

Contemporary Endocrinology
Series Editor: Leonid Poretsky

Dimiter Avtanski *Editor*

Adipose Tissue

Endocrine Functions, Health
Implications, and Future Perspectives

 Springer

Contemporary Endocrinology

Series Editor

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Preface

The understanding of adipose tissue has undergone a remarkable transformation in recent decades. Once viewed simply as a passive storage depot for excess energy, adipose tissue is now recognized as a dynamic endocrine organ with far-reaching effects on metabolism, inflammation, and overall health. This paradigm shift has profound implications for our understanding of obesity, diabetes, and related metabolic disorders, which collectively represent some of the most pressing public health challenges of our time.

In this volume, we aim to provide a comprehensive overview of adipose tissue as an endocrine organ and examine its complex biology and clinical significance. We explore the interplay between adipose tissue and various physiological systems, shedding light on how adipose dysfunction contributes to the pathogenesis of metabolic diseases that affect millions of people worldwide.

Our journey begins with an examination of the fundamental anatomy and physiology of adipose tissue, including the process of adipogenesis and the crucial roles played by both adipocytes and non-adipocytes. We then explore the metabolic functions of adipose tissue from energy storage and release to its involvement in glucose homeostasis and thermogenesis. A significant portion of this book is dedicated to unraveling the endocrine functions of adipose tissue, detailing the actions of various adipokines and their impact on insulin signaling and metabolic health.

Recognizing the critical importance of translating basic science into clinical practice, we present an in-depth analysis of the clinical implications of adipose tissue dysfunction. Through a series of studies, we illustrate the real-world impact of conditions such as obesity, lipodystrophies, and metabolic syndrome, emphasizing the importance of early detection and intervention. We also discuss the current management strategies, including lifestyle modifications and surgical interventions.

As we look to the future, we examine cutting-edge technological advances in adipose tissue research, including single-cell sequencing, multi-omics analyses, and artificial intelligence. These emerging technologies not only enhance our understanding of adipose tissue biology but also offer exciting possibilities for improved diagnostic and therapeutic approaches.

This book is intended for a diverse audience, including researchers, clinicians, and medical students at all levels. Our goal is to bridge the gap between basic science and clinical practice, facilitating connections that inform both future research directions and current patient care strategies.

The editor would like to express his sincere gratitude to the contributing authors for their exceptional work and to the staff at Springer Nature for their support in bringing this volume to fruition. We hope that this book will serve as a valuable resource in the ongoing efforts to understand and address the complex challenges posed by adipose tissue dysfunction in human health.

Salé, Morocco

Dimiter Avtanski

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Chapter 1

Significance of Adipose Tissue as an Endocrine Organ



Dimitar Avtanski and Radoslav Stojchevski

Abbreviations

ACTH	Adrenocorticotrophic hormone
A-FABP (<i>s.</i> FABP4)	Adipocyte fatty acid-binding protein
AGL (<i>s.</i> Lawrence syndrome)	Acquired generalized lipodystrophy
AGT	Angiotensinogen
AI	Artificial intelligence
AMPK	AMP-activated protein kinase
Ang II	Angiotensin II
ANGPTL-4	Angiopoietin-like protein-4
APL	Acquired partial lipodystrophy
ASC	Adipose-derived stem cell
AT	Adipose tissue
ATGL	Adipose triglyceride lipase
ATM	Adipocyte tissue macrophages
BAT	Brown adipose tissue
CAA	Cancer-associated adipocyte

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CAD	Coronary artery disease
CGL	Congenital generalized lipodystrophy
CTRP	C1q/TNF-related proteins
CVD	Cardiovascular diseases
DHEA	Dehydroepiandrosterone
ECM	Extracellular matrix
EGF	Epidermal growth factor
ER	Endoplasmic reticulum
EV	Extracellular vesicle
Fabp4 (<i>s. aP2</i>)	Fatty acid-binding protein 4
FetA	Fetuin-A
FFA	Free fatty acid
FGF	Fibroblast growth factor
FPLD	Familial partial lipodystrophy
GIP	Glucose-dependent insulinotropic polypeptide
GLP-1	Glucagon-like peptide-1
hADSC	Human adipose-derived stem cell
HGF	Hepatocyte growth factor
HIF-1 α	Hypoxia-inducible factor-1-alpha
HPA	Hypothalamic-pituitary-adrenal (axis)
HSD	Hydroxysteroid dehydrogenase
HSL	Hormone-sensitive lipase
IBD	Inflammatory bowel disease
IGF-I	Insulin-like growth factor 1
IL	Interleukin
IL-1Ra	Interleukin-1 receptor antagonist
ILC	Innate lymphoid cell
LCN2	Lipocalin-2
LH	Luteinizing hormone
MCP1 (<i>s. CCL2</i>)	Monocyte chemoattractant protein 1
Metnl	Meteorin-like (protein)
MetS	Metabolic syndrome
ML	Machine learning
MSC	Mesenchymal stem cell
NAFLD	Non-alcoholic fatty liver disease
NAMPT (<i>s. visfatin</i>)	Nicotinamide phosphoribosyltransferase
NK	Natural killer (cell)
PAI-1	Plasminogen activator inhibitor 1
PCOS	Polycystic ovarian syndrome
PDGF	Platelet-derived growth factor
PPAR α	Peroxisome proliferator-activated receptor-alpha
PVAT	Perivascular adipose tissue
RAAS	Renin-angiotensin-aldosterone system
RBP4	Retinol-binding protein 4
RIA	Radioimmunoassay
SAA	Serum amyloid A

scRNA-seq	Single-cell RNA sequencing
SeP	Selenoprotein P
SLE	Systemic lupus erythematosus
SNS	Sympathetic nervous system
SRD5A2	Steroid 5 alpha-reductase 2
SVF	Stromal vascular fraction
sWAT	Subcutaneous white adipose tissue
T2DM	Type 2 diabetes mellitus
TGF β	Transforming growth factor-beta
TNF	Tumor necrosis factor
UCP1	Uncoupling protein 1
uPA	Urokinase-type plasminogen activator
uPAR	Urokinase-type plasminogen activator receptor
UPR	Unfolded protein response
VEGF	Vascular endothelial growth factor
VLDL	Very-low-density lipoprotein
vWAT	Visceral white adipose tissue
WAT	White adipose tissue

Introduction

Adipose tissue (AT) has long been viewed as a mere energy reservoir and depository for storing excess energy as triglycerides. Contrary to this classical view, modern research has revealed that AT is more than an organ of energy storage. It is a dynamic endocrine organ with complex functions that regulates numerous physiological activities. It plays an important role in lipid and glucose metabolism, inflammation, and vascular homeostasis, releasing a variety of bioactive substances called adipokines, through which it communicates with other parts of the body. AT is today recognized for its role in promoting chronic low-grade inflammation, particularly in the context of obesity. The imbalance between pro- and anti-inflammatory factors secreted by AT contributes to the development of metabolic disorders such as insulin resistance, type 2 diabetes mellitus (T2DM), and cardiovascular diseases (CVDs).

This chapter introduces the endocrine function of AT, with particular reference to its diverse range of adipokines and how they contribute to metabolic, inflammatory, and systemic signaling activities. It also discusses how the deregulation of AT can be associated with the development of obesity and metabolic disorders; CVDs; endocrine, neurodegenerative, and immune diseases; and cancer. We attempted to outline the overall complexity of AT, highlighting its importance far beyond fat storage and how this understanding could be beneficial for developing new therapeutic targets and treatment principles for metabolic disorders.

Changing Perceptions of Adipose Tissue

Throughout the twentieth century, AT was viewed solely as a passive depot for energy storage in the form of triglycerides [1]. However, the remarkable progress in biochemistry, particularly with the invention of electron microscopy and the development of new techniques for cell isolation, uncovered intricate details of the AT anatomy and functions beyond those of passive energy storage. The introduction of radioimmunoassay (RIA) by Rosalyn Sussman Yalow and Solomon Berson in the 1950s [2] allowed for the quantification of hormones (such as insulin) circulating in AT. A milestone in AT research was the discovery of leptin in 1994 by Jeffrey M. Friedman [3], who recognized AT functions beyond passive energy storage and sparked research in the area. AT research has gained even greater momentum with the advancement in molecular biology and genetics, particularly with the advent of single-cell technologies, enabling researchers to analyze the whole genome, transcriptomics, proteomics, and metabolomics at the individual cell level [4]. One notable finding in AT research was the identification of significant amounts of brown AT in adult humans. This discovery opened new perspectives for therapeutic interventions aiming to increase energy expenditure in combating obesity and metabolic disorders.

Today, we comprehend AT as an active endocrine organ that secretes a myriad of factors playing diverse roles in lipid and glucose metabolism, inflammation, and vascular homeostasis. Through a dense network of nerves and vessels, AT is in constant communication with other organs in the control of homeostasis.

Adipose Tissue-Derived Endocrine Factors

Morphologically, AT can be classified into two main types: white adipose tissue (WAT) and brown adipose tissue (BAT), both of which are spatially distributed as separate depots possessing different secretory profiles and functions [5]. WAT is the predominant type of body fat and is divided into two significant subgroups: subcutaneous WAT (sWAT) stored beneath the skin and visceral WAT (vWAT) surrounding organs in the abdomen [6]. sWAT itself adds up to approximately 80% of the total body fat and serves as the main lipid storage [7]. It also plays a role in heat insulation, protection against infections, and mechanical stress [8]. On the other hand, vWAT is not typically present in large quantities in healthy individuals but is very active metabolically and continuously releases free fatty acids (FFAs) into the bloodstream. However, in a state of obesity, excessive fat accumulates in the vWAT and other ectopic locations, such as around the liver, heart, blood vessels, digestive organs, and kidneys, leading to insulin overproduction and resistance, inflammation, and arterial fat buildup [9, 10].

Although present in minimal amounts in adult humans, BAT is currently appreciated as an important regulator of metabolic health. In adults, BAT is mostly distributed in the upper back, above the clavicles, and around the vertebrae [11]. It derives its color from the high concentration of mitochondria within fat cells. The primary function of BAT is related to thermogenesis and energy expenditure through the conversion of FFAs into ATP via uncoupling protein 1 (UCP1)-facilitated oxidative

phosphorylation [12]. Similar to WAT, BAT is endocrine-active and characteristically secretes factors such as fibroblast growth factors (FGFs) and irisin [13, 14].

Besides classical WAT and BAT, a third type of AT (*beige* or *brite*) residing within WAT and comprising cells sharing characteristics of both WAT and BAT adipocytes has been identified. This tissue can successfully adapt to environmental stimuli and represents a promising target for metabolic interventions.

AT is an organ composed of adipocytes and a stromal vascular fraction (SVF) that includes preadipocytes, fibroblasts, and vascular smooth muscle, endothelial, and immune cells [15]. These components produce numerous communication molecules and regulators of metabolism that can be grouped into several major categories: adipokines, inflammatory and immunomodulatory components, growth and differentiation factors, metabolic regulators, and steroid hormones [16, 17]. Some AT-derived endocrine factors are listed in Table 1.1. Adipokines (such as leptin, adiponectin, and resistin) are a heterogeneous group of proteins produced

Table 1.1 Adipose tissue-derived endocrine factors and their association with obesity, type 2 diabetes mellitus, and cardiovascular diseases

Name	Obesity-associated changes in levels	Impact on T2DM	Impact on CVD	References
Adiponectin	Decreased	Enhances insulin sensitivity, reduces inflammation	Protective	[18–25]
Adipsin	Decreased	May promote insulin resistance	Limited data	[26]
Ang II	Increased	Contributes to insulin resistance	Promotes vasoconstriction, contributes to hypertension and oxidative stress	[27, 28]
Apelin	Increased	Decreases glucose metabolism, enhances glucose uptake, improves insulin sensitivity, reduces inflammation	Decreases blood pressure	[29–34]
Chemerin	Increased	Associated with insulin resistance and inflammation	Promotes atherosclerosis, links to MetS	[35–44]
CTRP1	Limited data	Potential benefit	Potential benefit	[45–51]
CTRP3	Decreased	Improves insulin sensitivity, reduces inflammation	Protects against atherosclerosis	[52–59]
CTRP5	Increased	Potential benefit	Potential benefit	[46, 47, 60–62]
CTRP9	Variable	Improves insulin sensitivity, reduces inflammation	Protects against atherosclerosis	[63–69]

(continued)

Table 1.1 (continued)

Name	Obesity-associated changes in levels	Impact on T2DM	Impact on CVD	References
IL-1 β	Increased	Impairs insulin signaling and β -cell function	Contributes to atherosclerosis and plaque instability	[70, 71]
IL-6	Increased	Contributes to insulin resistance and dyslipidemia	Promotes atherosclerosis and inflammation	[72–77]
Leptin	Increased	May increase risk	Increases risk	[78–84]
LCN2	Increased	May worsen insulin resistance and inflammation	Associated with atherosclerosis and heart failure	[85, 86]
MCP-1	Increased	Recruits inflammatory cells, promotes insulin resistance	Contributes to atherosclerosis	[87, 88]
Metnrl	Variable	Anti-insulin-resistant effects	Potential benefit	[89–92]
Nesfatin-1	Variable	May be protective, potential role in glucose regulation	Potential role in blood pressure regulation, heart rate, sympathetic nerve activity	[93–95]
Omentin	Decreased	Improves insulin sensitivity, reduces inflammation	Protects against atherosclerosis and vascular dysfunction	[96–100]
Progranulin	Increased	May increase risk	Complex/mixed	[101–105]
PAI-1	Increased	Contributes to insulin resistance, impairs fibrinolysis	Increases the risk of thrombosis, linked to CVD risk	[106, 107]
Resistin	Increased	May increase risk, may promote insulin resistance	May increase risk	[108–117]
SAA	Increased	Impairs insulin signaling, promotes inflammation	Marker of CVD risk, may promote atherosclerosis	[96, 118–120]
TNF	Increased	Promotes insulin resistance and inflammation	Contributes to endothelial dysfunction, atherosclerosis, and heart failure	[72, 121–128]
Vaspin	Variable	Mixed, improves insulin sensitivity	Potential protective role	[129–135]
Visfatin	Variable	Mixed	Mixed	[136–142]

Ang II angiotensinogen, *CTRP* C1q/TNF-related protein, *CVD* cardiovascular diseases, *IL* interleukin, *LCN2* lipocalin-2, *MetS* metabolic syndrome, *MCP1* monocyte chemoattractant protein 1, *MetS* metabolic syndrome, *PAI-1* plasminogen activator inhibitor-1, *SAA* serum amyloid A, *T2DM* type 2 diabetes mellitus, *TNF* tumor necrosis factor

particularly by the adipocytes [3, 143]. The inflammatory and immune-modulatory factors include various cytokines, chemokines, complement factors, and acute-phase proteins that play roles in the modulation of the inflammatory responses [144, 145]. AT also releases enzymes involved in lipid metabolism and inflammation, as well as lipid-based signaling molecules such as FFAs and triglycerides [146, 147]. The growth factors produced by AT regulate angiogenesis, adipogenesis, and tissue remodeling [148, 149]. Furthermore, AT is a significant source of steroid hormones, including estrogens, androgens, and glucocorticoids [150, 151]. The following sections discuss these categories of AT-derived compounds in more detail.

Adipokines

Adipokines are a large group of loosely classified signaling molecules unified by their production in the AT. These include substances with diverse chemical structures and roles in the control of energy balance, metabolism, and insulin action. Although the major source of adipokines is the adipocytes, other components of SVF, including preadipocytes, endothelial cells, fibroblasts, and immune cells (particularly macrophages), also contribute to adipokine production, albeit to a lesser extent [1]. Classical members of the adipokine group comprise leptin, adiponectin, resistin, and visfatin.

Initially discovered as a regulator of appetite by causing satiety, leptin is today considered a pleiotropic protein associated with energy homeostasis and immunity. Its main roles encompass controlling lipid turnover, energy expenditure, and the sustenance of glucose levels [152, 153]. It also activates the immune system [154, 155], modulates bone metabolism (particularly osteocalcin function) [156], and regulates reproduction [157]. Leptin acts as an adiposity signal, communicating with the brain in a negative feedback loop [156, 158, 159]. In contrast, adiponectin has opposing effects on balancing whole-body glucose and lipid regulation. It improves insulin sensitivity of the liver and skeletal muscles [160, 161] and regulates hepatic fatty acid oxidation [162, 163]. Resistin, gaining its name as a hormone that causes insulin resistance in peripheral tissues [108], is now also seen as a multifunctional hormone with various effects on inflammation, lipid, and vascular function. Resistin levels strongly correlate with the level of adiposity, peaking in obese individuals, and are used as predictive markers for metabolic syndrome (MetS) and T2DM [109]. Visfatin is another adipokine associated with metabolic diseases and is positively correlated with obesity indices [164, 165]. Other significant but less well-studied adipokines include apelin, omentin, vaspin, C1q/TNF-related protein (CTRP) family members (CTRP3 and CTRP9), nicotinamide phosphoribosyl-transferase (NAMPT, also known as visfatin), and retinol-binding protein 4 (RBP4).

The adipokine secretion profile varies significantly among different AT depots. For instance, sWAT produces higher levels of leptin and adiponectin than vWAT. In contrast, vWAT secretes more pro-inflammatory adipokines, such as interleukin (IL)-6 (IL-6), tumor necrosis factor (TNF), and monocyte chemoattractant protein 1

(MCP1, *s.* CCL2). The depot-specific adipokine profile contributes to the distinct metabolic and endocrine effects associated with different body fat distributions. For example, the increased pro-inflammatory adipokine secretion from vWAT is thought to contribute to the higher metabolic risk associated with visceral obesity [1, 166].

Inflammatory and Immune-Modulatory Factors

AT is a significant source of a diverse range of molecules that positively or negatively influence inflammation and immune responses [1]. These molecules can be broadly divided into pro-inflammatory and anti-inflammatory factors [16]. While adipocytes contribute to the production of these inflammatory factors, infiltrating immune cells, particularly macrophages, are major sources of pro-inflammatory cytokines in obese AT [145, 167]. Well-established pro-inflammatory factors secreted by AT include TNF, IL-6, IL-1 β , MCP1, and plasminogen activator inhibitor-1 (PAI-1) [144, 168]. Several other molecules with diverse physiological roles have emerged as key regulators of AT inflammation. These include lipocalin-2 (LCN2), chemerin, angiotensin II (Ang II), serum amyloid A (SAA), and adipokines such as adipsin, omentin, vaspin, and CTRP family members [98, 169–175]. The role of these factors in the inflammation of AT and their potential links to obesity-related conditions are currently areas of active investigation [176, 177].

On the other hand, AT also produces anti-inflammatory factors, such as adiponectin, IL-10, and IL-1 receptor antagonist (IL-1Ra), which help to counterbalance pro-inflammatory effects [16]. The balance between anti-inflammatory and pro-inflammatory adipokines is tightly regulated, and its disruption is associated with the pathogenesis of obesity-related complications [178, 179]. The following sections discuss the pro- and anti-inflammatory factors produced by AT in more detail.

Pro-Inflammatory Factors

Among the pro-inflammatory factors produced by AT, TNF, IL-6, IL-1 β , MCP1, PAI-1, LCN2, chemerin, Ang II, SAA, and adipsin play important roles in regulating AT physiology in health and disease [16, 177, 180–184]. AT dysfunction in obesity is associated with hypertrophy (enlarged adipocyte size) and hyperplasia (increased adipocyte numbers). These changes lead to disturbed adipocyte maturation and adipokine production, adipocyte cell death, and infiltration of adipocyte tissue macrophages (ATMs) [185–188]. MCP1 is one of the critical molecules recruiting macrophages to AT, amplifying the inflammatory response [181]. In lean AT, resident macrophages are predominantly of the anti-inflammatory M2 phenotype, while obesity induces a shift toward pro-inflammatory M1 macrophages [189]. The shift toward the production of pro-inflammatory adipokines may cause the progression of chronic low-grade inflammation, which, if persistent, could further lead to dyslipidemia, impaired glucose tolerance of peripheral tissues (such as skeletal

muscles and the liver), insulin resistance, T2DM, and CVD [190–195]. Among the pro-inflammatory adipokines, the levels of TNF (produced mainly by ATMs) and IL-6 correlate positively with AT hypertrophy and are important for the initiation of obesity-induced chronic inflammation and impaired insulin signaling [144, 145, 178, 196–198]. TNF and IL-6 can directly interfere with insulin receptor signaling pathways, leading to decreased insulin sensitivity in AT and other metabolic organs [199]. These pro-inflammatory factors act not only locally within AT but also systemically, affecting distant organs, such as the liver, muscle, and vasculature, contributing to whole-body metabolic dysfunction [200].

Anti-Inflammatory Factors

In addition to pro-inflammatory factors, AT produces various anti-inflammatory adipokines that are important for maintaining AT homeostasis and preventing the development of obesity-related metabolic disorders [16]. Among these factors, adiponectin, omentin, vaspin, and some CTRP proteins (such as CTRP3 and CTRP9) are well-characterized [201–203]. Adiponectin, the most abundant adipokine, enhances insulin sensitivity, reduces inflammation, and exerts cardioprotective effects [16]. Omentin improves insulin signaling and glucose uptake, whereas vaspin improves insulin sensitivity and reduces food intake [204]. CTRP3 and CTRP9 have emerged as important metabolic regulators with anti-inflammatory properties [205]. These anti-inflammatory adipokines counterbalance the effects of pro-inflammatory factors, helping to resolve inflammation, improve insulin sensitivity, and maintain metabolic homeostasis [206].

The balance between pro- and anti-inflammatory factors in the AT is essential for maintaining metabolic health. In obesity, this balance is often disrupted, with a decrease in the production of anti-inflammatory factors and an increase in the production of factors with pro-inflammatory action [178]. Understanding the roles of anti-inflammatory factors has opened new avenues for potential therapeutic interventions in obesity-related metabolic disorders [206].

Growth and Differentiation Factors

AT is a source of differentiation and growth factors that play a role in maintaining homeostasis, and its dysfunction contributes to the development of obesity-related complications. These factors support AT angiogenesis, growth, and development in both autocrine and paracrine manners while also having systemic effects, particularly in states of obesity [207]. Among these factors, the most prominent are FGFs, vascular endothelial growth factor (VEGF), and transforming growth factor-beta (TGF β) [208]. FGFs, particularly FGF21, participates in the regulation of glucose and lipid metabolism, VEGF is essential for AT vascularization, which is critical

for tissue expansion and metabolic health, while TGF β is involved in regulating adipocyte differentiation and extracellular matrix (ECM) remodeling [209]. Other important growth factors produced by AT include insulin-like growth factor 1 (IGF-I), which promotes adipocyte differentiation and glucose uptake, and hepatocyte growth factor (HGF), which is involved in adipogenesis and angiogenesis [210].

The growth and differentiation factors are primarily produced by the mesenchymal stem cells (MSCs) within the AT [211, 212], which possess multipotent characteristics that can differentiate into cells of mesodermal origin (such as adipocytes, chondrocytes, and osteoblasts). Additionally, adipose-derived stem cells (ASCs) (a subset of MSCs) can indirectly stimulate angiogenesis and neovascularization through the release of various paracrine factors [213, 214].

The expression and secretion of these growth factors are often dysregulated in obesity. For instance, VEGF levels may be insufficient to support healthy vascularization of the expanding AT, contributing to hypoxia and inflammation [186].

Angiogenic and Adipogenic Factors

The expansion of AT in obesity requires the formation of new blood vessels (angiogenesis) to transport oxygen and nutrients to the growing tissue [215, 216]. This process is regulated by AT through the production of various pro- and antiangiogenic factors. AT-derived growth factors, including VEGF, FGF21, insulin-like growth factor I (IGF-I), and platelet-derived growth factor (PDGF), promote angiogenesis within AT [148, 186, 207, 217–226] while also playing roles in adipogenesis (differentiation of mature adipocytes from precursor cells) [227]. VEGF is a potent stimulator of endothelial cell proliferation and migration, which is key for forming new blood vessels; FGF21 promotes angiogenesis and regulates glucose and lipid metabolism; and IGF-I stimulates angiogenesis and adipocyte differentiation [209]. In contrast, other factors, such as the serine protease inhibitors serpins (particularly PAI-1) and angiopoietin-like protein-4 (ANGPTL-4), regulate the action of the pro-angiogenic factors, thus contributing to the inhibition of angiogenesis [228, 229]. ANGPTL-4 inhibits angiogenesis by suppressing endothelial cell proliferation and migration, whereas PAI-1 can inhibit angiogenesis by interfering with the proteolytic cascades necessary for blood vessel formation [223]. Besides growth factors, evidence suggests that some adipokines, such as leptin and adiponectin, also regulate various aspects of angiogenesis [230]. Leptin promotes angiogenesis by stimulating endothelial cell tube formation and migration, whereas adiponectin has been shown to have both pro- and antiangiogenic effects depending on the context [148].

In rapidly expanding AT, angiogenesis may not keep pace with tissue growth, leading to areas of hypoxia. This hypoxia can trigger the expression of pro-angiogenic factors such as VEGF but can also contribute to inflammation and insulin resistance if prolonged [186].

Multifactorial Growth Factors

Besides the growth factors involved in the regulation of angiogenic processes, AT produces a variety of other growth factors with diverse functions, such as HGF and TGF β . HGF is involved in insulin signaling, glucose metabolism, β -cell homeostasis, and AT angiogenesis and is a major contributing factor to the pathophysiology of insulin resistance and T2DM [231]. HGF has been shown to induce insulin resistance in adipocytes by activating the PI3K/Akt signaling pathway, which leads to increased glucose uptake and reduced insulin sensitivity. Paradoxically, HGF also exerts protective effects on pancreatic β -cells, highlighting its complex role in metabolic regulation [232]. TGF β regulates adipose metabolism, inflammation, fibrosis, and angiogenesis. Studies have shown that blocking TGF β signaling protects against diet-induced obesity and insulin resistance [233–235]. TGF β expression is negatively associated with AT browning due to its inhibition of the expression of key thermogenic genes, such as UCP1. This suggests that TGF β signaling may be a potential therapeutic target for increasing energy expenditure in obesity [234]. Epidermal growth factor (EGF) is another multifactorial growth factor with pleiotropic effects on AT. Besides being an angiogenic factor, EGF regulates adipocyte differentiation through its receptor, EGFR. EGF expression is upregulated during adipocyte differentiation, whereas inhibition of EGFR signaling in human adipose-derived stem cells (hADSCs) suppresses adipogenic differentiation [236].

In addition, cross talk exists between these growth factors and adipokines. For example, adiponectin has been shown to modulate HGF expression, while leptin can influence TGF β signaling, highlighting the complex regulatory network within AT [237, 238].

The complex roles of these growth factors make them potential targets for therapeutic interventions. For instance, inhibition of TGF β signaling or modulation of HGF activity could potentially improve insulin sensitivity and metabolic health in obesity [239].

Metabolic Regulators

The major function of AT is to maintain metabolism by producing various metabolic regulatory molecules. Besides adipokines discussed earlier, other molecules, such as angiotensinogen (AGT), RBP4, adipose triglyceride lipase (ATGL), hormone-sensitive lipase (HSL), and adipocyte fatty acid-binding protein (A-FABP, also known as FABP4), are essential metabolic regulators exerting a significant impact on adipogenesis and energy homeostasis [240–242]. ATGL initiates lipolysis by hydrolyzing triglycerides to diglycerides, whereas HSL primarily acts on diglycerides to produce monoglycerides. This coordinated action regulates the release of fatty acids from the AT in response to metabolic needs [243].

AGT is a precursor protein of angiotensin II (Ang II), a component of the renin-angiotensin-aldosterone system (RAAS), that regulates fluid balance and blood

pressure [244, 245]. AGT also contributes to insulin resistance by interfering with insulin signaling pathways and promoting oxidative stress and inflammation [244, 246, 247]. RBP4 is associated with metabolic diseases and insulin resistance, whereas ATGL and HSL are involved in regulating lipolysis by influencing the release of fatty acids from AT into the bloodstream [248–250]. A-FABP acts as a fatty acid chaperone and hormone that influences lipid homeostasis, inflammation, and thermogenesis [251]. A-FABP not only facilitates fatty acid transport but also interacts with hormone-sensitive lipase to modulate lipolysis. Moreover, it has been implicated in cholesterol trafficking and inflammatory responses [251]. The diverse roles of these metabolic regulators make them potential targets for therapeutic intervention. For example, the inhibition of A-FABP or modulation of RBP4 levels has been explored as a strategy to improve insulin sensitivity and metabolic health in obesity [252].

The metabolic regulatory functions of AT vary depending on its location, with sWAT being more metabolically beneficial than visceral WAT [240]. This difference is evident in obesity, where elevated levels of Ang II associated with increased visceral fat contribute to hypertension and chronic inflammation, further exacerbating metabolic health [242, 246].

Steroid Hormones

AT produces enzymes necessary for de novo steroid biosynthesis from cholesterol and converts steroid precursors into active steroid hormones, including estrogens (estrone, estradiol, and estriol), androgens (androstenedione and testosterone), progestogens (progesterone), and glucocorticoids (cortisol and cortisone) [253–256]. AT also synthesizes dehydroepiandrosterone (DHEA), which can be converted to testosterone, estradiol, or other active sex hormones [257]. The conversion of steroid hormones in AT is catalyzed by locally produced steroidogenic enzymes such as 17 β -hydroxysteroid dehydrogenase (HSD17B); cytochrome P450 family members CYP11A1, CYP17A1, and CYP19; hydroxysteroid dehydrogenases HSD3B2 and HSD17B3; and steroid 5 α -reductase 2 (SRD5A2) [258–260]. The steroidogenic activity of AT is regulated by various factors, including hormones such as adrenocorticotrophic hormone (ACTH) and luteinizing hormone (LH), as well as local factors such as inflammatory cytokines and adipokines. This regulation ensures that steroid production in AT responds to both systemic and local metabolic needs [253].

AT-derived steroid hormones maintain metabolic processes and are important for the normal functioning of adipocytes and gender-related fat depot distribution [254]. The ability of AT to produce and metabolize steroid hormones exemplifies the concept of *intracrinology*, where cells can produce active hormones for their own use or for paracrine effects on neighboring cells without releasing significant amounts into the circulation [261]. The steroid-producing role of AT plays a significant role during the postmenopausal period in women when the main source of estrogen shifts from the ovaries to AT and other tissues [255]. AT-derived estrogens are important for maintaining metabolic health, particularly in postmenopausal women. They also contribute

to insulin sensitivity, lipid metabolism, and energy homeostasis. However, excessive estrogen production by AT can lead to adverse metabolic effects [262]. In addition to estrogens, glucocorticoids regulate various aspects of AT function, including adipocyte differentiation, inflammation, oxidative stress, and adipokine expression through the activation of glucocorticoid receptors [263, 264].

Dysregulation of AT-produced steroid hormones has been linked to obesity, insulin resistance, and polycystic ovarian syndrome (PCOS) [265, 266] and contributes to the development and progression of hormone-related cancers, such as breast and endometrial cancers [267, 268]. Understanding steroid hormone production in AT provides opportunities for developing new therapeutic interventions. One such potential option would be modulating the activity of specific steroidogenic enzymes in AT, which could potentially be used to treat hormone-related disorders or metabolic diseases.

Adipose Tissue and Systemic Signaling

The recognition of AT as an endocrine organ that controls whole-body metabolism and inflammatory responses has led to a reevaluation of the traditional definition of the endocrine system [1, 17, 240, 269, 270]. AT adapts to different physiological states, such as fasting, feeding, exercise, and stress. These adaptations involve changes in the production and secretion of adipokines, which in turn influence the function of other organs [270]. The endocrine function of AT produces hormones and responds to various endocrine signals, creating a complex network of feedback loops [271]. AT is in permanent communication with other organs and tissues with endocrine secretion, such as the hypothalamus, liver, stomach, intestine, and skeletal muscles [178, 180, 272–275]. The liver produces various hormones essential for metabolism and energy homeostasis [276, 277], while the stomach and intestines that secrete hormones, such as ghrelin and incretins, control appetite, energy balance, and glucose homeostasis [278].

The gut microbiome is another important factor that affects AT metabolism, inflammation, and energy balance [279–284]. It influences AT function through multiple mechanisms, including the production of short-chain fatty acids, regulation of bile acid metabolism, and modulation of the intestinal barrier. These interactions can affect AT inflammation, insulin sensitivity, and energy storage capacity [285].

The following sections discuss some of the major organs and tissues with endocrine functions that are closely associated with AT.

Hypothalamus

The hypothalamus is a brain region that regulates appetite, energy balance, and metabolism [286]. The AT and hypothalamus are involved in a complex bidirectional relationship. AT-derived hormones, such as leptin, adiponectin, and resistin, directly modulate hypothalamic function by targeting hypothalamic neurons to

regulate feeding behavior and thermogenesis [287–289]. Leptin, often called the *satiety hormone*, acts on the arcuate nucleus of the hypothalamus to suppress appetite and increase energy expenditure [290]. However, in obesity, leptin resistance can develop, leading to a breakdown of this regulatory mechanism [291]. In contrast, during periods of increased energy demand, the hypothalamus can mobilize energy stores by activating the sympathetic nervous system (SNS), which can lead to lipolysis in adipocytes and the release of FFAs in the circulation [292–297]. The sympathetic nervous system not only induces lipolysis but also regulates adipokine secretion and adipocyte differentiation. Chronic sympathetic activation, as observed in obesity, can lead to inflammation and insulin resistance in AT [294].

Disruption of the AT-hypothalamus interaction in obesity and metabolic conditions can lead to impaired hypothalamic function and AT dysfunction. AT dysfunction can affect hypothalamic function through various mechanisms. One such mechanism involves the infiltration of ATMs into the hypothalamus, leading to neuroinflammation and neuronal impairment [298, 299]. Hypothalamic inflammation, which is partly induced by saturated fatty acids and inflammatory cytokines, is now recognized as a key factor in the development of obesity and metabolic syndrome. Inflammation can lead to leptin and insulin resistance in the hypothalamus, further exacerbating metabolic dysfunction [298]. AT-derived extracellular vesicles (EVs) can act on the hypothalamus to modulate energy intake, serving as an additional way of communication between AT and the hypothalamus [300, 301]. The hypothalamic-pituitary-adrenal (HPA) axis is an important pathway through which the hypothalamus regulates AT function [287, 302]. Activation of the HPA axis triggers the release of glucocorticoids, which can influence AT metabolism and distribution [303]. Recent research has shown that the hypothalamus can induce *browning* of WAT through sympathetic activation, leading to increased energy expenditure. This represents another important aspect of the hypothalamus-AT interaction in energy homeostasis [304].

Liver

The liver is a central organ in energy and glucose regulation and serves as a significant site of fat storage [305]. The liver and AT actively exchange signals to maintain their metabolic homeostasis. AT-derived adiponectin, leptin, and resistin target liver function and regulate insulin sensitivity and glucose levels [274]. Decreased serum adiponectin levels in obesity are associated with hepatic adipokine resistance and the development of nonalcoholic fatty liver disease (NAFLD) [306, 307]. Adiponectin improves hepatic insulin sensitivity and shows anti-inflammatory and anti-fibrotic effects in the liver. It acts through AMP-activated protein kinase (AMPK) and peroxisome proliferator-activated receptor- α (PPAR α) pathways to enhance fatty acid oxidation and reduce gluconeogenesis [308].

In contrast, liver-produced growth factors such as IGF-I and FGF21 influence AT metabolism and insulin sensitivity [309]. FGF21, primarily produced by the liver, acts on AT to enhance glucose uptake, improve insulin sensitivity, and promote the

browning of WAT. In turn, AT sensitizes the body to the effects of FGF21, creating a feedback loop between these organs [310]. The liver also produces hepatokines, such as fetuin-A (FetA) and selenoprotein P (SeP), which can influence AT function. For instance, FetA has been shown to impair insulin signaling in adipocytes and promote inflammation in AT [311].

Dysregulation of AT function in obesity state can lead to an increased influx of FFAs to the liver, contributing to the development of NAFLD and other metabolic disorders [312]. The increased influx of FFAs to the liver in obesity overwhelms the liver's capacity for fatty acid oxidation and very-low-density lipoprotein (VLDL) secretion. This leads to hepatic lipid accumulation, which triggers inflammation and oxidative stress, key features of NAFLD progression [312]. Besides its interaction with AT, the liver engages in cross talk with other organs and tissues, including the pancreas, skeletal muscles, and brain, to maintain overall metabolic homeostasis [313].

Pancreas

The pancreas is a vital organ in both endocrine and exocrine systems. The pancreas secretes hormones, such as insulin and glucagon, which are essential for regulating blood glucose levels [314]. Insulin resistance occurs when tissues become less responsive to insulin, leading to decreased glucose uptake in the muscle and AT and impaired suppression of hepatic glucose production. This results in elevated blood glucose levels and compensatory hyperinsulinemia, which can eventually lead to β -cell exhaustion and T2DM [315]. Glucagon, produced by pancreatic α -cells, acts as a counter-regulatory hormone to insulin. It promotes hepatic glucose production and lipolysis in the AT. A balance between insulin and glucagon is essential for maintaining glucose homeostasis [316].

Adipokines secreted by AT can influence pancreatic function, thereby affecting insulin sensitivity [317]. Leptin regulates pancreatic function by promoting cell proliferation, glucose metabolism, and insulin secretion [318, 319]. Resistin affects various aspects of pancreatic function by impairing insulin action and contributing to insulin resistance [108]. On the other hand, adiponectin exerts its effects on the pancreas by promoting β -cell regeneration and improving pancreatic islet lipid metabolism [320]. IL-6 and TNF also impact pancreatic function and contribute to insulin resistance [144, 317, 321].

The incretin hormones glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), synthesized by the gut in response to food intake, enhance insulin secretion and sensitivity. Interestingly, AT has been shown to express receptors for these incretins, suggesting a direct link between incretin activity and AT function [322].

The expansion of AT and the resulting hypoxia in obesity leads to the release of adipocyte-specific fatty acid-binding protein 4 (Fabp4, *s. aP2*) and other factors, which can stimulate acute insulin secretion from β -cells [323, 324]. In the early stages of obesity, pancreatic β -cells often compensate for insulin resistance by

increasing insulin secretion. This compensation is supported by factors released from expanding AT, including Fabp4. However, chronic overstimulation can lead to β -cell dysfunction and eventual failure, contributing to T2DM [325].

Skeletal Muscles

AT and skeletal muscles interact extensively through the secretion of adipokines and myokines (cytokines and other peptides released by skeletal muscle cells that act in an endocrine, paracrine, and autocrine manner) to maintain metabolic homeostasis and regulate insulin sensitivity [326–331]. The cross talk between AT and skeletal muscles represents a complex endocrine loop where adipokines and myokines mutually influence each other's production and function [329]. AT-produced adiponectin enhances insulin sensitivity in skeletal muscles, promotes glucose uptake, and improves metabolic control [332]. Additionally, adiponectin and leptin can activate AMPK, thereby increasing skeletal muscle fatty acid oxidation [333, 334]. Conversely, myokines produced by the skeletal muscles can affect AT function. For example, irisin may increase the thermogenic capacity of WAT by promoting “browning,” a process characterized by the expression of UCPI and increased mitochondrial activity [335, 336]. IL-6 can exert both pro- and anti-inflammatory effects on AT and stimulate AT lipolysis [337–340]. Other important myokines include myostatin, which inhibits muscle growth and influences AT metabolism, and meteorin-like (Metrl), which promotes AT browning and improves insulin sensitivity [341].

AT dysfunction affects the cross talk between AT and skeletal muscles by increasing the influence of resistin and other pro-inflammatory cytokines on skeletal muscle insulin resistance, potentially leading to the development of metabolic disorders [108, 144, 342]. Intramuscular AT, which increases with obesity and aging, can directly affect muscle function and insulin sensitivity. Ectopic fat deposition can lead to local inflammation and impaired insulin signaling in muscle cells [343]. Exercise significantly alters AT-skeletal muscle cross talk as it increases the production of beneficial myokines, enhances AT insulin sensitivity, and promotes a favorable adipokine profile. Exercise-induced changes contribute to improved metabolic health and highlight the importance of physical activity in maintaining balance between these tissues [344].

Immune System

AT plays a key role in the initiation and modulation of both the innate and adaptive immune responses [345, 346]. AT hosts a diverse repertoire of immune cells, including macrophages, T and B cells, natural killer (NK) cells, innate lymphoid cells (ILCs), and eosinophils, which, alongside adipocytes, produce a variety of pro- and anti-inflammatory cytokines [347]. The balance and phenotype of these cells change

with obesity, contributing to the inflammatory state [348]. Adipokines, such as leptin and adiponectin, directly modulate immune cell function. Leptin promotes T-cell activation and inflammatory cytokine production, whereas adiponectin has anti-inflammatory effects, suppressing macrophage activation and promoting the generation of anti-inflammatory M2 macrophages [183].

Under healthy conditions, AT cytokines are maintained in tight balance, supporting normal immune responses against infections. In lean AT, macrophages are predominantly of the M2 anti-inflammatory phenotype; however, obesity induces a shift toward the M1 pro-inflammatory phenotype [167]. AT dysfunction leads to the infiltration and accumulation of immune cells within AT, promoting the development of low-grade chronic inflammation. This altered inflammatory state affects immune system function and triggers insulin resistance [349–351]. Chronic low-grade inflammation associated with obesity is often referred to as *metabolic inflammation* or *metaflammation*. This type of inflammation is unique because it is triggered by metabolic signals and involves many of the same molecular pathways activated during classical inflammation [195]. Conversely, in cases of malnutrition, the shrinking of AT diminishes immune system function, thus increasing susceptibility to infections [352–354].

Endothelium

AT interacts with the endothelium through endocrine and paracrine mechanisms and plays a role in angiogenesis and vascular function [148]. Many adipokines, such as TNF, IL-6, and VEGF, act as pro-angiogenic factors, while others, such as serpins, including vaspin and PAI-1, have antiangiogenic functions [355, 356]. Adiponectin promotes endothelial nitric oxide production, suppresses endothelial cell activation, and inhibits vascular smooth muscle cell proliferation, protecting against atherosclerosis [16].

TNF is a potent inducer of VEGF expression, one of the most powerful drivers of angiogenesis, promoting endothelial cell survival and proliferation [357, 358]. TNF also induces the expression of other pro-angiogenic factors, such as basic fibroblast growth factor (bFGF) and IL-8 [359, 360]. IL-6 also stimulates VEGF production by directly influencing endothelial cell proliferation, migration, and tube formation. It is important to note that TNF and IL-6 may also exert antiangiogenic effects, depending on the specific context [361]. In obesity, rapid AT expansion can outpace angiogenesis, leading to areas of hypoxia. Hypoxia triggers the expression of hypoxia-inducible factor-1-alpha (HIF-1 α), which in turn upregulates VEGF and other pro-angiogenic factors. However, chronic hypoxia can also contribute to inflammation and insulin resistance in AT [362].

PAI-1 is a primary inhibitor of urokinase-type plasminogen activator (PA), which activates plasmin, an enzyme that degrades the ECM [363]. Decreased ECM breakdown creates a physical barrier that hinders endothelial cell movement, which is crucial for angiogenesis [364]. Conversely, PAI-1 can bind to the uPA receptor

(uPAR), triggering a pro-angiogenic response through the modulation of cell adhesion and signaling pathways [365, 366]. Perivascular AT (PVAT), which surrounds most blood vessels, plays a unique role in vascular function. PVAT produces vasoactive substances that directly influence vascular tone and inflammation. In obesity, PVAT dysfunction contributes to vascular insulin resistance and endothelial dysfunction [367].

Serpins play diverse roles in cellular processes, particularly in reducing oxidative stress and improving endothelial cell survival [135]. They also suppress vascular inflammation, a major driver of vascular dysfunction and diseases such as atherosclerosis [368]. Moreover, serpins are involved in the regulation of fibrinolysis, and their overexpression can contribute to atherogenic changes [369].

The interaction between AT and endothelium has significant implications for metabolic health. Dysregulation of this interaction, as observed in obesity, contributes to endothelial dysfunction, a key early step in the development of atherosclerosis and other cardiovascular diseases. Understanding these interactions may reveal new therapeutic targets for obesity-related vascular complications [370].

Adipose Tissue Dysfunction

Adipose Tissue Hypertrophy

AT expansion occurs through hyperplasia (increase in cell number) or hypertrophy (increase in cell size) [371, 372]. The number of adipocytes in fat depots stabilizes during neonatal development and early childhood. Later in life, hypertrophic expansion typically occurs because of persistent overnutrition [373], as existing adipocytes capture and retain excessive circulating lipids [374]. As a result of an imbalance between energy intake and expenditure, AT initially expands because of subcutaneous hyperplasia. Overnutrition can also activate WAT browning in response to increased energy expenditure; however, this adaptive response is often insufficient to counteract the negative effects of AT hypertrophy [375]. After this process reaches its limit, hypertrophy occurs, which leads to AT dysfunction. Enlarged adipocytes have a reduced capacity for lipid storage. Consequently, excessive fat accumulates in visceral and ectopic sites, including the skeletal muscles, liver, and pancreas [376]. Hyperplasia is limited in conditions of extreme hypertrophic obesity, and further hypertrophic expansion causes lipotoxicity—a MetS that contributes to the onset of obesity-related diseases [377–379]. Adipocyte hypertrophy in obesity is manifested by pathological AT remodeling, which includes deregulated adipo- and angiogenesis, hypoxia, and adipocyte death. Dysregulated adipogenesis affects normal adipocyte secretion and, together with the increased infiltration of ATMs, leads to the development of chronic low-grade inflammation manifested by increased expression of pro-inflammatory factors (such as TNF, IL-6, and leptin) and decreased expression of anti-inflammatory factors (adiponectin and others) [186, 380, 381]. This dramatic change in AT links AT hypertrophy to many pathophysiological

conditions, including dyslipidemia, insulin resistance, T2DM, endothelial dysfunction, CVD, and NAFLD [382–384].

Insulin Resistance and Diabetes

AT dysfunction, in the context of obesity-induced hypertrophy, is the main driver for the development of insulin resistance and T2DM. As summarized from the previous sections, this is mediated through several mechanisms: (1) *altered adipokine secretion* (hypertrophic adipocytes exhibit a shift in their adipokine profile toward the production of pro-inflammatory cytokines, leading to a chronic low-grade inflammatory state) [16]; (2) *ectopic lipid accumulation* (as adipocytes reach their storage capacity, excess lipids are stored in non-AT such as the liver, skeletal muscle, and pancreas, which impairs insulin signaling in these tissues) [385]; (3) *chronic low-grade inflammation* (as mentioned above, the resulting chronic low-grade inflammation caused by dysfunctional adipocytes leads to activation of stress-response signaling pathways, such as JNK and IKK- β /NF- κ B, which interfere with insulin signaling) [195]; (4) *FFA influx* (hypertrophic adipocytes exhibit increased lipolysis, leading to elevated circulating FFAs, which can directly induce insulin resistance in the skeletal muscle and liver, and contribute to pancreatic β -cell dysfunction) [386]; (5) *AT hypoxia* (rapid AT expansion can outpace angiogenesis, resulting in areas of hypoxia, which can trigger the expression of pro-inflammatory factors and contribute to insulin resistance) [362]; and (6) *endoplasmic reticulum (ER) stress* (adipocyte hypertrophy induces ER stress, which can activate the unfolded protein response (UPR); chronic UPR activation can lead to insulin resistance through different mechanisms, including inhibition of insulin receptor signaling) [387].

The progression from insulin resistance to T2DM occurs when pancreatic β -cells can no longer compensate for the reduced insulin sensitivity by increasing insulin production. This β -cell failure is partly because of the lipotoxic and glucotoxic effects of chronic hyperglycemia and hyperlipidemia, as well as the impact of pro-inflammatory cytokines produced by dysfunctional AT [388].

Cardiovascular Diseases

AT dysfunction is also associated with the pathogenesis of various CVDs, including hypertension, atherosclerosis, coronary artery disease (CAD), and heart failure [273]. AT dysfunction contributes to CVDs through multiple mechanisms, including systemic inflammation, altered lipid metabolism, insulin resistance, and endothelial dysfunction. Excess visceral adiposity is associated with increased cardiovascular risk [389]. Among the cytokines produced by AT, adiponectin has particularly been shown to exert cardioprotective effects by maintaining endothelial function, reducing inflammation, and modulating lipid metabolism [390]. Adiponectin exerts its cardioprotective effects by activating AMPK and other

signaling pathways. This leads to improved endothelial function, reduced vascular inflammation, and enhanced insulin sensitivity [390]. In contrast, high levels of pro-inflammatory adipokines, such as leptin and resistin, are positively associated with the risk of cardiovascular events [391]. Other adipokines also play a role in cardiovascular health. For example, omentin-1 has anti-inflammatory and vasodilatory effects, whereas chemerin and visfatin are associated with increased inflammation and atherosclerosis risk [392]. Recent research has highlighted the existence of an *AT-myocardial axis*, in which dysfunctional AT, particularly epicardial fat, can directly influence cardiac function through paracrine effects [393].

Endocrine Disorders

Through endocrine secretion, AT also affects the function of other endocrine organs. AT dysfunction can disrupt the hypothalamic-pituitary-gonadal axis, alter steroid hormone metabolism, and influence thyroid hormone function through the secretion of various adipokines and inflammatory mediators [240]. Thus, AT dysfunction may lead to the development of endocrine disorders such as PCOS, Cushing's syndrome, hypogonadism, or thyroid dysfunction [394–397]. In PCOS, AT dysfunction contributes to insulin resistance and hyperandrogenism. Excess visceral adiposity leads to increased production of inflammatory cytokines and altered adipokine secretion, particularly decreased adiponectin and increased leptin levels, exacerbating the metabolic and reproductive features of PCOS [398]. Consequently, these conditions may worsen the chronic inflammatory state, alter adipokine secretion, and further contribute to metabolic disorders. The relationship between AT dysfunction and endocrine disorders is bidirectional. For instance, although obesity can contribute to thyroid dysfunction, thyroid hormones also play a crucial role in regulating AT metabolism and differentiation [399]. The interplay between AT dysfunction and endocrine disorders can create a vicious cycle, potentially leading to long-term health consequences, such as an increased risk of T2DM, CVD, and certain cancers.

Lipodystrophy

Lipodystrophies are a rare group of conditions characterized by abnormal fat distribution, i.e., loss of fat in some body parts and abnormal gain in others. They can be present at birth (congenital) or develop later in life and can affect the whole body (generalized) or only certain areas (partial) [400]. Lipodystrophies result from genetic mutations affecting adipocyte development, function, or survival or can be acquired due to autoimmune processes or medication side effects. Loss of functional AT leads to ectopic fat deposition in other organs, contributing to metabolic complications [401]. These conditions arise from factors such as impaired differentiation of fat cells and disrupted function or premature death of fat cells [402]. Lipodystrophies are often associated with dyslipidemia, insulin resistance, diabetes, hypertriglyceridemia, fatty liver disease, and CVD [400, 403].

Leptin deficiency is a hallmark of generalized lipodystrophy. Leptin replacement therapy has shown promising results in managing metabolic complications in patients with lipodystrophy, demonstrating the role of leptin in metabolic regulation [404]. Some of the known lipodystrophies are congenital generalized lipodystrophy (CGL), also known as Berardinelli-Seip syndrome, familial partial lipodystrophy (FPLD) or Köbberling–Dunnigan syndrome, acquired generalized lipodystrophy (AGL, also known as Lawrence syndrome), and acquired partial lipodystrophy (APL) or Barraquer-Simons syndrome. The extent of metabolic derangements related to these syndromes is positively correlated with the degree of lipoatrophy [405]. HIV-associated lipodystrophy, a common form of acquired partial lipodystrophy, is associated with antiretroviral therapies. It is characterized by peripheral fat loss and central fat accumulation, leading to metabolic complications similar to those observed in other forms of lipodystrophy.

Other Pathologies Related to Adipose Tissue Dysfunction

Immune Diseases

Given that AT is a source of numerous pro- and anti-inflammatory factors, dysfunction within AT may directly influence immune responses and contribute to immune diseases, such as inflammatory bowel disease (IBD), systemic lupus erythematosus (SLE), and rheumatoid arthritis [406]. Dysfunctional AT, particularly mesenteric fat, can contribute to the pathogenesis of IBD. Hypertrophied mesenteric adipocytes produce increased levels of TNF and IL-6, which can exacerbate intestinal inflammation [407]. In SLE, AT dysfunction may lead to disease progression through increased leptin production, which can promote autoantibody production and T-cell activation. Conversely, chronic inflammation in SLE can induce AT dysfunction, creating a potential feedback loop [408]. In rheumatoid arthritis, the AT surrounding the joints (infrapatellar fat pad) can become a source of pro-inflammatory adipokines and cytokines, contributing to joint inflammation and cartilage degradation. In addition, systemic AT dysfunction can exacerbate the inflammatory state in rheumatoid arthritis [409].

AT dysfunction can alter immune responses through multiple mechanisms, including the dysregulated production of adipokines and pro-inflammatory cytokines, changes in immune cell populations within AT, and alterations in systemic metabolic parameters that influence immune function [406].

Neurodegenerative Disorders

Adipokines also contribute to the pathogenesis of various neurodegenerative disorders. Leptin may affect neuronal apoptosis and exert neuroprotective effects by modulating inflammation and oxidative stress. Adipokines can influence neurodegenerative processes through multiple pathways, including modulation of neuroinflammation, oxidative stress, and insulin signaling in the brain. They can also affect the blood-brain barrier permeability and neuronal energy metabolism [410]. As a result, AT dysfunction may contribute to the pathogenesis of neurodegenerative

disorders, such as Parkinson's disease, multiple sclerosis, and Alzheimer's disease [411]. In Parkinson's disease, leptin has been shown to exert neuroprotective effects on dopaminergic neurons, potentially through the activation of neuroprotective signaling pathways and reduction of oxidative stress [412]. In multiple sclerosis, adipokines may induce disease progression via their effects on immune function and inflammation. For example, leptin can promote T-cell proliferation and pro-inflammatory cytokine production, potentially exacerbating autoimmune responses. Conversely, adiponectin may have anti-inflammatory effects that could be beneficial [413]. Altered levels of adipokines have been observed in Alzheimer's disease. For example, low levels of adiponectin are associated with an increased risk of cognitive decline, possibly owing to its anti-inflammatory and insulin-sensitizing effects. Conversely, elevated leptin levels may have neuroprotective effects, although leptin resistance in obesity may negate these benefits [414].

Modulating adipokine signaling or targeting their downstream effects could potentially offer novel neuroprotective strategies for these conditions [415].

Cancer

AT dysfunction may also contribute to the development and progression of different types of cancer. The mechanisms underlying this association include chronic inflammation, altered hormone signaling (especially in hormone-dependent cancers), dysregulated adipokine production, and changes in the tumor microenvironment [416]. Obesity is linked to the increased incidence and worsening outcomes of multiple cancers, including prostate, colon, endometrial, and premenopausal breast cancers [417]. Studies have demonstrated that AT-derived pro-inflammatory cytokines, such as leptin or resistin, positively influence cancer cell proliferation, migration, and invasion potential [418–420]. Leptin has been shown to promote cancer cell proliferation, migration, and invasion of various cancer types, often through the activation of JAK/STAT, PI3K/AKT, and MAPK. Conversely, adiponectin has anti-tumor effects, inhibits cell proliferation, and promotes apoptosis [421]. Recent research has highlighted the role of cancer-associated adipocytes (CAAs), which can be reprogrammed by cancer cells to support tumor growth. CAAs provide energy-rich fatty acids to cancer cells, secrete pro-inflammatory factors, and contribute to chemoresistance [422]. Further, obesity-induced inflammation and insulin resistance create a favorable microenvironment for tumor growth and metastasis [423].

Future Research Directions and Clinical Implications

AT research has seen a dramatic shift in recent years, revealing a complex role beyond fat storage. However, many questions regarding the endocrine activity of AT remain unanswered, necessitating further investigation. An immediate imperative is detailed characterization of the AT secretome and identification of new adipokines. Simultaneously, a comprehensive analysis of known cytokines and mechanistic

studies are needed to identify the signaling pathways involved in their actions. Defying the precise molecular mechanisms of action is important to determining the role of these factors in the pathogenesis of obesity-related metabolic disorders [424]. Future research should also explore the role of AT dysfunction in age-related metabolic decline and age-related diseases [425].

Another avenue that requires further exploration is the interaction between AT and other endocrine organs. As discussed above, AT has in a dynamic relationship with other endocrine organs, including the hypothalamus, liver, skeletal muscle, and pancreas. Further exploration is needed to define the precise mechanisms that mediate this dynamic communication. Recent studies have demonstrated the importance of AT-derived EVs in regulating systemic insulin sensitivity and glucose homeostasis [426, 427]. Further studies are needed to clarify the endocrine role of EVs in AT.

Obesity is a growing global issue that will continue to challenge humanity in the future. Research on the pathogenesis of obesity-related comorbidities will likely expand the understanding of the molecular mechanisms underlying these associations. These findings will eventually lead to the identification of new targets and strategies for the prevention and treatment of obesity and coexisting conditions. Research into methods to induce “browning” of WAT, increasing energy expenditure, represents a promising aspect of obesity treatment. Future studies should focus on identifying safe and effective ways to promote this process [375]. The interaction between the gut microbiome and AT function is an emerging area of research, and studies on how modulation of the gut microbiome influences adipokine production and AT metabolism would offer new therapeutic approaches [428]. It is also important to investigate the effects of environmental factors, such as increasing amounts of waste, climate change, and higher concentrations of pollutants and endocrine-disrupting chemicals on AT, especially its endocrine function [429].

Novel techniques that provide an unprecedented view of AT at single-cell and molecular levels are being developed, enabling better understanding of AT physiology and potentially offering new individualized therapies [4]. Obesity can be treated with novel pharmacological interventions, including adipokine receptor agonists and antagonists, which can modulate adipokine signaling and improve metabolic health [430]. Ultimately, exploring the therapeutic potential of ATMs and their secretome could lead to the development of cell-based therapies for the treatment of metabolic disorders and other comorbidities associated with obesity [431]. The application of artificial intelligence (AI) and machine learning (ML) to analyze large-scale AT data could potentially reveal new patterns and relationships affecting AT in health and disease [432].

Conclusion

In this chapter, we briefly introduce the main molecular factors produced by AT, which will be further discussed in more detail in subsequent chapters. We also explored the interaction of AT with other organs and tissues, as well as the clinical implications of our improved understanding of AT physiology for developing novel

treatments and individualized therapies for metabolic and cardiovascular diseases. Rapid advancements in technologies such as single-cell RNA sequencing (scRNA-seq), metabolomics, and advanced imaging techniques can uncover new therapeutic options to address the increasing prevalence of metabolic disorders that currently affect a significant portion of the world population. However, perhaps the most crucial principle is to look back to our evolutionary roots and appreciate a lifestyle that maintains a balance with our environment, emphasizing the importance of diet, physical activity, and stress management in maintaining AT health and overall metabolic well-being. As our understanding of AT as an endocrine organ continues to evolve, it promises to revolutionize our approach for treating and preventing obesity-related disorders. The implications of this research extend beyond individual health to global public health strategies, emphasizing the need for interdisciplinary approaches to tackle the worldwide challenges of metabolic disorders.

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Chapter 2

Anatomy and Physiology of Adipose Tissue



Yijie Huang, Yunwen Hu, Haiping Chen, Zhaohua Cai, and Ben He

Abbreviations

12,13-diHOME	12,13-Dihydroxy-9Z-octadecenoic acid
18F-FDG	Fluorine-18 fluorodeoxyglucose
9-PAHSA	9-Hydroxy-stearic acid
β_3 -AR	β_3 -Adrenergic receptor
Acetyl-CoA	Acetyl-coenzyme A
ADicerKO	Adipose Dicer knockout
AdipoR1 and AdipoR2	Adiponectin receptors 1 and 2
ADSC	Adipose-derived mesenchymal stem cell
AMPK α	AMP-activated protein kinase alpha subunit
aPVAT	Abdominal periaortic perivascular adipose tissue
ASC	Adipose stem cell
ATM	Adipose tissue macrophage
A-tPVAT	Anterior thoracic periaortic perivascular adipose tissue
BAT	Brown adipose tissue
BMAT	Bone marrow adipose tissue
cAMP	Cyclic adenosine monophosphate

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cBMAT	Constitutive bone marrow adipose tissue
CLSTN3 β	Calsyntenin 3 β
Col	Collagen
CT	Computed tomography
CXCL	C-X-C motif chemokine ligand
dAT	Dermal adipose tissue
DNL	De novo lipogenesis
EAT	Epicardial adipose tissue
ECM	Extracellular matrix
Elf5	E74-like factor 5
EPDR1	Ependymin-related protein 1
EV	Extracellular vesicle
eWAT	Epididymal white adipose tissue
FAHFA	Fatty acid esters of hydroxy fatty acid
FFA	Free fatty acid
FGF21	Fibroblast growth factor 21
GIP	Glucose-dependent insulinotropic polypeptide
GLUT	Glucose transporter
gWAT	Gonadal white adipose tissue
HFD	High-fat diet
hMSC	Human mesenchymal stem cell
HSC	Hematopoietic stem cell
HSL	Hormone-sensitive lipase
iBAT	Interscapular brown adipose tissue
IGF	Insulin-like growth factor
IL	Interleukin
ILCs	Innate lymphoid cells
iNKT cells	Invariant natural killer T cells
iWAT	Inguinal white adipose tissue
LepR	Leptin receptor
IPRAT	Lateral perirenal adipose tissue
L-tPVAT	Lateral thoracic periaortic perivascular adipose tissue
MAPK	Mitogen-activated protein kinase
MAT	Mesenteric adipose tissue
MCP-1	Monocyte chemoattractant protein 1
mEAT	Myocardial epicardial adipose tissue
MI	Myocardial ischemia
MI/R	Myocardial ischemia and reperfusion
miRNA	MicroRNA
mPRAT	Medial perirenal adipose tissue
MRI	Magnetic resonance imaging
MSC	Mesenchymal stem cell
MSCA1	Mesenchymal stem cell antigen-1
Msln	Mesothelin
MVB	Multivesicular compartment

Myh11	Myosin heavy chain 11
NE	Norepinephrine
NO	Nitric oxide
NOS1	Nitric oxide synthase 1
PA	Palmitic acid
PAME	Palmitic acid methyl ester
PAO	Palmitoleic acid (C16:1n7-palmitoleate)
PDGFR α	Platelet-derived growth factor receptor alpha
PET/CT	Positron emission tomography/computed tomography
PKA	Protein kinase A
PLC	Phospholipase C
PPAR γ	Peroxisome proliferator-activated receptor gamma
PRAT	Perirenal adipose tissue
PVAT	Perivascular adipose tissue
PVCF	Perivascular adipose tissue-derived contractile factor
PVRF	Perivascular adipose tissue-derived relaxing factor
sAT	Subcutaneous adipose tissue
scRNAseq	Single-cell RNA sequencing
SHRSP	Stroke-prone spontaneously hypertensive rats
SM22 α	Smooth muscle protein 22-alpha
SMC	Smooth muscle cell
SVF	Stromal vascular fraction
sWAT	Subcutaneous white adipose tissue
TNF α	Tumor necrosis factor-alpha
tPVAT	Thoracic periaortic perivascular adipose tissue
TZD	Thiazolidinedione
UCP1	Uncoupling protein 1
VSMC	Vascular smooth muscle cells
vWAT	Visceral white adipose tissue
WAT	White adipose tissue
Wt1	Wilms tumor 1

Overview of Adipose Tissue

Physiological Functions of Adipocytes

Adipose tissue can generally be classified into white adipose tissue (WAT) and brown adipose tissue (BAT). This binary classification was originally based on macroscopic and histological observations. Appearing yellow and homogeneous, WAT is primarily composed of uniform spherical adipocytes. These cells, also known as white adipocytes, exhibit a characteristic “ringlike” morphology, in which a single large lipid droplet occupies most of the space, thereby displacing organelles such as the mitochondria and nuclei to one side. Adipocytes in BAT are typically polygonal and smaller than those in the WAT. Their most prominent feature is the presence of

multiple small lipid droplets and abundant mitochondria, which impart a brown appearance to the tissue; hence, the origin of the name BAT [1, 2].

Adipose tissue is widely distributed throughout the body (Table 2.1). In rodents and humans, WAT is primarily distributed subcutaneously, as well as around internal organs such as the omentum and mesentery [3, 4] (Table 2.1). During the period from birth to adolescence, human WAT expands through hyperplasia (an increase in number) and hypertrophy (an increase in cell size) [5, 6]. The number of adipocytes remains relatively stable in adulthood in lean and obese individuals, with adipocytes turning over at a rate of 10% per year in human [6].

Unlike widely distributed WAT, BAT is relatively sparse. In mice, it is primarily distributed in the cervical, supraclavicular, axillary, perirenal-adrenal, and paravertebral regions, as well as around major arteries [7–9] (Table 2.1). The BAT distribution in humans differs slightly from that in rodents (Table 2.1). In infants and young children, BAT is primarily found in the same supraclavicular region [10]. However, as individuals grow older, most BAT is replaced with WAT [11]. The presence of metabolically active BAT in adults was first demonstrated in vivo using fluorine-18 fluorodeoxyglucose (¹⁸F-FDG) positron emission tomography/computed tomography (PET/CT) [12, 13]. Levy et al. [14] suggested that adult humans have three main BAT depots: the supraclavicular section located in the neck and above the

Table 2.1 Key characteristics of white, brown, and beige adipose tissue

	White	Brown	Beige
Macroscopic morphology	White color, less vascularization	Brown color, high vascularization	N/A
Microscopic morphology	Low dense mitochondrial with a big lipid droplet	High dense mitochondrial with several small lipid droplets	High dense mitochondrial with many intermediate lipid droplets
UCP1 expression	–	+++	+ (Baseline) ++ (Activated)
Distribution in mice	Omental, mesenteric, perirenal, gonadal (epididymal), aPVAT, interscapular, inguinal	Interscapular, cervical, axillary, perirenal, tPVAT	Inguinal (widely known), epididymal (cachexia)
Distribution in human	Omental, mesenteric, perirenal, gonadal, epicardial depot sAT (represented by thigh, abdominal depot)	Infant: Interscapular depot Adult: Suprascapular, cervical, axillary, paravertebral, mediastinal, perirenal depot	Uncertain
Thermogenic capacity	Low	High	Inducible
Function	Energy storage	Thermogenesis, metabolically healthy	Thermogenesis, metabolically healthy

UCP1 uncoupling protein 1, *aPVAT* abdominal periaortic adipose tissue, *tPVAT* thoracic periaortic adipose tissue, *sAT* subcutaneous adipose tissue

clavicle, the mediastinal zone situated around the spine and heart, and the infradiaphragmatic portion surrounding the kidneys/adrenal glands, pancreas, liver, and spleen. However, because of the intrinsic limits of PET/CT for measuring the uptake of ^{18}F -FDG tracer in tissues, research focusing on adult BAT often occurs under stimulation conditions, such as cold exposure. Consequently, these findings may not accurately reflect the physiological state of BAT.

Currently, it is widely accepted that in addition to its physical functions such as mechanical protection and heat insulation, adipose tissue also has metabolic and energy properties. White adipocytes take in fatty acids carried by circulating lipoproteins and convert them into triglycerides for storage in large lipid droplets within cells [15]. Serving as an energy reservoir, WAT depots initiate lipolysis during fasting and other catabolic states, releasing free fatty acids (FFAs) to supply other organs [15]. With abundant mitochondria and high expression of uncoupling protein 1 (UCP1), BAT can dissipate energy through the production of heat and is associated with maintaining the core temperature during cold exposure through a process referred to as nonshivering thermogenesis [16].

Furthermore, a series of specific cell markers have been identified that differentiate between classical brown and white adipocytes. For example, in rodents, brown adipocytes are characterized by high expression of *Ucp1*, *Prdm16*, and *Ppargc1a* [17–19], whereas white adipocytes are specifically identified by gene expression of *Hoxc8*, *Hoxc9*, and *Tcf21* [20, 21]. Along with the distinct morphological and physiological characteristics of BAT and WAT, the classification of “white” and “brown” has emerged as a standard paradigm for studying newly determined adipose tissue.

Of note, not all adipocytes remain metabolically static throughout life; rather, they exhibit dynamic changes. In response to certain stimuli, such as cold exposure [22] and exercise [23], inguinal adipocytes in mice exhibit a “browning” characteristic supported by a multilocular appearance, upregulation of BAT-specific marker genes such as *Ucp1*, *Prdm16*, and *Ppargc1a*, together with increased mitochondrial activity and respiration rates [24, 25]. After 5 weeks of warm adaptation, the cold-induced brown-like inguinal adipocytes in mice converted into white adipocytes with a dramatic decrement in *Ucp1* to an undetectable level, but with the acquisition of typical white features [26]. Combining the features of white and brown fat cells, the specific adipocytes specialized in inducible and reversible conversion are named beige/brite (brown-in-white) adipocytes in a humorous way, which is an example of the learning paradigm of adipose tissue. Specific markers of different adipocytes have been reviewed by some researchers with subtle disparities, which certainly need duplication and further demonstration [21, 27–29].

Questions remain to be answered about whether all adipocytes present the reversible pattern, whether all beige fat cells come from the conversion of white adipocytes or share the same origins as WAT, and which stage/factor in the developmental course serves as the determinant of the classification. Moreover, there remains a gap in our understanding of the detailed regulatory mechanisms of the conversion process. It is worth noting that a study combining PET/CT and histology proposed that the adipose tissue used to be considered BAT in the supraclavicular region of adult humans is actually composed of beige adipocytes [24], further verified by a gene

expression profile of human BAT samples isolated from many anatomical locations with a large array of beige cell-selective genes [30]. Therefore, caution must be exercised when applying the learning pattern and extrapolating the findings from experimental studies in mice to clinical applications in humans.

Endocrine Function of Adipocytes

The complex and highly active role of adipose tissue as an endocrine organ is widely recognized via the secretion of adipokines [31]. To date, the definition and constitution of adipokines have remained unclear and controversial. Some researchers have identified adipokines as peptides produced by adipocytes and/or other situated cells within adipose tissue [32–34]. To avoid ambiguity in the sources of the factors discussed below, adipokines are defined as the bioactive substances secreted by adipocytes (not equal to adipocyte-specific) to display an integral metabolic profile, performing in an autocrine, paracrine, and endocrine manner. Based on their ingredients, adipokines can be classified into three groups: inorganic molecules such as nitric oxide (NO) [35]; organic compounds such as peptides, lipokines, and microRNAs (miRNAs); and extracellular vehicles (EVs). Those produced by BAT are referred to as batokines habitually, while actually belonging to adipokines. Certain well-studied batokines that are preferentially secreted by BAT are also discussed below.

Main Polypeptides

Polypeptides derived from adipocytes, particularly leptin and adiponectin, are among the most extensively studied bioactive substances with endocrine function. Leptin, a 16 kDa protein hormone that is essential for metabolism and energy balance expressed by adipocytes, was discovered in 1994 [36]. Predominantly produced by subcutaneous WAT (sWAT) rather than visceral WAT (vWAT), leptin primarily exerts its effects by binding to the leptin receptor (LepR), which is widely distributed in the central nervous system, adipose tissue, heart, muscle, lungs, small intestine, and liver tissues [37, 38]. Not only exerts its appetite-suppressing effects by crossing the blood-brain barrier and acting on the hypothalamus, but leptin also interacts with hormones involved in regulating the body's substance and energy metabolism [39]. Leptin indirectly mediates the effects of insulin, glucagon, insulin-like growth factor (IGF), growth hormone, and glucocorticoids [40]. Loss of leptin or LepR in both rodents and humans not only leads to extreme obesity but also manifests elevated blood sugar levels and severe insulin resistance [41]. Moreover, hyperglycemia and insulin resistance also occur in individuals with lipodystrophy, a condition characterized by very low levels of leptin [41]. Although the regulatory mechanisms remain to be determined, these findings support the involvement of leptin in maintaining metabolic homeostasis.

Adiponectin, initially discovered in 1995, was first identified as a 30 kDa adipocyte complement-related protein by Scherer et al., who isolated it from 3 T3-L1 adipocytes [42]. Adiponectin is primarily secreted by adipose tissue and expressed in minimal amounts in other cell types [43–45]. It interacts with the conserved receptors AdipoR1 and AdipoR2, which are present in various tissues in both humans and rodents [46]. Adiponectin is ultimately degraded in the liver, following its circulation and action throughout the body [47]. Adiponectin activity is crucial for maintaining whole-body insulin sensitivity, as evidenced by observations of insulin resistance in mice lacking adiponectin [48] and, conversely, retained insulin sensitivity in obese mice with elevated adiponectin expression [49]. The ceramidase activity of adiponectin receptors regulates key metabolic pathways, including PI3K/AKT, AMPK, mitogen-activated protein kinase (MAPK), phospholipase C (PLC), and peroxisome proliferator-activated receptor gamma (PPAR γ), explaining the insulin-sensitizing effects of adiponectin through the modulation of ceramide levels that critically influence glucose and lipid metabolism [47]. Additionally, adiponectin exhibits potent anti-inflammatory and antifibrotic actions across multiple organs by engaging macrophages and fibroblasts [50–52], contributing to protection against diseases such as atherosclerosis [53], gestational diabetes [54], and nonalcoholic fatty liver disease [55]. This collective evidence highlights adiponectin as a critical endocrine hormone secreted by fat cells, with well-established roles in maintaining metabolic balance, especially under conditions of prolonged metabolic strain.

Main Lipokines

Lipokines are specific species of fatty acids and derivatives produced by adipocytes and have well-defined physiological roles in an endocrine manner [56]. In 2008, through genetic intervention in *de novo* lipogenesis (DNL) of WAT in obese mice, it was the first time to postulate a lipokine known as palmitoleic acid or C16:1n7-palmitoleate (PAO), a monounsaturated fatty acid [57]. PAO is capable of exerting an effect on many organs to increase systemic insulin sensitivity, thereby contributing to metabolic health. Rat muscle cells were found to increase glucose uptake by PAO by increasing the abundance of glucose transporters (GLUTs) GLUT1 and GLUT4 in the plasma membrane [58]. PAO also acts in an endocrine manner to decrease hepatic steatosis and promote the viability and mitogenesis of the insulin-producing pancreatic β -cells [59, 60].

Fatty acid esters of hydroxy fatty acids (FAHFAs) were first discovered in 2014 from lipidomic analysis of mice, derived from BAT, WAT, and the liver [58]. FAHFAs represent a new class of lipids with more than 24 members distinguished by the branched ester sites on hydroxy fatty acids that can be synthesized *in vivo* [58, 61, 62]. Most studies on the bioactive roles of FAHFAs have been in a pathological context. A systemic reduction in FAHFA levels is associated with the deterioration of the metabolic profile of insulin sensitivity in both mice and human [58]. Conversely, oral administration of the family member 9-hydroxy-stearic acid (9-PAHSA) can stimulate glucose uptake by adipocytes and promote insulin

secretion under hyperglycemic conditions in insulin-resistant mice [58]. The metabolic benefits of FAHFAs are further clarified to attenuate the inflammation of pancreatic tissue and promote β -cell survival in nonobese diabetic mice, showing the therapeutic potential of type1 diabetes [63].

Main Extracellular Vesicles and MicroRNAs

Despite the long-term debate of the nomenclature and classification [64], membrane-enclosed functional vesicles derived from a variety of cell types, including adipocytes, are referred to as extracellular vesicles (EVs)/exosomes in this section. EVs can be released by budding off the cell surface, or by fusion of internal multivesicular compartments (MVBs) with the plasma membrane [64, 65]. As a mixture of biochemical compounds, such as proteins, lipids, and miRNAs, EVs serve as channels for cell communication of metabolic signals [64]. The circulating levels of miRNAs and adipocyte-derived EVs are considered novel forms of adipokines.

Adipose tissues are a primary source of circulating exosomal miRNAs. This is supported by a dramatic reduction in circulating exosomal miRNAs observed in mice with adipose tissue-specific knockdown of the miRNA-processing enzyme Dicer (ADicerKO) and in patients with lipodystrophy [66]. The levels of circulating exosomal miRNAs in ADicerKO mice can be restored by transplantation of normal inguinal WAT (iWAT), epididymal WAT (eWAT), and BAT. However, impaired glucose tolerance tests markedly improved only in mice transplanted with BAT [66], indicating that BAT-derived miRNAs may contribute to the regulation of glucose metabolism. Throughout the circulation, exosomal miRNAs derived from adipocytes have a distant endocrine effect in other organs. Circulating exosomal miR-27a in exosomes released by adipose tissue can be taken up by the skeletal muscle, leading to obesity-related insulin resistance state in mice [67]. In addition, these fat-derived circulating miRNAs can act on other tissues such as the liver and muscles, to regulate mRNA translation and stability [66]. Exosomal miRNAs derived from adipose tissues can have different regional effects on the regulation of adipogenesis, adipocyte hypertrophy, and lipid accumulation [68]. In line with this, ADicerKO mice exhibit an abnormal fat distribution pattern characterized by the loss of intra-abdominal and subcutaneous white fat and an enlargement and “whitening” of interscapular brown fat [69]. Exosomal miRNAs can also be produced by adipose-derived mesenchymal stem cells (ADSCs). ADSC-derived exosomal miR-342-5p has been proposed as a potential mechanism for protecting endothelial cells against atherosclerosis [70]. The precise regulatory mechanisms of the cross talk between adipose tissue and adipose tissue-derived exosomal miRNAs and depot-specific disparity remain to be elucidated.

Main Batokines

Batokines are adipokines derived from BAT that play pivotal roles in promoting adipogenesis and angiogenesis as well as in conveying the advantageous metabolic effects associated with activated BAT [71]. A thorough classification and explanation of the multifarious functions of batokines have been comprehensively summarized by Villarroya et al. [72]. Some important batokines are mentioned below.

Fibroblast growth factor 21 (FGF21), a 23 kDa protein composed of 209 amino acids, which is abundantly secreted by BAT during thermogenesis, stimulates the uptake of FFAs and accelerates lipid metabolism in both WAT and BAT [73–75]. Its efficacy in managing obesity is well documented, demonstrating effects such as facilitating fat reduction and alleviating conditions such as hyperglycemia, insulin resistance, and dyslipidemia [76]. A recently discovered human batokine, ependymin-related protein 1 (EPDR1), has been found to improve the function of pancreatic β -cells and boost overall metabolic efficiency [77, 78]. 12,13-Dihydroxy-9Z-octadecenoic acid (12,13-diHOME) is a converting product of linoleic acid and is increasingly produced by BAT in response to exercise and cold exposure [79, 80]. 12,13-diHOME enhances the uptake of fatty acids by heart muscle cells and promotes their respiratory capability [81]. It also facilitates improved contraction and respiration in these cells through a mechanism dependent on nitric oxide synthase 1 (NOS1) [81]. Long-term administration of 12,13-diHOME counteracts the detrimental effects of a high-fat diet (HFD) on heart function and structural remodeling in mice [81]. EVs secreted by BAT facilitate interorgan communication and exert cardioprotective effects. A study further demonstrated that intramyocardial injection of BAT-derived EVs attenuates the injury caused by MI/R [82]. BAT miRNAs (miR-125b-5p, miR-128-3p, and miR-30d-5p) have been identified as cardioprotective factors in MI/R mice by suppressing the proapoptotic MAPK pathway, an effect that can be reversed when co-using BAT miRNA inhibitors [82].

In summary, adipokines play a vital role in metabolic homeostasis by releasing biochemical substances including polypeptides, lipokines, EVs, and exosomal miRNAs. However, until now, most studies have focused on systematic metabolic effects and circulating levels of certain adipokines, especially in the pathological context. There is still a large gap in our understanding of the cross talk between adipokines and their local physiological functions in adipose tissue.

The Integral Role of Other Cells and Extracellular Matrix (ECM) in Adipose Tissue

Adipose depots are composed of lobules crowded with adipocytes, supported by arterioles, regulated by neuronal processes, and separated by fibrous septa. Adipose tissue also comprises immune cells, fibroblasts, neuronal processes, etc. [83].

Immune Cells Within Adipose Tissue

Adipose tissue harbors a diverse population of innate and adaptive immune cells, which serve as critical regulatory factors for maintaining adipose tissue homeostasis. The substantial enrichment of anti-inflammatory immune cells, including M2-like macrophages, eosinophils, innate lymphoid cells (ILCs), regulatory T cells (Treg cells), invariant natural killer T cells (iNKT cells), and $\gamma\delta$ T cells in mouse WAT, establishes an anti-inflammatory microenvironment favorable for adipose tissue homeostasis [84, 85].

The role of adipose tissue macrophages (ATMs) as representative immune cells in adipose tissue deserves further investigation. As fundamental components of the innate immune system, ATMs are traditionally categorized into classically activated (M1-like) and alternatively activated (M2-like) macrophages [86, 87]. The M2-like phenotype of ATMs has been reported to control inflammation in the adipose tissue and regulate adaptive thermogenesis and adipogenesis. In response to cold exposure, macrophages are recruited to iWAT and alternatively activated by interleukin (IL)-4 (IL-4)/IL-13 produced by local eosinophils [88]. These alternatively activated macrophages induce the expression of tyrosine hydroxylase and promote catecholamine production, thereby promoting lipolysis and thermogenesis in adipose tissue [88]. In addition, macrophages regulate adipocyte biogenesis and ECM remodeling during adipogenesis. In β_3 -adrenergic receptor (β_3 -AR)-induced de novo adipogenesis, dying adipocytes would recruit M2-polarized macrophages to facilitate adipocyte clearance and express high levels of osteopontin, attracting a subpopulation of CD4⁺/platelet-derived growth factor receptor alpha (PDGFR α)⁺ progenitors [89]. In mice, M2-polarized macrophages exhibit physiological endocytosis of collagen, which reduces proinflammatory collagen fragments and is also associated with the physiological expansion of sWAT [90]. Notably, ATMs undergo massive changes in composition, distribution, and function during diet-induced obesity and aging, and novel ATM subpopulations have recently been identified [91–99]. Obesity and aging induce ATMs toward a proinflammatory phenotype. In both aged mice and older humans [100–102], M1-like macrophages were found to secrete more proinflammatory cytokines such as IL-6, tumor necrosis factor α (TNF α), and IL-1 β in adipose tissue, engaging in localized and systemic inflammation to influence insulin sensitivity and metabolic homeostasis [87].

Innervation in Adipose Tissue

The presence of sympathetic innervation in adipose tissue, which locally releases noradrenaline and drives lipolysis and thermogenesis in brown and beige adipocytes, is well-established [103–105]. Sympathetic nerves express tyrosine hydroxylase, a marker of noradrenergic neurons, and catalyze the synthesis of norepinephrine (NE) under conditions such as cold exposure and fasting [28, 104]. NE induces adipocyte lipolysis through the activation of the β_3 -ARs-cyclic AMP (cAMP)-protein kinase A (PKA) signaling pathway, which in turn phosphorylates

hormone-sensitive lipase (HSL), NE induce adipocyte lipolysis [106]. By subsequently coupling both $G_{\alpha s}$ and $G_{\alpha i}$, subunits of the G protein-coupled receptors for transmembrane signaling, NE interacts with β -ARs to activate the MAPK cascade to stimulate the gene expression of UCP1, the primary driver of uncoupled mitochondrial respiration and adaptive nonshivering thermogenesis in brown and beige adipocytes [107–109].

Abundant sympathetic innervation is observed in the iBAT of mice and supraclavicular fat pad of humans. It is now well-known that BAT is much more densely innervated by sympathetic nerves than WAT [110–112]. Sympathetic innervation also differs significantly between the subcutaneous and visceral depots. Mice iWAT exhibits a more abundant parenchymal sympathetic innervation than eWAT [113]. In addition, after 48 h of cold exposure, there is a more marked increase in the proportion of UCP1⁺ beige cells and higher sympathetic innervation density in the inguinal region than dorsolumbar regions [113].

The sympathetic innervation of thermogenic adipose tissue is typically regulated by a multitude of factors derived from adipocytes, including the transcription regulator PRDM16 and the neurotrophic factor S100b. The expression level of PRDM16 is associated with the density of sympathetic projections within the adipose tissue. Researchers found that there were no significant cold-induced regional differences in sympathetic innervation density in adipocyte-specific knockdown of PRDM16 mice [113], whereas overexpression of PRDM16 led to increased sympathetic innervation of beige adipocytes in iWAT in mice [114]. This is further supported by the abundant sympathetic innervation observed in regions with high levels of PRDM16 in iBAT in mice and the supraclavicular fat pad in humans [110, 111]. As a neurotrophic factor, S100b can stimulate sympathetic axon growth [115]. Recently, Zeng et al. showed that a previously unknown protein, calstentenin 3 β (CLSTN3 β), can bind to and enhance the protein expression of S100b, thereby promoting the sympathetic innervation of both brown and beige adipocytes [115].

Extracellular Matrix (ECM) of Adipose Tissue

Constituted by a complex amalgam of proteins, polysaccharides, and proteoglycans, ECM provides a dynamic mechanical and structural scaffold that simultaneously serves as a biochemical framework to facilitate intercellular communication [116]. The interactions between the peri-adipocyte ECM and its cognate cell surface receptors have been reviewed systematically [117].

The ECM is remodeled during adipogenesis. During the differentiation of human mesenchymal stem cells (hMSC) to adipocytes, significant elevation in laminin- α 4 and laminin- β 4 expression levels was observed, and specific laminin was integrated into the basement membrane [118]. In mice, laminin- α 4 was found to negatively regulate the thermogenic phenotype and pathways involved in mitochondrial biogenesis in adipocytes through the suppression of the AMP-activated protein kinase alpha subunit (AMPK α) [119].

High levels of collagen (Col) VI (Col VI) expression have been observed in obese adipocytes, and pericellular fibrosis is present in omental adipose tissue and subcutaneous adipose tissue of obese individuals [120–123]. Fibrosis restricts adipocyte hypertrophy but is associated with a reciprocal increase in adipocyte hyperplasia and may be linked to decreased insulin sensitivity, adverse outcomes of bariatric surgery, and difficulty in weight loss [124].

The ECM may determine the fate of progenitor cells in the adipose tissue. In human WAT, the ECM can be subdivided into septa and stroma, with the former exhibiting a higher concentration of fiber components, such as Col I, Col III, and elastin than the latter [125]. These two compartments constitute different niches for the CD45⁻/CD34⁺/CD31⁻ progenitors within the adipose lobules. In the stroma, there is enrichment of the mesenchymal stem cell antigen-1 (MSCA1)⁺ adipogenic subset, whereas in the septa, the CD271^{high} subsets with a high tendency for myofibroblast conversion are more abundant [125].

Adipose tissue is widely distributed throughout the body and exhibits a rich heterogeneity. Previously, adipose tissue was considered uniform, but current research has revealed differences across various fat depots and even within individual depots, including cellular origin, metabolic functions, and interactions with other organs. Next, we will elaborate on the anatomy, functions, and physiological roles of adipose tissue based on the location of the fat deposit.

Visceral White Adipose Tissue (vWAT)

The definition of vWAT remains unclear. Some researchers define vWAT as the adipose tissue surrounding intra-abdominal organs, whereas others consider retroperitoneal fat, including perirenal fat, as part of vWAT [126, 127]. One classification method defines genuine vWAT based on whether the fat depot drains into the portal vein, represented by fat depots around the omentum and mesentery [3]. The portal vein theory posits that the delivery of FFAs and proinflammatory cytokines from vWAT to the liver via the portal vein contributes to insulin resistance and metabolic deterioration observed in obese individuals [128]. However, in the broad sense, “visceral” should include the gonads and kidneys, and this section introduces the broader concept of vWAT.

Omental Adipose Tissue

The omentum is rich in adipose tissue and can be subdivided into greater and lesser omenta. The greater omentum has received more attention and been studied extensively. Although considered as WAT [129, 130], omental adipose tissue can undergo beige adipogenesis *in vitro* through a gut-derived peptide called glucose-dependent

insulinotropic polypeptide (GIP) [131], and by a thiazolidinedione (TZD) named rosiglitazone [132].

The omentum is microscopically composed of translucent membranous areas and highly vascularized adipose-rich regions, with different proportions and anatomical locations in humans and rodents with greater omenta [133]. The human greater omentum predominantly consists of fat cells [133, 134], while murine omental adipose tissue accounts for only 40% of the omentum [133]. The omental adipose tissue is enclosed by two layers of mesothelial cells to represent a substantial, flattened layer in human omentum [134–136] but is restricted as an adipose-rich rim of murine omentum [133]. Macroscopically, human omental fat resembles an apron hanging from the greater gastric curvature down to the level of the pubis symphysis with a surface area of 300 cm² to 1500 cm² [134, 137]. However, murine omental adipose tissue presents as a much smaller fat strip that extends along the anterior greater curvature of the stomach [133]. Nonetheless, human and mouse omenta share similar surface structures via electron microscopy [133], indicating that mice may be justified as experimental models to study omental adipose tissue to some extent.

Current studies on omental adipocytes have often been conducted in pathological contexts, and the physiological roles of omental fat depots remain to be elucidated. Clinical evidence has demonstrated that obesity-induced omental adipocyte hypertrophy is strongly associated with impaired systemic insulin sensitivity and hepatic steatosis in obese adults [138, 139], indicating that omental adipose tissue may contribute to obesity-related metabolic disorders. In addition, omental adipose tissue is found to promote the development of malignant tumors owing to its highly vascularized microenvironment and the biochemical signals it releases [140, 141].

Mesenteric Adipose Tissue

Mesenteric adipose tissue (MAT) extends proximally from the mesenteric attachment toward the mesentery base [142], referring specifically to the adipose tissue attached to the intestinal walls [143]. MAT can be regionally differentiated into small intestinal MAT and large intestinal MAT. Small intestinal MAT is not only characterized by smaller adipocytes but also contains a higher prevalence of fat-associated lymphoid clusters compared to large intestinal MAT [144]. Evidence from inflammatory bowel studies suggests that MAT may play a role in bowel immune regulation. In patients with Crohn's disease, bowel inflammation penetrates the adjacent adipose tissue along the mesentery [145]. Liu et al. [146] suggested that MAT is an independent determinant of metabolic syndrome and is associated with the thickness of the intima and media in human carotid arteries [146]. Furthermore, MAT also exhibits browning potential, as demonstrated by the ability of both human MAT and primary mesenteric adipocytes from Crohn's disease patients and healthy controls to induce browning [147]. However, it should be noted that research on MAT is currently limited. The close anatomical proximity of

MAT to surrounding tissues complicates sample collection, often resulting in vascular contamination, which has impeded comprehensive investigations into the role of the mesenteric fat pad in metabolic health [148, 149].

Perirenal Adipose Tissue

Perirenal adipose tissue (PRAT) surrounds the kidneys on both sides and is enclosed by a thick multilayered fibrous tissue known as the renal fascia [150]. The medial part of PRAT, referred to as medial PRAT (mPRAT), is found around the hilum of the kidney, where studies have discovered UCP1-expressing brown adipocytes [150]. In contrast, the lateral portion of the PRAT, termed lateral PRAT (lPRAT), mainly consists of white adipocytes [21]. Observations of age-related changes in human PRAT suggest gradual substitution of brown adipocytes with white adipocytes over time [151]. However, analysis of PRAT obtained from individuals in Siberia at the time of autopsy showed up to a 40% composition of brown adipocytes, demonstrating the capacity of PRAT to adapt to colder environments [152]. Additionally, dormant brown adipocytes, characterized by unilocular lipid droplets and a gene expression pattern that shares features with white adipocytes, yet with positive expression of UCP1, have been identified in the PRAT of adult kidney donors [153]. Therefore, PRAT is a unique visceral fat depot containing a mixture of brown and white adipocytes. Further studies are needed to investigate the origin and plasticity of cellular heterogeneity in PRAT.

Gonadal White Adipose Tissue

Gonadal white adipose tissue (gWAT) is sometimes termed periovarian WAT in females and epididymal WAT (eWAT) in males. gWAT, a specialized form of adipose tissue in mammals, envelops reproductive organs, specifically encompassing the uterus and ovaries in females and the epididymis and testes in males [149]. Periovarian WAT is situated in proximity to the ovaries, uterus, and bladder and plays a crucial role in the local endocrine milieu. In instances of obesity, observations indicate that gonadal and perirenal fat depots exhibit continuity, with fat accumulation surrounding the uterine horns and ovarian coalescing [149]. eWAT, on the other hand, is intimately associated with the epididymis, testicular tissues, and prominent vasculature supplying the epididymis, highlighting its integral role in structural support and potential metabolic influence on these reproductive structures. However, in humans, no corresponding gonadal fat region has been identified as that in mice. Therefore, whether gWAT in mice accurately represents vWAT in humans for research purposes remains a subject of ongoing debate.

Subcutaneous Adipose Tissue

Located beneath the skin, encapsulated by connective tissue and supported by blood vessels and nerves, subcutaneous adipose tissue (sAT) is widely distributed. Given the significant differences in the distribution patterns of sATs between mice and humans, this section will discuss sATs in mice and humans separately.

Mice Subcutaneous Adipose Tissue

In mice, sAT can be divided into anterior and posterior sATs [3]. The anterior sAT is primarily located along the midline and on both sides of the mouse, including fat depots located at the deep cervical, superficial cervical, interscapular, subscapular, and axillo-thoracic areas [154]. Posterior sAT is primarily found in the inguinal, dorsolumbar, and gluteal regions [154]. Typically, the term sWAT is used to refer to sAT; however, this oversimplifies the functional diversity of sAT. Indeed, because inguinal adipose tissue is the largest and most easily isolated fat depot among mouse sATs, it is considered the archetype of sATs, exhibiting typical WAT characteristics at room temperature and is commonly referred to as iWAT [155]. However, iWAT does not represent the entirety of sAT, as it exhibits much greater heterogeneity than previously thought. Upon cold exposure and exercise, iWAT activates thermogenesis, which is attributed to the reversible browning process of beige adipocytes [156–158]. Wu et al. isolated clonal beige adipocyte cell lines from mouse iWAT, which could be induced to activate thermogenesis [24]. Unlike posterior sAT, mouse anterior sAT appears brown, and interscapular fat depot displays visible brown and white components even at room temperature [154, 159]. The brown component of interscapular adipose tissue, commonly referred to as interscapular BAT (iBAT), is the largest brown adipose depot in mice and is the primary focus of BAT research [155].

Despite primarily exhibiting the characteristics of WAT, mouse iWAT demonstrates features distinct from those of vWAT. With the exception of inducible thermogenic activation under physiological stimuli such as cold exposure and exercise, iWAT appears less geared toward proliferation. In an HFD regimen, vWAT demonstrates an earlier onset of lipogenesis, observable as early as 4 weeks, whereas iWAT exhibits hypertrophy over an extended duration, typically not until 12 weeks [160]. Additionally, iWAT is distinguished by a reduced rate of macrophage infiltration, contributing to its diminished release of proinflammatory cytokines compared to vWAT [161]. Further studies have confirmed the critical anti-inflammatory role of CXCL14-expressing adipose stem cells (ASCs) from iWAT in obesity. This effect was achieved by suppressing the inflammatory CXCL12-CXCR4 pathway in monocytes, consistent with previous findings [162, 163]. This aligns with emerging evidence that iWAT ASCs inhibit monocyte infiltration in obesity [164], accentuating the specialized role that ASCs play in diverse adipose tissues under metabolic stress.

Human Subcutaneous Adipose Tissue

sAT is widely distributed throughout the human body. In infancy, interscapular adipose tissue comprises adipocytes that express genes characteristic of classical brown adipocytes [165]. However, with growth, BAT in the interscapular region eventually regresses [165]. In adults, the main sATs are primarily located in the abdominal region, buttocks, and thighs [166]. Specifically, adipose tissue found in the buttocks and thighs is collectively referred to as the gluteofemoral depot [167, 168]. Research has demonstrated that gluteofemoral sAT exhibits a reduced level of lipolytic activity compared to sAT in the abdominal region [169]. In humans, sAT may possess inducible thermogenic activation capabilities. Histological and molecular evidence suggests that human thigh adipose tissue upregulates thermogenesis-related genes such as UCP1 in response to cold stimulation, indicating the presence of browning [170, 171]. However, PET/CT imaging did not reveal an increase in glucose uptake in the sAT in response to cold stimulation [172, 173]. In one study, acute cold exposure decreased the local blood flow in human sAT, resulting in reduced glucose uptake [174]. Apart from the lower sensitivity of PET/CT, potentially leading to false-negative results, one possible hypothesis is that, under cold stimulation, sAT primarily serves as a thermal insulator through vasoconstriction, with the activation of thermogenesis requiring longer exposure time to manifest [16].

Perivascular Adipose Tissue

Anatomy of the Perivascular Adipose Tissue

Perivascular adipose tissue (PVAT) is defined as a unique fat depot surrounding blood vessels throughout the body (except for the cerebral vasculature), without any anatomical structural barrier [175–177]. According to this definition, PVAT can be subdivided into periaortic adipose tissue and organ-specific fat, encircling distinct organ vasculature. Therefore, broadly speaking, epicardial adipose tissue (EAT) and adipose tissue of the mesenteric bed and renal sinus should fall under the category of PVAT [178, 179]. However, EAT will be discussed separately, while the latter two are currently considered parts of mesenteric and perirenal adipose tissue and classified as vWAT. Moreover, in the existing literature, the term PVAT primarily refers to periaortic adipose tissue, with special emphasis on thoracic periaortic PVAT (tPVAT) and abdominal periaortic PVAT (aPVAT). Therefore, this section predominantly focuses on periaortic adipose tissue.

Thoracic Periaortic PVAT

The tPVAT extends from the aortic arch at the T4 vertebra to the T10–T11 vertebrae, namely, to the aortic hiatus of the diaphragm [180]. Microscopically, the majority of rodent tPVAT exhibit morphological characteristics of BAT, with adipocytes having round nuclei, abundant mitochondria, and small multilocular lipid droplets, whereas the remaining small areas structurally resemble WAT [181, 182]. A series of human autopsies validated that multilocular BAT-like cells in tPVAT immunochemically express high levels of UCP1, a unique marker of brown adipocytes [183]. Using microarray analysis of mice, tPVAT shares approximately identical global gene expression patterns with classical iBAT, with disparity lying in only 228 significantly different genes (0.79%) [181]. PVAT is reported to exhibit active thermogenesis similar to BAT in response to cold exposure in mice [35]. This is further supported by ^{18}F -FDG PET/CT studies in adult humans showing that cold-induced ^{18}F -FDG intake is markedly upregulated in the periaortic area [184].

Although sharing some similarities with BAT, it exhibits notable differences from classical BAT when exposed to external stimuli. In mice fed a HFD for 13 or more weeks, tPVAT and iBAT both showed resistance to the extent of inflammation. However, the appearance of BAT appeared “whiter,” and an unexpected distortion in the architecture of BAT lipid droplets was observed, a phenomenon not seen in tPVAT. Nevertheless, tPVAT developed a dissimilar manifestation, with swollen mitochondria and unfolding of cristae. These findings are supported by alterations in gene expression of HFD [181].

Intriguingly, further efforts were made in an experimental investigation to subdivide tPVAT into lateral tPVAT (L-tPVAT) and anterior tPVAT (A-tPVAT), presenting a quite discrepant picture [185]. More UCP1⁺ adipocytes are situated in A-tPVAT than in L-tPVAT. In addition, disparity lies in the biological activity. L-tPVAT had a significantly improved vasorelaxation effect on the aorta compared to A-tPVAT in the vascular ring experiment, whose biological basis and physiological regulatory role remain to be further explored.

Abdominal Periaortic PVAT

The aPVAT encompasses the abdominal aorta, from the aortic hiatus of the diaphragm to the femoral bifurcation [180]. Morphologically, adipocytes within the aPVAT, as observed via light and electron microscopy in both rodents and humans, are primarily unilocular, resembling those in WAT [182, 186, 187]. Human aPVAT has chemoattractant properties and secretes comparable amounts of chemokines as sWAT [187]. Given the growing evidence for the physiological and pathological roles of WAT, clarifying the similarities and differences between aPVAT and WAT may reveal the bioactivity and metabolic mechanisms of aPVAT, which warrant further study.

Difference Between tPVAT and aPVAT

These findings have encouraged researchers to hypothesize that tPVAT and aPVAT represent BAT and WAT, respectively, which are thought to act differently in their bioactive patterns. In response to stimuli, WAT tends to initiate the inflammatory pathway more than BAT. Corroborating this, an experimental study in an HFD-induced obese mouse model revealed that aPVAT explants were capable of promoting more macrophage migration than tPVAT explants, accompanied by a higher elevation in the mRNA abundance of macrophage markers and proinflammatory chemokines in aPVAT than in tPVAT [182]. In addition, aPVAT in rats was more inflamed than tPVAT, with a proinflammatory profile of gene expression and immune cell infiltration [186]. Further insights are awaited from clinical and experimental data to investigate the biological basis and functional links between the PVAT, WAT, and BAT.

In general, periaortic PVAT has attracted considerable attention owing to its unique anatomical location and relative convenience. PVAT is analogous to the comparatively well-studied WAT and BAT. tPVAT exhibits a BAT-like phenotype, capable of thermogenesis, whereas aPVAT resembles WAT, presenting a more proinflammatory pattern. Although questions remain to be answered, exploration of PVAT opens a window into the external environment of the vasculature and provides novel opportunities to identify the cross talk between PVAT and homeostasis of the cardiovascular system.

Origin of Perivascular Adipose Tissue

The Debate of Perivascular Adipose Tissue Origin

Evidence regarding the developmental origin of PVAT has yielded controversial results. Some studies have shown that progenitor cells of PVAT share a common developmental origin with vascular smooth muscle cells (VSMCs) [35, 185]. Smooth muscle protein 22- α (SM22 α), a putative calcium-binding protein, is expressed in mesenchymal populations around the dorsal aorta during mouse embryogenesis at embryonic day (E) 9.0 and is considered one of the earliest markers of VSMC [188]. A lineage-tracing study elucidated that adipocytes within the tPVAT primarily originate from SM22 α^+ progenitors, providing powerful support for this hypothesis [185]. Research has discovered that PPAR γ is an essential factor for adipogenesis *in vitro* and *in vivo* [189, 190]. Progenitor cells prenatally expressing PPAR γ are capable of proliferating and are the main source of the rapid growth of adipocyte development from birth to 1 month old in mice [191]. In an experimental study using a smooth muscle cell (SMC)-specific *Pparg* knockout mouse model with a genotype of *Pparg*^{fllox/fllox}; *SM22 α -Cre*; *ApoE*^{-/-}, there was no PVAT supposedly surrounding the aortic arch, thoracic and abdominal aorta, along with a significant reduction in mesenteric adipose tissue [35], further corroborating this hypothesis.

However, the dissenting voice is that PVAT develops from a fibroblastic lineage [192]. Single-cell RNA sequencing (scRNA-seq) analysis for stromal vascular fraction (SVF) separated from thoracic aortas at postnatal day (P) 3 (with nearly identical integration with E18) revealed several cell populations including SMCs, adipocytes, and a connective array of fibroblast cells. Fibroblast cell populations can be further classified into progenitor cells, intermediate cells, and preadipocytes. To verify whether SMCs serve as the origin of periaortic fat cells, Angueira et al. [192] used *Myh11-Cre;tdTomato* reporter mice as genetic lineage-tracing models. *TdTomato*⁺ adipocytes were not detected around the aorta at P3 in reporter mice, challenging the notion that PVAT shares a common origin with SMCs, as previously discussed. Furthermore, *ex vivo* experiments to estimate adipogenic potential showed that SMCs present nearly no ability to undergo adipocyte differentiation. In contrast, progenitor cells and preadipocytes of the fibroblast cell populations are capable of developing adipocytes, and preadipocytes display the strongest adipogenic potential. The supposition of periaortic PVAT arising from fibroblastic lineage was further demonstrated using genetic lineage-tracing models.

As Chang et al. [35] utilized the *SM22 α -Cre* expressed as early as E9.0 in mice in their studies, Angueira et al. [192] investigated SVF of periaortic PVAT at E18 and mainly at P3 in mice. The disparity in progenitor cells of PVAT may lie in the stages chosen differently to explore development during the embryonic period and after birth. This possibility cannot be ruled out because, in adult mice of 13 weeks old, the SVF of tPVAT encompasses a new cluster of SMCs contributing to PVAT formation [192]. More comprehensive research is necessary to define these conditions more clearly, emphasizing the need for more precise descriptions of the developmental trajectory.

Regional Differences in Perivascular Adipose Tissue Origin

The phenotypic and bioactive disparity along the aorta discussed above suggests that PVAT may be a heterogeneous tissue derived from different progenitor cells with local specificity. Administration of thiazolidinediones (TZDs), known as *PPAR γ* agonists, markedly augments the differentiation of preadipocytes with a high affinity to *PPAR γ* [193]. Precursor cells stemming from aortic explant from aortic rings in C57Bl/6 J mice were used *ex vivo* for adipogenesis using rosiglitazone as one of the TZDs, depicting different gene expression profiles of tPVAT and aPVAT [194]. Moreover, the results of transcriptome analysis and aortic ring array suggested that progenitor cells from tPVAT and aPVAT maintained their inherent identity to develop into transcriptionally more thermogenic and WAT-like adipocytes, respectively, with cell-autonomous traits, even *ex vivo* [194].

Except for what was mentioned above, developmental settings may be different in PVAT, even at different anatomical locations of the same arterial segment. Transcriptome analysis of L-tPVAT and A-tPVAT showed a massive discrepancy in gene expression for regulating development [185]. At the same time, a lineage-tracing study further validated that adipocytes derived from *Myf5*⁺ are located in

L-tPVAT rather than in A-tPVAT, reflecting that L-tPVAT is present at an earlier development stage [185].

Taken together, PVAT is a highly heterogeneous tissue derived from multiple progenitor and precursor cells, which remains to be precisely determined. It is crucial to acknowledge that current studies on the origins of PVAT are mainly conducted in experimental animal models, underlining that these findings have yet to be determined in humans.

Endocrine and Physical Function of Perivascular Adipose Tissue

The long-standing notion that PVAT provides structural support for the vascular system has led to its importance being overlooked. It was not until 1991 that PVAT was first demonstrated to attenuate the contractile effects of NE in the rat aorta *ex vivo* [195]. Given its close anatomical proximity to the vascular wall and the fact that human aortic arch PVAT was even observed with adipocytes infiltrating the adventitia under light microscopy [196], the physiological characteristics of PVAT have attracted enormous interest. Recently, PVAT has garnered considerable attention because of its role in vascular tone by mediating both vasodilation and vasoconstriction. It has been reported that PVAT secretes PVAT-derived relaxing factors (PVRFs) to blunt the agonist-induced vasocontractile impact in vascular protection, such as NO, palmitic acid methyl ester (PAME), and prostacyclin [35, 197, 198]. Vasocontractile effects may be modulated by PVAT-derived contractile factors (PVCFs), including catecholamines, angiotensin II, and chemerin [199–201]. Notably, the pinpoint mechanisms of PVAT in performing and balancing both converse functions remain unclear. Apart from the effects on vascular tone, studies have provided new insights into the role of PVAT in VSMC growth and migration by releasing growth factors and influencing the formation of neointima [202, 203].

As aging is an inevitable and natural biological process, its effect on PVAT remains unclear. Bioinformatics analysis revealed a decrease in the adipogenic differentiation competence of resident stromal cells within the PVAT into endothelial and brown fat cells, promoting vascular remodeling [204]. In line with this finding, the number of brown-like adipocytes within tPVAT was observed to decline in aged mice [185], which can be seen in the periaortic PVAT of aged rats with a decrement in anti-constrictive function [205]. In addition, aging results in older mice being more vulnerable to obesity by enhancing macrophage infiltration in the PVAT and exacerbating the alteration in the vascular wall to a more proinflammatory pattern than in younger mice [206]. In terms of inflammation, which plays a core role in atherosclerosis, PVAT has the potential to be a new predictor and therapeutic target for cardiovascular aging-related diseases, which requires further investigation.

Apart from the heterogeneous morphological, original, and functional disparities in PVAT discussed above, emerging evidence reveals that a significant gender gap

lies in PVAT as well. The Framingham Heart Study with 3246 participants concluded that the volume of tPVAT in women was higher than that in men, in line with a higher prevalence of excess tPVAT in women as aging [207]. Experimental data from stroke-prone spontaneously hypertensive rats (SHRSP) suggest that sex differences can be attributed to the decreasing vasodilation function of male PVAT [208]. Because the vasoprotective factor estrogen works as a vasodilator, an anti-inflammatory and antioxidant factor, a regulator of the RAAS system, and an inhibitor of the sympathetic nervous system [209–211], further research is required to identify the clinical significance and mechanisms of metabolic sexual disparity in PVAT.

Epicardial Adipose Tissue (EAT)

Anatomy of Epicardial Adipose Tissue

Epicardial adipose tissue (EAT) is characterized by unique properties that differentiate it from classical WAT and BAT. It is found between the myocardium (heart muscle) and epicardium (outer layer of the heart) and is supplied by the coronary arteries [212]. Approximately 80% of the heart surface is covered by epicardial fat, which accounts for approximately 20% of the total weight of the heart [213]. EAT is localized around the major coronary arteries, ventricular surface, and apex in humans, but it is primarily concentrated in the atrioventricular groove in mice and rats [214]. EAT can be categorized into two types: coronary EAT, which is directly adjacent to the coronary artery adventitia, and myocardial EAT, which is located over the myocardium [215]. The EAT surrounding the left atrium shows high expression of genes encoding arrhythmogenic factors [216], whereas the coronary artery EAT is characterized by high expression of genes that promote inflammatory adipokines and regulate glucose and lipid metabolism [216].

EAT possesses unique functionalities owing to its distinct anatomical location and direct contact with the heart but without fascial separation from the myocardium [212]. EAT safeguards the heart and coronary arteries by preventing mechanical deformation and shielding the heart from the impacts of low body temperature [217]. In neonates, the EAT has thermogenic characteristics and functions similar to BAT. However, as age increases, the function of EAT changes from thermogenesis to energy storage, and the BAT-like activity of EAT significantly decreases with age [218]. Additionally, the release of FFAs from adipocytes in the EAT may serve as a local and rapidly mobilizable energy supply for cardiomyocytes [219, 220]. Moreover, EAT protects myocardial cells from lipotoxicity by converting excess FFAs into fatty acyl-coenzyme A (acetyl-CoA), which is then stored as triacylglycerol in lipid droplets of adipocytes [221, 222].

Adipogenesis of Epicardial Adipose Tissue

Research on the origin of EAT is limited. A study involving embryos from miscarriages and ectopic pregnancies found that the precursor tissue of EAT appears as early as the beginning of the second gestational month (days 33–35 of gestation), and unilocular adipocytes are present by the eighth gestational month (week 32 of gestation) [223]. EAT formation begins in the atrioventricular grooves and progresses to the interatrial groove and right ventricle, eventually reaching the inter-ventricular groove [223]. In mice, EAT typically originates in the atrioventricular groove, which is derived from the epicardial component in embryos [224]. The EAT in the atrioventricular groove of mice appears between the first and second weeks after birth, and its formation depends on the expression of PPAR γ [224]. In addition, studies have shown the involvement of Wt1 (Wilms tumor 1) and Msln (mesothelin) cells in the development of EAT adipocytes [129, 225]. In a previous study using *Wt1^{CreERT2};Rosa26-mTmG* reporter mice, it was found that approximately 66% of epicardial adipocytes were originated from Wt1-expressing mesothelial cells during E14.5 to E16.5 [129]. By injection of the *Msln-Cre* adenovirus into *Rosa26-mTmG* embryonic hearts, a study revealed that the embryonic epicardium contributes to the formation of epicardial fat during development [225].

Endocrine Function of Epicardial Adipose Tissue

Similar to other adipose tissues, EAT possesses endocrine functions and secretes adiponectin, leptin, adrenomedullin, omentin, visfatin, resistin, and other adipokines [226]. For example, adiponectin secreted by EAT can alleviate cardiac dysfunction by regulating PPAR γ [227]. Furthermore, adiponectin directly reduces myocardial NADPH oxidase activity through endocrine or paracrine mechanisms, and its expression in the EAT is regulated by the paracrine effects of heart-released oxidation products [228]. Adiponectin can also protect cardiomyocytes from enlargement and reduce inflammation and fibrosis in the heart, thereby lowering the risk of adverse clinical events [229].

However, in terms of endocrine function, EAT behaves more like the so-called bad adipose tissue. Numerous studies have suggested that EAT promotes disease progression by secreting proinflammatory and pro-fibrotic mediators [216]. EAT-derived leptin induces metabolic syndrome-related myocardial injury through two pathways: mitochondrial oxidative stress, which leads to apoptosis, and inflammation via AP1 translocation [230]. High levels of IL-1 β , IL-6, monocyte chemoattractant protein 1 (MCP-1), and TNF α mRNA and protein have been observed in this tissue [231]. These inflammatory factors can contribute to the formation of atrial fibrillation [232]. Patients with coronary artery disease demonstrate mild inflammation of the EAT due to macrophage infiltration [231]. The proinflammatory, profibrotic, and proarrhythmic effects of EAT-derived EVs may play a role in

the development of cardiovascular diseases associated with obesity and abnormal adipose tissue accumulation [233].

Dermal Adipose Tissue

Anatomy of Dermal Adipose Tissue

Dermal adipose tissue (dAT) is a loosely structured dermal component composed of adipocytes that are functionally integrated into the skin [234, 235]. In rodents, it typically manifests as a substantial layer of adipose cells ranging from 2 to 15 cells in thickness, situated immediately within the reticular dermis, demarcated by a discrete muscle layer known as the panniculus carnosus [236, 237]. The human skin is distinguished by a prominent dAT layer that lacks a well-defined boundary with sAT, a feature attributed to an underdeveloped skeletal muscle infrastructure [234, 238]. During the growth phase, hair follicles interact closely with dermal adipocytes [237]. Additionally, sweat glands, ubiquitously present across the human skin, are embedded in the dermis and occasionally come into contact with the interface of dAT [239].

Over the past few decades, increasing attention has been paid to the importance of dAT in various biological processes. Presently, dermal adipocytes are acknowledged as a discrete, exceptional population distinguished by their unique biological characteristics that extend beyond mere metabolic functions [235, 240]. Many contemporary studies have elucidated the multifaceted involvement of dAT in an extensive array of physiological processes, including the regulation of hair follicle cycling [241], modulation of local immune responses during infections [242], and facilitation of wound-healing mechanisms [243, 244]. Segalla et al. [240] categorized dAT into at least three or four functional compartments within the dermis: near pilosebaceous units, sweat glands, fibroblasts/immune cells/connective tissue, and a diffuse, unclustered form with undefined roles. Recent studies have shown that dAT in mice undergoes reversible dedifferentiation and displays high plasticity depending on environmental changes [245]. In short, dAT exhibits fascinating, non-metabolic attributes, underscoring its specialized and intriguing nature [235, 240].

Origin of Dermal Adipose Tissue

During mouse skin development, adipose precursors emerge on E16.5 [246]. Multilocular adipocytes first emerge between E17.5 and E18.5 and rapidly multiply in number and size [247–249], peaking around P12. At P17, the dAT around the hair follicles began to collapse with a decrease in cell size rather than substantial cell apoptosis [249]. By P19–P23, dermal adipocytes shrink to less than half their size

[247, 249]. Mature dermal adipocytes dedifferentiate into smaller fibroblast-like adipocyte-derived precursor cells during the degenerative phase of hair follicles, which can re-differentiate back into mature adipocytes during the active growth phase of hair follicle [250]. The cyclical growth of dAT is a consequence of hypertrophy, involving an increase in the size of preexisting adipocytes, and hyperplasia, a process driven by the proliferation and differentiation of adipocyte precursors into mature, lipid-filled, unilocular adipocytes [241, 251, 252].

During the embryonic period, early mouse adipose precursors can be labelled with *Dlk1*-CreER [241]. Following E16.5, there is a dermal lineage specification in which cells expressing *Dlk1* are restricted to give rise to lower dermal derivatives including adipocytes [246]. In the adult mouse skin, a large portion of adipose progenitors can be marked using *Pdgfra*-CreER [241]. PDGFR α ⁺ progenitor cells also have the ability to differentiate into fibroblasts, which can participate in wound-healing [246]. The proliferation of both adipocyte stem cells and preadipocytes critically relies on PDGF α /PDGFR α signaling, and mesenchymal cell-specific deletion of PDGF α in mice impedes dAT expansion during this period [252]. This highlights the importance of PDGF α /PDGFR α signaling in regulating the hyperplastic growth of dAT.

The origin and development of dAT are distinct from those of the traditional WAT and BAT. However, multiple adipocyte precursor populations have been identified in murine dAT, all sharing common cellular surface markers (CD34, CD29, and Sca1) with adipocyte precursors from other WAT depots [241, 253]. Lin⁻, CD24⁺, CD29⁺, CD34⁺, and Atn1⁺, a marker set originally developed for visceral and subcutaneous adipose stem cells [253, 254], can also be used to sort dermal adipose progenitors for quantification and gene expression profiling [252]. Similar to vWAT, CD24⁺ skin progenitors represent the early adipose stem cells necessary for the long-term maintenance of dAT [252]. Within this framework, CD24⁺ cells denote an adipocyte stem cell pool, whereas CD24⁻ cells represent committed pre-adipocytes [252, 255]. Both CD24⁺ and CD24⁻ adipocyte precursor subsets can proliferate; however, the CD24⁺ adipocyte stem cell population experiences preferential expansion, giving rise to approximately 20% of new adipocytes [241, 252].

Bone Marrow Adipose Tissue (BMAT)

Anatomy of Bone Marrow Adipose Tissue

Bone marrow adipose tissue (BMAT) contributes to over 10% of total body fat and represents a distinctive category of adipose tissue with unique functional characteristics [256, 257]. BMAT functions as a modulator of skeletal homeostasis and energy metabolism, which fills 50–70% of the bone marrow cavity in the human body [258]. Both murine and human bone marrow adipocytes exhibit a large lipid droplet, enveloped by a very thin layer of cytoplasm, with the cell nucleus situated

peripherally, and they express comparable levels of adiponectin and leptin as white adipocytes [259]. The average diameter of these marrow adipocytes is generally less than that of subcutaneous and visceral white adipocytes, usually measuring between 40 and 65 micrometers [260].

There are two types of BMAT: constitutive BMAT (cBMAT), which is located within the yellow marrow of distal bones and has little to no hematopoiesis, and regulated BMAT (rBMAT), which is found in proximal bones with active hematopoiesis and bone remodeling [261–263]. cBMAT exists in the medullary canal at the junction of the sacrum and ankle, whereas rBMAT develops within the bone marrow of long bones after birth, extending from beneath the growth plate to the metaphysis and entering the diaphysis [264]. cBMAT plays a suppressive role in hematopoiesis, potentially by preserving hematopoietic stem cells (HSCs) in a quiescent state, as elegantly demonstrated by research from the Daley laboratory [265]. In relation to the skeletal system, the volume of cBMAT, as assessed by techniques such as osmium staining and micro-CT in rodents or *magnetic resonance imaging* (MRI) in humans, is inversely proportional to bone mass [266, 267]. Conversely, rBMAT exhibits a more adaptable nature, functioning as an adipose tissue with endocrine and paracrine effects on hematopoietic and skeletal remodeling processes [256]. A high rBMAT volume is frequently, albeit not universally, correlated with reduced bone mass [268, 269]. However, these findings regarding BMAT have only been confirmed in mice, and whether they hold true for human BMAT remains to be determined.

Adipogenesis of Bone Marrow Adipose Tissue

Previous studies have shown that the source of adipocytes in the bone marrow differs from that in WAT [270]. The bone marrow exists in two forms: red and yellow. The red marrow is active in blood cell formation, and its red color is derived from abundant erythrocytes [271]. The yellow marrow is mostly filled with fat cells, defining its color, as it also contains some primitive blood cells [271]. During growth, bone marrow transitions from red to yellow as fat accumulates, particularly in long bone shafts and trabecular regions by early adulthood, with fat comprising 20–25% of the adult skeletal mass [271]. BMAT typically expands first at the ends of long bones and then progresses toward the shaft, moving toward the ends [272, 273]. As this occurs, the red marrow reduces and eventually occupies only specific sites such as the ribs, sternum, certain vertebrae, sacrum, and coccyx by approximately 40 years of age [272, 273].

Bone marrow adipocytes originates from mesenchymal stem cells (MSCs), which have the potential to differentiate into both adipocytes and osteoblasts [274]. *PPARG* is recognized as a key regulator that governs the process of adipocyte differentiation during the development of bone marrow adipocytes. Deletion of *Pparg* results in a decrease in the number of bone marrow adipocytes [275]. Additionally, haploinsufficiency of *Pparg* has been associated with a notable increase in bone

mass [276]. Bone marrow adipocytes originate from heterogeneous lineages. Lineage-tracing studies have revealed the origins of MSCs, showing that they derive from Osterix1-positive cells found in neonatal bone marrow [277]. However, in adult but not young mice, MSCs have been associated with cells that express LepR [274]. Notably, the leptin signaling pathway is instrumental in managing both the development of bone marrow adipose tissue and bone formation in adult mice [278].

Bone marrow adipocytes are undeniably derived from the mesenchymal progenitor cells that inhabit the bone marrow. Nonetheless, the exact lineage hierarchy of these adipocytes within BMAT, as well as the molecular pathways governing their differentiation, is yet to be fully elucidated.

Endocrine Function and Physiology of Bone Marrow Adipose Tissue

BMAT plays a pivotal role in the maintenance of bone marrow homeostasis. It is also involved in regulating hematopoiesis and osteoblastogenesis. In contrast, BMAT significantly contributes to energy metabolism, highlighting its multifaceted influence on both the hematological and skeletal systems, as well as overall metabolic health.

BMAT is a complex and dynamically active endocrine adipose depot located in non-hematopoietic bone marrow niches that interacts with hematopoietic cells and bone tissue [279]. Nguyen et al. proposed that adipocytes might facilitate hematopoiesis by secreting leptin [280]. Notably, in the early stages of postnatal development, endothelial and stromal cells expressing LepR are demonstrated to exhibit the highest levels of stem cell factor [281], which is a crucial component for the development and maintenance of hematopoietic stem cells. Furthermore, crucial molecules, such as CXCL12, IL-3, IL-8, CSF3, and LIF, are expressed in bone marrow adipocytes, directly promoting the survival of HSCs [282]. According to a report by Corre et al. [283], bone marrow adipocytes can produce cytokines such as IL-7, IL-15, EPO, and TPO, which directly promote hematopoiesis through the induction of lymphoid and myeloid differentiation of HSC clonogenic progenitors. Bone marrow adipocytes express or produce factors that participate in regulating the differentiation of HSCs into lymphocytes, granulocytes, megakaryocytes, and erythrocytes, but their specific role is not yet clear [284]. For instance, the reduction in B lymphocyte production is associated with an increase in adipose tissue in the bone marrow, a part of which promotes the generation of myeloid-derived suppressor cells [285]. These cells inhibit the production of B lymphocytes via the secretion of IL-1. During in vitro co-culture with HSCs in vitro, bone marrow adipocytes can support megakaryocyte maturation and promote platelet production [286].

To some extent, marrow adipocytes have been shown to exert a suppressive effect on bone formation. Indeed, there is evidence suggesting that the deletion or reduction of marrow adipocytes leads to enhanced bone formation [287]. In vitro studies

have shown that adipocytes derived from MSCs can induce differentiation of MSC-derived osteoblasts into adipocyte phenotypes [288]. The lipotoxicity of FFAs produced by bone marrow adipocytes is mediated by their action as natural ligands for PPAR γ , inducing activation of PPAR γ in MSCs, pre-osteoblasts, and osteoblasts, promoting adipogenesis and transforming osteoblasts into adipocytes by inhibiting *Runx2* activity [279, 289]. Furthermore, within the FFAs produced by bone marrow adipocytes, palmitic acid impairs osteoblast formation and mineralization by inhibiting the Wnt/ β -catenin and BMP2/*Runx2*/Smads pathways and also induces apoptosis and autophagy dysfunction in bone cells [279, 290, 291].

Notably, BMAT possesses endocrine functions and is also subject to regulation by endocrine factors. It exhibits endocrine/paracrine roles by secreting peptides, such as leptin and adiponectin, as well as cytokines, including IL-6, IL-1 β , and TNF α [292]. In addition, compared to epididymal adipocytes, there is an upregulation of IL-6, IL-1 β , and TNF α gene expression in mouse bone marrow adipocytes, indicating that BMAT has inflammatory potential [293]. In 2014, Cawthorn et al. [256] demonstrated that BMAT acts as an endocrine organ and contributes significantly to circulating adiponectin levels under various conditions in control mice, genetically modified mice (Ocn-Wnt10 mice), rabbits, and humans. Research conducted on human cell cultures has demonstrated that marrow adipocytes exhibit high levels of leptin expression and secretion [294]. Further research is needed to explore the effects of adipokines such as leptin and adiponectin on bone. Expansion of BMAT is regulated by growth hormone, with a marked increase in BMAT occurring in pituitary-ectomized rats, an effect that is mitigated by the introduction of external growth hormone [295].

Furthermore, the BMAT is innervated by sympathetic and sensory axons, which can potentially influence its adaptation to different skeletal sites [296]. It is directly responsive to adrenergic signals and can be modified by the neural regulation of surrounding cells, indicating multiple potential mechanisms for the neural regulation of BMAT metabolism [296].

Mammary Adipose Tissue

Primarily composed of epithelial cells and adipocytes, the mammary gland functions as an exocrine organ responsible for milk production and secretion [297, 298]. Enveloping the ducts and alveoli, the mammary fat pad is a crucial component of the mammary gland, occupying most of the breast [299]. Because the mammary gland is an appendage of the skin, mammary adipose tissue is considered by some researcher to be a type of sAT [298, 299]. An early ultrastructural study suggested that adipocytes within the mammary gland are derived directly from perivascular mesenchymal cells. Throughout the differentiation process, these cells gradually accumulate lipids, ultimately acquiring the morphological characteristics of typical white adipocytes [300]. However, the remarkable functional and morphological changes in the mammary gland during the cyclical lactation process indicate that

mammary adipose tissue exhibits characteristics distinct from those of typical sAT, such as iWAT. Although mammary adipose tissue constitutes the primary component of the breast stroma, it has received much less attention from researchers than the mammary parenchyma in studies targeting the mammary gland. In adipose tissue-focused research, mammary adipose tissue is often excluded because of concerns regarding the potential confounding effects of mammary epithelial cells. Nevertheless, there is growing recognition of the role of mammary adipose tissue in mammary development and lactation.

Mammary adipose tissue plays a critical role in postnatal development of the mammary gland. In lipodystrophic mice, mammary gland development remains impaired, even with exogenous estradiol supplementation, as evidenced by the absence of duct terminal end buds [301]. Loss of adipose tissues at 2 weeks and 7 weeks after birth results in decreased duct branching points and terminal end buds, as well as excessive lobulation in mice, respectively [302]. These findings suggest that adipose tissues are essential for the formation of the ductal network during puberty and for maintaining proper lobular architecture. Mammary adipose tissue, a crucial component of the breast stromal microenvironment, has been primed to contribute significantly. Signaling molecules secreted by mammary adipose tissue are crucial for regulating mammary epithelial cells. Conditioned media derived from fully differentiated adipocytes inhibits apoptosis of mammary epithelial cells [303]. The genetic deletion of functional leptin or lack of leptin receptors results in the complete loss of ductal epithelial development, and this defect can be reversed by restoring leptin signaling [304]. Mice overexpressing adiponectin have exhibited abnormal mammary growth and incomplete ductal development [305]. Interestingly, the “white” phenotype of adipocytes may be essential for mammary gland development. As mentioned above, mammary adipose tissue is primarily composed of white adipocytes, while the presence of typical brown adipocytes remains uncertain. An *in vivo* experiment showed that browning of mammary adipose tissue by a β 3-AR agonist is associated with inhibited mammary development [306]. Additionally, proliferation of mammary epithelial cells is suppressed when co-cultured with brown adipocytes *in vitro* [306].

During lactation, most of the mammary fat pad is replaced by the expanded ductal system and developed alveoli [307]. A plausible hypothesis for the disappearance of mammary adipose tissue during lactation is that adipocytes undergo delipidation to provide the necessary substrates and energy for milk production and secretion. The anabolic processes of mammary adipose tissue in lactating mice were inhibited [308]. The number of lactating offspring and the duration of lactation are determining factors for the extent of mammary adipose tissue depletion, with adipose tissue proximal to the mammary epithelial tissue being consumed more extensively [309]. Adipocytes may be an alternative source of secretory alveoli in addition to ductal stem cells. In late-pregnancy mice, a single large lipid droplet appears in the cytoplasm of alveolar cells, which displays characteristics of both epithelial and adipocyte cells [310]. Immunohistochemical analysis using perilipins 1 and 2 revealed a population of cells with an intermediate adipoe epithelial phenotype in the mammary fat pad of mice during pregnancy and lactation [311]. These cells highly

express E74-like factor 5 (Elf5), a key regulator of alveologenesis, and both transient and stable ectopic expressions of Elf5 in cultured adipocytes induce the expression of whey acidic protein [311]. Furthermore, using the Cre-loxP recombination system, it has been shown that mouse mammary adipocytes may directly transdifferentiate into secretory epithelial cells during pregnancy [312]. These temporary lipid-containing secretory alveolar cells that are derived from adipocytes during lactation are defined as “pink adipocytes” by Cinti et al. [310]. Mammary adipose tissue also promotes gland involution. Lipid tracking and lipidomics results indicate that adipocytes within mammary adipose tissue receive lipids from alveoli, and removal of mammary adipose tissue impedes mammary gland involution [313].

Summary

This chapter briefly introduces the anatomy and physiology of the adipose tissue. The classification of adipose tissue by “color” has evolved from simply reflecting its appearance to now representing the metabolic and thermogenic states of adipocytes, establishing a paradigm in adipose tissue research. Unilocular white adipocytes primarily store energy, whereas multilocular, mitochondria-rich brown adipocytes are mainly involved in thermogenesis. Accumulating evidence indicates the existence of beige adipocytes, which lie between white and brown adipocytes and can be inducibly activated for thermogenesis. Adipose tissue also functions as an endocrine organ, playing essential roles in metabolic regulation and other physiological functions by secreting polypeptides, lipokines, EVs, and exosomal miRNAs. Immune cells, neural innervation, and ECM collectively influence the adipocyte phenotype and local microenvironment in adipose tissue.

Adipose tissue, distributed widely throughout the body, demonstrates substantial heterogeneity, with adipocytes in various fat depots and even within the same depot, showing notable disparities in origin, phenotype, and physiological functions. Furthermore, adipose tissue is dynamic, manifesting structural and functional alterations in response to physiological stimuli or at specific stages of the life cycle. A comprehensive understanding of adipose tissue biology is important for the development of future therapies.

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Chapter 3

Metabolic Function of the Adipose Tissue



Gergana Deevska

Abbreviations

β -AR	β -Adrenergic receptor
AA	Amino acid
ABCA1	ATP-binding cassette transporter protein A1
ABCG1	ATP-binding cassette transporter protein G1
ABHD5	Alpha/beta hydrolase domain-containing protein 5
ACAT	Acyl-CoA:cholesterol acyltransferase
ACC	Acetyl-CoA carboxylase
acyl-CoA	Acyl coenzyme A
AdipoR	Adiponectin receptor
AGPAT (<i>s. LPAAT</i>)	1-Acylglycerol-3-phosphate O-acyltransferase
AMP	Adenosine monophosphate
AMPK	Adenosine monophosphate-activated protein kinase
apoA-I	Adipolipoprotein A-I
aSMase	Acid sphingomyelinase
ATGL	Adipose triacylglycerol lipase
ATRA	All-trans retinoic acid
BAT	Brown adipose tissue
BCAA	Branch chain amino acids
CCT	CTP:phosphocholine cytidylyltransferase
CDP	Cytidine diphosphate
CDS	Chanarin-Dorfman syndrome
CE	Cholesterol ester

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C/EBP	CCAAT/enhancer-binding proteins
CERS	Ceramide synthase
ChREBP	Carbohydrate-response element-binding protein
CPT	CDP-choline:1,2-diacylglycerol phosphotransferase choline
DAG	Diacylglycerol
DES1	Dihydroceramide desaturase 1
DGAT	Diacylglycerol acyltransferase
DHAP	Dihydroxyacetone phosphate
DNL	De novo lipogenesis
eNOS	Endothelial nitric oxide synthase
ER	Endoplasmic reticulum
ETC	Electron transport chain
FAS	Fatty acid synthase
FA	Fatty acid
FC	Free cholesterol
FFA	Free fatty acid
G3P	Glycerol-3-phosphate
G6P	Glucose-6-phosphate
GAPDH	Glyceraldehyde-3-phosphate dehydrogenase
GCS (<i>s. UGCG</i>)	Glucosylceramide synthase
GLP	Glucagon-like peptide
GLUT	Glucose transporter
GPAT	Glycerol-3-phosphate acyltransferase
GPCR	G protein-coupled receptor
GPD1	Glycerol 3-phosphate dehydrogenase
GPDH	3-Glycerol phosphate dehydrogenase
HDL	High-density lipoprotein
HK	Hexokinase
HMP	Hexose-monophosphate
HSL	Hormone-sensitive lipase
iNOS	Inducible nitric oxide synthase
iPFK2	Inducible 6-phosphofructo-2-kinase
IR	Insulin receptor
IR-A	Insulin receptor isoform A
IR-B	Insulin receptor isoform B
KSR	3-Ketosphinganine reductase
LCFA	Long-chain fatty acid
LD	Lipid droplet
LDH	Lactate dehydrogenase
LDLR	Low-density lipoprotein receptor
LPA	Lysophosphatidic acid
LPAAT (<i>s. AGPAT</i>)	Lysophosphatidic acid acyltransferase
LRP1	Low-density lipoprotein receptor-related protein 1
MDH	NAD-dependent malate dehydrogenase
MGL	Monoacylglycerol lipase

NO	Nitric oxide
PA	Phosphatidic acid
PAP (<i>s. Lipin</i>)	Phosphatidic acid phosphatase
PC	Phosphatidylcholine
PDC	Pyruvate dehydrogenase complex
PDK	Pyruvate dehydrogenase kinase
PDP	Pyruvate dehydrogenase phosphatase
PE	Phosphatidylethanolamine
PEPCK-C	Phosphoenolpyruvate carboxykinase
PFK	Phosphofructokinase 1
PI	Phosphatidylinositol
PK	Pyruvate kinase
PKA	cAMP-dependent protein kinase
PKL	Liver-specific pyruvate kinase
PKM	Pyruvate kinase muscle isoenzyme
PKR	Red blood cells-specific pyruvate kinase
PL	Phospholipid
PLTP	Phospholipid transfer protein
PPAR	Peroxisome proliferator-activated receptor
RA	Retinoic acid
RAR	Retinoic acid receptor
ROS	Reactive oxygen species
S1P	Sphingosine-1-phosphate
SM	Sphingomyelin
SMS1	Sphingomyelin synthase
SPHK	Sphingosine kinase
SPT	Serine palmitoyltransferase
SR-BI	Scavenger receptor class B type 1
TAG	Triacylglycerol
TCA	Tricarboxylic acid
TG	Triglyceride
TR	Thyroid receptor
UCP1 (<i>s. thermogenin</i>)	Uncoupling protein-1
UGCG (<i>s. GCS</i>)	UDP-glucose:ceramide glucosyltransferase
VLDLR	Very low-density lipoprotein receptor
WAT	White adipose tissue

Introduction

Adipose tissue is a complex metabolically active organ consisting of two functionally distinct tissue types, white adipose tissue (WAT) and brown adipose tissue (BAT), which differ in size and body distribution. WAT is the largest organ distributed throughout the body and is designed to store considerable amounts of energy

in the form of triacylglycerols (TAGs). Nearly all TAGs in the body are found in adipocytes, the primary cell type of adipose tissue, with less than 5% located in other tissues such as skeletal muscle cells, liver, and pancreas. WAT adipocytes are unique cells in terms of size and expansion capacity. They contain a single centrally located LD) consisting of TAGs and cholesteryl esters (CEs) surrounded by a phospholipid (PL) monolayer and LD-specific proteins. These unilocular cells are dynamically altered in response to the nutrient condition. During periods of nutrient excess, extra nutrients are converted into TAGs through lipogenesis. TAGs accumulate within LD, causing adipocyte to expand by several folds in size. During nutrient deprivation, stored TAGs are broken down to release free fatty acids (FFAs) via lipolysis, and different body tissues are used to fulfill their energy needs. This is referred to as TAG turnover, which is a slow process central to maintaining whole body energy homeostasis in a healthy adult individual [1].

Conversely, BAT comprises only a small percentage of adult human adipose tissue, localized primarily to the supraclavicular and paravertebral spaces [2, 3]. However, it does not play a role in energy storage. Instead, it dissipates stored energy to produce heat and regulate body temperature, thereby playing a role in thermogenesis [4]. Brown adipocytes are morphologically different from white adipocytes and contain numerous tiny LDs and well-developed mitochondria that express high levels of uncoupling protein-1 (UCP1 or thermogenin). A third type of adipocytes, namely “beige” or “brite,” has been described in recent years [5]. Although located within WAT, they are morphologically and metabolically similar to brown adipocytes.

Moreover, white adipocytes can be converted into beige adipocytes in response to specific environmental, neuronal, and hormonal stimuli [6]. This unique morphological and metabolic plasticity of adipose tissue underlies its crucial role in maintaining energy homeostasis and ultimately in regulating metabolism and body weight. In addition, the function of adipose tissue as an endocrine organ requires a highly active protein synthesis machinery to produce and secrete hundreds of small peptide hormones and other metabolites (collectively known as “adipokines” from WAT and “batokines” from BAT). They further contribute to the crosstalk between cells and tissue types and ensure adequate whole-body homeostatic control. This chapter focuses on the critical role of adipose tissue in whole-body energy homeostasis by exploring the major metabolic pathways in different adipocyte types, summarizing their regulatory mechanisms and potential impact on human health and disease.

Role of Adipose Tissue in Energy Homeostasis

The primary role of the adipose organ in regulating whole-body energy homeostasis is to (1) act as a dynamic energy reservoir, ensuring that an adequate supply of energy substrates for other tissues is maintained within healthy ranges under different physiological states; (2) convert chemical energy into heat via non-shivering

thermogenesis under certain stress conditions; and (3) communicate with the rest of the body via endocrine signals to achieve a higher level of regulatory control of energy homeostasis.

The role of adipose tissue in dynamic energy storage and release within the human body is attained by WAT. This tissue type plays an integral role in maintaining energy homeostasis, ensuring that energy is stored during periods of excess caloric intake and released when the body needs it, such as during fasting or times of increased energy demand. The consumption of more calories than required for immediate energy expenditure leads to the conversion of extra energy into TAG molecules via lipogenesis and their storage in adipocytes as LDs. These LDs can expand in size and number as more energy is stored, allowing the WAT to adapt to the changing energy needs of the body. During fasting or with increased energy demand, the body relies on the energy stored in white adipocytes to meet its energy needs. The release of stored energy from adipose tissue occurs through lipolysis. TAG molecules are hydrolyzed to FFAs and glycerol, which are released into the bloodstream for use as energy substrates by other tissues, such as the muscle and liver. Lipogenesis and lipolysis metabolic pathways are described in greater detail in section “Central Metabolic Pathways in Adipocytes” of this chapter. These processes are regulated by a complex signaling network that involves various hormones and enzymes. They ensure metabolic flexibility and a consistent energy supply, which are essential for survival.

Non-shivering thermogenesis, a heat-generating process that prevents hypothermia without muscle shivering, is a unique feature of brown and beige adipocytes [7]. Thermogenesis is regulated by environmental factors such as cold exposure as and the sympathetic nervous system. In addition to its central role in regulating body temperature, it supports the maintenance of energy balance within the body by dissipating excess energy as heat, thus enhancing energy expenditure. Notably, recent studies have provided compelling evidence that the thermogenic-mediated functions of brown/beige fat extend beyond heat generation and play an active role in regulating glucose and lipid metabolism, insulin sensitivity, and overall adipose tissue homeostasis [8]. Hence, regulation of the number and function of brown/beige adipocytes is emerging as a promising strategy for developing novel approaches that support the management of excess body adiposity and diabetes [9]. An in-depth overview of the process of non-shivering thermogenesis and its underlying regulatory mechanisms is provided in section “Regulation of Adipose Tissue Metabolism” of this chapter.

Efficient crosstalk between adipose tissues and other tissues and organs in the human body is essential for maintaining a continuous, well-balanced homeostatic state. This is achieved by the secretion of a large number of factors with hormonal, autocrine, and paracrine properties. These factors include peptides, hormones, growth factors, binding proteins and precursors, a variety of novel signaling lipids and lipid mediators, certain inflammatory mediators, and exosomal miRNAs [10]. They are named adipokines and batokines and represent a complex and poorly understood network of biochemical mediators produced in WAT and BAT, respectively, in response to metabolic, environmental, and genetic triggers aimed at

communicating with other tissues to maintain homeostasis and adapt to changes [11]. The endocrine roles of adipose tissue are discussed more comprehensively in other chapters of this book.

Central Metabolic Pathways in Adipocytes

Lipid Metabolism in Adipose Tissue

Lipids comprise a diverse group of molecules with unique structures, functions, and metabolic pathways that govern their synthesis and turnover. The primary energy storage lipid molecule in adipose tissue is the glycerolipid TAG. It is the primary neutral lipid that accumulates inside LD and comprises the hydrophobic core of dynamic cellular organelles. The LD surface is composed of polar, amphipathic lipids, which are relatively minor, but important lipid intermediates with specific functions. These include cholesterol, several different phospholipids, and sphingolipids.

TAG Synthesis and Turnover

TAG synthesis occurs via two distinct pathways: the glycerol-3-phosphate (G3P) pathway and the acyl coenzyme A (acyl-CoA): monoacylglycerol (MAG) pathway. Both pathways involve multiple steps taking place at the endoplasmic reticulum (ER) membranes. The activity of the MGAT pathway in humans is limited to small intestinal enterocytes during the process of active absorption of dietary fat due to the abundance of the digestion product sn-2 MAG. In adipocytes, the major pathway that takes place is the G3P pathway. It comprises four sequential steps, in which three FFAs are added to a glycerol backbone to form TAG. This pathway was originally named the “Kennedy pathway” in honor of Kennedy and his colleagues, who identified the enzymes of the TAG pathway in the 1950s and 1960s [12, 13]. It begins with acylation of G3P at the sn-1 position by a long-chain acyl-CoA thioester, a step catalyzed by the enzyme glycerol-3-phosphate acyltransferase (GPAT). The product of this first step is lysophosphatidic acid (LPA). The GPAT-catalyzed reaction is the rate-limiting step of the de novo TAG synthesis pathway. In mammals, four isoforms of GPATs (GPAT1–4) have been identified and characterized as having different subcellular localizations, substrate preferences, and tissue-specific expression profiles [14]. GPAT1 and GPAT2 are localized in the mitochondrial outer membrane, whereas GPAT3 and GPAT4 are localized in the ER membrane.

Moreover, GPAT1 and GPAT2, although expressed to some degree in WAT, appear to have limited contribution to the total activity of G3P conversion to TAG [15–17]. GPAT3 and GPAT4, on the other hand, are both expressed in WAT. GPAT3 is the predominant isoform expressed in WAT, accounting for as much as 80% of

total GPAT activity [14, 18]. GPAT4, in addition to its expression in WAT, has also been found in BAT. Although the mRNA abundance of this isoform is high in adipose depots, the data suggest that most of the GPAT activity in adipocytes is provided by GPAT3 [19]. Its expression and activity are further significantly upregulated during adipocyte maturation [18].

A second acylation at the sn-2 position of LPA by acyl-CoA:1-acylglycerol-3-phosphate O-acyltransferase (AGPAT or LPA acyltransferase (LPAAT)) produces a second intermediate of this pathway, phosphatidic acid (PA). As many as 13 genes encoding proteins with similar structures and sequence similarities to previously characterized glycerolipid acyltransferases have been identified and named *Agpat 1–13*; however, only AGPAT1, 2, and 3 have been shown to catalyze the esterification of LPA to form PA [13, 20]. WAT expresses all three AGPAT isoforms; however, AGPAT-2 and -3 are barely detectable. AGPAT2 is critical for TAG synthesis in this tissue type and its expression is twofold greater than AGPAT1. Deficiency of AGPAT2 in humans results in the Berardinelli-Siep form of congenital lipodystrophy, indicating that the different isoforms cannot compensate for its loss [21].

In step 3 of this pathway, PA is hydrolyzed by the enzyme phosphatidic acid phosphatase (PAP, also called Lipin) to form diacylglycerol (DAG). PAP catalytic activity is Mg^{2+} -dependent, and in mammalian cells, there are three isoforms (PAP1–3) with distinct structural similarities and tissue-specific expression patterns. All three PAP isoforms are expressed in human fat, with PAP1 being the primary lipin enzyme in both WAT and BAT [22]. Mutations in this isoform lead to a marked lipodystrophy phenotype in mice, whereas humans with mutations in the gene encoding PAP1 exhibit no defects in adipogenesis or reduction in adiposity, suggesting the existence of a yet-to-be-identified compensatory mechanism for DAG synthesis in adipocytes [23]. DAG is not only the immediate precursor for the synthesis of TAG but also a vital branch-point intermediate that intersects the synthesis of TAG and the major phospholipids that compose the phospholipid monolayer of LD, phosphatidylcholine (PC), and phosphatidylethanolamine (PE).

The fourth and final esterification step in the TAG synthesis pathway is catalyzed by diacylglycerol acyltransferase (DGAT). Two genes have been identified in mammalian cells that encode structurally distinct enzymes that catalyze the same biochemical reaction: *DGAT1* and *DGAT2* [24, 25]. Both enzymes are highly expressed in cells and tissue types that actively produce TAG, including white and brown adipose tissues [26]. It appears that the two DGAT enzymes can compensate for each other in adipose tissue, suggesting that they do not possess completely distinct functions and are most likely not essential for TAG storage in adipocytes [27].

Lipolysis is the metabolic pathway through which TAG is completely catabolized to FFAs and glycerol. It is the primary turnover pathway for TAG molecules that occurs in the cytosol of adipocytes. In white adipose tissue, the primary function of lipolysis is to generate FFAs that are excreted into the circulation and used for energy production in other tissues, therefore participating in the maintenance of whole-body energy homeostasis. Conversely, fatty acids (FAs) generated via lipolysis are intracellularly used as substrates for β -oxidation and energy production in brown adipocytes. Lipolyzed FAs may also be re-esterified back to TAG or activated

for use in the synthesis of other FA-containing intracellular lipids, such as phospholipids, cholesteryl esters, and sphingolipids.

The central pathway of adipocyte lipolysis is catalyzed by three main lipases, namely adipose triacylglycerol lipase, hormone-sensitive lipase, and monoacylglycerol lipase, which work coordinatively to remove the FA moieties of TAGs, sequentially releasing the glycerol backbone.

The removal of the first FA from the TAG molecule producing DAG is catalyzed by the enzyme adipose triacylglycerol lipase (ATGL, also known as desnutrin, PNPLA2, and calcium-independent phospholipase A2 ζ), which is the major TAG-specific hydrolase highly expressed in adipose tissue [28–30]. This is the rate-limiting step in TAG degradation *in vivo* [31]. ATGL is a LD-associated enzyme that possesses the highest substrate specificity towards TAG, but can also hydrolyze DAG, although at a much lower level. In addition, it is not currently known whether ATGL may have specificity towards the *sn* position of the FAs in TAG, their chain length, or saturation level. Consistent with the key role of this enzyme in TAG lipolysis, ATGL-null mice show increased white adiposity, and silencing ATGL in human adipocytes significantly reduces lipolysis, whereas overexpression has the opposite effect [31, 32]. Humans lacking functional ATGL, however, do not have increased adiposity despite the presence of multisystem TAG storage underlying severe pathologies [33].

For optimal activity, ATGL requires the presence of a specific activator protein known as alpha/beta hydrolase domain-containing protein 5 (ABHD5, also known as CGI-58). CGI-58 is an essential component of the lipolytic system capable of potentially inducing the activity of ATGL in tissue extracts from adipose tissue [34]. Genetic defects in this activator protein result in the neutral lipid storage disease Chanarin-Dorfman syndrome (CDS), characterized by intracellular accumulation of TAG in LDs of most tissues and ichthyosis [35].

The second step in TAG turnover involves the release of another FA from DAG to produce MAG under the catalytic activity of the enzyme hormone-sensitive lipase (HSL). This name originates from the fact that lipase is under hormonal regulation [36]. HSL was historically the first identified neutral lipase in adipose tissue and, for many years, was considered the sole key player in TAG hydrolysis, catalyzing the rate-limiting reaction until the discovery and characterization of ATGL [37]. Recent advances in our understanding of the role of HSL in TAG hydrolysis indicate that although it has broad substrate specificity towards tri-, di-, and monoacylglycerols, as well as cholesterol and retinyl esters, the rates of hydrolysis of DAG are much higher than those of other substrates and at least tenfold higher than for TAG [38]. The structural and functional properties of HSLs and their different modes of regulation have been extensively studied over the past five decades and are well characterized (reviewed in [38]). Briefly, during lipolysis, HSL translocates to the surface of the LD in response to hormonal stimuli that reversibly activate phosphorylation sites located within the regulatory domain of the enzyme via cAMP-dependent protein kinase (PKA) and intracellular levels of cAMP. In adipose tissue, in addition to post-translational modifications, protein-protein interactions with specific LD-associated proteins, such as perilipins, vimentin, and FABP, have also been to

play an important role in regulating HSL activity [39–41]. In humans, mutations in the gene encoding the HSL protein result in more than 50% decreased expression and lead to adipose tissue dysfunction presenting with features of lipodystrophic phenotype [42, 43].

Lipase catalyzes the final step in TAG hydrolysis, in which the third FA is released from MAG to yield free glycerol monoacylglycerol lipase (MGL). This enzyme is ubiquitously expressed in various tissues, with high levels in adipose tissue. In contrast to the other two lipases, MGL does not hydrolyze other glycerolipids and possesses specificity towards the hydrolysis of monoacylglycerols at both the sn-1- and sn-2-position of the FA residue [44, 45]. Although this enzyme has been extensively studied for its critical role in the brain endocannabinoid signaling system [46], its physiological role in adipose tissue lipolysis remains to be elucidated.

A shared noteworthy characteristic of ATGL, HSL, and MGL is the existence of regulatory mechanisms at the level of protein interaction partners that modulate enzyme activity, localization, stability, or affinity to other proteins. Deficiency of many of these proteins with regulatory and/or supporting functions leads to pronounced alterations in the metabolism of TAG and other neutral lipids, often resulting in adipose tissue dysfunction and consequent pathologies [47].

Cholesterol Storage and Efflux

Cholesterol is the second most abundant neutral lipid accumulating in adipocytes LDs. As much as one-fourth of total body cholesterol is stored in adipose tissue, which could increase to one-half of the adipose tissue hypertrophy and hyperplasia associated with obesity [48, 49]. Interestingly, nearly all LD-associated cholesterol is free cholesterol (FC), with less than 6% cholesterol esters (CE) [50]. This is consistent with the finding that acyl-CoA:cholesterol acyltransferase (ACAT), an enzyme that catalyzes the esterification of cholesterol with long-chain FAs (LCFAs), has relatively low expression levels of in mouse adipose tissue compared to other tissues [51]. Furthermore, the rate of de novo cholesterol synthesis in adipocytes has been reported to be negligent. Instead, these cells acquire cholesterol via lipoprotein uptake via several different receptor-mediated mechanisms, including the low-density lipoprotein receptor (LDLR), scavenger receptor class B type 1 (SR-BI), low-density lipoprotein receptor-related protein 1 (LRP1), and very low-density lipoprotein receptor (VLDLR) [52–55]. Diet is the primary source of adipocyte cholesterol, as evidenced by earlier studies demonstrating that dietary cholesterol levels are more strongly correlated with adipocyte cholesterol content than with plasma cholesterol concentrations [48, 56]. Circulating triglyceride (TG)-rich chylomicrons deliver dietary cholesterol to the adipose tissue, where uptake occurs in association with TG accrual through the above-mentioned membrane-anchored lipoprotein receptors.

The removal of cholesterol from adipocytes is achieved through efflux via two ATP-binding cassette transporter proteins, ABCA1 and ABCG1, and SR-BI [57].

ABCA1 acts to efflux excess cellular FC to adipolipoprotein A-I (apoA-I), forming nascent high-density lipoprotein (HDL) particles in circulation, contributing to systemic HDL biogenesis [58]. SR-BI, on the other hand, transfers cholesterol to the mature circulating HDL. It was initially shown that ABCA1 and SR-BI are the primary adipocyte-expressed transport systems for cholesterol efflux in adipose tissue [59]. However, more recent studies, implicated ABCG1 as a significant player in adipose tissue cholesterol homeostasis and overall lipid storage capacity [60, 61]. Both ABCA1 and ABCG1 expression levels in adipose tissue and FC efflux appeared to be proportional to adipocyte size and cellular TAG content. However, the mechanism underlying this association remains to be elucidated.

Adipocyte phospholipid transfer protein (PLTP) has recently been identified as an additional contributor to cholesterol efflux in adipose tissue. It stimulates adipocyte FC efflux and contributes a small but significant pool of plasma HDL cholesterol, which illustrates a necessary but not yet well-understood link between phospholipids and cholesterol efflux in this cell type [62].

Synthesis and Remodeling of Major Phospholipids in Adipose Tissue

The major LD-associated surface phospholipids in mammalian cells are PC, PE, and phosphatidylinositol (PI). Compared with other membranes, LDs are relatively deficient in phosphatidylserine and phosphatidic acid but are enriched in some lysophospholipids [63]. The metabolic steps for synthesizing the three major phospholipids found in adipocyte LDs—PC, PE, and PI—are summarized below. Notably, these phospholipids share a common intermediate with the TAG biosynthetic pathway. DAG is a precursor for the synthesis of PC and PE, whereas phosphatidic acid is used to synthesize PI.

The initial step in PC synthesis begins with the import of extracellular choline inside adipocytes and its rapid phosphorylation to phosphocholine by the cytosolic enzyme, choline kinase. In the subsequent reaction, phosphocholine is converted to cytidine diphosphate (CDP)-choline by CTP:phosphocholine cytidyltransferase (CCT), the rate-limiting reaction for PC biosynthesis. The final reaction in this pathway is the transfer of choline from CDP-choline to DAG in a reaction catalyzed by CDP-choline:1,2-diacylglycerol choline phosphotransferase (CPT), an integral membrane protein localized primarily to the ER [64, 65].

PE is synthesized via the CDP-ethanolamine pathway, which is composed of several reactions that closely parallel those of the CDP-choline pathway for PC synthesis. The cytosolic enzyme ethanolamine kinase first activates the amino alcohol ethanolamine to phospho-ethanolamine. Subsequently, CTP reacts with the phosphorylated amine to produce CDP-ethanolamine in a reaction catalyzed by the cytosolic enzyme CTP: phosphoethanolamine cytidyltransferase. In the final step of PE synthesis via this pathway, the integral ER membrane protein CDP-ethanolamine:1,2-diacylglycerol ethanolaminephosphotransferase converts CDP-ethanolamine and DAG to PE [65, 66].

PI is produced from phosphatidic acid (PA) via conversion to CDP-diacylglycerol, which then serves as a precursor for the biosynthesis of several acidic phospholipids, including phosphatidylinositol (PI). In the first step, CDP-diacylglycerol synthase catalyzes the reaction between CTP and PA, resulting in the formation of CDP-diacylglycerol, which is then used in a subsequent reaction to provide the DAG skeleton for the synthesis of PI. This step is catalyzed by the enzyme PI synthase [65].

The degradation and remodeling of phospholipids are achieved by different enzymatic activities of a large group of intracellular phospholipases that vary considerably in structure, function, and tissue expression. They hydrolyze phospholipid substrates at specific ester bonds and play a vital role in the remodeling of existing PL, as well as in the generation of a wide array of bioactive second messenger molecules that play a role in cell signaling [67].

Sphingolipid Metabolism in Adipose Tissue

Sphingolipids (SLs) are a diverse class of lipid molecules that contain the long-chain amino alcohol sphingosine as the backbone. They are ubiquitously found in all mammalian cells, including adipocytes, as critical structural components of cellular membranes [68]. In addition, several class members have been shown to function as signaling molecules [69]. The importance of SLs in adipose tissue structure and function has emerged in the past decade as our understanding of adipocyte biology has advanced. Adipocytes are unique cells as they must respond rapidly to whole-body energy conditions by expanding or reducing their size to accommodate lipid storage or lipid mobilization, respectively. To achieve this, they must be equipped with essential metabolic pathways to produce and degrade sphingolipids that respond to the energy demands of the body.

Changes in adipocyte size can occur rapidly, which may demand an acute increase in *de novo* sphingolipid biosynthesis to maintain the proper lipid composition in the plasma membrane and growing LD(s). Several SL species are present in LDs at relatively low concentrations and their specific functions are poorly understood [70]. *De novo* sphingolipid biosynthesis occurs in the ER. It begins with condensation of L-serine and saturated fatty acyl-CoA (most commonly palmitoyl-CoA) to form 3-ketosphinganine. This is the rate-limiting step in the pathway catalyzed by serine palmitoyltransferase (SPT) [71]. Adipose tissue-specific deletion of the catalytic subunit of this enzyme in mice resulted in the normal development of adipose tissue early in life, with progressively increasing cell death and inflammation with age [72]. Adipocyte-specific SPTLC2-deficient (aSPTLC2-KO) mice have markedly reduced adipose tissue mass, resulting in impaired fat distribution, causing systemic insulin resistance and severe lipodystrophy [73]. This unequivocal evidence emphasizes the significance of these lipids in maintaining a healthy adipose tissue.

In the second step, 3-ketosphinganine reductase (KSR) produces sphinganine, which is subsequently acylated to form dihydroceramide by dihydroceramide

synthases, often referred to as ceramide synthases (CERS). These are a family of enzymes that differ in their specificity for fatty acyl chain length and saturation. CERS1/4 mainly produces C18-Cer, CERS5/6 results in the formation of C16-ceramides, and CERS2 generates very long-chain ceramides, predominantly C24-ceramides. The possible pleiotropic roles of the individual enzymes in adipose tissue are yet to be elucidated; however, the significance of CERS 5 and CERS 6 yielding C-16 ceramide is well illustrated by the consequences of their deletion in animals. Mice deficient in CERS6 exhibit reduced C16:0 ceramide levels in white and brown adipose tissue when placed on a high-fat diet, which in turn results in suppressed adipose inflammation and increased β -oxidative capacity [74]. Similarly, loss of CERS5 is associated with reduced weight gain, reduced white adipose tissue inflammation, and improved glucose levels in animal models of diet-induced obesity [75].

The 4,5-trans-double bond is introduced in the sphingoid backbone of dihydroceramide by the enzyme dihydroceramide desaturase 1 (DES1), yielding ceramide [76]. Although germline ablation of this gene has been shown to result in lethality [77], its removal from adult animals resulted in healthy animals with reduced adipose tissue depots and liver mass, as well as improved lipid and glucose handling [78]. Furthermore, adipose tissue-specific ablation of this gene in obese rodents resulted in improved whole-body glucose metabolism, reduced weight gain by reducing adipose tissue mass, and resolved hepatic steatosis independent of adipose tissue browning.

Once synthesized in the ER, ceramide is transported to the Golgi apparatus, where it is used for the synthesis of all complex sphingolipids, including sphingomyelin (SM) and glycosphingolipids (cerebrosides and gangliosides), as well as other metabolites, such as ceramide-1-phosphate and sphingosine [71]. In the Golgi apparatus, ceramide is converted to SM by sphingomyelin synthase (SMS) 1 (SMS1). Ablation of SMS1 enzyme in animals results in reduced body weight and loss of fat tissue mass, accompanied by a severe lipodystrophic phenotype [79, 80]. Overexpression of this enzyme in a human liver cell line is associated with decreased TAG synthesis and LD formation [81]. However, whether similar phenomena occur in adipocytes remains to be elucidated. A second enzyme, namely SMS2, with the same catalytic activity, exists in mammalian cells, and it is primarily localized to the plasma membrane, where it contributes to lipid remodeling in cell signaling [82]. SMS2-null mice appear to have normal adipose tissue development and function, with no reported severe abnormalities [80].

The addition of glucose to ceramide in the Golgi apparatus is facilitated by glucosylceramide synthase (GCS or UDP-glucose:ceramide glucosyltransferase (UGCG)), leading to the production of the first cerebroside, glucosylceramide, which can be further transformed into more complex glycosphingolipids including gangliosides [83]. Pharmacological targeting of this step in animal models of obesity leads to decreased glycosphingolipid content and has been shown to suppress

adipogenesis, reduce the formation of white adipocytes, improve overall adipocyte function, and reduce inflammation in adipose tissue [84, 85]. Thus emphasizes the significance of these lipids in maintaining a healthy adipose tissue.

Ceramide is one of the several key metabolites in this pathway that possesses bioactive properties that mediate cell signaling and regulate various cellular processes. It has been extensively studied in the context of adipose tissue biology, obesity, diabetes, and cardiometabolic diseases [86].

Ceramide can also be produced via the turnover pathway of complex sphingolipids that involve different lysosomal acid hydrolases, and can be recycled by the reacylation of sphingosine. Lysosomal degradation of SM is catalyzed by acid sphingomyelinase (aSMase), which releases the phosphocholine group from the SM-regenerating ceramide. Mice deficient in this enzyme are protected against diet-induced adipose tissue expansion, hyperglycemia, and insulin resistance via liver-mediated metabolic adaptations as well as adipose tissue-specific changes associated with the absence of adipocyte hypertrophy and increased expression of genes associated with brown adipocyte differentiation [87, 88].

Lysosomal degradation of glycosphingolipids is achieved by the action of specific acid hydrolases that release the respective glyco- moiety to produce ceramide. Acid ceramidase then catalyzes the diacylation of ceramide to release sphingosine. This enzyme has been shown to be activated in mouse adipose tissue overexpressing adiponectin receptors (AdipoRs), resulting in improved overall metabolic health when animals are challenged with a high-fat diet [89, 90].

In the next step, sphingosine can be phosphorylated by either isoform of sphingosine kinase (SPHK1,2) to form sphingosine-1-phosphate (S1P), another crucial bioactive sphingolipid with robust cell-signaling properties. This is the final step in the turnover pathway before the sphingoid backbone is entirely degraded to hexadecenal and phosphoethanolamine, a reaction catalyzed by S1P lyase [91]. A noteworthy characteristic of S1P in adipocytes is its role as a key mediator of the lipolysis metabolic pathway and leptin secretion, supported by the dose-dependent increase in glycerol released by adipocytes treated with S1P *in vitro* [92]. In addition, depletion of SPHK1 in mice results in increased expression of adipogenesis markers and anti-inflammatory molecules in adipose tissue, whereas it abrogates pro-inflammatory molecules, suggesting that this enzyme is required for lipolysis-driven adipose tissue inflammation [93]. SPHK2 deficiency appears to play a similar role in adipogenesis regulation [94]. S1P lyase deficiency in mice was accompanied by decreased adipose tissue depots. However, the metabolic changes are liver-mediated rather than adipocyte-specific [95].

Although sphingolipids are a minor class of lipids, they are crucial for maintaining metabolically healthy adipose tissue. Therefore, the preservation of structurally and functionally healthy sphingolipid metabolism is an essential determinant of health.

Glucose Metabolism in Adipose Tissue

Although adipose tissue contributes less than 10% to whole-body glucose disposal following a meal, its critical role in systemic glucose homeostasis is well documented. Adipocytes express at least four glucose transporters (GLUTs), GLUT1, GLUT4, GLUT8, and GLUT10 [96]. Of these, the most abundantly expressed is GLUT4, which is also the major insulin-regulated glucose transporter. Several seminal studies elegantly demonstrated that GLUT4-mediated glucose transport into adipocytes regulates whole-body glucose homeostasis, and disruption of this process leads to disease states, such as insulin resistance and diabetes [97]. Moreover, the activity of GLUT4 has been associated with enhanced lipogenesis via activation of the nuclear transcription factor carbohydrate-response element-binding protein (ChREBP), illustrating the existence of an important cross-talk between the two metabolic pathways in adipose tissue [98].

Intracellular glucose is phosphorylated to glucose-6-phosphate (G6P) by the enzyme hexokinase (HK). This irreversible step effectively traps this sugar molecule inside the cell and commits it to further metabolism. Mammalian cells have four isoforms (1–4) of this enzyme, hexokinase, which catalyzes the phosphorylation of glucose to glucose 6-phosphate with broad substrate specificity and the ability to phosphorylate other hexoses. Adipocytes express HK1–3, with HK2 having the highest expression among the three isoforms [99]. Loss of HK2 activity in the adipose tissue of mice resulted not only in reduced glucose disposal by adipocytes but also in increased glucose production in the liver, contributing to the development of glucose intolerance. Similarly to the knockdown of GLUT4, the loss of adipose HK2 was accompanied by decreased lipogenesis and increased FA release in WAT, further emphasizing the role of adipose tissue glucose metabolism in healthy whole-body glucose and lipid homeostasis [100]. G6P can enter one of two major pathways in adipocytes: glycolysis followed by the tricarboxylic acid (TCA) cycle or hexose-monophosphate (HMP) shunt.

Glucose Metabolism Via Glycolysis and TCA Cycle

Glycolysis is a central metabolic pathway used by all tissues, including adipose tissue, for glucose oxidation to provide energy as ATP and intermediates in other metabolic pathways. It consists of nine steps divided into two phases, in which G6P is metabolized into two pyruvate molecules. The rate-limiting step of glycolysis is the reaction catalyzed by phosphofructokinase (PFK) 1 (PFK-1). This irreversible phosphorylation reaction is the most important control point and is subject to allosteric and hormonal regulation, which determines the overall rate of glycolysis. In mammalian tissues, PFK is a tetramer composed of four subunits encoded by different genes that are arranged in a tissue-specific manner to form homo- and heterotetramers. The tissue-specific arrangement results in three different isoforms of PFK with specific tissue distributions, namely PFK M-type, L-type, and C-type (or PF in

humans) [101]. Silencing of the PFK M isoform in mice results in reduced fat depots and lower body weight, most likely because of glycolytic oscillations responsible for enhancing the production of the TAG backbone precursor α -glycerophosphate [102].

PFK-1 in adipose tissue is controlled by the available concentrations of the substrates ATP and fructose 6-phosphate as well as by other regulatory molecules. It is inhibited by ATP and citrate and activated by 5'-AMP, phosphorylation via cyclic AMP-dependent protein kinase, and fructose 2,6-bisphosphate, similar to its regulation in other tissues [103]. This enzyme has been reported to play a role in adipocyte TAG synthesis, lipogenesis, diet-induced systemic insulin resistance, and adipose tissue inflammatory response, which further illustrates the interconnectivity between glucose and lipid metabolism in adipose tissue [104].

The last regulatory step in glycolysis is the conversion of phosphoenolpyruvate to pyruvate, catalyzed by pyruvate kinase (PK). In mammalian tissues, four different PK isoenzymes are expressed in a tissue-specific manner: liver-specific PK (PKL), red blood cells—specific PK (PKR), and two muscle isoforms (PK muscle isoenzymes PKM1 and PKM2), which are generated via alternative splicing of the respective encoding gene and are differentially expressed in various tissues [105, 106]. Adipocytes exhibit high levels of PKM2 expression. PKM2 and PKM1 possess both overlapping and non-overlapping functions with PKM1 and share some similarities with the liver isoform [107]. The expression of both PKM isoforms is increased by thermogenic activation in BAT; however, silencing of PKM2 in mature brown adipocytes leads to augmentation of the expression of selected thermogenic genes, revealing a novel role of the glycolytic pathway in BAT [108, 109].

The fate of the final product of glycolysis, pyruvate, in adipocytes depends on the energetic state of the cell, oxygen availability, and metabolic demands of the body. Pyruvate can be reduced to lactate by lactate dehydrogenase (LDH) to regenerate NAD^+ and allow for the continuation of glycolysis. Although counterintuitive, adipocytes actively produce lactate, with as much as 70% of the ingested glucose being converted to this metabolite, a magnitude similar to that observed in skeletal muscles [110, 111]. Moreover, recent studies have demonstrated that lactate production is prioritized in adipocytes, further supporting the idea that glucose metabolism in adipose tissue is essential for whole-body glucose homeostasis [112]. Finally, adipocyte-derived lactate may play roles beyond being an intermediate of glycolysis, such as acting as a sensing and signaling molecule and mediating inflammation [112, 113].

An alternative pathway for further pyruvate metabolism, which occurs in tissues with high oxidative capacity, is oxidative decarboxylation by the pyruvate dehydrogenase complex (PDC). PDC is a sizeable multi-enzyme complex built from multiple copies of the three enzymes. It irreversibly converts pyruvate into acetyl-CoA, a key metabolite that can be further degraded in the TCA cycle to carbon dioxide and water, releasing the energy utilized to synthesize ATP via oxidative phosphorylation. The activity of mammalian PDC is regulated through the phosphorylation–dephosphorylation cycle. Phosphorylation, resulting in inactivation of the complex, is catalyzed by pyruvate dehydrogenase kinase (PDK), and dephosphorylation and the resultant reactivation is catalyzed by pyruvate dehydrogenase phosphatase

(PDP). The most abundant PDK isozyme in adipose tissue is PDK4, which has been implicated in BAT lipogenesis, thermogenesis, and glyceroneogenesis [114].

Several intermediates produced during glucose metabolism in adipocytes serve as substrates for the synthesis of metabolic precursors utilized in the process of lipogenesis, realizing critically important crosstalk between different metabolic pathways in adipose tissue.

DHAP and Synthesis of Glycerol-3-Phosphate

Dihydroxyacetone phosphate (DHAP) is a glycolytic metabolite produced in a reaction that cleaves fructose-1,6-bisphosphate into two three-carbon molecules. It can be subsequently reduced to yield G3P, which provides a glycerol backbone for TAG synthesis. The reaction is catalyzed by cytosolic glycerol 3-phosphate dehydrogenase (GPD1) and provides an essential link between glucose metabolism and TAG synthesis because adipocytes are unable to re-use glycerol released during lipolysis because they do not express glycerol kinase. Instead, glycerol is transported through the blood to the liver, where it expresses the kinase that phosphorylates glycerol and produces glycerol 3-phosphate. GPD1 utilizes NADH as a coenzyme and is primarily regulated at the transcriptional level by peroxisome proliferator-activated receptor (PPAR)-gamma (PPAR γ) in adipose tissues. Its levels have been reported to increase during adipogenesis [115].

G3P is in constant demand in adipose tissue owing to the ongoing TG/FA recycling that exists in adipocytes, especially in situations when recycling is increased. Interestingly, a growing body of evidence suggests that this pathway may not be the major source of G3P in triglyceride synthesis. A biosynthetic pathway for producing G3P from sources other than glucose and glycerol, glyceroneogenesis, is emerging as an important source of carbon for the glycerol backbone of TAG in mammalian cells, including adipocytes [116].

Glyceroneogenesis, Oxaloacetate, and Pyruvate

Glyceroneogenesis was discovered due to the finding that WAT contains both pyruvate carboxylase and the cytosolic form of phosphoenolpyruvate carboxykinase (PEPCK-C) [117]. Until this discovery, these two enzymes were believed to be involved only in gluconeogenesis. Glyceroneogenesis is initiated by the carboxylation of pyruvate to oxaloacetate and its entry into the TCA cycle, where it is reduced to malate by NAD-dependent malate dehydrogenase (MDH). Malate is transported out of the mitochondria via the dicarboxylate shuttle and re-oxidized back to oxaloacetate by the cytosolic form of the former enzyme, which is subsequently decarboxylated to phosphoenolpyruvate by PEPCK-C and converted to 1,3-bisphosphoglycerate via a reversal step of glycolysis. In the next step, this metabolite is oxidized to glyceraldehyde-3-phosphate by glyceraldehyde-3-phosphate dehydrogenase (GAPDH), which exists in equilibrium with DHAP via

isomerase. In the final step, DHAP is reduced to 3-glycerol phosphate by 3-glycerol phosphate dehydrogenase (GPDH), as described above [116]. The relative contribution of this pathway to G3P synthesis, compared to glycolysis, is approximately 50% in humans and as much as 80% in rodents. In adipose tissue, it increases during fasting and appears to be the major pathway glyceride-glycerol synthesis in adipose tissue of rats fed a diet supplemented with sucrose for 5 days, accompanied by a significant elevation in the rates of lipogenesis [118, 119]. Taken together, these observations suggest that glucose is most likely not the major precursor of the glycerol backbone for TAG synthesis in adipose tissue, indicating the simultaneous occurrence of both glyceroneogenesis and glycolysis in this tissue type.

Acetyl-CoA and De Novo Lipogenesis (DNL)

The conversion of acetyl-CoA to palmitate via FA synthesis *de novo*, followed by palmitate conversion to other FAs and their subsequent incorporation into TAG and storage in LDs, is known as *de novo* lipogenesis (DNL). In humans, FA synthesis occurs primarily in the liver and lactating mammary glands and, to a lesser extent, in adipose tissue. Approximately 20% of palmitate in TAGs is derived from DNL in the human adipose tissue [1]. *De novo* FA synthesis occurs in the cytosol where acetyl-CoA carboxylase (ACC) and FA synthase (FAS) work together to produce palmitate, the predominant FA produced by FAS [120]. Palmitate can be subsequently elongated and/or desaturated to produce a diverse range of FA species. This process requires energy such as ATP and the availability of the reducing equivalents NADPH to incorporate carbons from acetyl-CoA into the growing FA chain. NADPH is a product of oxidative reactions in the HMP shunt, which provides another link between glucose and lipid metabolism [121]. Numerous studies in animal models and humans have demonstrated that DNL in adipose tissue is metabolically beneficial and decreases insulin resistance, obesity, and high-fat diet [122].

In summary, glucose metabolism in adipose tissue, although a quantitatively insignificant contributor to whole-body disposal of glucose, is qualitatively a critical player in the maintenance of healthy systemic glucose homeostasis.

Protein and Amino Acid Metabolism in Adipose Tissue

A distinct feature of adipose tissue that has been extensively studied and characterized in the last decade is its function as an endocrine organ that actively secretes hundreds of hormones and small peptides acting in endo-, para-, and autocrine fashion to crosstalk with the rest of the cells and tissues in the body. This requires highly active protein synthesizing cellular machinery to ensure adequate control of transcription and translation of newly synthesized proteins and proper folding and post-translational modification to form a final functional

protein product. In adipocytes, these processes use pathways and mechanisms that are most likely not different from those in other tissue types. Although the role of adipose tissue in systemic protein and amino acid (AA) metabolism is not well understood, a growing body of research is focusing on deciphering the role of specific AAs.

In the recent decade, a considerable body of evidence has suggested that adipose tissue is capable of metabolizing significant quantities of branch-chain amino acids (BCAAs), leucine, isoleucine, and valine, and it is second only to skeletal muscle in its capacity to catabolize these AAs [123, 124]. More recent studies utilizing selective downregulation of specific BCAA metabolic enzymes in animals have demonstrated that adipose tissue can modulate circulating BCAA levels *in vivo* [125]. Although the physiological importance of adipose tissue BCAA oxidation remains obscure, these observations support the idea that coordinated downregulation of BCAA oxidative enzymes may dramatically alter adipose tissue BCAA oxidative flux. Consistent with this is the reported downregulation of BCAA oxidative enzyme expression in adipose tissue of obese patients [126]. Studies in BAT using stable isotope tracing showed that in this tissue type, the contribution of BCAA carbons as downstream substrates in the TCA cycle is far less than the respective contributions of glucose, lactate, and FAs [127, 128]. However, their carbon skeleton can be efficiently utilized for *de novo* lipogenesis in brown adipocytes [129].

Additionally, brown adipocytes use BCAA as a key nitrogen source for synthesizing non-essential amino acids and their downstream products, including Glu, Ala, Asp, N-acetyl-AAs, and glutathione. Many of these molecules are actively secreted by BAT, and when the BCAA-nitrogen flux into brown adipocyte mitochondria is impaired, this results in decreased circulating BCAA-derived metabolites accompanied by increased oxidative stress and decreased hepatic insulin signaling [130]. Taken together, these studies suggest that active BCAA uptake to BAT is critical as a nitrogen donor for metabolite synthesis, rather than being used as carbon fuel for thermogenesis.

Another amino acid of particular importance for adipose tissue function is L-arginine (L-Arg), which acts as a precursor for synthesizing the signaling molecule nitric oxide (NO) via the NOS pathway. In this pathway, L-Arg is converted to NO via one of several NOS enzymes that differ in tissue expression and dependency on Ca^{2+} [131]. Human and rat adipocytes predominantly express endothelial (eNOS) and inducible (iNOS) nitric oxide synthase enzymes [132, 133]. Subsequent studies revealed that eNOS is most likely the major source of NO production in both white and brown adipocytes and plays an essential role in maintaining normal glucose and lipid metabolism, mitochondrial biogenesis, oxidative phosphorylation, reactive oxygen species (ROS) generation, and adipokine secretion [134]. Modulating NO-mediated pathways through dietary supplementation with L-arginine has been suggested as a potential therapeutic strategy against metabolic syndrome and dyslipidemia [135].

Thermogenesis in Adipose Tissue

Thermogenesis is a metabolic process in which the body utilizes energy substrates to produce heat as the primary end-product of metabolism. This process reflects the thermodynamic inefficiency of utilizing substrates for ATP generation in mammals, which results in heat production. Heat generation, in turn, is a vital contributor to the regulation of body temperature. Thermogenesis is used to describe a facultative or adaptive process of heat generation “on-demand” in response to external stimuli, such as cold exposure or nutrient oversupply. In mammals, thermogenesis can be shivering or non-shivering. Shivering thermogenesis is characterized by involuntary irregular muscular activity resulting in heat generation. On the other hand, nonshivering thermogenesis is defined as an increase in metabolic heat production that is not associated with muscle activity. The primary site for non-shivering thermogenesis is the adipose tissue, mainly brown and beige adipocytes.

Non-shivering thermogenesis is achieved via the uncoupling of oxidative phosphorylation from ATP production during electron transfer in the mitochondrial electron transport chain (ETC), releasing extra energy as heat instead of preserving it as ATP. In normal mitochondria, ATP synthesis is coupled with electron transport via the H^+ gradient. When the H^+ gradient in the inner mitochondrial membrane is disrupted, protons are allowed to flow back into the matrix without flowing through the ATP synthase, resulting in uncoupling and heat generation. This process is mediated by UCP1, which is localized to the inner mitochondrial membrane and facilitates proton leakage [136]. UCP1 is highly expressed in BAT, whose brown color is secondary to the high mitochondrial content underlying its thermogenic potential, and is the best-characterized thermogenic effector in mammals [137]. UCP1-dependent thermogenesis is regulated by both exogenous and endogenous stimuli.

The most prominent activator of BAT thermogenesis is cold exposure, which results in increased metabolic activity and concomitantly increased thermogenesis. This process includes the upregulation of GLUT1 and GLUT4 enhanced expression of the glycolytic enzymes HK, LDH, and PFK, which stimulate glucose metabolism, providing sufficient electron donors to supply electrons to the ETC [138].

Another well-characterized stimulus includes β -adrenergic activators that mediate β -adrenergic signaling via β 3-adrenergic receptors (β 3-ARs) in rodents and β 2-AR in humans [139, 140]. Signaling through these receptors initiates downstream signaling cascades that affect cellular metabolism and initiate the transcription of thermogenic genes. This leads to increased UCP1 protein levels, lower FFA storage in WAT, and higher FFA oxidation and storage in BAT [141, 142]. Thermogenic genes can also be upregulated via the stimulation and activation of thyroid receptors α and β ($TR\alpha$ and β), which are expressed in both WAT and BAT [143]. Other activators of thermogenesis include exercise, and natural extracts are effective in activating adipocytes to gain thermogenic capacity, while simultaneously enhancing metabolic regulation. In addition, numerous mechanisms for activating thermogenesis beyond UCP1 have been identified and characterized to varying extents [9, 144].

Thermogenesis is the key activity that leads to the modulation of systemic metabolism and improvement of energy expenditure, which are two fundamental mechanisms that may be beneficial against obesity and diabetes. Therefore, pharmacological and genetic manipulations of this metabolic process have been explored as promising approaches to treat this disease and may provide future avenues for drug development.

Regulation of Adipose Tissue Metabolism

Adipose tissue plays a critical role in regulating systemic glucose and lipid metabolism and secretes bioactive molecules that affect almost every cell and tissue in the body. Therefore, well-coordinated and timely regulation of different metabolic pathways in this tissue type is essential for maintaining whole-body metabolic health. Any dysregulation may ultimately result in dysfunctional adipose tissue and initiate pathological changes in other cells and tissues, subsequently leading to disease. The regulation of adipose tissue metabolism is under hormonal and nutritional control achieved at the level of regulating specific metabolic enzymes and pathways to meet the demands of the whole body to maintain a balance in the availability and accessibility of energy substrates to other tissues underlying the essential function of adipose tissue in energy homeostasis.

Hormonal Regulation

The two major hormones that are master regulators of metabolism are insulin and glucagon which will be discussed in this chapter. Other hormones, including steroid hormones, estrogen and androgens, glucocorticoids, and thyroid hormones, employ additional hormonal control of adipose tissue metabolism. The effects of these hormones are less well understood as regulators of normal adipocyte metabolism and are better known for their roles in disease states such as obesity, as discussed elsewhere [145].

Insulin

Insulin is produced in pancreatic β -cells and is released in response to increased blood glucose and nutrient availability. It binds to the insulin receptor (IR) expressed on the surface of many tissues, including the adipose tissue. There are two IR isoforms, IR-A and IR-B; however, IR-B is much more specific to insulin and mediates most of its metabolic effects [146]. This isoform is the predominant isoform expressed in adipocytes. Insulin binding to IR triggers downstream signaling cascades that result primarily in altered cellular metabolism and secondary changes to

gene expression levels to activate intracellular metabolic pathways and utilize the available substrates.

Adipocytes are also susceptible to insulin exposure. The binding of insulin to adipose tissue insulin receptors results in changes in all metabolic pathways described in this chapter. Insulin affects glucose metabolism in adipose tissue by increasing the rate of glucose transport across the cell membrane, followed by an increase in the rate of glycolysis via the activation of HK and PFK. The effects on lipid metabolism include a decreased rate of lipolysis, lowering of FFAs in the plasma, and stimulation of the lipogenic pathways of fatty acid and triacylglycerol synthesis. High insulin levels favor the dephosphorylated form of HSL, which is inactivated and inhibits lipolysis of stored TAG. Insulin also upregulates lipoprotein lipase (LPL), an extracellular enzyme attached to the endothelial cells of the capillary walls in many tissues, particularly adipose tissue. LPL acts on circulating lipoproteins to release FFAs, which can enter adipocytes and be stored as TAG molecules [147]. Insulin can also affect protein metabolism in adipocytes by increasing the rate of AA transport and protein synthesis [148].

Glucagon

Glucagon is one of several counterregulatory hormones that counteract the effects of insulin in the human body. The others include the catecholamines epinephrine and norepinephrine, cortisol, and growth hormone. It is produced in pancreatic α -cells from a larger proglucagon peptide and is secreted in response to low blood glucose levels. Encoded by the proglucagon gene, the proglucagon peptide is subject to post-translational processing via specific convertase enzymes expressed in a tissue-specific manner to produce glucagon in pancreatic α -cells and other peptides, namely glucagon-like peptides (GLPs), GLP-1, GLP-2, oxyntomodulin, and glicentin in L-cells of the intestine and brain, respectively [149]. The effects of glucagon in different tissues are mediated by glucagon binding to the glucagon receptor, a member of the class II G protein-coupled receptor (GPCR) superfamily [150]. Glucagon receptors are expressed in adipocytes, but to a lesser extent than in liver and kidney cells [151]. Upon binding to its receptor, glucagon activates a downstream signaling cascade mediated by c-AMP-dependent activation of several signaling proteins, including PKA activation and subsequent phosphorylation of downstream targets aimed at mobilizing TAG stores to release energy substrates for use by other tissues [152]. The primary effect of glucagon on lipid metabolism is inhibition of FA synthesis through phosphorylation and subsequent inactivation of ACC by adenosine monophosphate (AMP)-activated protein kinase (AMPK). This facilitates the transport of FA into the mitochondrial matrix for β -oxidation. In addition, glucagon stimulates HSL in adipocytes, promoting lipolysis independently of sympathetic nervous system innervation, resulting in increased FFAs in the circulation, which bind to albumin and are delivered to the liver and other peripheral tissues [153–155]. However, catecholamines appear to be the primary activators of lipolysis in adipose tissue.

In addition to regulating lipid metabolism in adipose tissue, glucagon also plays a pivotal role in controlling energy expenditure via thermogenesis in BAT. It has been shown to increase energy expenditure by stimulating oxygen consumption and heat production in vitro and in vivo [156–158]. Cold exposure increases circulating glucagon levels and the concomitant stimulation of non-shivering thermogenesis [159]. Acute glucagon administration affects energy expenditure via BAT-dependent and -independent mechanisms, which are poorly understood [145].

The glucagon regulation of different metabolic pathways in adipose tissue is complex and not yet fully understood, most likely involving multi-directional cross-talk between the adipose tissue, the brain, and potentially other vital peripheral organs.

Nutritional Regulation

The regulation of adipose tissue metabolism by the availability of macronutrients for providing energy fuels during the feed-fast cycle in the body is mediated through the fluctuating circulating levels of the abovementioned hormones, insulin and glucagon, in response to food intake. The effect of certain micronutrients, such as vitamins, minerals, and other minor dietary components such as bioactive dietary compounds (or nutraceuticals), on different metabolic pathways within adipocytes is an emerging field of research. However, data on the effects of specific nutrients and the underlying mechanisms, particularly in humans, are unclear. Moreover, most dietary interventional studies have focused on the impact of nutrition on disease states such as insulin resistance and obesity.

Specific vitamins and dietary compounds have been implicated in the regulation of adipose tissue metabolic properties by affecting lipid turnover and proper adipose tissue functional integrity. These molecules act as modulators of cellular signaling at the molecular level and affect gene expression of key regulators of food intake, lipid metabolism, adipogenesis into white, beige and brown adipose tissue, thermogenesis, lipotoxicity, adipo/cytokine synthesis, and inflammation [160]. Only a few of these nutritional regulators that are important for adipose tissue metabolic integrity are summarized here.

Bioactive Dietary Compounds

Nutraceuticals are a large group of chemically different molecules that do not typically provide energy. Instead, they are minor constituents of our diet, often added as spices such as cinnamon, rosemary, ginger, pepper, saffron, garlic, onion, turmeric, chili, and others. They contain specific biologically active compounds such as curcumin, catechins, capsaicin, gingerol, resveratrol, and berberine, which have been shown to have beneficial health effects. In adipose tissue, nutraceuticals modulate

cellular signaling pathways involved in the storage and dissipation of energy and enhance satiety, ultimately leading to weight loss. The underlying mechanisms of these effects include increased thermogenesis and reduced lipid accumulation in adipocytes by regulating the expression of related transcription factors such as CCAAT/enhancer-binding proteins (C/EBPs) and PPAR γ as well as modulating the activities of certain enzymes related to lipogenesis, such as ACC, FAS, and GPDH [161]. Each individual bioactive compound has a specific mode of action in the control of metabolic functions in adipose tissues, some of which have been studied and summarized in more detail [160].

Another essential property of these compounds is their anti-inflammatory and antioxidant properties. In vitro studies have shown that they decrease preadipocyte proliferation and differentiation, and viability. These effects are mediated by interference with specific signaling pathways involved in inflammation.

Vitamins

Fat-soluble vitamins A, D, and E have emerged as regulators of adipose tissue metabolism. Adipose tissue is one of the primary storage depots for these micronutrients, where their intracellular concentration is usually proportional to the LD size.

Vitamin A in the human diet is present in two forms: retinyl esters and β -carotene or other carotenoids like xanthophylls and zeaxanthins [162]. Endogenously, carotenoids are converted to retinol, which is subsequently oxidated to 9-*cis*-retinoic acid (RA) and all-trans RA (ATRA), which are the biologically active metabolites that act as important regulators of gene transcription via retinoid acid receptors (RARs) [163]. RA is involved in the regulation of several metabolic processes that govern adipogenesis and lipogenesis in adipocytes. The mechanisms underlying these effects remain largely speculative [164]. In addition, RA regulates the expression of genes that affect lipid metabolism in adipocytes, such as UCP1 and UCP3, and plays a role in regulating thermogenesis in rodent BAT [165]. However, in humans, these effects are minimal [166].

The active form of vitamin D, calcitriol (1,25(OH) $_2$ D), exhibits anti-inflammatory activity in adipocytes, suggesting that it may help decrease adipose tissue inflammation associated with obesity and metabolic dysfunction. Furthermore, a vitamin D-deficient diet results in reduced expression of lipid oxidation-related genes, such as PGC1- α , PPAR α , UCP1, and others in the adipose tissue [167, 168]. Although most of these studies have been conducted in animals and data from human studies are yet to be obtained, based on the detrimental effects of vitamin D deficiency on adipose tissue metabolism, it has been suggested that it plays a beneficial role in adipose tissue metabolism and functional integrity.

Vitamin E (α -tocopherol) is the far less studied fat-soluble vitamin. It acts as a fat-soluble antioxidant and signaling molecule that mediates a number of cellular events relevant to fatty acid uptake, metabolism, accumulation, storage, and release, as well as adipokine secretion and release from adipose tissue [169–171].

Conclusion

Adipose tissue is a complex metabolic organ designed to respond appropriately to changes in nutritional status by undergoing dynamic remodeling, including quantitative and qualitative alterations in its structure. To accommodate these changes, it must be able to quickly adapt to intracellular metabolism and provide a continuous supply of energy donors to maintain whole-body energy homeostasis. This is achieved by the coordinated regulation of the metabolism of lipids, glucose, and certain amino acids highlighted in this chapter. The regulation of adipose tissue metabolism is under the coordinated action of two hormones, the master-metabolic regulators insulin and glucagon. Additional regulation exists via certain nutrients; however, their significance has mainly been studied in animals, and their role in humans is unclear.

The metabolic integrity of adipose tissue is an essential determinant of overall adipocyte health, assuring the proper synthesis and release of hundreds of molecules that act as endocrine mediators in other tissues. These include a variety of peptides, microRNAs, and lipids, all of which are direct products of adipose tissue metabolism.

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Chapter 4

Endocrine Functions of the Adipose Tissue



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Abbreviations

ACRP30	Adipocyte complement-related protein (s. adiponectin)
AdipoR	Adiponectin receptor
AgRP	Agouti-related protein
AHN	Arcuate hypothalamus nucleus
AMPK	Adenosine monophosphate-activated protein kinase
ANGPTL2	Angiopoietin-like protein 2
BAT	Brown adipose tissue
BMI	Body mass index
CAP1	Adenylyl cyclase-associated protein 1
CCN4 (s. WISP1)	Cellular communication network factor 4
CSF	Colony-stimulating factor
CTRP	C1q/TNF-related protein
CXCL10	C-X-X motif chemokine ligand 10
DCN	Decorin
DHEA	Dehydroepiandrosterone
DHEA-S	Dehydroepiandrosterone sulfate
EGF	Epidermal growth factor
EMT	Epithelial-to-mesenchymal transition
EV	Extracellular vehicle
FSTL1	Follistatin-like 1
GABA	Gamma-aminobutyric acid
G-CSF	Granulocyte CSF

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GLP-1	Glucagon-like peptide-1
GLP-1RA	Glucagon-like peptide-1 receptor agoist
IL	Interleukin
LCN2	Lipocalin-2
LEP-R	Leptin receptor
LH	Lateral hypothalamic (area)
LPS	Lipopolysaccharide
MC4R	Melanocortin-4 receptor
MCP-1	Monocyte chemoattractant protein-1
M-CSF	Macrophage colony-stimulating factor
Metrl	Meteorin like
miRNA	MicroRNA
NPY	Neuropeptide Y
NRG4	Neuregulin-4
PAI-1	Plasminogen activator inhibitor-1
POMC	Proopiomelanocortin
PPAR α	Peroxisome proliferator-activated receptor-alpha
PVN	Paraventricular nucleus
RBP4	Retinol binding protein 4
RELM	Resistin-like molecules
ROR1	Receptor tyrosine kinase-like orphan receptor 1
SFRP5	Secreted frizzled-related protein 5
STAT3	Signal transducer and activator of transcription 3
T2DM	Type 2 diabetes mellitus
TBI	Traumatic brain injury
TLR4	Toll-like receptor 4
TNBC	Triple-negative breast cancer
TNF	Tumor necrosis factor
VH	Ventromedial hypothalamic (nucleus)
VMH	Ventromedial hypothalamic (nucleus)
WAT	White adipose tissue
WISP1 (<i>s. CCN4</i>)	Wingless-type inducible signaling pathway protein 1
11 β -HSD1	11beta-hydroxysteroid dehydrogenase type 1
17 β -HSD	17beta-hydroxysteroid dehydrogenase
α -MSH	α -melanocyte stimulating hormone

Introduction

This chapter focuses on how the adipose tissue transmits endocrine signals to other cells, tissues, and organ systems. By definition, “endocrine” is a type of signaling between cells where signaling molecules (hormones) are secreted by specialized endocrine cells and carried through the circulatory system to act on target cells, tissues, and organs at a distance. The term hormone was first used by the British

physiologist Ernest Starling about 120 years ago to describe the biochemical messengers that travel from endocrine cells to target cells along the circulatory system and coordinate physiological activities and the growth and development of various parts of the organismal bodies [1, 2].

Historically, the main physiological functions of white adipose tissue (WAT) have predominantly focused on long-term energy storage, thermal insulation, and mechanical protection [3]. In the 1960s and the 1970s, brown adipose tissue (BAT) was experimentally proven to be the site of non-shivering thermogenesis in rodents [4]. The concept that adipose tissues can also have endocrine functions was confirmed after the discovery of the first two most characteristic adipocyte secretory products, leptin [5] and adiponectin [6], in 1994–1995.

Overview of Adipokines

The modern view and understanding of cell signaling functions of adipose tissue is that the cross-talk between fat cells and their environment is mediated in three main ways: (1) nutritional mechanisms (cell signaling pathways that are affected by the availability of nutrients), (2) neural pathways (information pathways connecting neurons to other neurons), and (3) molecular signal messengers (through autocrine, paracrine, and endocrine routes) collectively termed adipokines or adipocytokines (from Greek *adipo*-, fat; *cytos*-, cell; and *-kinos*, movement) [7]. Currently, adipose tissue is considered to be a dynamic secretory tissue/organ that generates a myriad of adipokine molecules, noncoding RNAs, extracellular vesicles (EVs), transferring signals to multiple other cells, tissues, and organs of the body [8].

The first adipokine (adipsin) was discovered in 1987 when adipose tissue was first reported to be the main site for the metabolism of sex steroids [9], and the production of adipsin as a new endocrine factor was found to be significantly down-regulated in rodent obesity [10]. As scientific discoveries related to the endocrine function of adipose tissue progressed in the next couple of decades, the identification and characterization of leptin in 1994 further validated the concept that adipose tissue has an important function as an endocrine organ. In 2012, it was reported that more than 600 adipose tissue secretory proteins had already been identified [11], potentially providing a broad databank of adipokines to identify novel biomarkers or signaling factors associated with metabolic diseases. In the current decade, the number of confirmed adipokines has increased significantly (Table 4.1) [11].

Some cytokines, such as tumor necrosis factor (TNF), were first discovered a decade before the concept of adipokines was developed in the late 1980s when the first adipokines were identified. Since the discovery of the first adipose tissue-derived adipokine (adipsin in 1986 [24]), followed by the discovery of leptin, resistin, and others, the interest in the developmental, functional, and pathophysiological aspects of adipose tissue has grown significantly [8]. This increased research focus and interest in adipose tissue has coincided with the exponential increase in global rates of obesity- (and type 2 diabetes mellitus (T2DM)-) related morbidity and

Table 4.1 List of some of the more notable currently known adipokines

Adipokine	Year of discovery	Structure	Function
Leptin	1994 [5]	167 AA polypeptide	Influence appetite/satiety
Adiponectin	1995 [6]	244 AA polypeptide	Modulates glucose regulation and fatty acid oxidation
Apelin	1998 [12]	77 AA pre-proprotein	G-protein-coupled APJ receptor
Chemerin	1997 [13]	14 kDa protein	Adipocyte differentiation and stimulation of lipolysis
Interleukin-6 (IL-6)	1986 [14]	26 kDa glycoprotein	Mediator for obesity-derived chronic inflammation in insulin resistance
Monocyte chemoattractant protein-1 (MCP-1)	1989 [15]	8 kDa protein glycoprotein	Inhibits insulin-stimulated glucose uptake and alters adipocyte gene expression
Visfatin	2004 [16]	53 kDa protein	Insulin-mimetic, promotes vascular inflammation and atherosclerosis
Retinol binding protein 4 (RBP4)	1968 [17]	21 kDa protein	Potentially linked to insulin resistance and metabolic diseases
Intelectin-1 (omentin)	2001 [18]	34 kDa protein	Regulation of energy metabolism, insulin sensitivity, and reproduction
Plasminogen activator inhibitor-1 (PAI-1)	1983 [19]	46 kDa glycoprotein	Elevated in insulin resistance, obesity, and metabolic syndrome
Serpin A12 (Vaspin)	2005 [20]	47 kDa glycoprotein	Insulin sensitizing effect and inhibition on food intake
Progranulin	2003 [21]	68 kDa glycoprotein	Growth-promoting, neuroprotective and anti-inflammatory
C-X-C motif chemokine ligand 10 (CXCL10)	1985 [22]	9 kDa protein	Pro-inflammatory, correlates positively with obesity and type 2 diabetes
Tumor necrosis factor (TNF)	1975 [23]	52 kDa homotrimer protein	Classical, pleiotropic pro-inflammatory cytokine/adipokine

mortality in recent decades [25, 26]. Adipose tissue-produced signaling molecules are among the major tissue-organs mechanisms for controlling food intake and involve interplay between the gut, brain, muscle, and other organs [27]. Current efforts are devoted to developing novel therapeutic approaches for regulating adipokine and neuropeptide functions to combat morbidity and mortality related to the increased incidence of obesity and T2DM.

Leptin

In 1994, leptin was discovered in the Laboratory of Dr. Jeffery Friedman as a new hormone product of the obese (*ob*) gene after his team worked on characterizing genetically obese (*ob/ob*) mice [5]. This groundbreaking discovery confirmed the earlier hypothesis of Dr. Douglas Coleman, who first proposed decades ago that an undiscovered hormonal system regulates body weight and appetite. For these contributions to science, Dr. Coleman and Friedman received the 2010 Albert Lasker Basic Medical Research Award for discovering the hormone leptin, which regulates appetite and body weight, proving the strong connection between obesity and genetics.

In the last century (circa 1940–1990), pioneering research focused on various regions of the brain through experimental lesions (and/or stimulations) led to the discovery of a “satiety center” in the ventromedial hypothalamic (VMH) nucleus. During the same period, a “hunger center” was identified in the lateral hypothalamic (LH) area of animal brains. These earlier reports showed that VMH and LH nuclei lesions can result in abnormal feeding behavior in animals and humans [28, 29]. The current view on this topic is that the ventromedial hypothalamic (VH) nucleus represents the brain’s main satiety center, and when stimulated, the VMH nucleus causes a sensation of fullness (and reduces feeding behavior). Destruction of the VMH nucleus leads to overeating and weight gain. In 1995, it was further discovered that leptin regulates metabolism and appetite by suppressing the synthesis or release of neuropeptide Y (NPY) in the arcuate hypothalamus nucleus (AHN) [30].

The molecular mechanism by which leptin communicates with the brain to signal satiety involves leptin transmembrane receptors (LEP-R), which have molecular structure similar to the class I family of cytokine receptors (including receptors for interleukins (ILs), growth hormone, prolactin, etc.) [31, 32]. Specifically in the context of brain mechanisms to signaling satiety, the leptin receptors isoform b (LEP-Rb) has been most important and found in the ventromedial, arcuate, lateral, and dorsomedial hypothalamic nuclei, which are crucial in regulating energy balance and body mass [32, 33]. Further studies have shown that leptin can inhibit the neural pathways activated by appetite stimulants, also known as orexigenic pathways, resulting in reduced food and energy intake. Leptin can also affect anorexiogenic pathways to suppress appetite [34].

The mechanisms of action of leptin on the main neuronal centers that regulate/cause hyperphagia or hypophagia constitute a relatively simple algorithm of interactions in which leptin interacts via leptin receptors in the melanocortin system. In this system, NPY and agouti-related protein (AgRP) are well-known peptides with orexigenic effects in the brain’s hypothalamus region, affecting two specific neuronal circuits [35, 36]. The two main neuronal populations in the melanocortin system are orexigenic appetite-increasing NPY/AgRP neurons and anorexiogenic appetite-suppressing proopiomelanocortin (POMC) neurons, both located in the AHN. Once stimulated by various circulating hormones such as leptin, insulin, or ghrelin, these neurons can significantly change the appetite, feeding, and metabolic rates. The

regulation of these neuronal circuits in the AHN brain area is critical for maintaining the body's energy balance, and lesions or dysfunction in these circuits could produce significant changes in food intake (hyperphagia/obesity or hypophagia/starvation) [37]. In addition, in AHN, the prohormone POMC is post-translationally cleaved into several smaller peptides, one of which results in the formation of α -melanocyte stimulating hormone (α -MSH).

During a "fed state," leptin binds to LEP-Rb receptors expressed at the surface of POMC neurons to signal for the initiation of the POMC cleavage in order to produce the active form of the hormone α -MSH. Next, the anorexigenic effects of the α -MSH neuropeptide are signaled to a population of MC4R second-order neurons into the paraventricular nucleus (PVN) by a mechanism in which α -MSH binds to the melanocortin-4 receptors (MC4Rs) [38, 39]. Leptin could upregulate the frequency of action potentials in anorexigenic POMC neurons by depolarizing through a nonspecific cation channel and suppressing inhibition by local orexigenic NPY/gamma-aminobutyric acid (GABA) neurons [40].

During a "starvation/hunger state," there is an increase in the activity of AgRP- and NPY-expressing neurons. Hunger signals stimulate the release of NPY in AHN, which binds to its G protein-coupled receptors to increase feeding behavior and storage of calories. Increasing levels of NPY and the overall stimulation of this pathway promote feeding behavior. There are five known mammalian NPY receptors, Y1R-Y5R (in primates, including humans, Y3R is non-functional), which have been grouped into the same family because they all bind NPY regardless of their overall low sequence similarity [41]. It would be conflicting for both pathways to operate simultaneously; therefore, the NPY system also releases AgRP, an antagonist of MC4R [40, 42, 43].

An increased level of leptin in the blood could be used as a marker of leptin resistance, which is known to correlate with other inflammatory markers and to predict cardiovascular risk in obese individuals [44]. Leptin resistance could be defined by reduced sensitivity (or failure in response of the brain) to leptin, marked by a decrease in the potency of leptin to suppress appetite (and affect the basal metabolic rates). Leptin resistance results in increased food intake, leading to an increase in body mass index (BMI), causing overweight and obesity, which increases morbidity and mortality from cardiovascular diseases and other metabolic disorders [45].

In summary, leptin regulates food intake, metabolic rate, and body mass through the above-mentioned mechanisms. Furthermore, adipose tissue (through leptin production) also affects reproductive function and system [46] and plays a vital role in fetal growth [47, 48], proinflammatory immune responses [49, 50], cardiovascular system angiogenesis [51, 52], and lipolysis [53–56]. Leptin resistance is a significant challenge in the treatment of obesity. However, recent discoveries in the functional relationships between leptin, glucocorticoids, and glucagon-like peptide 1 (GLP-1) receptor agonists (GLP-1RA) have increased the hope for effective future therapies [57, 58].

Adiponectin

In 1995, the polypeptide adiponectin was discovered to be produced exclusively in adipocytes in the laboratory of Dr. Philipp Scherer [6], who first described it as a new hormone and adipokine, which was later discovered to be also biosynthesized in the placenta [59], muscles [60, 61], and even in the brain [62]. Adiponectin is a 244-amino-acid-long polypeptide that is abundant in plasma at higher levels compared to most other hormones [63]. In the mid-1990s, circulating adiponectin levels were found to be inversely correlated with overall adiposity and fat mass, making it unique than most other adipokines, including leptin [64].

Adiponectin (also known as Acrp30, GBP-28, apM1, and AdipoQ) is traditionally considered a “guardian angel adipocytokine” because it has multiple positive systemic (pleiotropic) effects [65]. Unlike other hormones, this adipokine has been reported to significantly improve metabolic health and homeostasis when secreted by adipose tissue at higher levels. In such situations (abundant adiponectin in circulation), it has been proven to increase insulin sensitivity, improve lipid clearance, and reduce systemic inflammation [66]. Numerous studies have shown that increasing adiponectin levels improves metabolic health by enhancing glucose tolerance [67], decreasing liver steatosis and fibrosis [68], and producing a more metabolically healthy obesity phenotype of obesity in diabetic swine [69] and adiponectin transgenic mouse models [70, 71]. On the opposing end of the spectrum for the adiponectin physiological effects, several studies have shown that decreased adiponectin levels can lead to glucose intolerance and hyperlipidemia [72–74]. Furthermore, previous studies using both type 1 and type 2 diabetic mice have shown that a single injection of purified recombinant 30 kDa (Acrp30) adiponectin results in a 2–3-fold elevation in circulating Acrp30 levels, producing a transient decrease in basal glucose levels and a reduction in hyperglycemia (without increasing blood insulin levels) [75].

It is important to note that there is no consensus in the scientific literature or community regarding the effects of adiponectin, which has been reported to have both pro-inflammatory and anti-inflammatory effects [76]. Numerous previous studies have reported the potential beneficial effects of increased circulating adiponectin toward favoring insulin-sensitizing, anti-atherogenic, and anti-inflammatory effects. Conversely, other studies in human cohorts (mostly in patients with autoimmune diseases) have shown that adiponectin might have a pro-inflammatory function, where the pathophysiology of the autoimmune disease might correlate with elevated adiponectin levels. For example, it has been previously reported that high serum levels of adiponectin could be positively associated with the severity of inflammation and pathological progression in systemic lupus erythematosus [77, 78], rheumatoid arthritis [79], chronic kidney disease [80], inflammatory bowel disease [81], and cystic fibrosis [82].

The most likely reason (and mechanism) for the existence of such conflicting dualism of the pro-inflammatory and anti-inflammatory effects of adiponectin’s biological functions is that it circulates in the blood in multiple isoforms. Multiple

studies have confirmed that adiponectin in the blood exists in at least three different molecular weight forms: (1) low-molecular-weight trimers, (2) middle-molecular-weight hexamers, and (3) high-molecular-weight multimers [83]. Additionally, after its synthesis, adiponectin undergoes a series of post-translational modifications via glycosylation and hydroxylation [84]. During this process, three major oligomeric isoforms of adiponectin are created: a 60 kDa low-molecular-weight trimer, a 150 kDa middle-molecular weight hexamer, and a high-molecular-weight multimer (420 kDa). In these isoforms, the structural differences are in the multiple lysine residues of adiponectin, where the isoforms differ in the extent of hydroxylation and subsequent glycosylation. Furthermore, in human adiponectin isoforms, the post-translational modification of isoform variants includes several hydroxylated proline residues and an intermolecular disulfide bond formed at the cysteine residue at the N-terminus. With these modifications, adiponectin's low molecular isoform in its active form is a 60 kDa glycoprotein, which is a trimer of adiponectin 28 kDa monomers joined by their C-terminal globular and collagen-like domains. If trimers multimerize further, this leads to the production of 150 kDa hexamers and 420 kDa multimers, each comprising 12–32 monomers [76].

Another potentially important mechanism explaining the dual pro-inflammatory and anti-inflammatory effects of adiponectin is the natural variety of adiponectin receptors in various tissues and organs. Both adiponectin receptors (AdipoR1 and AdipoR2) exhibit structural similarity, with 67% amino acid overlap and similar organization of their intracellular NH₂-terminal and extracellular COOH-terminal domains [85]. In addition, both receptors are differentially expressed in tissues and organs, with AdipoR1 being broadly expressed and present in skeletal muscle and the liver, whereas AdipoR2 is predominantly expressed in the liver [86]. Experimental genetic studies have shown that the removal or disruption of AdipoR1 receptors decreases adiponectin-induced 5' adenosine monophosphate-activated protein kinase (AMPK) activation at the cellular level, and disturbances of AdipoR2 result in decreased peroxisome proliferator-activated receptor- α (PPAR α) activation [87]. Additionally, T-cadherin (a cell surface protein lacking transmembrane and cytoplasmic domains common to all other cadherins) has also been reported as a receptor for adiponectin. T-cadherin binds and participates in adiponectin signaling of both 150 kDa hexamers and 420 kDa multimers but not for globular or 60 kDa low-molecular isoforms in various muscle tissues [88].

Adiponectin has been extensively studied for its potential as a therapeutic target for drug development, aiming to reduce the morbidity and mortality of T2DM and metabolic syndrome [89]. The lack of sufficient knowledge or understanding of the mechanisms determining the specific pro- or anti-inflammatory properties of adiponectin isoforms, receptors, and post-translational modifications has slowed down the development of potential anti-inflammatory therapeutics against metabolic disorders and autoimmune diseases. More research is needed to decipher the underlying mechanisms controlling adiponectin isoform and receptor levels, and the body's response to their interactions under different metabolic conditions. Another challenge in drug development targeting adiponectin is the technical problems in accurately measuring adiponectin isoforms in biological samples and the absence of

universal standards in research laboratories. Finally, dietary interventions can be used as pivotal modulators of adiponectin levels, creating non-pharmacological and non-invasive opportunities for intervention in prediabetes and metabolic syndrome management [90].

Resistin

In the early 2000s, resistin was discovered in the laboratory of Dr. Mitchell A. Lazar from the University of Pennsylvania [91]. The name of this adipokine originates from its ability to interfere with the physiological effects of insulin. Resistin is a 12.5 kDa cysteine-rich polypeptide secreted from white adipocytes [92], and when it was discovered in mice, it was hypothesized to be a major molecular factor linking obesity and diabetes [91]. In obese rodents, plasma levels of adipocyte-produced resistin are significantly increased and are strongly related to insulin resistance [93]. However, in contrast to rodents, human resistin is predominantly expressed and secreted by macrophages, and its levels increase under inflammatory conditions [94]. Studies have demonstrated a correlation between increased resistin levels and insulin resistance [95], microvascular complications in patients with T2DM [95], and cardiovascular disease events in older adults [96].

Resistin induces inflammation in many chronic inflammatory diseases, infectious diseases, and inflammation-associated cancers [97]. More recently, multiple reports have suggested that resistin is part of the host defense system as an innate immunity peptide that exhibits broad-spectrum antimicrobial effects by modulating immunity [98].

In recent years, it has become clear that the physiological role of resistin is more complex than that originally described or anticipated. Resistin in humans and rodents has variations in its molecular structure, and three isoforms (resistin-like molecules (RELM)- α , β , and γ) have been identified and described in the literature [99]. The receptor downstream signaling of resistin remains unknown, and therefore, the molecular mechanisms of resistin action are poorly understood [100]. However, multiple studies have suggested potential receptors for resistin isoforms, such as decorin (DCN) [101], mouse receptor tyrosine kinase-like orphan receptor 1 (ROR1) [102], toll-like receptor 4 (TLR4) [103], and adenylyl cyclase-associated protein 1 (CAP1) [104]. The signaling between RELM- α , - β , and - γ (resistin isoforms) and various possible receptors is complex and adds to the pleiotropic nature of the physiological action of resistin in health and disease.

Furthermore, multiple studies have indicated that resistin expression is not limited only to adipocytes and macrophages but is also present and expressed by various cells from other organs and systems, including the skeletal muscle, stomach, small and large intestine, adrenal gland, brain, and pituitary gland [105, 106]. Resistin can be overexpressed in the brain after traumatic brain injury (TBI), and this increase could lead to the systemic elevation of plasma resistin levels. After acute TBI (<6 h), elevated resistin levels have shown a strong correlation with a

worse clinical prognosis for patients [107]. However, under normal healthy conditions, the plasma range of resistin in humans has been identified to be between 7 and 22 ng/ml [108, 109], and some proinflammatory cytokines, such as TNF [110], IL-6 [111], and lipopolysaccharide (LPS) [112], can upregulate resistin gene expression and increase the serum levels of resistin [113–115].

Owing to the inherent complexity of resistin, the research focus in this field has shifted from viewing it as a molecular link between obesity and insulin resistance to its newly emerging role as a biomarker of cancer promotion and progression in obese subjects [116–118]. In addition, resistin has been proposed as an inflammatory marker in human atherosclerosis [119] and rheumatoid arthritis [120] because its pro-inflammatory properties are superior to those of its insulin resistance-inducing effects.

Cytokines and Steroid Hormones

As previously described in this chapter, many adipokines have pro- or anti-inflammatory properties. Some initially discovered cytokines molecules, such as TNF, have been later proven to be adipokine (molecules that are made by fat cells in the body).

In 1975, Dr. Lloyd J. Old from the Memorial Sloan Kettering Cancer Center, New York, discovered TNF as a new cytotoxic factor produced by macrophages [23]. More than two decades later, in 1997, it was discovered that adipocytes under obese conditions also produce TNF mRNA and elevated TNF protein levels [121].

Currently, TNF is a well-studied cytokine with a pleiotropic function that can regulate immune function, cell differentiation, proliferation, apoptosis, and energy metabolism [122]. Generally, cytokines within adipose tissue can be produced by any of the main adipose tissue cell types (adipocytes, preadipocytes, and other cell types). Previous studies utilizing mRNA expression approaches to study TNF have shown that adipocytes can synthesize TNF along several interleukins (more specifically, IL-1 β [123] and IL-6 [124]).

Other adipocyte-produced signaling molecules with immunological actions include two categories of factors related to families of complement system products and macrophage colony-stimulating factors (CSFs) (M-CSFs).

As an example of a complement system product, a 30 kDa adipocyte complement-related protein (ACRP30) was reported 25 years ago as a secreted protein with an unknown function at the time, which was exclusively expressed in differentiated adipocytes [125]. After numerous studies have been completed in recent years, the protein is now known as adiponectin, which is one of the best-known adipocytokines with well-documented pro- and anti-inflammatory functions [126].

An example of adipocyte-produced CSFs is granulocyte CSF (G-CSF). G-CSF is a 174-amino acid polypeptide with a molecular weight of 45–50 kDa and is highly expressed primary preadipocytes isolated from mammary fat pads of human breast cancer patients [127]. Treatment approaches using recombinant human G-CSF

protein in cell lines of triple-negative breast cancer (TNBC) can enhance the epithelial-to-mesenchymal transition (EMT), migration, and invasion of cancer cells by activating the signal transducer and activator of transcription 3 (STAT3).

Some additional, relatively less studied adipokines associated with the pathogenesis of obesity and T2DM include the following pro- and anti-inflammatory factors [128]: follistatin-like 1 (FSTL1) (a glycoprotein with potential proinflammatory functions that contribute to angiogenesis, immune response regulation, and cell proliferation [129]), wingless-type inducible signaling pathway protein 1 (WISPI, or CCN4) (known to be upregulated in obesity and induce a pro-inflammatory response in macrophages *in vitro* [130]), asprosin (found in 2016 as a novel adipokine cleavage product of profibrillin, utilizing a cAMP second messenger system to modulate hepatic glucose production and appetite stimulation [131]), secreted frizzled-related protein 5 (SFRP5) (discovered in 2010 to have inhibitory effects on the Wnt signaling pathway; known effects include anti-inflammatory and insulin-sensitizing action and positively associated with insulin sensitivity [132, 133].), meteorin-like (metrnl, or subfatin) (identified as a novel adipokine in 2014; has some positive metabolic effects in obesity, T2DM, and dyslipidemia), neuregulin-4 (NRG4) (an epidermal growth factor (EGF)-like signaling molecule; reduced levels may be causally linked to obesity-related impaired glucose metabolism [134]), TFA5 (also known as FAM19A5) is a 14 kDa type I transmembrane protein with known functions linked to inflammation, differentiation, and cognition [135]; its silencing in adipocytes significantly promotes vascular smooth muscle cell activation; downregulation of TFA5 during obesity may trigger cardiometabolic diseases [136]).

Adipose tissue functions as an endocrine organ that secretes numerous peptide hormones and other bioactive molecules (such as steroids, which can be biosynthesized *de novo* from cholesterol in WAT [137]) that can act in auto-, para-, and endocrine ways to regulate systemic metabolism. The higher mass of dysfunctional adipose tissue in obesity may cause or exacerbate metabolic abnormalities that lead to T2DM [138], cardiovascular diseases [139], and multiple types of cancer [140].

Although the adrenal gland is the primary source of circulating corticosteroids, and gonads are the primary source of sex hormones, adipose tissue expresses an almost full range of enzymes needed to produce, convert, and activate steroid hormones [141]. In postmenopausal individuals, estrogen production, is shifted to other body sites, including adipose tissue [142]. After menopause, adipose tissue plays a leading role in estrogen production, and circulating C19 steroid precursors androstenedione, dehydroepiandrosterone (DHEA), and DHEA sulfate (DHEA-S) serve as reservoirs for extragonadal estrogen synthesis [143].

Adipose tissue can also actively synthesize androgens with the help of the 17 β -hydroxysteroid dehydrogenase (17 β -HSD), an essential enzyme in sex steroids conversion. A literature review can bring multiple studies that have reported that 17 β -HSD expression in obesity is systemically increased, which suggests that it can be an important factor contributing to circulating androgen excess in obesity [144]. Animal studies have reported that the whole steroidogenic enzymatic set and testosterone biosynthesis capacity were found in the fat depots of female rats [145].

These findings support the hypothesis that adipose tissue may contribute substantially to hyperandrogenism in obese women.

Furthermore, adipocytes can process and activate existing circulating androgens, and, by converting less potent androgens into more potent hormones, can further modulate the production of testosterone and androstenedione through the actions of various adipocytokines [146]. Androgens have been reported in the literature to contribute to adipocyte proliferation and differentiation. They stimulate adipocytokine production and promote visceral adipose tissue accumulation, adipogenesis, lipid storage, and lipolysis. Androgens can also modulate body fat distribution patterns in humans through spot and depot-specific effects on the cells of each fat compartment [147].

Cortisol can also be produced and secreted locally by adipose tissue to some extent. Obesity, along with chronic exposure to stress and inadequate sleep, has been reported to negatively affect the hypothalamic-pituitary-adrenal axis and elevate systemic cortisol levels. This results in upregulated activity of the 11β -HSD1 enzyme, which locally increases cortisol synthesis in adipose tissue under obesity and stress conditions [148].

Adipose tissue produces cortisol by the activity of the 11β -HSD1 enzyme in adipocytes [149], although 11β -HSD1 mostly increases the local glucocorticoid concentrations within adipose tissue and does not seem to contribute significantly to systemic cortisol concentrations [150]. Increased long-term exposure to elevated cortisol levels is known to be strongly related to abdominal obesity [151] and increased blood cholesterol, triglycerides, blood glucose, blood pressure, muscle weakness, and mass [152–154]. Cortisol has been validated in many studies as a potent steroid hormone that affects adipose tissue in many direct and indirect ways, influencing insulin sensitivity, fatty acid metabolism, adipocyte differentiation, adipokine expression, and body fat distribution [149, 155].

Regulation of Adipokine Secretion

Regulation of adipokine secretion is an important topic because mechanisms and factors regulating adipokines levels in circulation could be used to develop new pharmacological and lifestyle treatments for metabolic syndrome, type 1 and 2 diabetes, cancer, autoimmune conditions, and other more or less common diseases [156–158]. Unfortunately, due to adipokines signaling complexity and their pleiotropic systemic effects, only a few clinical trials have shown limited success for adipokine-based treatments in improving cardiometabolic health [158].

In the previous sections of this chapter, detailed information was provided on individual adipokine secretion and how it might be influenced by various pathological conditions, such as obesity, inflammation, and diabetes. For example, the inflammatory regulator IL-6 has emerged in recent decades as one of the potential mediators of obesity-derived chronic inflammation with insulin resistance [159]. In

recent years, more details emerged regarding the molecular mechanisms regulating the expression and circulating levels of IL-6. For example, it has been experimentally demonstrated that IL-1 β and TNF exhibit cooperativity in regulating IL-6 expression in adipocytes depending on CREB binding and H3K14 acetylation [123].

Additionally, microRNAs (miRNAs) have been discovered as regulators controlling diverse biological processes (including adipokine secretion) at the level of post-transcriptional repression. For example, miR-146b is known as a factor that can downregulate cytokine signaling (suppress the expression of inflammatory genes) in the inflammatory process, and it has been shown in mature adipocytes that miR-146b can be highly expressed in response to an increase in levels of TNF and IL-6 [160]. This proves miRNAs can be important regulators of adipokine production in obesity complications.

The mechanism of IL-6 signaling starts with binding to its cellular receptor (IL-6R α) as a dimeric complex to form a trimeric receptor complex, further activating the intracellular JAK/STAT3 pathway. Recruiting JAKs to the membrane leads to their activation and triggers the phosphorylation of tyrosine on a cytoplasmic tail subunit of the receptor at docking sites for STAT proteins. As a final step, the phosphorylated STAT3 translocates into the nucleus to activate target transcription [161].

Other categories of specific molecular factors that have been identified to regulate adipokine secretion include sphingolipids, namely ceramides, which accumulate at high concentrations in the liver and muscle of obese and diabetic rats [162]. Ceramides are part of the sphingolipids which are containing the organic aliphatic amino alcohol sphingosine. Their general molecular structure consists of a long-chain sphingoid base (sphingosine, sphinganine, or phytosphingosine) and an additional fatty acid linked to the sphingoid base to form the ceramide backbone [163]. In early studies of obese and T2DM patients, plasma ceramide levels have been found to be strongly correlated with diminished insulin sensitivity [164]. In 2007, endogenously increased ceramide synthesis came into the spotlight as a potentially major molecular factor leading to increased insulin resistance in humans in vivo [165]. Sphingolipid metabolism studies in relation to the regulation of specific adipokines have shown that adiponectin potently stimulates ceramidase activity through its two receptors (AdipoR1 and AdipoR2). As a result of this interaction, ceramidase activity initiates pleiotropic actions of adiponectin [165]. Meanwhile, other molecular regulators that inhibit adipocyte differentiation, such as interferon, retinoic acid, IL-1, and TNF, have also been found to interfere with adiponectin secretion [166].

In recent years, it has been established that multiple circulating factors, including insulin, growth hormone, glucocorticoids, sex steroids, and thyroid hormones, significantly affect adipokine secretion and regulation [167]. In the last decade, a strong association between resistin or adiponectin levels and free thyroxine was discovered in newly diagnosed hypo- and hyperthyroidism patients compared with healthy control populations [168]. This establishes and reaffirms the hypothesis of a complex interplay between the adipose tissue and endocrine system.

Conclusion

This book chapter provides details from early historical and recent studies illustrating the complexity of adipose tissue as an active endocrine organ with a significant impact on metabolic and hormonal regulation. The bioactive molecular secretions of adipocytes (known as adipokines) can affect other tissues and organs locally and distantly via autocrine, paracrine, and endocrine routes. When these effects impact the immune system and have systemic inflammatory effects, adipokines are referred to as pro-inflammatory adipocytokines to emphasize their significant immunological systemic effects. Adipokines can be classified into three major categories: **(1)** Pro-inflammatory (including TNF, leptin, IL-6, resistin, RBP4, lipocalin-2 (LCN2), IL-18, angiopoietin-like protein 2 (ANGPTL2)), that are positively related to body weight, fat mass, insulin resistance, and general pro-inflammatory properties [169]; **(2)** Anti-inflammatory adipokines, (such as adiponectin, some C1q/TNF-related proteins (CTRPs), progranulin, omentin-1, and other new emerging adipokines) that may protect against the complications of obesity by exerting anti-inflammatory or antioxidant effects [170]; and **(3)** Mixed type or neutral adipokines, which include adipokines that have not been well studied or have shown both pro- and anti-inflammatory effects depending on the context (such as adiponectin in certain autoimmune or genetic conditions, as well as relatively new adipokines such as TAF5/FAM19A5, NRG4, etc.) whose effects on inflammation and the immune system are not yet fully understood.

The endocrine functions of WAT and BAT play a significant role in adipose tissue dysfunction, with possible clinical implications and opportunities for the development of new biomarkers or targets for the pharmacological treatment of diseases such as metabolic syndrome, type 1 and 2 diabetes, cancer, autoimmune conditions, and other common diseases that disturb the homeostasis of adipose tissue. However, it is important to note that adipokines are not the only factors involved in these conditions, and other factors such as insulin resistance, inflammation, and genetic predisposition also play significant roles.

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Chapter 5

Adipose Tissue Dysfunction: Clinical Implications and Complications



Just Dronkers, Michelle Lobeek, Laura M. G. Meems, and Thomas M. Gorter

Abbreviations

AF	Atrial fibrillation
AGL	Acquired generalized lipodystrophy
APL	Acquired partial lipodystrophy
AT	Adipose tissue
BMI	Body mass index
BP	Blood pressure
CAD	Coronary artery disease
CGL	Congenital generalized lipodystrophy
COPD	Chronic Obstructive Pulmonary Disease
CV	Cardiovascular
CVD	Cardiovascular diseases
DAG	Diacylglycerol
EAT	Epicardial adipose tissue
EMA	European Medicines Agency
ER	Endoplasmic reticulum
FA	Fatty acid
FDA	Food and Drug Administration
FFA	Free fatty acid
FPLD	Familial partial lipodystrophy
GIP	Glucose-dependent insulinotropic polypeptide
GLP-1	Glucagon-like peptide-1
GLUT4	Glucose transporter type 4
HAART	Highly active antiretroviral therapy

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HALS	HIV-associated lipodystrophy syndrome
HbA _{1c}	Hemoglobin A _{1c}
HDL-C	High-density lipoprotein cholesterol
HF	Heart failure
HFpEF	HF with preserved ejection fraction
HFrfEF	HF with reduced ejection fraction
IL-6	Interleukin-6
INSR	Insulin receptor
MetS	Metabolic syndrome
MHO	Metabolically healthy obese
MUO	Metabolically unhealthy obese
PC	Pyruvate carboxylase
PKC	Protein kinase C
RAAS	Renin-angiotensin-aldosterone system
SAT	Subcutaneous adipose tissue
SGLT-2	Sodium-glucose cotransporter 2
T2DM	Type 2 diabetes mellitus
TNF	Tumor necrosis factor
VAT	Visceral adipose tissue
VTE	Venous thromboembolism
WC	Waist circumference

Introduction

The worldwide prevalence of obesity has increased to epidemic proportions and in 2022, more than one billion people in the world were obese [1]. Obesity, a metabolic disease typically characterized by the accumulation of visceral and ectopic fat, is a major contributor to the development of cardiovascular (CV) risk factors, such as hypertension, type 2 diabetes mellitus (T2DM), dyslipidemia, and CV diseases (CVD), and therefore greatly contributes to increased morbidity and mortality rates. Beyond overall obesity, the onset and progression of CVD are driven by adipose tissue (AT) dysfunction. However, the spectrum of obesity consists of individuals with metabolic healthy and unhealthy obesity. Furthermore, the pathophysiological transformation from healthy to dysfunctional AT is complex and has been the focus of research in recent years. The treatment of obesity has greatly evolved over the years and consists mainly of lifestyle behaviors, such as caloric restriction and physical activity, and surgical and/or pharmacological weight loss interventions. This chapter discusses the pathophysiology and clinical implications of obesity and AT dysfunction, reviews the pathophysiological role of AT dysfunction in the development of CV risk factors and disease, presents several real-world cases of adiposity-related CVD, and summarizes the available non-pharmacological and pharmacological treatments for obesity and AT dysfunction.

Adipose Tissue Dysfunction

Pathophysiology of Obesity

Adipose tissue (AT) has pleiotropic functions under physiological conditions. It serves as protection for organs and body parts, exerts effects on reproduction, and is most importantly involved in energy homeostasis. AT serves as storage of triglycerides in periods of excess energy that may be released during energy deprivation [2]. However, if this energy balance is disrupted with prolonged periods of excess energy, adipocytes can no longer adequately store this energy, resulting in AT dysfunction. In response to the altered energy balance, three important consecutive changes occur in dysfunctional AT. First, AT expands by increasing adipocyte size (hypertrophy) and/or by proliferation and differentiation of pre-adipocytes (hyperplasia) [2]. The extent of hypertrophy and hyperplasia is limited, especially in the visceral AT (VAT) [3]. As a result, intracellular pathways are activated leading to reactive oxygen species production and endoplasmic reticulum (ER) stress (Fig. 5.1) [4]. Second, expansion of AT increases the demand for nutrients and oxygen that are accommodated by increased angiogenesis, i.e., the sprouting of new blood vessels [5]. This angiogenic capacity is, however, reduced in AT of obese individuals, contributing to enhanced adipocyte stress [6, 7]. Third, adipocyte stress stimulates the secretion of pro-inflammatory cytokines, resulting in the infiltration of immune cells (Fig. 5.1) [4, 8]. Severe AT inflammation is characterized by the accumulation of immune cells surrounding dying adipocytes and this histological pattern is known as a crown-like structure [9]. Infiltrated immune cells contribute to a local pro-inflammatory environment by secreting inflammatory factors in the circulation that ultimately leading to a systemic low-grade inflammation.

In the late 1960s, it was observed that obese individuals had a higher free fatty acid (FFA) turnover rate than lean individuals, suggesting that AT in obese individuals releases more fatty acids (FAs) [10]. This process of lipolysis is induced by tumor necrosis factor (TNF) and interleukin-6 (IL-6), both pro-inflammatory cytokines (Fig. 5.1) [11, 12]. The enhanced lipolysis by inflammatory signals was also confirmed in humans as infusion of IL-6 in healthy men [13] or release of IL-6 by exercise increased FFA levels [14]. The enhanced FFA release subsequently induces ER stress that further aggravates adipocyte inflammatory signaling [15, 16]. This results in a detrimental feedback loop that maintains the pro-inflammatory environment in AT and continues to increase FFA release. Elevated circulatory FFA levels are particularly important for the development of T2DM and metabolic syndrome (MetS).

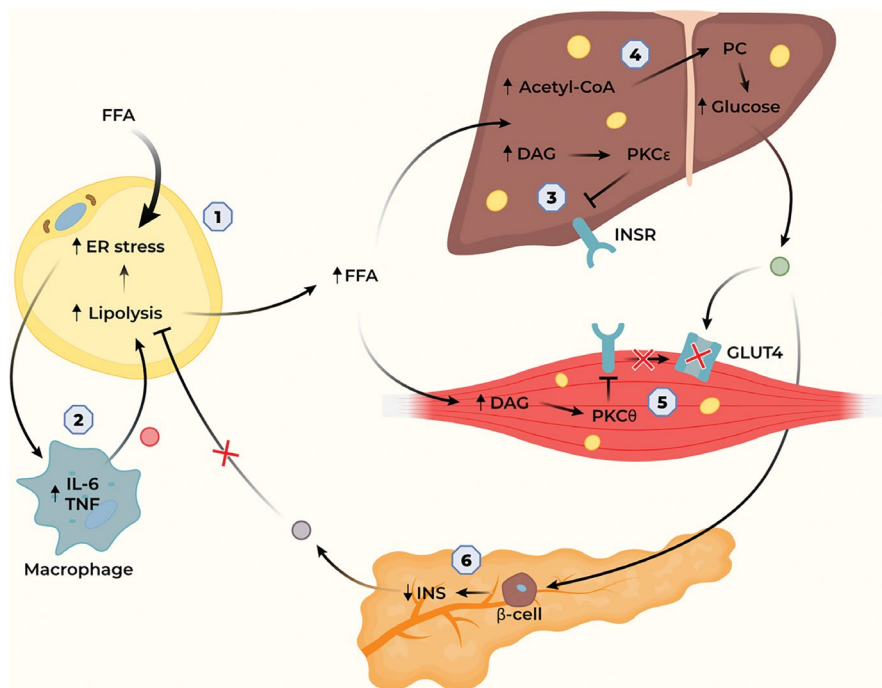


Fig. 5.1 Molecular mechanism of dysfunctional adipose tissue leading to insulin resistance. (1) If the storage capacity of FFA in adipocytes is reached, ER stress increases, which subsequently enhances lipolysis and FFA release. (2) ER stress results in the secretion of chemoattractants and infiltration of immune cells. These cells produce pro-inflammatory cytokines that further increase lipolysis and ER stress. (3) Excess circulating FFAs are stored in the liver, which increases DAG. This activates PKCε, which inhibits INSR and leads to hepatic insulin resistance. (4) Acetyl-CoA levels increase with elevating FFA levels, which activates PC and increases glucose production and secretion. (5) Similar to the liver, DAG-PKCθ-INSR prevents the translocation of GLUT4 to the cellular membrane and the uptake of glucose, leading to glycemia. (6) Prolonged glycemia hampers insulin production in pancreatic β-cells, eventually leading to a decline in circulating insulin and loss of the anti-lipolytic effect of insulin. FFA free fatty acid, ER endoplasmic reticulum, DAG diacylglycerol, PKC protein kinase C, INSR insulin receptor, Acetyl-CoA Acetyl co-enzyme A, GLUT4 glucose transporter type 4, IL-6 interleukin-6, TNF tumor necrosis factor, PC pyruvate carboxylase

Clinical Implications of Obesity

In modern well-developed societies, food is abundantly available and physical activity is limited, resulting in a positive energy balance (e.g., higher intake than usage). The body resolves this state of excess energy by accumulating AT, which leads to an increased body weight. Individuals become overweight, classified as a body mass index (BMI) ≥ 25 kg/m², and if the excess energy state persists, a BMI ≥ 30 kg/m² may be observed categorizing individuals as obese [17]. However, AT distribution may vary greatly between individuals with similar BMI. As illustrated in Fig. 5.2, women accumulate fat predominantly in subcutaneous AT (SAT),

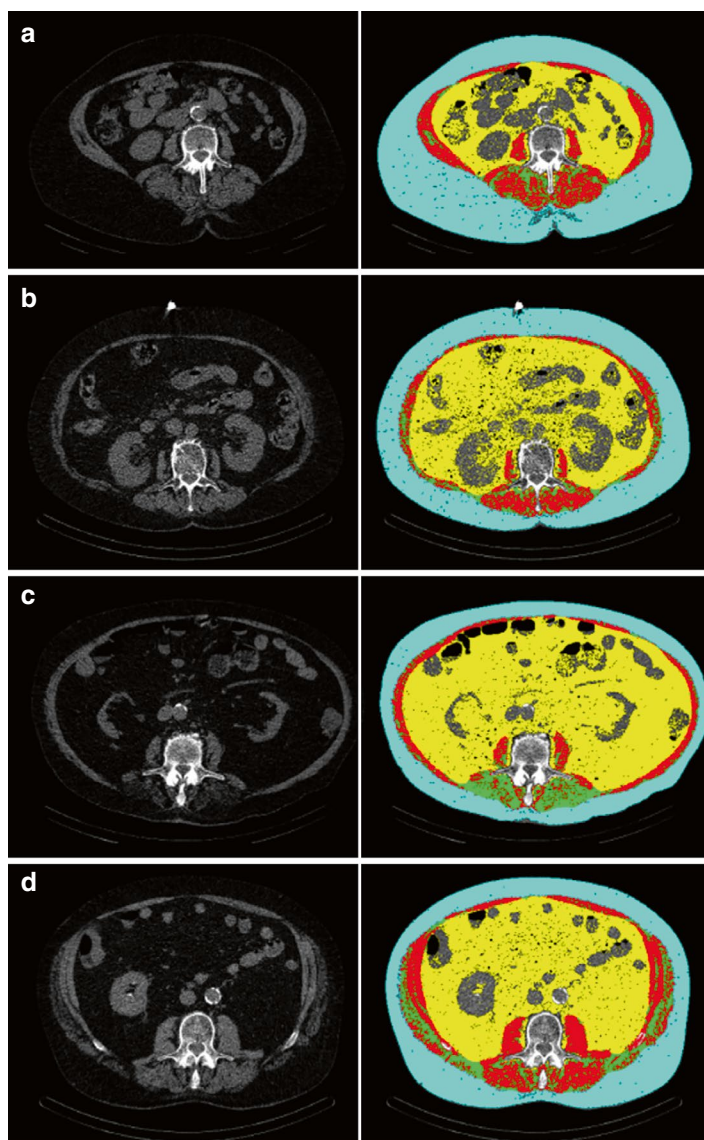


Fig. 5.2 Varying adipose tissue distributions among four individuals with obesity. (a) A 73-year-old woman with a BMI of 34 kg/m^2 , a high amount of SAT, and a moderate amount of VAT. She was diagnosed with hypertension and HF with preserved ejection fraction. (b) A 67-year-old woman with a BMI of 34 kg/m^2 , high amount of SAT, and high VAT. She was diagnosed with atrial fibrillation with no history of T2DM, hypertension, CAD, dyslipidemia, or stroke. (c) An 87-year-old man with a BMI of 34 kg/m^2 , a moderate amount of SAT, and a high amount of VAT. He was diagnosed with HF with a preserved ejection fraction, atrial fibrillation, and chronic kidney disease. (d) A 63-year-old man with a BMI of 35 kg/m^2 and a high amount of SAT and VAT. He was diagnosed with CAD and underwent coronary artery bypass grafting. Cyan and yellow illustrate the measured SAT and VAT volume, respectively. BMI body mass index, SAT subcutaneous adipose tissue, VAT visceral adipose tissue, HF heart failure, T2DM type 2 diabetes mellitus, CAD coronary artery disease

Table 5.1 Characteristics of four individuals with various adipose tissue distributions despite the same BMI

Individual	A	B	C	D
Age, years	73	67	87	63
Gender	Woman	Woman	Man	Man
BMI, kg/m ²	34	34	34	35
SAT, cm ²	323	349	244	303
VAT, cm ²	185	344	527	389
WC, cm	115	128	129	128
EAT, ml	155	218	369	321
<i>Presence of risk factors</i>				
Hypertension	Yes	No	Yes	Yes
Type 2 diabetes	No	No	No	No
Atrial fibrillation	No	Yes	Yes	No
Heart failure	Yes	Yes	Yes	Yes
Dyslipidemia	No	No	No	Yes
Myocardial infarction	No	No	No	Yes
Renal disease	No	No	Yes	No
History of stroke	No	No	No	No
COPD	Yes	No	No	No

BMI body mass index, *EAT* epicardial adipose tissue, *SAT* subcutaneous adipose tissue, *VAT* visceral adipose tissue, *WC* waist circumference, *COPD* chronic obstructive pulmonary disease.

while men are prone to store fat in VAT. However, even within the same sex, the tendency towards accumulation in a particular depot differs. Notably, each individual has a variable CV risk profile despite their similar BMI (Table 5.1).

Obese individuals who are relatively healthy (i.e., absence of other cardiometabolic disorders) are classified as metabolically healthy obese (MHO). Conversely, obese individuals with prevalent cardiometabolic diseases are classified as metabolically unhealthy obese (MUO). However, different classification criteria exist with distinct cutoff values that complicate the identification of particular MHO patients [18]. Although these MHO patients are viewed as rather healthy, the risk of CVD is still greater than that in their lean counterparts [19]. In addition, almost 50% of MHO patients progress to MUO over a follow-up of 12 years [20]. This indicates that early lifestyle management and weight loss therapies should be recommended for all obese individuals, irrespective of their MHO or MUO classifications.

Therefore, obesity is not a benign condition and may impair daily life (Fig. 5.3). Obese individuals score 4.9 points lower than lean individuals on a health-related quality of life questionnaire that encompasses five levels: mobility, self-care, activities, pain, and anxiety [21]. Higher BMI is associated with anxiety and depression, especially in children, and self-esteem may be affected contributing to a worse mental health status [22]. Furthermore, obesity has a profound impact on the body posture and structure. Greater abdominal fat leads to a shift of the center of gravity to the front of the feet, reducing the control of posture and overall stability. This may increase the risk of osteoarthritis, as obesity and poor posture increase knee and hip

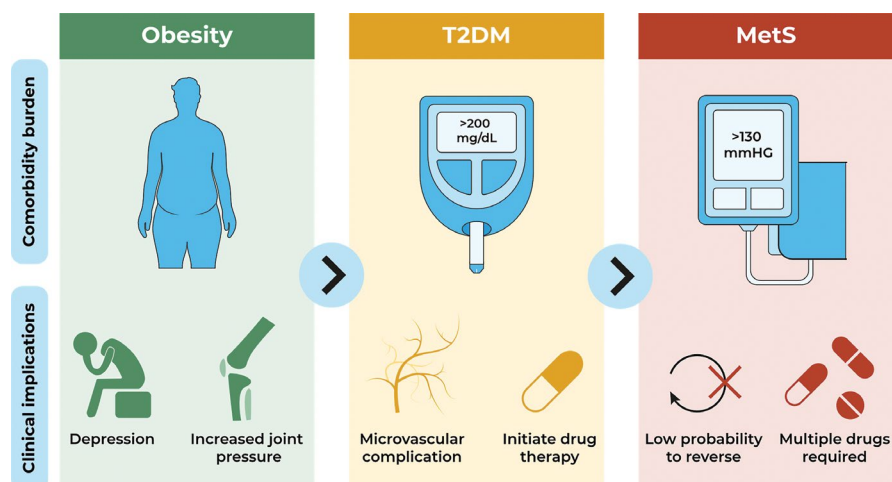


Fig. 5.3 Clinical manifestations of obesity, type 2 diabetes, and metabolic syndrome. The development of obesity, T2DM, and MetS is associated with multiple clinical manifestations. The manifestations become more severe with the progression from obesity to MetS, and they may accumulate; individuals with T2DM and MetS will also carry the burden of obesity-related health issues. *T2DM* type 2 diabetes mellitus, *MetS* metabolic syndrome

joint pressures. The combination of altered posture and structure modifies the gait pattern, which impairs daily activities including walking or climbing stairs [23]. As a result, both depressive thoughts (lack of motivation) and reduced mobility will make it harder to reduce weight by exercise or diet.

Insulin Resistance and Diabetes

Obesity and Risk of Type 2 Diabetes

T2DM is a common comorbidity associated with obesity, and the most common initial signs and symptoms of diabetes are increased urination, thirst, and tiredness. Individuals may also experience impaired wound healing and frequent infections [24]. Diabetes is diagnosed if one of the following criteria applies: 8-h fasting plasma glucose ≥ 126 mg/dL, 2-h plasma glucose ≥ 200 mg/dL during a 75 g oral glucose tolerance test, or hemoglobin A_{1c} (HbA_{1c}) $\geq 6.5\%$ [25]. The elevated glucose levels are a result of insulin insensitivity; organs are not able to respond to insulin signaling to increase the uptake of glucose.

Indeed, obesity substantially increases the risk of T2DM. In a large cohort study in 1,647,826 adolescent men, the risk of developing T2DM within the next 40 years was nearly 40% in men with a BMI ≥ 35 kg/m² [26]. Especially the gain in body weight early in life, as well as the total duration of obesity, is important regarding

the development of T2DM [27, 28]. Waist circumference, as surrogate for VAT, was also shown to be associated with the risk of T2DM, particular in patients with low BMI [29, 30]. In patients who already have T2DM, higher proportion of VAT was also associated with insulin resistance and poor glycemic control [31].

Pathophysiology: Adipocyte Dysfunction and the Development of Insulin Resistance

As discussed in the pathophysiology of obesity, adipocytes have limited capacity for FFA storage, leading to increased circulating FFAs. FFAs may potentially originate from VAT, as they are prone to inflammation-mediated lipolysis, thereby releasing FFAs in the portal vein [11]. Excess FFAs are stored ectopically in organs that are not designed as lipid storage organs (e.g., the liver, pancreas, and muscle), leading to organ lipotoxicity and impaired organ function [32]. In stable isotope experiments, it was shown that around 60% of triglycerides in the liver of nonalcoholic fatty liver disease arose from circulating FFAs [33].

FFAs play a pivotal role in insulin sensitivity in the liver and muscle. Accumulation of FFAs in the liver results in high intracellular levels of diacylglycerol, an intermediate product of triglyceride esterification (Fig. 5.1). This activates protein kinase C ϵ (PKC ϵ), which inhibits downstream insulin receptor signaling [34, 35]. This is supported by clinical evidence as hepatic diacylglycerol content is the best predictor of insulin resistance and highly correlates with activation of hepatic PKC ϵ [36]. Skeletal muscles are affected by FFAs in a similar fashion to the liver. Lipid accumulation increases diacylglycerol in the muscle and activates PKC θ , leading to impaired insulin signaling [12, 37].

Additionally, FFAs derived from AT enhance hepatic acetyl co-enzyme A which allosterically stimulates pyruvate carboxylase, the first enzyme in the gluconeogenesis pathway, thereby increasing hepatic glucose production [38]. Glucose is released from the liver, stimulating β -cells in the pancreas to produce insulin to clear circulating glucose. However, at this stage, many organs are insulin insensitive; aberrant insulin signal transduction impairs glucose transporter type 4 (GLUT4) translocation to the cell membrane, which is the main route of insulin-stimulated glucose uptake in cells [39]. The skeletal muscles play a central role, as over 80% of glucose is stored in this system [40]. Therefore, skeletal muscle insulin insensitivity is the main driver of hyperglycemia. Following prolonged hyperglycemia, pancreatic β -cells function eventually declines [41]. As insulin is a potent inhibitor of adipocyte lipolysis and gluconeogenesis, loss of insulin signaling to the adipocytes further stimulates FFA release and enhances glucose release from the liver (Fig. 5.1) [38]. At this stage, an insulin insensitivity individual is likely to be diagnosed with T2DM.

Clinical Implications of Insulin Resistance and Type 2 Diabetes

The diagnosis of T2DM has many health implications (Fig. 5.3), and individuals with diabetes are often stigmatized [42]. This may exacerbate mental health issues that are already observed in those with obesity. Additionally, hyperglycemia results in physiological complications that are proportional to its magnitude and duration [43]. Traditional complications are related to microvascular dysfunctions affecting dense microcapillary network (retinopathy, peripheral neuropathy, and nephropathy). Larger vessels are also affected by diabetes, which leads to macrovascular dysfunction (coronary heart disease, stroke, and peripheral vascular disease) [44]. These macrovascular complications will be discussed in the *Cardiovascular disease* section of this chapter.

It is estimated that 26% of T2DM patients in the USA show signs of retinopathy, defined as retinal microvascular aberrations, and in around 5% of these patients, vision is severely threatened [45]. The retina is the first microvascular system that is affected by hyperglycemia and retinopathy may be observed in people even before the diagnosis of T2DM [46]. Diabetic neuropathy, affecting around 30% of T2DM patients, is defined as peripheral nerve dysfunction that may lead to pain, numbness, and the loss of mechanoreception in the extremities [47]. Finally, diabetic nephropathy is defined as proteinuria >500 mg in 24 h, with an estimated prevalence between 20% and 50% of diabetic patients [48]. Persistent and untreated nephropathy may progress to chronic kidney disease which is a risk factor for many CVD [49].

To prevent complications, it is imperative that glucose levels remain stable at low levels. Adequate dietary interventions and exercise could facilitate the normalization of glucose levels and contribute to T2DM remission [50]. However, many T2DM patients are not able to maintain these lifestyle interventions. Metformin is used as first line drug intervention to control their glucose levels [51]. In severe diabetic patients with an HbA_{1c} > 9% or glucose levels >300 mg/dl supplementation with insulin may be considered [52]. Newly developed weight and glucose lowering drugs, sodium-glucose cotransporter 2 (SGLT-2) inhibitors and glucagon-like peptide-1 (GLP-1) agonists, may be used to resolve glycemia and are especially recommended in patients with high CV risk of or established CVD. GLP-1 agonists are advised for patients who benefit from a dual weight and glucose-lowering regimen and are preferred to insulin in T2DM patients when possible [17].

Metabolic Syndrome

Obesity and Metabolic Syndrome

MetS is a condition in which an individual experiences multiple metabolic complications. It is defined as having ≥ 3 of the following metabolic impairments [53]: (1) elevated waist circumference (population-specific cut-off), (2) triglycerides

≥ 150 mg/dL, (3) high-density lipoprotein cholesterol (HDL-C) < 40 mg/dL in men and < 50 mg/dL in women, (4) hypertension defined as systolic or diastolic blood pressure (BP) ≥ 130 mmHg or 85 mmHg, respectively, or (5) fasting glucose levels ≥ 100 mg/dL.

Waist circumference is a measure that correlates with the amount of VAT irrespective of BMI, indicating that excess VAT is particularly abundant in individuals with MetS [54]. This is corroborated by the observation that VAT volume (as measured by computed tomography) is more strongly associated with components of MetS compared to SAT volume [55, 56]. Obesity is also related to dyslipidemia, a disturbance in lipid balance reflected by increased circulating triglycerides and cholesterol or decreased HDL-C levels [57]. In addition, a strong linear association of BMI with systolic and diastolic BP is observed, and obesity increases the risk of developing hypertension [58, 59]. Each combination of the metabolic impairments could define MetS. However, hypertension was the most prevalent comorbidity in individuals with MetS, with a prevalence of 85% in MUO and 35% in MHO. Notably, the prevalence of dyslipidemia increases five-fold to 45%, and hyperglycemia increases six-fold to 60% in MUO compared to MHO [60].

Obesity and Hypertension

In addition to the release of FFAs and secretion of pro-inflammatory cytokines, adipocytes can secrete factors that play a role in BP regulation. Components of the renin-angiotensin-aldosterone system (RAAS), the primary system for BP regulation, are expressed in AT. In obesity, the RAAS becomes dysregulated, leading to its overactivation, thereby contributing to elevated BP in obese individuals [61–63]. In particular, perivascular AT surrounding blood vessels in the mesenteric area expresses high levels of RAAS components, underscoring the detrimental role of AT [64].

Additionally, it has been observed that rodents and humans with leptin deficiency have a lower BP despite a higher fat mass. Leptin may act via neuronal circuitry to influence BP, as inhibition of leptin signaling in neurons reduces BP in obese mice [65]. The reduction in circulating adiponectin, an important protective adipokine in obesity, also correlates with higher BP levels [66]. Adiponectin-knockout mice, which were fed a high-salt diet to induce hypertension, had more severe hypertension than their wild-type counterparts on the same diet. The increase in BP was ameliorated by adiponectin therapy, suggesting a protective role for adiponectin in obesity-related hypertension development [67].

Obesity, particularly VAT adiposity, is a strong predictor of increased aortic stiffness, which contributes to enhanced BP [68, 69]. Female mice with a deletion of the mineralocorticoid receptor are protected to western diet-induced vascular stiffness. This is potentially mediated by aldosterone, as it may bind to the mineralocorticoid receptor and subsequently reduce endothelial nitric oxide synthase activity, which is

a key component in endothelial relaxation signaling [70]. In addition, VAT increases pressure in the abdominal cavity [71], and increased renal fat is independently associated with hypertension [72, 73]. Excess VAT accumulation within the rigid kidney capsule may therefore compress the kidneys and increase intrarenal congestion, leading to a higher BP [74].

Clinical Implications

The additional burden of multiple metabolic impairments further deteriorates the lives of patients with MetS (Fig. 5.3). There is a bidirectional association of MetS and depression; the risk of depression is increased in MetS individuals and vice versa [75]. The overall quality of life appears unaffected in MetS patients but may be reduced in MetS patients with a high BMI [76]. Compared to more obvious signs and symptoms in obesity and diabetes, individuals with either dyslipidemia or hypertension are asymptomatic that may explain the unaltered quality of life. However, both dyslipidemia and hypertension increase the risk of incident CVD and CV mortality [77–79]. Screening for metabolic complication in obese individuals is therefore key in preventing CVD at a later stage in life.

If these risk factors are not adequately addressed and an individual progresses to MetS, lifestyle interventions are first used to resolve or control MetS. This consists of changing dietary intake, both quality and quantity, and increasing physical activity, which is beneficial for all MetS components [50]. Nevertheless, persistent or severe metabolic impairments will additionally benefit from the use of specific drugs. Dyslipidemia may be treated with statins that lower lipid levels, primarily by inhibition of the enzyme that catalyzes cholesterol biosynthesis [80]. The use of statins is also recommended to prevent CVD especially in individuals with a high CV risk [81]. Hypertension can be treated with multiple agents, including diuretics, calcium channel blockers, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers. Although stage I hypertension (BP ≥ 130 –139/80–85 mmHg) is used as cutoff criteria for MetS, anti-hypertensive drugs are only prescribed in individuals with a CVD risk score greater than 10% or stage II hypertension (BP $\geq 140/90$ mmHg) [82]. Considering that many MetS components are included in these risk prediction scores, it is likely that patients with elevated BP require antihypertensive therapy irrespective of their hypertension stage.

Patients with MetS may require more than one intervention to alleviate their symptoms and reduce the risk of CVD. Although lifestyle interventions are central to MetS therapy, the majority of MetS patients require supplementation with metformin, statins, or antihypertensive drugs. The prescription of these drugs is complicated by individual dose and response effects, and requires titration to assess the optimal dose that is monitored throughout life. Daily lifestyle modifications and drug use are additional burdens for patients with MetS. Despite the efficacy of the intervention, self-reported adherence to therapy is low. Around 50% is nonadherent to medication and even 90% does not adhere to lifestyle modifications [83]. MetS is

therefore a difficult metabolic disorder to reverse and should be prevented already in early stages of obesity.

Lipodystrophy

Lipodystrophy encompasses several metabolic disorders. It is characterized by partial or complete loss of major AT in the abdominal or gluteal area, concomitant with, in many cases, accumulation of fat in other regions of the body [84]. These conditions are classified by etiology into two main groups: acquired and inherited (congenital). Each of these groups can be further stratified into generalized (whole-body) or partial (specific regions) lipodystrophy (Table 5.2).

Types of Lipodystrophies

- 1. **Congenital generalized lipodystrophy (CGL)** is a rare autosomal recessive disorder characterized by significant reduction in SAT throughout the body [85]. Approximately 250 cases are described and the estimated prevalence ranges from 0.1 to 1 in a million [86]. The development of CGL is attributed, although not exclusively, to mutations in the *AGPAT2* or *BSCL2* gene. Both genes are involved in adequate storage of FAs in lipid droplets of adipocytes [84].

Table 5.2 Characteristics of lipodystrophy

	Congenital lipodystrohy		Acquired lipodystrophy		
	Generalized (CGL)	Partial (FPLD)	Generalized (AGL)	Partial (APL)	HALS
Prevalence	0.9 per million	1.5 per million	0.1 per million	0.2 per million	40-70% in patients on HAART
Fat distribution	Loss of subcutaneous fat	Loss of subcutaneous fat extremities and abdomen. Increased face, neck, and visceral cavity	Subcutaneous fat and pads extremities reduced	Loss starts in the face and spreads to abdomen	Lipodystrophy and/or hypertrophy Face, arms, and femoral-gluteal region
Etiology	<i>AGPAT2</i> or <i>BSCL2</i> mutation	<i>LMNA</i> mutation	Inflammatory disorders	Inflammation	HAART in HIV patients

CGL Congenital generalized lipodystrophy, *FPLD* Familial partial lipodystrophy, *AGL* Acquired generalized lipodystrophy, *APL* Acquired partial lipodystrophy, *HALS* HIV-associated lipodystrophy syndrome, *HAART* highly active antiretroviral therapy.

2. **Inherited familial partial lipodystrophy (FPLD)** is an autosomal dominantly inherited condition with loss of specific AT depots and prevalence is roughly estimated at 1.5 cases per million individuals [86]. The most common type of FPLD is type 2, also known as Dunnigan-type lipodystrophy, caused by genetic mutations in the *LMNA* gene. Mutations in or lack of *LMNA* are implicated in the inhibition of adipocyte differentiation and increased lipolysis [87, 88]. FPLD develops in puberty and leads to atrophy of SAT in the extremities and the abdomen. In addition, AT accumulates in the face, neck, and visceral cavity [85]. Notably, genetic screening for mutations in *LMNA* showed that FPLD prevalence is potentially higher than expected with estimates of 1 in 7000. Although many patients with this mutation lack the diagnosis of lipodystrophy, they have a high burden of metabolic disorders [89].
3. **Acquired generalized lipodystrophy (AGL)** has a similar clinical picture as CGL, which includes greatly reduced SAT volumes, but may additionally exhibit a decrease in intra-abdominal fat or fat pads in the extremities [90]. AGL is a rare condition with less than 0.1 cases per million that is predominantly diagnosed in childhood or early adolescence [86]. Although around 50% of AGL are of idiopathic origin many cases are attributed to inflammatory disorders, either excessive SAT inflammation or autoimmunity [90].
4. **Acquired partial lipodystrophy (APL)** is characterized by the cranial to caudal progression of fat loss. It starts in the face and eventually spreads to the abdomen, affecting all AT in between. Lipoatrophy is not observed in the lower extremities or gluteal region, but these regions accumulate excess fat. The prevalence of APL is also low, with estimates around 0.2 cases per million [86]. Similar to AGL, inflammation is associated with the development of APL, but metabolic complications are scarcely observed in patients [90]. This may be related to the preserved storage function of AT around the hips, thereby limiting circulating FFA levels and preventing metabolic disorder development.

Most cases of acquired lipodystrophy occur in HIV-infected patients treated with highly active antiretroviral therapy (HAART). Survival of HIV patients is greatly reduced by HAART, but approximately 40–70% of patients exhibit HIV-associated lipodystrophy syndrome (HALS) concomitant with metabolic perturbations as an adverse effect of therapy [91]. Although both lipoatrophy and AT hypertrophy can be observed in these patients, AT loss occurs commonly in the face, arms, and femoral-gluteal region [92]. The exact pathophysiology of HALS is unknown, but certain HAARTs may impair adipocyte differentiation, induce reactive oxygen species, and enhance adipocyte lipolysis [84, 93].

Metabolic Complications and Implications of Lipodystrophy

Similar to obesity, lipodystrophy results in increased FFA levels, primarily due to limited or inadequate lipid storage in adipocytes. Although the exact mechanisms linking lipodystrophies to metabolic complications, such as diabetes, ectopic lipid accumulation, and dyslipidemia remain elusive, it is likely that pathways similar to obesity-related metabolic complications are involved. Therefore, patients with lipodystrophy may potentially benefit from the treatment strategies utilized in obesity. In most cases, it is recommended that patients eat healthy and exercise regularly [84], except for patients with severe lipoatrophy and low body weight, as exercise may lead to further AT loss [94]. T2DM in lipodystrophy patients can be managed by standard of care drugs: metformin or insulin [95, 96]. However, these drugs are solely prescribed if the patient is diagnosed with diabetes, as these drugs are not approved by the Food and Drug Administration (FDA) for lipodystrophy [84]. To treat dyslipidemia, statins may be prescribed but use is warranted in HALS patients as statins interact with antiretroviral drugs [97].

Additionally, the general appearance of patients with lipodystrophy may be affected by the excessive loss or accumulation of fat in specific regions, which can impact their mental state. In particular patients with HALS exhibit loss of fat in their face, which can be reconstructed with cosmetic surgery via various implantation techniques, either exogenous silicone or endogenous fat [98, 99]. Conversely, FPLD patients with excess fat in the neck may benefit from repeated AT removal via lipectomy or liposuction [85].

Cardiovascular Disease

Obesity and Risk of Cardiovascular Disease

As described earlier, obesity and visceral adiposity are strongly related to CV risk factors, such as insulin resistance, dyslipidemia, hypertension, sympathetic nervous system, RAAS activation, and systemic inflammation [55, 100]. These obesity-related risk factors are causative for the development of CVD, such as atherosclerosis, heart failure (HF), stroke, and atrial fibrillation [101]. While increased BMI is associated with a higher incidence of CVDs, large inter-individual variations exist in the amount and distribution of VAT, which alter CV risk. Overweight and obese individuals with a low amount of AT often have a better CV risk profile than individuals with a higher amount of AT [102–105]. Additionally, obese individuals with high amount of upper body AT localization (e.g., intra-abdominal AT and increased triglyceride content in specific organs such as the liver and heart) are at higher risk compared with obese individuals with predominantly gluteal-femoral fat [106]. Basically, individuals with an excess amount of VAT have an increased risk for the development of CVD, independent of their BMI [107, 108].

Obesity Paradox

The partially dissociated relationship between BMI and VAT is important to interpret the obesity paradox. This paradox states that obesity is associated with an increased risk of CVD, especially HF. However, among patients with HF, those with a higher BMI have a better prognosis than those with a lower BMI. For a large part, this observation results from methodological flaws, such as confounding, selection bias, reverse causality, and because BMI and VAT are not always mutually related. Therefore, other measures that more specifically estimate the burden of visceral adiposity, for example waist circumference, are a better reflection of individual risk [109]. Interestingly, in patients with HF, these alternative anthropometric measurements showed no evidence of an obesity paradox [110].

Atherosclerosis and Thrombo-Embolic Disease

Obesity and visceral adiposity drive insulin resistance, atherogenic dyslipidemia, hypertension and the release of pro-inflammatory and pro-thrombotic factors, and these factors are closely related to the development of atherosclerosis and thrombo-embolic disease [111]. Obesity was previously shown to be associated with incident peripheral artery disease [112], stroke [113], and coronary artery disease (CAD) [114, 115]. However, increased BMI and its associated traditional risk factors, especially the metabolic consequences of visceral adiposity, seem most important in the risk of these atherosclerotic diseases [116–118], and the ancillary effects of AT dysfunction may explain these findings. For instance, it was shown that VAT volume was associated with arterial inflammation, independent of established risk factors [119].

A specific VAT depot of interest in relation to CAD is epicardial adipose tissue (EAT) which is the VAT situated between the outer wall of the myocardium and the visceral layer of the pericardium. EAT is mainly located in the atrioventricular and interventricular grooves and has an unobstructed relation with the myocardium and the coronary arteries [120]. Similar to VAT, EAT can transform from healthy AT into a pro-inflammatory and pro-atherogenic AT depot. EAT dysfunction is associated with CAD through inflammation, oxidative stress, endothelial damage, and lipid accumulation [120].

Venous thromboembolism (VTE), including deep vein thrombosis and pulmonary embolism, is highly common in the general population and even more in patients with obesity and contributes to increased morbidity and mortality. Obesity and visceral adiposity are associated with higher incidence for VTE [121, 122]. Although immobilization or hospitalization for trauma or critical illness exert a direct effect on VTE risk, the number of VTE cases is predominantly attributed to individuals with obesity who are hospitalized or had undergone knee or hip surgery [123–125]. As such, the presence of obesity is included in risk prediction models for

VTE, for instance to guide clinicians on prophylactic treatment with anticoagulation in hospitalized or post-surgical patients [126].

Heart Failure

Obesity is independently associated with the development of HF. The increased risk for HF is 5 and 7% per 1-unit increase in BMI for men and women respectively [127]. Obesity seems more strongly associated with HF with preserved ejection fraction (HFpEF) as compared to HF with reduced ejection fraction (HFrEF) [128]. In large clinical trials of patients with HF, the average BMI of patients with HFpEF was ~ 30 kg/m², whereas in HFrEF populations, the average BMI was ~ 28 kg/m². Beyond BMI, especially the amount of pericardial AT, located on the outer layer of the pericardial sac, was independently associated with the incidence of HFpEF [129]. In HFpEF, the amount of EAT was higher than matched controls without HFpEF [130].

Obesity leads to neurohormonal activation, sodium retention, and plasma volume expansion, thereby increasing metabolic rate and stress of the heart [131]. Furthermore, several ancillary mechanisms beyond obesity, such as intra-myocardial lipo-toxicity, systemic inflammation and endothelial dysfunction, may lead to adverse myocardial remodeling, hypertrophy, and diastolic dysfunction ultimately resulting in HF [131]. These mechanisms may be more pronounced in patients with HFpEF than HFrEF, particular in women with HFpEF [128].

In patients with HF, the presence of obesity is associated with lower quality of life, more HF symptom burden and impaired exercise tolerance. While obesity and associated plasma volume expansion are related to increased cardiac filling pressures [132], it seems that especially an abundance of VAT and EAT is associated with impaired hemodynamics and exercise intolerance [133–135].

Atrial Fibrillation

Obesity is independently associated with the development of atrial fibrillation (AF) [136–138]. In particular, the risk for AF increases when other anthropometric indices of obesity, such as waist circumference, waist-hip ratio, and fat mass, were used [139, 140]. Besides the onset of AF, obesity and visceral and epicardial adiposity are also associated with AF progression [141, 142], and with higher rates of recurrent AF after ablation [143]. The association between the development of AF in the setting of obesity is mediated through several mechanisms, including (1) hemodynamic and functional impairments associated with neuro-hormonal and RAAS activation and sodium retention leading to hypertension, plasma volume expansion, increased cardiac filling pressures, and ultimately left atrial stretch and enlargement [137, 138, 144, 145] and (2) left atrial electrical remodelling and conduction delay

due to peri-atrial AT expansion and fibro-fatty infiltration concomitant with local inflammation [146–150].

Obesity Treatment

Obesity is a treatable disease, and the cornerstone of obesity treatment is a combined lifestyle behavioral intervention focused on diet, caloric restriction, physical activity, and/or psychological interventions. Individuals who experience insufficient weight loss with lifestyle modifications alone may be offered pharmacological or surgical weight loss interventions. Dietary interventions may lead to modest weight loss in the short term but maintaining a durable weight loss may be quite difficult [151]. On the contrary, surgical weight loss interventions (e.g., Roux-Y gastric bypass) lead to a weight reduction ranging from 25% to 30% that sustains for over 5 years [152]. The field of pharmacological weight loss intervention has greatly evolved over the years, especially with the advent of GLP-1 receptor-modifying drugs, such as semaglutide, which may lead to sustained weight reduction in the range that was previously only seen after bariatric surgery.

Non-pharmacological Treatment of Obesity

Most randomized controlled trials investigating non-pharmacological interventions for obesity have used a lifestyle intervention including caloric restriction, typically with a 500–750 kcal/day energy deficit, combined with increased physical activity. An average weight reduction of 5–10% can be achieved with such intervention, but maintaining a longstanding weight reduction is difficult. A standard, moderate-intensity aerobic exercise program alone is associated with a modest weight loss of 1.5–3.5 kg and an average fat loss of 1.3–2.6 kg [153]. The Diabetes Prevention Program randomized individuals with a BMI ≥ 24 kg/m² and prediabetes to lifestyle interventions or metformin. Lifestyle intervention was associated with a reduced risk for T2DM, and with a greater reduction in body weight and HbA_{1C} as compared to metformin [154]. The Look AHEAD trial randomized 5145 overweight and obese patients with T2DM to either an intensive lifestyle intervention or control group. While lifestyle intervention led to an 8.6% reduction in body weight after 1 year, compared to 0.7% reduction in the control group, lifestyle intervention was not associated with lower risk of CV events [155]. Weight loss achieved at the end of the study was 6.0 and 3.5% in the intervention and control groups, respectively. Although a subgroup of individuals who lost >10% body weight had a 21% lower risk of CV events [156]. In a post-hoc analysis of the Look AHEAD trial, it was shown that at 1 year, the intervention group lost 5.6 kg fat and 2.3 kg lean mass, but regained 100% fat between years 1 and 8 [157].

The most recent guideline from the American Society of Metabolic and Bariatric Surgery states that bariatric surgery is recommended for individuals with a BMI ≥ 35 kg/m², regardless of the presence, absence, or severity of co-morbidities [158]. Furthermore, bariatric surgery should be considered for individuals with metabolic disease and a BMI of 30–34.9 kg/m² [158]. Bariatric surgery has sustained beneficial effects, not only on CV risk factors and metabolic control but also on CV mortality and CVD [159].

Pharmacological Treatment of Obesity

Anti-obesity medications have a long history of use. Early drugs used for the treatment of obesity in the 1930s and the 1940s, such as 2,4-dinitrophenol, had serious side effects and were withdrawn from the market. More recent drugs, such as sibutramine and rimonabant, were also withdrawn because of serious CV and psychiatric side effects, respectively. Currently, six drugs have been approved by the FDA and the European Medicines Agency (EMA) for the treatment of obesity: orlistat, naltrexone/bupropion, liraglutide, semaglutide, and setmelanotide. The latter is prescribed to treat rare obesity-related monogenetic deficiencies. Tirzepatide is a dual glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 agonist. Orlistat inhibits the breakdown of fat in ingested food. It leads to modest weight loss but is also associated with common gastrointestinal side effects, such as oily rectal leakage, fecal urgency, and fecal incontinence. Naltrexone/bupropion increases satiety and reduces food cravings and is associated with modest weight loss of 5–6% [160]. Liraglutide is the first GLP1 agonist to be used as a specific treatment for obesity and was investigated in the SCALE program. Liraglutide 3.0 mg *o.i.d.* was associated with a weight reduction ranging from 6% to 8% [161, 162]. In the subsequent STEP trials, semaglutide 2.4 mg once weekly was associated with an average weight reduction ranging from 10% to 15% [163–165]. Semaglutide was the first anti-obesity drug that also demonstrated a reduction in CV events. In the SELECT trial, semaglutide was associated with lower incidence of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke [166]. Semaglutide was also tested in patients with obesity-related HFpEF in the STEP-HFpEF trial. Semaglutide was associated with improved symptoms and physical capacity, greater improvements in exercise function, and greater weight loss as compared to placebo [167]. Interestingly, weight reduction with semaglutide in HFpEF was also associated with a reduction in C-reactive protein levels. This suggests that beyond weight loss, there may also be a reduction in systemic inflammation possibly due to lower burden of AT dysfunction [168]. The dual GIP and GLP-1 agonist tirzepatide has been tested in the SURMOUNT trials and tirzepatide 15 mg once weekly was associated with weight reduction averaging from 15% to 21% within 72 weeks [169–171].

Treatment of Adipose Tissue Dysfunction

While most studies on anti-obesity treatment have focused on weight loss, reduction in CV risk factors and CV events, relatively limited attention has been paid to the potentially beneficial effects on the underlying AT dysfunction. Such insights are important to understand the extent and mechanisms through which these anti-obesity treatments also improve CV risk beyond general weight reduction.

In an ancillary analysis from the Look AHEAD trial in 100 patients, mean VAT decreased by 8.0% in the intervention group, but this decrease was not associated with improvement in CV risk [172]. In another, smaller cross-sectional study, strict adherence to dietary guidelines was associated with less visceral and liver fat, adjusted for total body fat [173].

Bariatric surgery leads to an important reduction in VAT, especially in patients with T2DM [174]. Beyond a significant reduction in fat mass, bariatric surgery improves AT dysfunction, shifting it to more healthy tissue with improved lipolysis regulation, beneficial adipokine secretome, and decreased local and systemic inflammation, and several of these effects are weight loss-independent [175]. As such, bariatric surgery is increasingly being referred to as metabolic surgery.

In addition, several drugs have been shown to specifically reduce visceral and ectopic fat depots and partly resolve AT dysfunction. For instance, liraglutide has been shown to induce the browning of white AT in mice, demonstrated by upregulated lipolytic activity, enhanced expression of brown AT, and mitochondrial-specific genes [176]. Furthermore, in patients with non-alcoholic steatohepatitis, liraglutide was associated with a reduction of metabolic dysfunction, AT insulin resistance, and AT inflammation [177]. Also, semaglutide seems to have beneficial effects on AT dysfunction since proteins related to the regulation of lipid uptake, lipid storage, and lipolysis were downregulated in white AT of mice [178]. While anti-obesity treatments lead to various grades of body weight and VAT reduction, all anti-obesity strategies described may lead to a reduction in EAT volume and potentially to a change in its proinflammatory state [179]. Especially SGLT-2 inhibitors and GLP-1 agonists may have a beneficial effect on EAT by reducing its volume and lowering its inflammatory response [180–182].

Conclusion

Obesity is becoming one of the most important treatable risk factors for CVD. Moreover, in addition to being a traditional CV risk factor, unhealthy obesity with AT dysfunction is also a disease of its own. Knowledge of the transition of physiological, healthy AT to pathophysiological, unhealthy AT dysfunction, as well as the interplay between AT dysfunction and the development of CVD, has greatly evolved over the years. Major steps have been set in the treatment of obesity,

especially with the development of new pharmacological agents that achieve weight loss that approaches the amount of weight loss following bariatric surgery. However, apart from general weight loss strategies, some important knowledge gaps remain regarding the treatment of AT dysfunction. Future studies are urgently needed to better prevent and treat AT dysfunction to reduce the societal burden of CVD.

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Chapter 6

Adipose Tissue Angiogenesis and Clinical Implications



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Abbreviations

AARP	Anti-angiogenic recombinant protein
ACs	Adipocytes
AT	Adipose tissue
BAT	Brown adipose tissue
CSD1	Stearoyl-co-enzyme A desaturase 1
Dll4	Delta-like 4
DM	Diabetes mellitus
ECs	Endothelial cells
ED	Endothelial dysfunction
eNOS	Endothelial nitric oxide synthase
FABP	Fatty acid-binding protein
FFA	Free fatty acid
FGF21	Fibroblast growth factor 21
FOXO1	Forkhead box protein O1

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GLUT1	Glucose transporter 1
GPIHB1	Glycosylphosphatidylinositol-anchored high-density lipoprotein binding protein 1
IGF-I	Insulin-like growth factor 1
IR	Insulin resistance
LpL	Lipoprotein lipase
miRNA	microRNA
ncRNA	Non-coding RNA
NO	Nitric oxide
PDGF	Platelet-derived growth factor
PDGFR β	Platelet-derived growth factor receptor-beta
SIRT1	Silent information regulator 1, <i>s.</i> Sirtuin 1
T2DM	Type 2 diabetes mellitus
VEGF	Vascular endothelial growth factor
VLDL	Very low-density lipoprotein
VLDLR	Very low-density lipoprotein receptor
α -SMA	Alpha-smooth muscle actin

Introduction

Brief Overview of Adipose Tissue Angiogenesis

Adipocytes (ACs) and endothelial cells (ECs) represent two closely interconnected cell lines, determining each other's functions through constant and intriguing interplay. As a cornerstone for these facts, we can consider the results of studies indicating the presence of precursor cells with dual differentiation capacity into both adipocytes and EC within the adipose tissue (AT) blood vessels [1, 2].

The vasculature of the AT can be considered an orchestrator of internal shifts. The initial signal for this process is believed to originate from both the ACs themselves during dynamic modulation, marked as tissue remodeling (hypertrophy and hyperplasia), and from the metabolic signals accompanying these alterations. New blood vessel formation represents the response of healthy AT to increased demand for oxygen and nutrients due to its expansion. This well-coordinated angiogenic response maintains adequate oxygenation and prevents hypoxia. However, in obesity, due to rapid tissue growth and an imbalance of anti-angiogenic and pro-angiogenic factors, insufficient vasculature becomes prominent, contributing to the onset of inflammation and hypoxia, ultimately leading to the formation of dysfunctional AT [3].

Importance of Understanding Adipose Tissue Vascularization

Given these findings along with the shared pathophysiological grounds of broad-spectrum diseases involving dysfunctional AT, there is a distinct need for active investigation of its vascularization. This is aimed at identifying effective preventive strategies and therapeutic modalities [2, 4].

Unique Vascularization of Adipose Tissue

Description of the Vascular Structure in Adipose Tissue

The analogy of a multifaceted picture of AT can also be extended to the diverse subclasses of ECs, which vary in function and transcriptional profiles. The potential for constant communication between AT and ECs is based on the fact that every adipocyte in a state of physiological nourishment is supplied by at least one micro-vascular vessel. The unique vascularization of AT is reflected by the presence of non-permeable blood vessels, namely, continuous capillaries, whose structure is based on a continuous basement membrane and tight junctions between ECs. Thus, it is evident that molecular transport is a highly sophisticated process in this tissue, strictly controlled by transport systems, without possible paracellular leakage as a form of transport typical for ECs in other organs [2, 5].

Role of Vascularization in Adipose Tissue Function

Role of Vasculature in Targeted Nutrient Transport

The significant and distinctive role of AT ECs is evident in their regulation of the qualitative-quantitative influx of lipids, both during and between meals, into tissue depots [5].

Free Fatty Acid Uptake

A notable instance of paracrine communication between ECs and AT is exemplified by the uptake of triglyceride-rich lipoproteins from the bloodstream. This process is mediated by lipoprotein lipase (LpL), which is bound to the luminal endothelial surface via a protein serving its anchoring known as glycosylphosphatidylinositol-anchored high-density lipoprotein binding protein 1 (GPIHBP1), given that ECs do not synthesize this enzyme. The role of LpL is in forming transportable patterns of triglyceride-rich lipoproteins known as free fatty acids (FFAs) [5, 6].

Trans-endothelial Vesicle-Mediated Transport

Recalling the fact that the AT endothelium is of a continuous type, the scientific debate regarding potential mechanisms for further transport of liberated FFA towards tissue depots has progressed from assumptions of ECs being filled with numerous pores to eventually identifying, via electron microscopy, a type of transport labelled as vesicular transcytosis. It has been determined that these cells possess many surface vesicles, varying in type, thereby maintaining the constancy of interstitial fluid and plasma transport. Caveolae are the most abundant vesicle type in the AT. Their formation is regulated by cavins 1 and 2 and caveolins 1 and 2 [5, 7]. They exhibit a wide range of roles, far beyond transport, as they are considered to participate in the process of angiogenesis, signal transduction, and nitric oxide (NO) production. Thus, their loss in large arteries is believed to protect against the development of atherosclerotic plaques owing to reduced lipid transcytosis. However, diminution of caveolae in adipocytes and microvasculature, leads to the onset of type 2 diabetes mellitus (T2DM), disrupting the capacity for lipid storage [5].

Trans-endothelial Receptor-Mediated Transport

The role of individual proteins in receptor-mediated transendothelial transport remains unclear, but several ligand-binding proteins have been established. Within the domain of FFA transport, ECs expression of fatty acid-binding proteins (FABPs), scavenger receptor CD36, and fatty acid transport proteins (FATPs) 3 and 4 have been reported. It is also essential to recall the potential role of the very low-density lipoprotein (VLDL) receptor (VLDLR) in serving as a receptor for a few lipoproteins. Specifically, it is believed to promote both LpL-mediated release of FFA and vesicular transcytosis. It is speculated that ECs are expressed it in multiple tissues, including AT [5, 8, 9].

Adipocytokines, FFAs, and Glucose Transport

The uniqueness of AT is also reflected in the fact that it not only takes up a large quantity of FFAs, but also releases them into the bloodstream. Conceptualizing AT as a sizeable endocrine gland is comparable to molecule release from other endocrine glands, which occurs via fenestrated capillaries. In contrast, AT is characterized by continuous capillaries; thus, metabolites are released from AT through direct release via trans-endothelial transport into the bloodstream or through the lymphatic system. An exciting interplay has been established between AT, ECs, and glucose. Specifically, AT takes up significant amounts of glucose, and ECs themselves, besides transporting glucose, utilize it as a metabolic substrate and fuel, given their low percentage of mitochondria. Glucose uptake by ECs is believed to occur predominantly via glucose transporter 1 (GLUT1) and is insulin-independent [5, 10].

The Contributions of Adipose Tissue Angiogenesis to Overall Vascular Health

Angiogenesis is considered a crucial and central component of the processes underlying both AT development and its intricate connections with systemic metabolism, exerting influence on progenitor cell proliferation, tissue remodelling, regulation of adipocyte metabolism, and comprehensive adipocyte communication with the rest of the organism. Furthermore, focusing on pathological processes, it is evident that endothelial dysfunction (ED) is a hallmark of obesity. Recent perspectives emphasize the significance of the bidirectional relationship between these two pathological entities, as obesity was previously thought to lead to ED. In contrast, it is now understood that changes in ECs function can also positively influence adipocyte metabolism alterations [2, 4].

Mechanisms of Regulation of Angiogenesis

Regulation of Angiogenesis Is in Adipose Tissue

The multistep process of angiogenesis in AT encompasses the following phases: [1] ECs activation and proliferation in response to stimulating factors, [2] infiltration and invasion of ECs into the AT, and [3] formation of lumen and capillary networks within the tissue [4].

However, the role of the vasculature in AT is far more complex than the traditionally understood roles of the vascular system, and herein lies in the intriguing relationship between adipocytes and ECs. While the vasculature of AT does create a microenvironment that supports adipocyte differentiation, adipocyte precursors (preadipocytes) and endothelial precursor cells are believed to reside in close proximity within AT, facilitating their interactions during adipogenesis and angiogenesis. It is important to note the substantial resemblance between markers expressed by adipocytes and pericytes [2, 5]. However, although adipocytes and pericytes express similar markers, such as platelet-derived growth factor receptor-beta (PDGFR β) and alpha-smooth muscle actin (α -SMA), they have distinct roles and express different sets of markers specific to their cell types. The initial basis for a deeper understanding of the significance of the angiogenic process in AT was the discovery that AT expansion is halted by its inhibition. However, subsequent scientific findings have confirmed that this conclusion could be more complex, presenting a new perspective that provides insight into the onset of metabolic perturbations due to downstream regulation of angiogenesis. The formation of new vasculature is conditioned by the secretion of factors that stimulate this process, designated as pro-angiogenic factors, predominantly from the vascular endothelial growth factor (VEGF) family. Among these key regulators, VEGF-A provides chemoattractant

and mitogenic messages directed toward ECs, leading to their multiplication and phenotypic differentiation [4].

Intersignaling originating from the Notch signaling pathway through the delta-like 4 (DLL4) mediates communication between angiogenesis and VEGFs. However, the interaction between Notch signaling and VEGFs is complex and context-dependent, with Notch able to both positively and negatively regulate VEGF signaling, depending on the specific cell types and conditions involved [2, 4]. Activation of these factors results in body weight loss via heightened thermogenesis and energy expenditure as well as a reduction in hypoxia and related metabolic comorbidities associated with obesity [5]. Angiogenesis represents a fascinating entity, as evidenced by the observation that it can act as a protective and exacerbating factor. Specifically, animal models [11, 12] have shown that the effect depends on the time of application of the anti-angiogenic therapy. If administered to previously healthy subjects during weight gain, it leads to ectopic accumulation of AT by inhibiting its expansion, resulting in the onset of insulin resistance (IR). Conversely, when applied in cases of pre-existing obesity, this therapy can lead to the removal of pro-inflammatory factors and improvement in AT dysfunction [4, 5].

Role of HIF-1 α in Angiogenesis Regulation

Obesity is marked by a decrease in capillary density and thinning of capillary networks due to the rapid expansion of AT, resulting in a notable increase in the distance between adjacent microvasculature that leads to reduced tissue oxygenation, macrophage infiltration, and inflammation promotion, all characteristic features of tissue hypoxia [4, 5]. Hypoxia-inducible factors (HIFs) are activated during this state. HIF-1 comprises two subunits, HIF-1 α and HIF-1 β , and it serves as a functional transcription factor [4]. The role of HIF-1 α in AT has not yet been fully elucidated, despite it being identified as a critical regulator of the hypoxia response, and its effects may also be specific to different tissue depots. The findings from obese animal model studies [13, 14] have contributed to the proposition of potential roles for HIF-1 α . It is considered to be involved in the tissue response to hypoxia by interfering with tissue mitophagy, inflammation, and fibrosis processes, and its effects on angiogenesis are context-dependent and potentially tissue-specific [14–16]. However, its role is highly heterogeneous, as demonstrated by its varied effects on preadipocytes and adipocytes in terms of differentiation and subsequent function [2].

Additionally, there are challenges in extrapolating the results obtained from animal models considering the substantial differences between human and rodent biology [17]. Specifically, HIF-1 α levels are increased in the AT of obese mice [18]. In contrast, in human models, increased HIF-1 α levels have been observed only in a specific group of obese individuals with obesity hypoventilation syndrome, leading to the scientific hypothesis that different types of hypoxia may induce varying alterations in HIF-1 α [19]. For instance, early and transient activation of HIF-1 α occurs

after exposure of C57Bl/6J mice to intermittent hypoxia, followed by further changes, including decreased levels of endothelial nitric oxide synthase (eNOS) and VEGF, capillary reduction, dominance of a pro-inflammatory macrophage phenotype, and an increase in insulin resistance. However, these changes were not observed under prolonged hypoxic condition [20]. Nevertheless, one potential indirect role of HIF-1 in improving vascular density is the induction of platelet-derived growth factor (PDGF) expression, which is believed to aid in forming capillary-like tubular networks [2, 19, 21].

Mechanisms of Adipose Tissue Adaptation to Changing Metabolic Needs through Angiogenic Processes

The specific role of the unique AT vasculature can be discussed regarding two fundamental mechanisms of tissue expansion: hyperplasia and hypertrophy. The primary difference between these two processes is that hyperplasia is predominantly genetically determined and occurs physiologically during growth and development. In contrast, AT hypertrophy reflects the capacity for lipid storage during its lifespan. AT expansion is accompanied by dynamic perturbations at the stromal vascular fraction level. However, the fundamental difference between hyperplasia and hypertrophy is rooted in the temporal determinant of vascular development, which precedes and accompanies hyperplasia while lagging behind hypertrophy, thus representing dysfunction onset [1, 3].

Hyperplasia of AT

AT development via hyperplasia is synchronized with microvasculature evolution. Although specific to the growth period, as previously mentioned, there is potential for this later AT expansion, albeit with individual variation. This mode of expansion was positively associated with metabolic health. These assumptions indicate the significance of angiogenesis in this process. The presumed mechanisms are very complex, including the involvement of different genes and signaling pathways, with a wide range of metabolic and growth factors, such as insulin-like growth factor 1 (IGF-I), which are crucial in endothelial cell proliferation. IGF-I is pivotal in conditions such as pregnancy and post-acute myocardial infarction, representing striking examples of hyperplastic AT expansion during adulthood [3, 22].

Hypertrophy of AT

Hypertrophy, as a modality of AT expansion, is characteristic of a response to hypercaloric intake, representing the starting point for metabolic dysfunction, and is thus particularly distinctive for ACs within the abdominal depot. Specifically, hypertrophy is accompanied by disruption of the capillary architecture. Scientific premises supporting these findings include direct interference with signaling pathways during hypernutrition and insufficient angiogenesis, further leading to hypertrophy development, formation of a niche by hypertrophic adipocytes impermeable to vascular development, and, ultimately, combined dysfunction of adipocytes and the capillary network [3, 23].

The Regulatory Role of MicroRNAs in Angiogenesis in AT

MicroRNAs (miRNAs) are a class of small (19–25 nucleotides long) non-coding RNAs (ncRNAs) that play a significant role in post-transcriptional regulation by binding mRNA and suppressing translation or causing their degradation, thus impacting the metabolism in multiple ways [24]. Approximately 2600 miRNAs are present in the human genome [25]. In AT, they are important regulators of AC differentiation, lipogenesis, and angiogenesis and are essential for developing obesity and T2DM [26].

According to the action they perform, miRNAs regulating AT can be categorized into two primary groups: miRNAs that impair angiogenesis (miR-34a, miR-124, miR-29, etc.) and miRNAs that can be affected by pro- or anti-angiogenic factors (miR-21, miR-210, miR-296, etc.) [27].

MiR-34a targets the *SIRT1* (silent information regulator 1, s. sirtuin 1) gene and upregulates *FOXO1* (forkhead box protein O1) and p53 (*TP53*) genes in endothelial progenitor cells, inhibiting angiogenesis. However, its downregulation promotes brown AT (BAT) formation by up-regulating *SIRT1* and *FGF21* (fibroblast growth factor 21) genes [27, 28]. The miR-29 family has been proven effective in inhibiting angiogenesis in vitro and is under-expressed in numerous malignant diseases. However, miR-29a overexpression in adipocytes is associated with IR; therefore, neither miR-34a nor miR-29a is a suitable therapeutic option [29]. miR-124-3p has known anti-angiogenic and anti-obesity potential; it increases the thermogenesis of BAT targeting the *SCD1* (stearoyl-co-enzyme A desaturase 1) gene (*SCD*) [29]. miR-126b-5p inhibits tumor angiogenesis in various cancers but stimulates angiogenesis after injury and contributes to diet-induced adipogenesis by increasing lipid deposition and insulin resistance, similar to miR-221 and miR-222 [27, 30, 31].

miR-21 and miR-210 promote angiogenesis induced by hypoxia and seem to be associated with the exacerbation of IR in the pathophysiological progression from obesity to T2DM [27, 32]. miR-296 and miR-155 enhance angiogenesis in AT, cancer, and vascular diseases by up-regulating VEGF expression [27, 28]. miRNA let-7f improves hypoxia-induced angiogenesis, shows elevated expression in visceral

AT in obese patients, and the miRNA-26 family inhibits angiogenesis and adipogenesis by targeting SMAD1–Id1–p21^{WAF/CIP1}/p27 and Fbx19 signaling, respectively [27, 33, 34]. Additionally, miR-132-3p in exosomes originating from BAT has been found to reduce the expression of lipogenic genes in the liver [35].

miRNAs play an essential role in angiogenesis, making them potential indicators for metabolic disorders and a powerful novel therapeutic strategy, considering that their overexpression can be regulated by antisense and anti-miRNA oligonucleotides and underexpression by synthetic miRNA (miRNA mimics) [36].

Clinical Implications of Adipose Tissue Angiogenesis

Considering the clinical implications and AT angiogenesis-targeted approach, it is essential to note that specific interactions within this intriguing relationship remain unclear. This pertains primarily to the role of the vasculature during various metabolic conditions in maintaining AT homeostasis. Additionally, the role of hypoxia in stimulating angiogenesis during the spread of AT is still unclear. Despite the complexity of the relationship between these two cellular populations, recent discoveries in single-cell transcriptomics have revealed many different populations within the ACs themselves [3, 37, 38].

New findings beyond the simple inhibition of angiogenesis for obesity treatment highlight the complexities of therapies in this domain. These insights introduce a novel therapeutic concept based on the promotion of angiogenesis, applicable not only to obesity but also to diabetes mellitus (DM). This emerging approach challenges previous paradigms and opens new avenues for clinical intervention in metabolic diseases [38].

In the domain of paradoxical regulation of angiogenesis, we have examples of therapies leading to overall improvements in metabolic health and reductions in adiposity. For instance, the angiogenesis inhibitor TNP-470 application to leptin-deficient *ob/ob* mice resulted in these benefits [39]. However, whether this was solely due to angiogenesis inhibition remains debatable, given that the drug also suppresses food intake [3]. Other compounds tested as anti-angiogenic inhibitors, including ALS-L1023 [40], anti-angiogenic recombinant protein (AARP) (a.k.a. CTT peptide-endostatin mimic-kringle 5) [41], angiostatin, and VEGF inhibitors also result in weight loss, but the underlying mechanisms remain unclear [4]. Considering all this, the potential of angiogenesis modulation as a therapeutic tool in obesity treatment has become apparent and prudent [3, 4].

Conclusion

When discussing the potential therapeutic impact of drugs targeting angiogenesis for obesity treatment, it is essential to consider combining these drugs with existing therapies, including those from the field of obesity management and anti-inflammatory agents. There is an urgent need for rapid scientific efforts in this area to achieve the desired clinical outcomes, which would benefit patients suffering from obesity, a disease of pandemic proportions. Furthermore, this research could unravel the intriguing and enigmatic communication between AC and ECs and the various cellular populations involved in this process.

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Chapter 7

Technological Advances in Adipose Tissue Research and Clinical Practice



Radoslav Stojchevski and Dimitar Avtanski

Abbreviations

AI	Artificial intelligence
ASC-1	Alanine serine cysteine transporter 1
ASCs	Adipose-derived mesenchymal stem cells
ASPC	Adipose stem and progenitor cells
AT	Adipose tissue
BAT	Brown adipose tissue
BMI	Body mass index
CLI	Cerenkov luminescence imaging
CT	Computed tomography
CU	Contrast ultrasound
CVD	Cardiovascular diseases
DL	Deep learning
FACS	Fluorescent-activated cell sorting
IRT	Infrared thermography imaging
ML	Machine learning
MRI	Magnetic resonance imaging
MSCs	Mesenchymal stem cells

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NAFLD	Non-alcoholic fatty liver disease
NGS	Next-generation sequencing
NIRS	Near-infrared spectroscopy
NIRTRS	Near-infrared time-resolved spectroscopy
PAT2	Proton-coupled amino acid transporter 2
P2RX5	Purinergic receptor P2X ligand-gated ion channel 5
PET	Positron emission tomography
sc-seq	Single-cell sequencing technology
scATAC-seq	Single-cell assay for transposase-accessible chromatin using sequencing
scDNA-seq	Single-cell DNA sequencing
scEpi-seq	Single-cell epigenome sequencing
scRNA-seq	Single-cell RNA sequencing
SCP	Single-cell proteomics
snmC-seq	Single-nucleus methylome sequencing
snRNA-seq	Single-nucleus RNA sequencing
T2DM	Type 2 diabetes mellitus
WAT	White adipose tissue

Introduction

Adipose tissue (AT) is a complex and dynamic organ that plays crucial roles in energy homeostasis and metabolic health. It is composed of adipocytes and a stromal vascular fraction with cells containing a heterogeneous population, including pre-adipocytes, mesenchymal, progenitor, and immune cells such as T cells and macrophages [1, 2]. AT secretes adipokines, cytokines/chemokines, and vasoactive molecules with systemic and local effects. Dysregulation of these bioactive molecules due to obesity contributes to a cascade of metabolic disorders, including type 2 diabetes mellitus (T2DM), hypertension, cardiopathy, atherosclerosis, and cancer [3–6].

Recent technological advances have transformed our understanding of AT involvement in endocrine processes, metabolic regulation, immunity, and its interactions with other organs. Single-cell sequencing provides detailed information about AT cellular composition and how individual cells respond to various conditions, such as obesity, insulin resistance, or inflammatory signals [7]. Multi-omics technologies, including genomics, transcriptomics, epigenomics, and metabolomics, provide insights into the complexity of the molecular pathways and interactions that contribute to the overall function of AT [8]. *In vivo* imaging offers a real-time and non-invasive look into AT distribution, the mechanisms behind AT dysfunction, and the efficacy of potential treatments. With the combination of artificial intelligence (AI) and machine learning (ML) technologies, these techniques can revolutionize the future of AT research [9, 10].

AI, as a subfield of computer science, is anticipated to be a promising tool in future medicine and healthcare. The digitalization of healthcare combined with AI-driven devices and ML algorithms has transformed medical practice, improving clinical data management, disease diagnosis, risk assessment, disease prevention, and drug

discovery. AI has shown remarkable success in dissecting the complexities associated with AT using automated information retrieval from large-scale magnetic resonance imaging (MRI), computed tomography (CT) scans, and multi-omics data. This system reduces human error, improves predictions, and enhances clinical outcomes for AT dysfunction [11, 12]. ML models trained on multi-omics data can identify biomarkers and novel molecular pathways associated with inflammation, immune response, adiposity, and cardiovascular diseases (CVD), which can predict risk assessment, patient outcomes, and treatment plans for metabolic diseases and CVD [13].

This chapter summarizes the transformative impact of modern technology in AT research and presents new insights into the importance of targeting AT in clinical practice.

Single-Cell Sequencing in Adipose Tissue Research

Before the high-throughput sequencing era, researchers used fluorescent-activated cell sorting (FACS) to study AT heterogeneity. This method of identifying different cell types within AT is based on the presence or absence of specific cell surface markers. The sorted cells were then propagated and analyzed using downstream analyses. The cell surface markers used for white, brown, and beige adipocytes were alanine serine cysteine transporter 1 (ASC-1), proton-coupled amino acid transporter 2 (PAT2), and purinergic receptor P2X ligand-gated ion channel 5 (P2RX5), respectively [14]. Adipose stem and progenitor cells (ASPC) were sorted based on a specific combination of cell surface markers (Lin⁻/CD34⁺/CD29⁺/SVA1⁺/CD24⁺) [15]. Lineage tracing via Cre-recombinase has been employed to identify adipocyte precursors and characterize mature adipocytes within murine white AT (WAT) [16]. However, the lack of single markers limits the use of FACS and lineage-based strategies for identifying APSC heterogeneity.

Microarray analysis was the first high-throughput genomic method used to identify differentially expressed genes in distinct samples, a technology that significantly advanced drug development and basic research [17, 18]. However, because it relies on preset probes for a specific set of genes, its capacity to detect all genes and/or non-coding RNAs is limited. Next-generation sequencing (NGS) technologies, which emerged within the last two decades, addressed this limitation. Early NGS primarily focused on bulk RNA sequencing of whole tissues or isolated cell populations and could not identify distinct cell subsets [19].

To overcome the limitations of bulk RNA sequencing, single-cell transcriptome sequencing (scRNA-seq) was developed as the first single-cell sequencing technology (sc-seq) [20–22]. It provides detailed information about the variations between different cell clusters and facilitates the study of various cell-to-cell interactions. scRNA-seq is an effective method for exploring the cellular composition and dynamics of the stromal cells in AT. It offers comprehensive insights into cellular identities, gene expression profiles, and changes in cellular states under both normal and pathological conditions. Even more, scRNA-seq can help characterize cellular responses by identifying specific pathways modulated in the process [23]. Zheng

et al. [24] utilized scRNA-seq to reveal the heterogeneity among mesenchymal stem cells (MSCs), immune cells, mesothelial cells, and endothelial cells in WAT, which are crucial in maintaining AT homeostasis and influencing disease development.

Although a promising technique, scRNA-seq has several limitations that must be considered. These include prolonged enzymatic treatment involved in the cell isolation protocol, which may modify the gene expression profile of sensitive cells. Additionally, difficulties arise in isolating cells on the same day as tissue extraction, particularly with large human and animal tissue samples. Moreover, mature adipocytes often prove too large for effective analysis using scRNA-seq. These major challenges with scRNA-seq can be effectively overcome by utilizing single-nuclei RNA sequencing (snRNA-seq) [25–27]. snRNA-seq can be performed on fresh or frozen tissue samples and is not dependent on the enzymatic digestion of tissue to obtain single viable cells [28–30]. Since nuclei are much smaller than whole cells, using snRNA-seq makes it easier to identify the nuclei of all cell types, including larger cells such as adipocytes and neurons.

Another single-cell technique, single-cell proteomics (SCP), has enabled a thorough and extensive examination of protein expression at an individual cell level, which can provide even more detailed knowledge into AT heterogeneity, functional states, and disease mechanisms. Various types of SCP, including bottom-up and top-down proteomics, allow analyses of protein interactions, signaling pathways, and post-translational modifications [31], thus potentially revolutionizing AT research and identifying novel biomarkers and therapeutic targets. Other techniques within sc-seq and omics analyses include single-cell genome sequencing (scDNA-seq), single-cell epigenome sequencing (scEpi-seq), single-cell sequencing assay for transposase-accessible chromatin (scATAC-seq), and single-nucleus methylome sequencing (snmC-seq), among others [32]. With this new technology, it is possible to profile the AT at a single-cell level, which helps to better understand the cellular and molecular landscape of AT structure, heterogeneity, and function [33, 34].

Multi-omics Analyses in Adipose Tissue Research

Recent technological developments in high-throughput sequencing and mass spectrometry enabled researchers to perform integrative multi-omics analyses, combining data from genomics, transcriptomics, proteomics, metabolomics, epigenomics, and microbiota studies.

Genomics has opened up a new range of opportunities for identifying genetic variants that influence AT development and function [35]. The corresponding gene expression profiles indicative of critical regulators and pathways for adipogenesis, metabolism, and inflammatory response are identified by transcriptomics [36]. Proteomics is a high-throughput molecular tool for describing protein expression patterns, thus identifying the major functional proteins that may be involved in various metabolic processes [37]. Metabolomics provides the platform for analyzing a wide array of small molecules involved in adipocyte metabolic pathways and lipid

metabolism [38]. Epigenomics focuses on DNA methylation and histone modifications and their effect on gene expression and AT phenotype [39, 40]. Finally, microbiota analyses explore the interactions between the gut microbiome and AT that have an impact on metabolic health and inflammation [41, 42]. Multi-omics analyses allow scientists to analyze complex biological data and find novel correlations between different molecular layers within the AT. These new perspectives can lead to a better understanding of the AT function and its role in metabolic health and diseases.

Through the multi-omics approach by proteomic/transcriptomic analysis of visceral and subcutaneous pig AT, researchers revealed several depot-specific dysregulations of proteins involved in glucose and lipid metabolism as a response to energy stress, such as insulin deficiency or hyperglycemia [43]. Another study has combined transcriptomics, non-coding RNAomics (miRNAomics), and epigenomics to investigate the aging-related changes in the subcutaneous AT composition, structure, and function of female individuals [44]. In addition, Yang et al. [45] carried out transcriptomic/metabolomic analyses and revealed distinct patterns of differentially expressed genes and metabolites between adipose-derived mesenchymal stem cells (ASCs) from various sites, including subcutaneous, perirenal, and epididymal AT. These multisite ASCs exhibit diversity in gene expression and metabolite profiles, which may have potential relevance in associated diseases. Moreover, Si et al. [46] provided a detailed molecular profile of how air pollution affects AT, lipid metabolism, and mitochondrial function in mice by conducting metabolomic, lipidomic, and transcriptomic analyses.

In-depth analysis of multi-omics data sets is essential for advancing research on AT. It is an effective approach for uncovering novel therapeutic targets for obesity, T2DM, and other metabolic diseases.

***In Vivo* Imaging and Visualization of Adipose Tissue**

In vivo imaging involves several advanced techniques that allow a non-invasive observation of AT in living organisms for research or diagnostic purposes. Key *in vivo* imaging methods include positron emission tomography (PET), magnetic resonance imaging (MRI), computed tomography (CT), ultrasound imaging, and near-infrared spectroscopy (NIRS), among others. They provide valuable information about the distribution, dynamics, function, and metabolic activity of AT.

One particularly effective approach for imaging AT involves a combination of PET and CT. While PET depends on the emission of positrons from isotope-labeled molecules, CT utilizes X-rays to create images based on differences between tissue densities. This combination of techniques allows the capture of distinct metabolic changes within the body. As AT is less dense, it has specific X-ray attenuation properties, allowing for visualization using CT scans [47]. At the same time, PET imaging highlights areas of high metabolic activity using radiotracers, such as 2-deoxy-2-[18F]-fluoro-D-glucose (18F-FDG) [48]. Using the PET/CT technique,

researchers have identified brown AT (BAT) depots in the body and established correlations between their presence and variables including age, BMI, and glucose levels [49–51]. However, both PET and CT techniques are radiation-based, limiting their use. To address this concern, alternative radiation-free methods, such as MRI, are gaining attention. MRI relies on differences in the resonance frequencies of water and fat protons in a magnetic field, which allows for a cost-effective capturing of images of soft tissues at any anatomical angle. MRI is an effective method for visually distinguishing between WAT and BAT based on the difference in the water and fat content of these tissues [52].

Apart from the techniques described above, other imaging techniques are also efficient for exploring AT. These techniques include infrared thermography imaging (IRT), near-infrared spectroscopy (NIRS), near-infrared time-resolved spectroscopy (NIRTRS), contrast ultrasound (CU), Cerenkov luminescence imaging (CLI), and ultrasonography. IRT employs infrared-sensitive cameras to evaluate temperature distribution patterns and detect BAT by monitoring skin temperature, mainly in the interscapular region [51, 53]. NIRS relies on the varying absorption of oxy- and deoxyhemoglobin and offers a method for assessing tissue oxygen perfusion in highly vascularized BAT [54]. NIRTRS enables the analysis of BAT activity by measuring hemoglobin concentration and mitochondrial density. Similarly, CU can detect BAT activation by detecting its heat patterns and blood flow. In conjunction with standard optical imaging instruments, CLI is a quicker and less expensive replacement for PET imaging [55].

Raman spectroscopy is a powerful and non-invasive tool for exploring AT anatomy and physiology. Its method is based on measuring the inelastic scattering of light by molecules with a laser source providing the necessary excitation light. Compared to the other techniques discussed above, Raman spectroscopy has the least interference from water and has proven to be very efficient in tracking the distribution and composition of lipid droplets within cells [56, 57]. This technique can successfully visualize subcutaneous AT; however, it might be challenging for deeper AT depots such as perivascular or visceral AT [58].

In recent years, the outdated view of AT as a mere passive energy storage and insulator has already been reassessed. Modern physiology recognizes AT as a crucial endocrine organ with a significant role in actively regulating metabolic processes. This new understanding has profound implications in clinical imaging. Existing techniques must be re-evaluated to meet current demands, and new methods need to be developed to provide even more detailed insights into AT's role at various levels of granularity [59]. Moreover, high throughput techniques and *in vivo* imaging generate a vast amount of data that requires accurate interpretation. The incorporation of advanced computational approaches such as AI and ML aids researchers in efficiently processing and analyzing multi-omics and imaging data. In the following section, we will explore the advantages of AI and ML in AT research.

Artificial Intelligence and Machine Learning in Adipose Tissue Research

AI involves the development of computer systems capable of performing tasks that typically require human intelligence by utilizing algorithms, data, and computing power. ML is a subset of AI that can analyze large-scale data and extract features to improve over time as it is exposed to more data. ML can be further categorized as either supervised or unsupervised. As the name suggests, in supervised ML, the algorithm trains itself when exposed to input data with designated output labels. In unsupervised ML, the algorithm trains itself without any labels entered into the algorithm and finds hidden features in the data. Another subset of AI, deep learning (DL), involves artificial neural network algorithms that can handle structured data without human intervention and learn and predict high-level abstractions in the data. DL models can be 1D or 2D, as applied in image analyses [11, 12].

AI and ML are powerful tools for studying the physiology and molecular etiology of AT. They have proven extremely useful in analyzing high-throughput data from genomic, transcriptomic, proteomic, epigenomic, and metabolomic studies. AI and ML can help identify subtle changes in gene or protein expression and identify indistinct patterns and correlations that may evade human analyses [13]. Investigating multi-omics data through AI models leads to discovery of novel biomarkers and developing targeted therapeutics by identifying the molecular pathways involved in metabolic diseases, T2DM, and CVD [60].

AI has rapidly integrated into medicine and healthcare and is widely used in maintaining patient records, disease management, facilitating drug discovery, and improving medical diagnostic devices. AI has accelerated disease diagnosis by automating data-intensive stages, thereby improving the accuracy of diagnoses. Recent studies have demonstrated that unsupervised ML can identify subtypes in patients with persistent atrial fibrillation based on adipocyte markers [61, 62]. Another study by Castañé et al. [63] highlighted the use of ML to identify specific lipids that serve as predictive biomarkers for non-fatty acid liver disease (NAFLD). Incorporating AI/ML algorithms and methodologies with diagnostic tools, such as MRI and CT scans, has revolutionized the field of healthcare technology, leading to accurate and precise diagnostic, therapeutic, and decision-making processes. Body composition imaging is a breakthrough concept in quantifying AT segmentation. Manual segmentation analyses are tedious and time-consuming, whereas AI has automated this process with precision and accuracy [64]. In addition to their role in data analyses, disease diagnosis, and risk prediction, AI and ML are highly effective in personalizing healthcare and therapy planning. Personalized medicine empowers healthcare providers to tailor treatment approaches, recommend accurate medications and dosages, and improve diagnostic accuracy across all diseases, including AT-related disorders [65].

Recent technological advancements have improved the real-time monitoring of body parameters using advanced sensors available in wearable forms, such as

smartwatches. They can easily record personalized data in real-time, including BMI, oxygen level, heart rate, and fat proportion. In this regard, AI helps clinicians deliver personalized lifestyle interventions such as behavioral, physical, or nutritional modifications to prevent AT-related diseases [66, 67]. Thus, AI has immense potential to revolutionize personalized healthcare for individuals with AT-related conditions, including obesity, using advanced data-driven computational techniques and predictive analytics.

Although AI has successfully advanced the fields of medicine and healthcare, it is still associated with several significant challenges. The biggest challenges are the lack of high-quality data, risks of bias in data interpretation, and ethical and regulatory issues associated with healthcare [68]. As the field evolves, AI and other advancements in AT research are expected to increase their contribution to improving patient outcomes, diagnostic accuracy, treatment efficacy, and overall understanding of metabolic diseases and related conditions.

Clinical Trials on Adipose Tissue Reduction

The AT has a major role in various biological processes, including energy storage, hormone secretion, and metabolic regulation. However, excessive accumulation of AT, especially visceral AT, is linked with multiple metabolic disorders such as obesity, T2DM, CVD, and cancer [4, 69]. The growing prevalence of these conditions highlights the urgent need for effective strategies and therapies to reduce excessive AT and its negative impact on health that focus on weight loss and prevention of weight regain. To achieve this, both lifestyle and pharmacotherapeutic interventions are being evaluated in ongoing clinical trials, which are summarized in Table 7.1.

Conclusion

Recent technological advancements have revealed the dynamic nature of AT and highlighted their important role in elucidating the complex cellular and molecular mechanisms that support its function. Cutting-edge technologies such as single-cell sequencing and multi-omics analyses are crucial for understanding the role of AT in metabolic diseases such as obesity and T2DM. Applying innovative methods in AT research provides deeper understanding and potential identification of novel diagnostic biomarkers and therapeutic targets.

Integrating various imaging techniques has significantly advanced our knowledge on AT far beyond its traditional role as a passive energy reservoir. These techniques are essential for developing a broad perspective of AT's anatomy and physiology, revealing its active role in metabolic regulation.

Table 7.1 List of completed (phases 3 and 4) and ongoing (recruiting in phases 1, 2, 3, and 4) clinical trials related to AT reduction

ClinicalTrials.gov ID	Official title	Condition	Intervention/treatment	Phase	Status
NCT03241563	A Randomized, Double-blind Comparison Trial of Subcutaneous Sodium Deoxycholate Injections With or Without Triamcinolone for Reduction of Submental Fat	Fat reduction	Drugs: Sodium Deoxycholate, Triamcinolone	4	Completed
NCT04897867	CoolSculpting® Elite: Multi-Country Study to Evaluate Patient Satisfaction for Non-Invasive Fat Reduction in Abdomen, Flanks, Upper Arms, Inner Thighs, Outer Thighs and Submental Area	Non-invasive fat reduction	Device: CoolSculpting® Elite System with CoolSculpting® Elite applicators	4	Completed
NCT03510598	Fat Reduction in the Submental Area –a Sequential Treatment Approach With CoolMini and KYBELLA®	Body fat disorder	Device: The ZELTIQ CoolSculpting System Drug: Kybella 20 mg in 2 mL injection	4	Completed

(continued)

Table 7.1 (continued)

ClinicalTrials.gov ID	Official title	Condition	Intervention/treatment	Phase	Status
NCT02163902	A Multicenter, Double-blind, Nontreatment, Long-term Follow up Study of Subjects Who Completed ATX-101 (Deoxycholic Acid Injection) Clinical Trials ATX-101-11-22 or ATX-101-11-23 for the Reduction of Localized Subcutaneous Fat in the Submental Area	Submental fat: Healthy	Drug: ATX-101	3	Completed
NCT02123134	A Multicenter, Double-blind, Placebo-controlled Safety Study of ATX-101 (Deoxycholic Acid) Injection for the Reduction of Localized Subcutaneous Fat in the Submental Area in Subjects 65 to 75 Years of Age	Moderate to severe convexity of submental fat: safety, efficacy	Drug: ATX-101	3	Completed
NCT02035267	A Multicenter, Double-blind, Placebo-controlled Safety Study of ATX-101 (Deoxycholic Acid) Injection for the Reduction of Localized Subcutaneous Fat in the Submental Area in Subjects With Clinician-Reported Submental Fat Rating Scale (CR-SMFRS) Grade 1 or CR-SMFRS Grade 4	Moderate to severe convexity of submental fat: safety, efficacy	Drug: Deoxycholic acid	3	Completed

(continued)

Table 7.1 (continued)

ClinicalTrials.gov ID	Official title	Condition	Intervention/treatment	Phase	Status
NCT02010359	Omega-3 PUFA Suppress Adipochemokines	Obesity	Drug: Lovaza	4	Completed
NCT03849729	Effectiveness and Tolerability of Phentermine in the Reduction of Intrahepatic Fat Infiltration, Adipose Tissue and Postoperative Complications in Patients Under Bariatric Surgery	Obesity, morbid obesity, bariatric surgery, non-alcoholic fatty liver, weight loss	Drug: Phentermine	4	Completed
NCT00299325	A Randomized, Double Blind, Two-arm Placebo Controlled, 12-Month Study of the Effects of Rimonabant 20 mg Once Daily on the Amount and the Activity of Visceral Fat in Abdominally Obese Patients With Metabolic Syndrome	Metabolic syndrome	Drugs: Rimonabant, Placebo (for Rimonabant) Other: Mild hypocaloric diet	3	Completed
NCT00147264	A Randomized, Double Blind, 2X2 Factorial Design Study to Evaluate the Effects of Telmisartan vs. Placebo, and of a Low-Glycemic Diet vs. Control Diet, in Reducing Intra-Myocellular Lipids In Individuals With Abdominal Obesity	Metabolic syndrome X	Drug: Telmisartan (Micardis®) vs. Placebo Behavioral: Low-Glycemic Index Diet vs. Control Diet	3	Completed

(continued)

Table 7.1 (continued)

ClinicalTrials.gov ID	Official title	Condition	Intervention/treatment	Phase	Status
NCT01305577	Phase 3, Multicenter, Randomized, Double-blind, Placebo-controlled Study of ATX-101 (Sodium Deoxycholate Injection) Versus Placebo for the Reduction of Localized Subcutaneous Fat in the Submental Area	Moderate or severe submental fullness	Drug: Deoxycholic acid injection	3	Completed
NCT01294644	Phase 3, Multicenter, Randomized, Double-blind, Placebo-controlled Study of ATX-101 (Sodium Deoxycholate Injection) Versus Placebo for the Reduction of Localized Subcutaneous Fat in the Submental Area	Moderate or severe submental fullness	Drug: Deoxycholic acid injection	3	Completed
NCT01426373	Multicenter, Open-label Study of ATX-101 (Sodium Deoxycholate Injection) for the Reduction of Localized Subcutaneous Fat in the Submental Area	Moderate or severe submental fullness	Drug: Deoxycholic acid injection	3	Completed
NCT02397499	A Multi-Center, Randomized, Double-Blinded, Placebo-Controlled Study Evaluating the Safety and Efficacy of LIPO-202 for the Reduction of Central Abdominal Bulging Due to Subcutaneous Fat in Non-Obese Subjects	Central abdominal bulging	Drug: LIPO-202	3	Completed

(continued)

Table 7.1 (continued)

ClinicalTrials.gov ID	Official title	Condition	Intervention/treatment	Phase	Status
NCT02398188	A Multi-Center, Randomized, Double-Blinded, Placebo-Controlled Study Evaluating the Safety and Efficacy of LIPO-202 for the Reduction of Central Abdominal Bulging Due to Subcutaneous Fat in Non-Obese Subjects	Central abdominal bulging	Drug: LIPO-202	3	Completed
NCT00353054	A Double-Blind, Randomized, Placebo Controlled, Parallel Group Study to Evaluate the Effect of Calcium/ Vitamin D Supplementation (Caltrate 600+ D) on Body Weight and Fat Loss in Overweight and Obese Individuals on a Weight-Reducing Program	Obesity, overweight	Drug: Caltrate® 600 + D Behavioral: Weight loss intervention	4	Completed
NCT01546142	Multicenter, Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study of ATX-101 (Sodium Deoxycholate Injection) Versus Placebo for the Reduction of Localized Subcutaneous Fat in the Submental Area	Moderate or severe submental fullness	Drug: Deoxycholic acid injection	3	Completed

(continued)

Table 7.1 (continued)

ClinicalTrials.gov ID	Official title	Condition	Intervention/treatment	Phase	Status
NCT01542034	Multicenter, Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study of ATX-101 (Sodium Deoxycholate Injection) Versus Placebo for the Reduction of Localized Subcutaneous Fat in the Submental Area	Moderate or severe submental fullness	Drug: Deoxycholic acid injection	3	Completed
NCT01423617	Double-blind, Randomized, Placebo-controlled, Bicentric Study to Evaluate the Safety and Efficacy of Xenitol in Reducing Body Weight of Overweight Subjects	Overweight	Dietary Supplement: Xenitol	3	Completed
NCT04142749	A Multi-center, Randomized, Double-blind, Placebo-controlled, Parallel, Phase III Clinical Trial to Evaluate the Efficacy and Safety of Oltipraz	Non-alcoholic fatty liver disease	Drug: Oltipraz	3	Completed
NCT03361176	A Randomized, Double-blind, Dose-ranging Trial of Subcutaneous Sodium Deoxycholate Injections With or Without Low Dose Triamcinolone and Low Dose Lidocaine for Reduction of Submental Fat With Reduction of Pain and Swelling	Adiposity	Drug: Injectable sodium deoxycholate Combination Product: Injectable sodium deoxycholate with Triamcinolone acetate	4	Completed

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Table 7.1 (continued)

ClinicalTrials.gov ID	Official title	Condition	Intervention/treatment	Phase	Status
NCT01407393	Double-blind, Randomized, Placebo-controlled, Bicentric Clinical Investigation to Evaluate Safety and Efficacy of Glucosanol in Reducing Body Weight in Overweight and Obese Subjects	Overweight and obesity	Device: Glucosanol	4	Completed
NCT02068339	A Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel Phase 3 Clinical Trial to Evaluate the Efficacy and Safety of Oltipraz for Liver Fat Reduction in Patients With Non-Alcoholic Fatty Liver Disease Except for Liver Cirrhosis	Non-alcoholic fatty liver disease	Drugs: Oltipraz (90 mg and 120 mg)	3	Completed
NCT02007434	A Single Center, Double-blind, Parallel-group, Two Factor Patient-Experience Management Study of ATX-101 (Deoxycholic Acid Injection) for the Reduction of Localized Subcutaneous Fat in the Submental Area	Moderate or severe submental fullness	Drugs: Deoxycholic Acid Injection, Lidocaine/Epinephrine, Loratadine, Ibuprofen Other: Cold Compression chin strap	3	Completed

(continued)

Table 7.1 (continued)

ClinicalTrials.gov ID	Official title	Condition	Intervention/treatment	Phase	Status
NCT01233349	Double-blind, Randomized, Placebo-controlled, Bicentric Clinical Investigation to Evaluate Safety and Efficacy of Litramine TM in Reducing Body Weight in Overweight and Obese Subjects	Overweight, obesity, weight loss	Device: Litramine	3	Completed
NCT03877406	Decrease in Body Fat and Increase in Ketone Body After 6-month Treatment of Empagliflozin in Korean Patients With Type 2 Diabetes	Diabetes Mellitus Fat; Intolerance, Pancreas	Drug: Empagliflozin (10 mg), Hypoglycemics Oral	4	Recruiting
NCT06256445	A Multicenter, Randomized, Double-blind, Placebo-controlled, Phase III Clinical Study to Evaluate Efficacy and Safety of AYP-101 for the Reduction of Submental Fat in Adults	Healthy	Drug: Polyene phosphatidylcholine	3	Recruiting
NCT06005441	A Phase 2b, Randomized, Placebo-Controlled Factorial Study to Evaluate the Efficacy, Safety and Tolerability of CBL-514 Injection Compared With CBL-A1 and CBL-A2 for Reducing Abdominal Subcutaneous Fat	Subcutaneous fat	Drugs: CBL-514 injection, CBL-A1 Injection, CBL-A2 Injection	2	Recruiting

(continued)

Table 7.1 (continued)

ClinicalTrials.gov ID	Official title	Condition	Intervention/treatment	Phase	Status
NCT04392206	A Phase I, Open Label Study of Allogeneic Adipose Derived Mesenchymal Stem Cells in Reducing Anastomotic Stenosis in Primary Arteriovenous Anastomoses	End-stage renal disease	Drug: Adipose Derived Mesenchymal Stem Cells	1	Recruiting

The transformative impact of AI, particularly through ML and DL, is evident in medicine and healthcare. AI improves patient outcomes, diagnostic accuracy, treatment efficacy, and the overall understanding of metabolic diseases by analyzing large-scale, high-throughput data from various omics studies.

Finally, the importance of ongoing clinical trials on AT reduction lies in their potential to advance the medical knowledge and treatment options for obesity and related conditions. These trials evaluate the effectiveness of new interventions and provide valuable data for improving existing therapies, thus enhancing the quality of life and addressing the global health challenge of obesity.

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Chapter 8

Targeting Adipose Tissue: Therapeutic Strategies and Future Directions



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Abbreviations

AAV	Adeno-associated virus
Ad	Adenovirus
ATM	Adipose tissue-derived macrophage
AT-MSC	Adipose tissue-derived mesenchymal stem cells
BAT	Brown adipose tissue
BMI	Body mass index
cfDNA	Cell-free DNA
CNS	Central nervous system
CPT1	Carnitine palmitoyltransferase 1
CVD	Cardiovascular disease
DA	Dopamine
DRG	Dorsal root ganglion
ECM	Extracellular matrix
EMA	European Medicines Agency
ER	Extended-release
FDA	Food and Drug Administration
FFA	Free fatty acid
GIPR	Gastric inhibitory polypeptide receptor
GWAS	Genome-wide association studies
HFD	High-fat diet
KSR2	Kinase suppressor of Ras 2
MAOI	Monoamine oxidase inhibitor
MC4R	Melanocortin 4 receptor
NE	Norepinephrine
NK	Natural killer (cell)
PDGF	Platelet-derived growth factor
OPA1	Optic atrophy 1
PET	Positron-emission tomography
PM	Precision medicine
PRIME	Priority Medicines
SAT	Subcutaneous adipose tissue
SNS	Sympathetic nervous system
SR	Sustained-release
T2DM	Type 2 diabetes mellitus
TNF α	Tumor necrosis factor-alpha
UCP1	Uncoupling protein-1
VEGF	Vascular endothelial growth factor
WAT	White adipose tissue

Introduction

Self-awareness of the dangers of being overweight and maintaining a healthy lifestyle are the ideal strategies for combating obesity. Lifestyle intervention, pharmacotherapy, and bariatric surgery are the primary treatments of obesity [1]. Nevertheless, comprehensive therapies should be aligned with severe obesity coexisting with chronic diseases such as lipodystrophies, metabolic syndrome, insulin resistance, type 2 diabetes mellitus (T2DM), and cardiovascular disease (CVD). Based on the recent advances in understanding the pathogenesis of obesity-induced chronic diseases, recent research focuses on the intercellular networks of adipose tissue linking the disorders of immunometabolism with energy storage. These findings are essential for the development of new therapeutic strategies targeting adipose tissue.

There is still unmet need for the effective treatment of these obesity-related metabolic disorders. Therefore, in-depth and comprehensive analysis of the underlying mechanisms is crucial for designing innovative approaches. In this chapter, we summarize the gaps in the current understanding of adipose tissue pathophysiology and provide insights into the potential therapies for metabolic disorders that target adipose tissue.

Current Therapeutic Strategies

Severe overweight is associated with chronic metabolic diseases. Approaches to weight control that are synchronously beneficial for compromising chronic metabolic diseases are needed. The main existing therapeutic strategies and clinical practice guidelines for managing adipose tissue-related conditions are lifestyle interventions, pharmacological treatments, and bariatric surgery [2].

Lifestyle Interventions

Lifestyle interventions as the preferred obesity management include dietary and activity modifications with minimal side effects and socio-economic burden [3]. Low-calorie diets and increased daily activities are tailored to individuals with obesity [4]. High-intensity lifestyle interventions result in a mean weight loss of 5–8%, and approximately 60% of participants have more than 5% weight loss compared to their initial weight within 1 year [2]. High-intensity lifestyle interventions demonstrated similar results compared to joint intervention with pharmacotherapy and low-to-moderate-intensity lifestyle [2]. Histological analysis has shown improved mitochondrial biogenesis, decreased adipocyte size and lipid content, and low-grade inflammation in white adipose tissue (WAT) under dietary and exercise

interventions [5]. In addition, lifestyle interventions revive metabolic homeostasis and reduce the incidence of T2DM by 58% in obesity, which overrides the 31% reduction with metformin treatment [6]. Nevertheless, it is a challenge to persistently adhere to lifestyle interventions without achieving the desired effect of reducing body mass.

Pharmacological Treatments

Pharmacotherapy is indicated adducting with lifestyle interventions when an individual has a body mass index (BMI) ≥ 30 kg/m² or BMI ≥ 27 kg/m² + at least one comorbid condition, such as diabetes mellitus, hypertension, hyperlipidemia, or sleep apnea [4].

The Food and Drug Administration (FDA) criteria for new drug approvals should strictly follow the guidelines: placebo-adjusted weight loss >5% at 1 year or >35% of patients achieving weight loss >5% (which must be at least twice that induced by placebo), additionally showing evidence of metabolic improvements including blood pressure, lipid content, and glycemia [7]. Currently, the major FDA-approved anti-obesity medications include orlistat, lorcaserin, liraglutide (the only injectable formulation), phentermine/topiramate extended-release (ER), and naltrexone sustained-release (SR)/bupropion SR [7] (Table 8.1). Orlistat, a pancreatic and gastric lipase inhibitor, results in fat malabsorption and a net energy absorption disorder [8]. Lorcaserin, a 5-HT_{2c} (5-hydroxytryptamine receptor 2C) agonist, induces satiety to dampen food intake [9]. Liraglutide is a GLP1 receptor agonist that delays gastric emptying and inhibits food intake [10]. Phentermine, the most widely prescribed anti-obesity medication, was approved by the FDA in 1959 for ages >16 years [11]. Phentermine is a sympathomimetic amine that reduces appetite and food consumption. However, the prescription of phentermine is limited for short-term use (≤ 90 days) owing to its potential adverse effects [11]. Either phentermine/topiramate ER, a combination of sympathomimetic amine and ER antiepileptic drug, or naltrexone SR/bupropion SR, a combination opioid antagonist and amino-ketone antidepressant, acts on the central nervous system (CNS) to cumulatively suppress food intake [12]. Clinical trials for three monotherapies (orlistat, lorcaserin, and liraglutide) and two combined medications (phentermine-topiramate and naltrexone-bupropion) showed approximately 5–10% weight loss compared to the initial body weight within 1 year trials [2]. However, every anti-obesity medication has contraindications and common adverse effects, which are concerns for physicians recommending pharmacotherapy, especially for the long-term use of weight-loss medications.

Table 8.1 Current anti-obesity medications

Drug (Trade name)	Mechanisms of action	Administration	Contraindications	Adverse effects
Orlistat (Xenical, Alli)	Inhibits gastric and pancreatic lipases to reduce intestinal fat digestion	120 mg orally before meals, three times daily	Malabsorption syndrome, cholestasis, pregnancy	Flatulence, bloating, diarrhea
Lorcaserin (Belviq)	Activates hypothalamic neurons through 5-hydroxytryptamine receptor 2C to promote satiety	10 mg orally twice daily or 20 mg once daily	Pregnancy	Headache, dizziness, fatigue, dry mouth, constipation, upper respiratory tract-like symptoms; hypoglycemia in patients with diabetes
Liraglutide (Saxenda)	GLP-1 receptor agonist. Reduces appetite	Starting dose 0.6 mg, increased weekly by 0.6 mg to a maximum of 3.0 mg subcutaneously once daily	Family or personal history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2, pregnancy	Nausea, hypoglycemia, diarrhea, constipation, vomiting, headache, decreased appetite, dyspepsia, abdominal pain, fatigue, dizziness, increased lipase levels
Phentermine– topiramate (Qsymia)	Sympathomimetic amine, anorectic and ER antiepileptic drug. Suppresses food intake and increases energy expenditure	Starting dose 3.75 mg/23 mg for 2 weeks, recommended dose 7.5 mg/46 mg, maximum dose 15 mg/92 mg	Glaucoma, hyperthyroidism or monoamine oxidase inhibitors (MAOIs) used within 14 days, hypersensitivity to sympathomimetic amines, pregnancy	Insomnia, dry mouth, constipation, paresthesia, dizziness, dysgeusia
Naltrexone– bupropion (Contrave, Mysimba)	Opioid receptor antagonist, dopamine (DA) and norepinephrine (NE) reuptake inhibitor. Increases energy expenditure and suppresses food intake	One tablet (8 mg Naltrexone/90 mg of bupropion) daily for 1 week, dose increased by one tablet per day weekly, maximum 2 tablets twice a day at week 4	Uncontrolled hypertension, seizure disorders, anorexia nervosa or bulimia, chronic opioid use, MAOIs used within 14 days, alcohol or drug withdrawal, pregnancy	Nausea, constipation, headache, vomiting, dizziness, dry mouth, diarrhea

Bariatric Surgery

Bariatric surgery is more effective than lifestyle and pharmacological interventions in weight loss for long-term survival [13, 14]. It is considered for individuals with BMI ≥ 40 kg/m² or BMI ≥ 35 kg/m² + risk factors when other weight-loss attempts have failed [4]. For the Asian population, the BMI thresholds for bariatric surgery should be adjusted to BMI ≥ 27.5 kg/m² [15]. There are three standard surgical techniques: restrictive procedures for food limitation, such as gastric bypass sleeve gastrectomy; operations limiting the absorption of food calories (such as biliopancreatic diversion); and combined operations (such as biliopancreatic diversion with duodenal or distal gastric bypass) [16]. The laparoscopic technique is regarded as the first choice for bariatric surgery because of its safety and lower risks of complications [17]. The mechanisms are ill-defined, except for restriction of food intake, malabsorption of food calories, enhanced metabolic rate, increased satiety, heightened activities of other gastrointestinal hormones, elevated circulating bile acids, and tuned gut microbiome activities [18]. Weight loss can reach approximately 25% of the initial body weight within one-year post-surgery. Although bariatric surgery improves the quality of life [19], there are still several limitations, including high costs, risks of short/long-term complications, and weight regain in approximately 5–20% of patients [2].

Adipose Tissue as a Potential Therapeutic Target

Adipose tissue-secreted adipokines are crucial regulators of numerous physiological processes, including energy storage and release, lipid metabolism, glucose homeostasis, and thermogenesis. Recent research findings suggest potential targets within adipose tissue as therapeutic interventions for metabolic homeostasis, insulin resistance, and many other related diseases.

Targeting Thermogenic Adipose Tissue

Brown adipose tissue (BAT) is characterized by high mitochondrial content and a relatively smaller capacity of fat storage compared with WAT, which has low mitochondrial content and unilocular lipid droplets [20]. BAT is responsible for non-shivering thermogenesis and energy expenditure [21]. An investigation using positron-emission tomography (PET) observed cold activation with substantial amounts of metabolic activity in BAT of healthy adults [22]. Beige adipocytes, which belong to WAT, have a thermogenic attribute like that in BAT. Although beige adipocytes contain small lipid droplets, the number of mitochondria increases after cold exposure or exercise stimulation. Activation of adipocyte thermogenesis can

promote energy balance, improve insulin sensitivity, and reduce the risk of obesity-related diseases [23]. Uncoupling protein-1 (UCP1) plays a core role in the thermogenic function of brown/beige adipocytes and directly separates mitochondrial combustion energy to produce heat [23]. BAT activation and WAT browning can be induced by cold exposure and pharmacological activation using β_3 AR agonists [24]. Of late, TGR5 agonists and FGF21 replacement therapy may be the nascent potential drugs targeting thermogenic activation in obese individuals [25]. Motivated by these findings, several strategies based on diet-induced BAT thermogenesis have been developed to enhance sympathetic nervous system (SNS) activity. Effective ingredients, such as capsaicin, capsinoids, tea caffeine, and catechins, in these foods induce thermogenesis that suppresses obesity [25].

Targeting Macrophages in Adipose Tissue

Adipose tissue-derived macrophages (ATMs) accumulate in the extracellular matrix (ECM) and actively express proinflammatory cytokines in obese individuals [26]. ATMs maintain adipose tissue homeostasis in the steady lean state, engulf dead cells, release lysosomal enzymes, and take up free fatty acids (FFAs) [27]. Adipocyte apoptosis recruits activated anti-inflammatory M2 macrophages to the adipose tissue [28]. Chronic nutrient overload in adipocytes causes excessive oxidative stress and hypoxic conditions in adipose tissue, triggering the accumulation of ATMs and an unbalanced phenotypic switch between proinflammatory M1 and anti-inflammatory M2. M2 ATMs produce the anti-inflammatory cytokine IL-10, which preserves insulin sensitivity by directly counteracting TNF [29]. Conversely, M1 ATMs produce inflammatory cytokines, including tumor necrosis factor- α (TNF α) [30]. Tipping the balance from M2 ATMs towards M1 ATMs in obesity determines the processes of several human pathologies, such as T2DM and CVD. In addition, ATMs-induced chronic low-grade inflammation can mediate tumor initiation, progression, and metastasis [31, 32]. The depletion of ATMs in obese tumor-bearing mice induces tumor necrosis and arrests tumor angiogenesis [33]. ATMs can produce a platelet-derived growth factor (PDGF) and vascular endothelial growth factor (VEGF)-family ortholog (Pvf3) to regulate energy storage in adipose tissue, and blockade of this growth factor ortholog can redirect excess lipids to thermogenesis in BAT [34]. Therefore, ATMs may be druggable targets for the clinical prevention and treatment of obesity-induced metabolic disorders.

Targeting Fibrosis in Adipose Tissue

Fibrosis usually occurs in chronic inflammation during a pathological repair process. WAT undergoes expansion with hyperplasia (formation of new adipocytes) and hypertrophy (enlargement of adipocytes), with activated inflammatory

conditions that initiate the fibrotic repair process during obesity [35]. Fibrosis is the cumulative production of stiff ECM, where dynamic remodeling is lost due to physical constraints on expansion [36]. Inhibited expression of Collagen VI, a marker of fibrosis in adipose tissue, releases the limitation of expansion in adipocytes for improved homeostasis in obese mice [37]. Although bariatric surgery could effectively reduce fat mass in obesity, WAT fibrosis cannot be reversed [38]. The investigation demonstrated that fibrosis is negatively associated with the success of bariatric surgery [39]. Eplerenone, a mineralocorticoid receptor antagonist, suppresses fibrosis in WAT. The combination of eplerenone and bariatric surgery could be a potential therapeutic approach to prevent fibrosis in obese individuals [40, 41].

Targeting Visceral and Ectopic Fat

The distribution and accumulation of ectopic adipose tissue are determinants of metabolism in lean and obese individuals [42]. Subcutaneous adipose tissue (SAT) dysfunction, such as chronic low-level inflammation and insulin resistance, limits its expandability [43]. Released FFAs lead to ectopic adipose tissue deposition, which in turn aggravates the progression of inflammation and insulin resistance and increases systemic FFA content [43]. Hepatic, epicardial, perivascular, and visceral adipose tissues contribute to atherosclerosis and cardiometabolic disease [44–46]. Re-distribution of adipose tissue by increasing the tolerability of SAT and ectopic adipose tissue browning could be an effective approach to ameliorate metabolic diseases [47, 48].

Novel Therapeutic Approaches

Advancements in adipose tissue research have revealed the cellular and molecular pathophysiology of obesity and the underlying mechanisms of its comorbidities. Motivated by these findings, novel therapeutic strategies, including gene therapy, cell-based therapies, and precision medicine, are emerging to address the global obesity epidemic.

Gene Therapy

The approaches to gene therapies include replacing (a disease gene with a healthy gene), inactivating (a disease gene), and introducing a gene [49]. Given that the gene delivered by the adeno-associated virus (AAV) does not integrate into the

patient genome with respect to low immunogenicity, stability of the viral capsid, and long-term effects in vivo, AAV is the most popular approach in clinical trials [50]. Mice with a mutation in leptin (*ob* gene) exhibit obesity and severe diabetes [51]. Subsequently, introducing the leptin gene carried by adenovirus (Ad) rescued obesity and diabetes in *ob/ob* mice [52]. AAV8, a serotype of AAVs, has been demonstrated to effectively mediate the transduction in WAT and BAT in mice, indicating that AAV8 may be an ideal tool for further studies of adipose pathophysiology and the development of therapeutic strategies [53]. For instance, the overexpression of Akt2 using AAV8 in BAT of mice achieved thermogenesis through the mTORC2-Akt2 pathway [54]. Rec2, an engineered serotype of recombinant AAV (rAAV), effectively transfects BAT by oral administration, providing a new avenue to genetically manipulate BAT function [55]. In addition, a brain-adipose circuit controls the energy expenditure in adipocytes by using AAV [56]. Adenovirus-mediated human kallistatin injection in gonadal WAT improves adipose tissue remodeling and function in high-fat diet (HFD)-fed mice [57].

Cell-Based Therapies

Cell-based therapy is defined as injecting, grafting, or implanting live cells into patients to treat or cure diseases [58]. Cell-based therapy has been successfully applied to the transplantation of allogeneic human hematopoietic stem cells for bone marrow regeneration [58]. Preclinical investigations have validated that mesenchymal stromal cell (MSC)-based therapies mitigate obesity and metabolic syndromes induced by a high-fat diet in mice [59]. Dysfunctional adipogenic precursors can be reprogrammed and induced to differentiate into beige adipocytes for use in potential cell-based therapies [60]. Using CRISPR technology to overexpress UCP1 in human white adipocytes can give rise to brown-like adipocytes that prevent diet-induced obesity and ameliorate metabolic syndrome in mice. These CRISPR-engineered human brown-like adipocytes have the potential for clinical applications in obesity and the associated metabolic syndrome [61]. Ex vivo gene therapy approaches have facilitated research on cell-based therapies and achievements in preclinical studies. Implantation of carnitine palmitoyltransferase 1 (CPT1) (a mitochondrial enzyme) in adipocytes derived from adipose tissue-derived mesenchymal stem cells (AT-MSC) improves weight loss and glucose intolerance in obese mice [62]. Natural killer (NK) cells are currently considered a new cell source for cell-based therapy of obesity-associated cancer in clinical applications [63]. With the expansion of technologies and the understanding of pathological mechanisms, we look forward to novel therapeutic strategies for clinical applications.

Precision Medicine

Precision medicine (PM) is a revolution relative to traditional medicine, including diverse aspects from diagnosis to treatment. Advances in genome sequencing technology, molecular classification of clinical markers for diagnosis and treatment, drug target design, clinical cohort studies, and biomedical big data analysis algorithms support the development of PM. For instance, under clinical assessment and molecular profiling of cancer, predicted cancer genomics can guide specific therapies for a patient [64]. The well-established and widely used sequencing plasma circulating cell-free DNA (cfDNA) technique in prenatal diagnosis has enormous potential for multiple cancer screening [65]. To date, a WAT-on-chip system provides human-based, autologous, and immunocompetent information to recapitulate tissue heterogeneity, and this system can become a tool for PM application in metabolic diseases [66]. In addition, a multicenter collaboration must define and characterize methodologies for diagnosing asymptomatic adults with immunometabolic risk [67].

Gaps in Understanding and Future Research Directions

The Gaps in our Current Understanding of Adipose Tissue Physiology and Its Clinical Implications

Basic research on adipose tissue regarding metabolic disorders in obese individuals is compelling since the obtained scientific knowledge can be applied to only a small proportion of obese patients [68]. First, most investigations are preclinical studies taken on rodents, in which the conclusions acquired need further translation into humans [69]. Second, in addition to the adipose tissue itself, metabolic interactions among multiple systems in the body should be dissected. For instance, it has been demonstrated that adipose tissue communicates with the central and peripheral nervous systems to maintain whole-body energy homeostasis [70]. Additionally, when nutrient overload activates multi-systemic inflammatory responses in the liver, musculoskeletal tissue, pancreas, and hypothalamus, individuals are subject to insulin resistance and glucose intolerance [30, 71]. However, clinical therapies mainly focus on addressing the persistent complications of obesity rather than directly targeting adipose tissue itself. Finally, current technologies for analyzing adipose metabolism, especially for metabolic mining in humans, are relatively limited. Multi-technology combinations and technological innovation are particularly necessary.

Ongoing Research in Uncovering Adipose Tissue's Complexities

We have a limited understanding of the fate of adipocytes and of how adipogenesis is governed by both internal and external signals. In addition, the adipose tissue is simultaneously an independent entity, while also contributing to a cascading multi-systemic metabolic disorder. Hence, exploration of obesity should not only encompass drawing a blueprint of whole-body fat metabolism but also regarding adipose tissue as a metabolic crossroad linking back and forth to other organs.

Neuronal Regulations

The CNS bidirectionally communicates with adipose tissue by collecting peripheral nerve information and responding to sympathetic nerve outflow [72, 73] (Fig. 8.1). More specifically, the CNS neurochemically modulates BAT sympathetic nerve activity on thermoregulation and metabolic alterations in response to cutaneous and deep body thermoreceptor signals [75]. Dorsal root ganglia (DRG) sensory neurons arrest local sympathetic function, linking the role of vagal baroreceptors in modulating blood pressure [70]. Sensory nerves also serve as essential modulators for adipose tissue

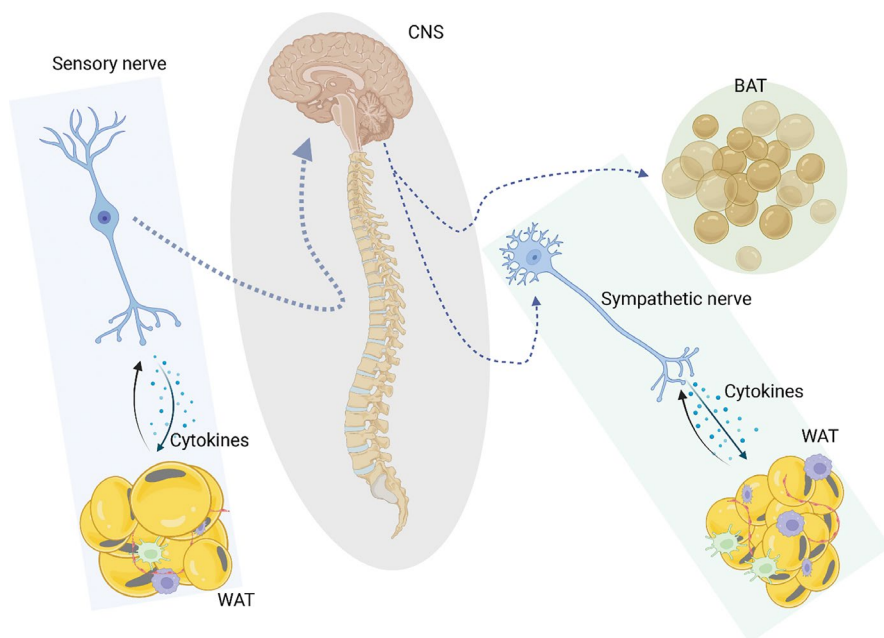


Fig. 8.1 Adipose tissue microenvironment in regulating systemic metabolism through signaling to local nerve fibers. *BAT* brown adipose tissue, *WAT* white adipose tissue, *CNS* central nervous system. (Modified after ref. [74] and created with BioRender.com)

activities and overall metabolic homeostasis [70]. Infiltrated endothelial and immune cells in adipose tissue finely tune the processes of neurotransmitter tone and blood flow with nerve fibers that favor adipose tissue browning, adipocyte activities, and energy expenditure [74]. However, using current research and measurement techniques, it is challenging to discern sequential responses in either nerve or adipose tissue building.

Immunometabolism

The joint exploration of inflammation and metabolism has led to the concept of immunometabolism, a field in which many questions remain unanswered. Activated or recruited immune cells in adipose tissues secrete a variety of cytokines that contribute to local and systemic metabolic aberrations [30]. The interconnected, often overlapping intracellular signals in inflammation pose a significant challenge to research. Both pro- and anti-inflammatory cytokines originating from the innate and adaptive immune systems contribute to unhealthy WAT conditions, including fibrosis and metabolic disorders [76, 77]. Hence, in-depth analysis of immunoregulation in obese patients must extend beyond individual cytokine interactions to encompass a broader system-level perspective [76].

Adipose Tissue Browning

Targeting brown and beige adipose tissues is a promising therapeutic strategy to increase energy expenditure and potentially address excess nutrition. [^{18}F] fluorodeoxyglucose-PET/CT and [$^{123/125}\text{I}$]-beta-methyl-p-iodophenyl-pentadecanoic-SPECT/CT imaging, used with and without thermogenesis induction, can detect thermogenically active adipose tissue areas in rodents and humans [78]. The exploration of thermogenic adipocytes provides us with a better understanding of the fundamental role of external and internal factors, including cold, exercise, central nervous system, immune system, hormones, metabolites, and alternatively activated cells, in regulating and inducing adipose tissue browning. However, the physiological mechanisms involved in brown and beige adipose tissues remain unclear in humans.

Potential Future Research Directions

Neuronal Regulations

The brain picks up peripheral information via electrical signals or adipose tissue-secreted cytokines and subsequently returns integrated signals to adipocytes through the noradrenergic sympathetic pathway [70]. To date, substantial unmet needs still

exist to achieve clinical treatment. First, advanced technologies and methodological techniques are urgently required observing the interaction among adipose tissue, sensory nervous systems, and sympathetic nervous systems, as well as to dissect synaptic junctions and electrochemical structures formed in transparent processed adipose tissue and nerves. Second, several key aspects, such as the time and type of innervation, axonal subtypes, branching patterns, and neuropeptide release responses to circumstances, remain unclear. The organ-targeted single-cell RNA-seq approach can identify endogenous signals for finding the putative receptors [79]. Long-term calcium imaging techniques can reveal projection-specific neuronal or DRG activity in vivo to confirm the signals [70].

Immunoregulation

Transient inflammation is essential for tissue remodeling [80]. The time at which the anti-inflammatory status switches to a chronic proinflammatory status is crucial for preventing metabolic disorders in an individual. Persistent inflammation in adipose tissue, particularly visceral adipose deposits, is a determinant of the development of chronic diseases. It explains why the cumulative abdominal adipose tissue is correlated with a high risk of death [81]. The limited success of interventions focused on a single cytokine or receptor in patients with obesity highlights the need for new therapeutic approaches. Combining therapies targeting multiple immune cell types or upstream signaling pathways could potentially provide greater efficacy [30].

Adipose Tissue Browning

Human active adipose tissue, comprising brown and beige adipose tissues, can potentially fuel energy expenditure [82]. One promising strategy is the direct injection of mitochondria into adipose tissue, leading to browning via the enhanced expression of optic atrophy 1 (OPA1)/UCP1 [83]. Pharmacological approaches can also activate the CNS to stimulate BAT and burn excess calories [84]. Moreover, genetic engineering techniques can increase the expression of β 3-adrenergic receptors and transcriptional co-regulators (such as Prdm16 or FOXC2) in WAT to promote browning [85, 86]. These strategies demonstrate the potential of inducing thermogenic function in human brown/beige adipose tissue, leading to increased energy expenditure.

Anti-fibrosis

Fibrosis is a hallmark of ECM dysregulation in dysfunctional WAT [87]. Although no specific anti-fibrosis drug exists for adipose tissue, several potential pro-fibrotic targets have been identified, such as anti-endotrophin and anti-PDGR α [88]. To

date, the most effective anti-fibrotic interventions are dietary modulation, exercise, anti-inflammation, and anti-obesity-associated T2DM [88]. Given the difficulty of explicitly targeting fibrosis, a comprehensive understanding of the mechanisms driving adipose tissue fibrosis is essential for preventing metabolic disorders.

Personalized Medicine and Tailored Interventions

A one-drug-fits-all model yields unsatisfactory results in treating obesity due to patient heterogeneity. Although common symptoms exist, obese individuals may also experience variations in their symptoms. Additionally, conditions, such as Cushing syndrome, can contribute to obesity and its complications [89]. This finding emphasizes that patients presenting with similar clinical symptoms may have vastly different underlying causes. Hence, PM can provide customization of health-care under precise analysis that guides the prescription of treatment, with medical decisions, treatments, practices, or products being tailored to the patient's needs [90].

Clinical decision-making is driven by a checklist and personal experience. The diagnostic “measure” is important. PM can encompass genetic, genomic, geographical, environmental, radiological imaging, and clinical symptom information to accurately predict a person's treatment [91, 92].

A patient's molecular and cellular analysis or genetic content can guide the choice of treatment. For example, ^{99m}Tc -methoxyisobutylisonitrile, used clinically in cardiac perfusion and parathyroid imaging, can localize to the supraclavicular adipose tissue because of its relatively high blood flow and mitochondrial density [93]. [^{123}I]-Metaiodobenzylguanidine, a radiolabeled norepinephrine analog and a marker of sympathetic innervation, can simultaneously visualize metabolic activity and innervation in BAT [94]. ^{18}F -fluoro-thiaheptadecanoic acid, a fatty acid tracer, has been used to quantify BAT oxidative metabolism and glucose and non-esterified fatty acid turnover [95]. Hence, the combined techniques of mitochondrial implantation and contrast-enhanced imaging can mediate adipose tissue browning. The systemic identification of active adipose deposits using this functional analysis clearly guides medical and surgical interventions.

Severe and persistent obesity often has underlying genetic components. Genome-wide association studies (GWAS) have identified numerous loci linked to BMI, including genes influencing waist and hip circumferences [96]. One notable example is the kinase suppressor of Ras 2 (KSR2), which is implicated in the early onset of severe obesity accompanied by food intake disorders and metabolic dysregulation [97]. Additionally, mutations in melanocortin 4 receptor (MC4R) and gastric inhibitory polypeptide receptor (GIPR) have been associated with extreme obesity. Notably, these variants exhibited a considerably stronger effect on BMI than the common variants [98]. MC4R deficiency, a monogenic syndrome, can now be precisely treated with a medication-granted Priority Medicines (PRIME) designation by the European Medicines Agency (EMA) [69]. Furthermore, studies have indicated that enhancer activity (H3K4me1 and H3K27ac) in adipose tissue may

regulate gene expression related to metabolism and insulin resistance [96]. Combining genetic screening with BMI analysis revealed the enrichment of neuronal genes in adipose tissue that influenced energy expenditure. This offers a promising avenue for the future targeting of certain central obesity and associated metabolic disorders via genetic re-editing.

Compared to molecular or genetic targets, the environmental drivers of obesity pose a significant challenge for PM. However, clustering techniques can help tackle this complexity by analyzing geographical, environmental, and clinical data algorithms. Integrating these clusters with healthcare AI can pinpoint the “right patient” for targeted interventions. Clustering provides a starting point for treatment, but the ultimate goal is to develop effective real-world applications for these treatments. However, the gap between preclinical findings and patient outcomes remains a significant obstacle. First, a deeper understanding of adipose tissue physiology and its clinical implications is needed. Then, scientists and clinicians must collaborate with engineers to translate preclinical findings into well-defined codes for use in AI systems. This integration will enable the dissemination of knowledge and facilitate PM strategies.

Conclusions

As part of the global challenge of blunting the chronic disease epidemic, multifaceted efforts must be made to prevent and treat obesity. The promotion of healthy living in modern environments is a crucial goal. Pharmacotherapy combined with accessible lifestyle programs remains the mainstay of treatment for those already facing obesity and its associated chronic conditions. The current treatments for obesity-related conditions entail a growing global, multidisciplinary network of certified medical professionals and the exploration of innovative therapeutic strategies. We have emphasized the ongoing evolution of adipose tissue research and its potential to transform healthcare. We hope our efforts can marginally hasten a healthier state of living for everyone.

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