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Chapter 9

The Heterogeneity of White Adipose Tissue

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http://dx.doi.org/10.5772/intechopen.76898

Abstract

The increasing prevalence of obesity is a major factor driving the worldwide epidemic of type 2 diabetes and metabolic syndrome. Adipose tissue not only stores energy, but also controls metabolism through secretion of hormones, cytokines, proteins, and microRNAs that affect the function of cells and tissues throughout the body. Accumulation of visceral white adipose tissue (WAT) leads to central obesity and is associated with insulin resistance and increased risk of metabolic disease, whereas accumulation of subcutaneous WAT leads to peripheral obesity and may be protective of metabolic syndrome. While much attention has been paid to identifying differences between white, brown and brite/beige adipocytes, there is growing evidence that there is functional heterogeneity among white adipocytes themselves. This heterogeneity, includes depot-specific differences in development, inflammation, and endocrine properties. In addition to the depot-specific differences, even within a single fat depot, WAT is composed of developmentally and phenotypically distinct subpopulations of adipocytes. The following chapter will introduce this concept of white adipocyte heterogeneity.

Keywords: heterogeneity, subpopulations, inflammation, microRNA, and adipokine

1. Introduction

The prevalence of obesity, characterized by excess of adipose tissue, has been increasing worldwide and represents one of the most significant public health problems of our time. Obesity is associated with numerous comorbidities, including type 2 diabetes, coronary heart disease, hypertension, hepatosteatosis, and even cancer. Adipose tissue is organized in discrete depots in specific locations throughout the body. This chapter will briefly introduce the two major types of fat, brown and white. We will introduce the major different WAT depots and more fully elaborate the physiology of two more recently defined depots: the dermal and

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bone marrow adipose tissue. We will then focus on visceral and subcutaneous white adipose tissue and discuss the differential developmental, inflammatory, and endocrine properties of these depots. The depot-specific expression and roles of inflammatory cytokines, adipokines, and novel signaling molecules, including lipokines and microRNAs will be discussed. Finally, we will discuss emerging literature that demonstrate WAT is composed of developmentally and phenotypically distinct subpopulations of adipocytes.

2. White, brown, and brite adipose tissue

The two major forms of adipose tissue include white adipose tissue (WAT) or brown adipose tissue (BAT). Although these tissues are characterized by lipid accumulation, these two tissues differ dramatically in morphology, developmental lineage, and function. WAT, is characterized by adipocytes with large unilocular droplets and is present in far greater amounts than BAT. WAT acts as the primary reserve for surplus energy in the body, storing excess nutrients as triacylglycerol (TAG). In contrast, the brown adipocytes actively dissipate energy through the production of heat. Brown adipocytes contain multilocular lipid droplets distributed throughout the cell. Brown adipocytes contain more mitochondria than white adipocytes, which, along with an increased capillary density, is responsible for the brown color of BAT [1]. In the unique thermogenic property of brown fat is due to the presence of uncoupling protein-1 (UCP1). UCP1 allows the reentry of protons pumped across the inner mitochondrial membrane by respiratory chain enzymes. This converts the energy of the mitochondrial proton gradient into heat. The importance of UCP1 to brown fat function is evident in studies of mice with targeted UCP1 ablation, which results in cold intolerance, with variable effects on WAT accumulation and obesity [2, 3].

The identification of a third adipocyte type, termed “brown-in-white”, “brite”, or “beige” that has many of the functional characteristics of BAT while being dispersed throughout WAT depots. Like its BAT, beige fat has the capacity for thermogenesis, expresses UCP1, and can be activated in response to cold exposure or adrenergic stimulation [4]. Although brown adipocytes are largely derived from Myf5-expressing expressing lineage, evidence exists that beige adipocytes are formed from both transdifferentiation of unilocular white adipocytes and from a unique Myf5 negative precursor population within subcutaneous depots [5, 6]. However, more recent evidence suggests the presence of functionally distinct populations of beige adipocytes [7] that are molecularly distinct from brown and white adipocytes in both mice and humans [8, 9]. Since the discovery that most humans possess active BAT, primarily in the supraclavicular regions [10–13], increasing the amount and activation of both BAT and beige AT to combat obesity has been an extremely active avenue of research.

3. White adipose tissue depots

WAT serves multitude of functions including storage of lipid, maintenance of insulin sensitivity, and endocrine signaling [14]. Adipocytes in WAT are characterized by low cytoplasmic volume, unilocular lipid droplets, and lower numbers of mitochondria compared to BAT. WAT can be categorized into two major subdivisions based on the anatomical locations

or depots: subcutaneous (fat under the skin in the hypodermis region) and visceral. Increase in visceral fat is related to the increased risk of metabolic disorders such as type 2 diabetes and cardiovascular diseases [15, 16], whereas subcutaneous fat is not and may even be protective against metabolic derangements [17]. The differences between these two types of WAT are attributable to both intrinsic differences in the cells that comprise these depots as well as differences in the micro-environment between adipose tissue depots.

3.1. Subcutaneous adipose tissue

In rodents, subcutaneous WAT is divided into subcutaneous anterior fat (SAF) and subcutaneous posterior fat (SPF). SAF can be further subdivided into cervical, axillary, interscapular, and subscapular, and SPF is divided into dorsolumbar, inguinal, and gluteal [18]. In humans, two subcutaneous fat regions are also recognized: upper and lower body fat, where they correspond approximately to SAF and SPF, respectively. Upper body subcutaneous fat consists of superficial and deep layers separated by the Scarpa's fascia. Superficial fat is compact, consistent in thickness, and metabolically less active compared to deep layer fat [19]. Lower body subcutaneous fat is primarily made up of adipose tissue around the gluteal and femoral (gluteofemoral) regions [20, 21]. Accumulation of gluteofemoral fat is associated with improved glucose tolerance [22], negatively correlated with insulin resistance [17], and associated with reduced aortic calcification related to cardiovascular diseases [23]. However, the protective effect of abdominal subcutaneous fat is disputed, potentially as a result of the presence of deep subcutaneous fat, which has been suggested to behave similar to visceral fat regarding metabolic parameters such as insulin-stimulated glucose utilization [24]. There has been no evidence of multiple subcutaneous AT layers in rodents, such as is the case in humans.

3.2. Visceral adipose tissue

Visceral fat is generally regarded as intra-abdominal adipose tissue that surrounds internal organs. Under this definition, the major human visceral depots are: the omental, retroperitoneal, perirenal, mesenteric, and pericardial depots [18, 20]. Notably, only the mesenteric and omental adipose tissues drain directly into the portal circulation, and thus release of free fatty acids (FFAs) and pro-inflammatory cytokines from these depots is directly delivered to the liver and promotes the development of hepatic steatosis and insulin resistance [21, 25]. Mice have similar visceral adipose tissues to humans including the mesenteric, perirenal, pericardial, and retroperitoneal fat depots. However, rodents have a well-developed perigonadal fat pad, which is largely absent in humans, while rodents have a paucity of omental adipose tissue (**Table 1**).

The enlargement of visceral adipose tissue is largely detrimental to the functions of the surrounding organs. Pericardial fat, including both epicardial and pericardial AT, is associated with metabolic disorders and low-grade inflammation, resulting in type 2 diabetes and cardiac complications. Increase thickness of pericardial AT is associated with the increase of diastolic pressure and fasting insulin [26, 27], arterial calcium [28], and severity of coronary artery disease [29]. Similarly, an increase in perirenal (fat between renal fascia and capsule) and pararenal AT (immediately external to renal fascia) thickness is correlated with glomerulopathy [30], increased frequency of chronic kidney disease in type 2 diabetic patients [31], and hypertension due to compression of low-pressure structures in the renal sinus such as veins,

	Subcutaneous	Visceral	Other
Humans	Upper body: superficial and deep abdominal (separated by Scarpa's fascia)	Omental, retroperitoneal, perirenal, mesenteric, pericardial	Bone marrow, dermal
	Lower body: gluteofemoral (butt and thigh)		
Rodents	Anterior: cervical, axillary, interscapular, subscapular	Perigonadal, perirenal, pericardial, mesenteric, retroperitoneal	Bone marrow, dermal
	Posterior: dorsolumbar, inguinal and gluteal		

Table 1. Major adipose depots in humans and mice.

lymphatic vessels, and ureters [32, 33]. Increased mesenteric fat is associated with increased risks of cardiovascular diseases [34], Crohn's disease [35], and hepatic insulin resistance and hepatosteatosis [36]. Together, these studies show that increased visceral, but not subcutaneous fat deposition, is associated with numerous disease states and metabolic derangements.

3.3. Other white adipose tissues

3.3.1. Dermal white adipose tissue (dWAT)

Recent research has drawn attention to a newly recognized adipose depot, the dermal white adipose tissue (dWAT) [37]. dWAT is the widespread adipose tissue found in the reticular region of the dermis, and in mice is separated from the subcutaneous adipose tissue by a striated muscle layer. In mice, evidence suggests that adipocytes from dWAT develop independently from subcutaneous depot [38]. On the other hand, human dWAT is not clearly separated from the underling subcutaneous depot and is defined by dermal cones that concentrate around hair follicles [39]. Clusters of dWAT are more densely distributed in areas that are highly-prone to scaring [40]. In fact, dWAT is now known to be associated with numerous functions including scar formation, wound healing, and cutaneous fibrosis [41–45]. The wound healing mechanism involves inflammatory response and closing of the area by fibroblast migration, which the latter is mediated by adipocyte activation. This process is characterized by an intra-conversion between adipocytes and myofibroblasts and also contributes to the fibrosis observed in scar formation and autoimmune diseases (i.e. scleroderma) [37, 46, 47].

In addition to wound healing effect, dWAT plays an important role in hair follicle cycling. Preadipocytes, but not mature adipocytes in the dWAT have been suggested to activate the growth of hair follicles [48, 49]. As dWAT develops independently from subcutaneous depot, its emergence in embryonic stage coincides with the development of hair follicles, at least in murine fetuses [38], further supporting the relationship between dWAT and hair follicle development.

Dermal adipose tissue has also been suggested to function in other processes including protection of skin from bacterial infection and whole-body thermoregulation. Infection with *S. aureus* promotes rapid proliferation of pre-adipocytes, leading to large expansion of dWAT and increased production of antimicrobial cathelicidin [50], suggested a protective response of dWAT to bacterial infection. Loss of syndecan-1, an important adipocyte differentiation protein, leads to reduced thermoregulation and loss of dWAT, implying a role of dWAT in regulating temperature [51].

3.3.2. Bone marrow adipose tissue (BMAT)

Bone marrow adipose tissue (BMAT) is, as the name suggests, is located within the bone marrow. Bone marrow adipocytes are known to share common origin with osteocytes, chondrocytes and hematopoietic cells, as indicated by lineage tracing models [52]. As a fat depot, BMAT makes up 10% of human fat mass and up to 70% volume of bone marrow [53]. The BMAT adipocytes consist of two types in mice: constitutive bone marrow adipocytes (cBMA) and regulated BMA (rBMA) [54]. cBMAs are large adipocytes that densely populate regions of distal tibia and caudal vertebrae. These adipocytes develop early in life, contain high levels of unsaturated fatty acids, and are resistant to insulin and beta-adrenergic stimuli. On the other hand, rBMAs are distributed across the trabecular regions of proximal tibia, distal femur, and lumbar vertebrae. These adipocytes are smaller and have higher saturated fat than cBMAs and subcutaneous adipocytes [55]. Additionally, rBMAs respond to beta-adrenergic stimuli and dietary changes [54]. Interestingly, BMAs exhibit characteristics of both WAT and BAT and express both WAT and BAT markers. BMAs express adipogenic markers and resemble WAT in terms of the unilocular appearance and the capability to secrete adiponectin and leptin [56, 57]. However, like BAT or brite adipocytes, the distribution of these cells are dependent on temperature and location within the body [54, 58]. The BAT characteristics of BMAT decrease with age and in pathological condition such as diabetes [59].

Numerous physiological and pathological processes influence BMAT physiology. BMAT expansion occurs in normal aging, primarily due to an increase in rBMA over time [54, 60]. Expansion of BMAT and reduction of bone volume are observed in human subjects with osteoporosis [61]. Steroid hormones also modulate BMAT expansion, as both estrogen deficiency [62, 63] and excess glucocorticoids, observed in Cushing's disease, have also been shown to increase BMAT [64, 65]. On the other hand, in a location and subtype dependent manner, leptin potentially antagonizes adipogenesis in bone marrow as observed in both caloric restriction and leptin-deficiency [66–70]. Furthermore, high-fat diet (HFD) causes BMAT expansion and bone loss [71–73]. Treatment of type 2 diabetes with thiazolidinedione (TZD) increases BMAT mass. Although the relationship between increased BMAT and reduced cortical and trabecular bone mass remain controversial, these studies could possibly discourage TZD administration to patients with high risk of bone fracture [72, 74–77].

The physiological functions of BMAT in normal and pathological conditions are beginning to be explored. Inflammatory cytokines have been found to be secreted by BMAT and the secretion of these molecules may be altered by diet induced obesity [71, 78, 79]. Bone marrow adipocytes have also been shown to produce adiponectin. Particularly during caloric restricted state and anorexia nervosa during which all adipose tissues except BMAT are depleted, BMAT is a major source of circulating adiponectin [53, 80–83]. Additionally, BMAT influences hematopoiesis and osteogenesis in the marrow environment. BMAT has been shown to negatively regulate hematopoiesis [84] and bone marrow adipocytes may also play a role in bone remodeling. Increased bone marrow adipocytes leads to the increased expression of RANKL, which induces the activity of osteoclasts and reduces bone density [85]. Similarly, osteoporosis is accompanied by a marked increase BMAT mass [86]. Future studies will add to our understanding of the regulation and physiological contribution of BMAT.

4. Intrinsic differences between visceral and subcutaneous adipocytes

Recent lineage tracing studies have indicated that visceral and subcutaneous WAT are derived from different developmental lineages [87]. This finding supports earlier findings that preadipocytes and adipocytes from these depot have intrinsic depot-specific differences in both gene expression and function.

In general, preadipocytes derived from subcutaneous regions are more pro-adipogenic and readily differentiate into adipocytes, whereas visceral preadipocytes express anti-adipogenic genes and require additional components for differentiation [88–91]. The increased differentiation of subcutaneous-derived preadipocytes may due, at least in part, to high levels of expression of pro-adipogenic genes, PPARy and C/EBPs coupled with the high number of rapidly replicating preadipocytes derived from subcutaneous tissue [92–96]. These intrinsic differences could contribute to the protective effect of subcutaneous fat during obesity, where hyperplasia in subcutaneous fat allows the uptake of excess fat and prevents ectopic deposition. On the contrary, visceral fat has lower lipoprotein lipase activity and higher rates of catecholamine-induced lipolysis. This leads to an increase in free fatty acid release from visceral adipose tissue into the portal circulation [97–100]. These differences in gene expression, differentiation, and replication are retained after numerous passages of cultured subcutaneous and visceral preadipocytes, thus revealing intrinsic, cell-autonomous differences which contribute to the regional differences in mature adipocytes.

In addition to the large differences between visceral and subcutaneous adipocytes, inter-depot differences also exist even with subcutaneous and visceral adipose tissue. Within subcutaneous depot, abdominal preadipocytes express higher pro-adipogenic marker PPARγ, are more susceptible to apoptosis upon inflammatory cytokine exposure, and are smaller in size due to increased lipolysis compared to gluteofemoral subcutaneous fat [90, 99, 101]. Similarly, not all visceral adipose tissues are the same. Mesenteric adipocytes are intermediate between abdominal subcutaneous and omental in terms of replication and differentiation [92, 93, 95, 96]. Furthermore, the perirenal depot contains a higher percentage of rapidly dividing cells than perigonadal fat [96, 102–104]. Together, these studies demonstrate that variations in subcutaneous and visceral depots are dependent not only on anatomical location, but also upon the intrinsic properties of the adipocytes found within the depots.

5. Associations of WAT depots with metabolic health

As previously mentioned, accumulation of visceral fat, termed central obesity, is associated with increased risk of diabetes, and cardiovascular diseases [23, 105–107] while subcutaneous fat has been linked to protection from metabolic diseases [17, 22, 108]. The differential effects of subcutaneous and visceral adipose tissue on metabolism have been directly tested by transplantation and surgical removal of adipose tissue. While transplanting subcutaneous adipose tissue improved the glucose tolerance of the recipient animals, transplantation of visceral fat

did not have this effect [109, 110]. Similarly, removal of visceral fat restores insulin sensitivity in rats and in humans, but removal of subcutaneous did not improve metabolic profiles [111–113]. Thus, visceral WAT is strongly associated with metabolic syndrome. The following section of this chapter will discuss the depot-specific regulation of inflammation, immune cells, and cytokines and how these factors impact whole-body physiology.

5.1. The role of immune system in obesity-related metabolic syndrome

Macrophages have an established role in regulating angiogenesis during tissue repair [114]. In the early expansion of obese adipose tissue, remodeling of extracellular matrix occurs along with increased angiogenesis to support growing adipocytes [115, 116]. However, continued hypertrophy of adipocytes in later stage of obesity leads to reduced oxygen tension, and expression of hypoxia-inducible factor 1α (HIF1α) is induced in the adipose tissue. HIF1α has been shown to be elevated in obese mice and humans [117–120]. Increased HIF1α is associated with the development of fibrosis, inflammation, and insulin resistance [119, 121–123].

The negative impacts of visceral fat depots on metabolism are, at least in part, attributable to the macrophage infiltration and inflammation that occur primarily in the visceral adipose tissue. The immune system plays an intricate role alongside of adipose dysfunction during the development of obesity-related metabolic syndrome. Obesity-induced metabolic disease is now classified as a chronic-inflammatory disease due to the presence of immune cells and elevated levels of inflammatory cytokines. In lean mice and humans, low levels of macrophages are found in adipose tissue. However, obese mice and human subjects have an increased number of macrophages, especially in the visceral adipose tissue, with numbers correlating with the increased size of adipocytes and body fat mass [124, 125]. The Infiltrating macrophages in obesity are polarized towards a classically activated M1 pro-inflammatory phenotype and surround dying adipocytes in the form of multinucleated giant cells and crown-like structures [126, 127]. The number of alternatively-activated M2 macrophage number does not change during obesity but is overwhelmed by the increased presence of recruited M1 macrophages, leading to an overall shift in the ratio of these macrophages [128].

Macrophage recruitment relies on chemoattractant proteins, such as monocyte chemoattractant protein (MCP)-1 or chemokine (C-C motif) ligand 2 (CCL2). The initial dose of MCP-1 release was found to be secreted by pre-adipocytes [129], supporting the hypothesis that initial recruitment of macrophages is necessary for extracellular matrix remodeling and tissue expansion. Post-recruitment, macrophages are activated by other immune cells, in particular cytotoxic cells, initiating an inflammatory cascade. Adipose CD8 cytotoxic T cells that normally kill virus-infected cells are activated by obese adipocytes, which leads to subsequent activation and M1 polarization of macrophages. This macrophage polarization event precedes macrophage infiltration and occurs as an early response to high-fat-diet (HFD) exposure in mice [130]. Natural killer (NK) cells, which are cytotoxic cells that participate in innate immunity, recruit and activate macrophages through secretion of MCP-1 and IFN-γ. Activated macrophages, in return, recruit via the secretion of CCL3, CCL4, and CXCL10, and stimulate the proliferation of NK cells through release of IL-15 [131]. Other immune cells, including B and different types of T cells, indirectly contribute to pro-inflammation state of

adipose tissue. B cells are important participants of humoral immunity, secrete inflammatory cytokines (IL-8, IL-6, IFN-γ), and activate both CD4 and CD8 T cells [132]. B cells support adipocyte hypertrophy and the pro-inflammatory T-cell function in obesity/T2D through cellular contact-dependent mechanisms. Thus, reducing the interaction between antigen presenting B cells and T cells decreases the inflammatory response and can lead to improvements in glucose and insulin metabolism [132, 133]. While the effects of pro-inflammatory immune cells are principal regulators of adipose tissue in the obese state, anti-inflammatory cells (i.e. M2 macrophages, regulatory T cells (Treg), and T helper type 2 cells (Th2)) also have defined roles in adipose tissue homeostasis [134].

5.2. Inflammatory cytokines

The macrophage infiltration which occurs during obesity, particularly visceral adipose tissue, lead to increased local and systemically levels of inflammatory cytokines [135]. In the following section, we will discuss the regulation and action of some of the major inflammatory cytokines within adipose tissue.

5.2.1. Tumor necrosis factor-α (TNF-α)

TNF-α was the first identified cytokine derived from adipose tissue macrophages that links both obesity and inflammation. TNF-α mRNA and protein levels have been shown to be elevated during obesity in the adipose tissue both animal models and human subjects. Increased TNF-α is positively correlated with increased degree of obesity and circulating insulin level, whereas TNF-α level decreases with weight loss and increased insulin sensitivity [136–140]. These effects are directly attributable to TNF-α, as infusion of a TNF-α neutralizing antibody, or ablation of TNF-α or its receptor in mice leads to improved insulin sensitivity [140–142]. Despite these clear results in mouse models of obesity, the use of TNF-α neutralizing antibodies and inhibitors has had inconsistent success in treating insulin resistance and glucose intolerance in obese human subjects [143–146].

TNF-α affects a myriad of various pathways to alter adipose tissue metabolism. TNF-α impairs insulin signaling via downregulation of insulin receptor through phosphorylation of insulin receptor substrate-1 (IRS1) and suppresses adipogenesis by controlling the transcriptional regulation and activity of the adipogenic factors PPARγ and C/EBPs [14, 147, 148]. Furthermore, TNF-α induces lipolysis through the downregulation of anti-lipolytic genes perilipin, FSP27 and G0S2 and inhibition of lipoprotein lipase activity. TNF-α can directly cause apoptosis in visceral pre-adipocytes and adipocytes [149–155]. Taken together, the actions of TNF-α function to reduce adipocyte size and number, leading to the release of free fatty acids into the circulation.

5.2.2. Interleukin-6 (IL-6)

Interleukin-6 (IL-6) is secreted by numerous cell types including the adipocytes and macrophages, with only 10% of IL-6 being contributed by adipocytes [124, 156, 157]. Multiple lines of evidence point to visceral adipose tissue as the major contributor of circulating IL-6 [158, 159]. Like TNF-α, IL-6 also negatively regulates insulin signaling through degradation of IRS1 [148].

5.2.3. Interleukin-1 receptor antagonist (IL-1Ra)

IL-1Ra is a natural antagonist to inflammatory cytokine interleukin-1α and β. IL-1Ra is expressed in numerous tissues, and is highly expressed in adipose tissue during obesity, and its expression is positively correlated with leptin level. Indeed leptin is capable of inducing IL-1Ra; and as a negative feedback loop, IL-1Ra antagonizes leptin activity [97, 160]. Targeting IL-1Ra has intriguing therapeutic potential, as treatment of diabetic patients with a recombinant human interleukin-1-receptor antagonist increased insulin secretion from pancreatic islets [161]. Interestingly, a single nucleotide polymorphism in IL-1Ra is highly associated with body fat mass [162].

5.2.4. Plasminogen activation inhibitor-1 (PAI-1)

PAI-1 is another inflammatory cytokine more highly expressed in visceral than subcutaneous adipose tissue. In human subjects. Plasma PAI-1 level correlates with body mass index [163]. PAI-1 is expressed in mature adipocytes, monocytes, as well as other stromovascular cells from the adipose tissue [164, 165]. Ablation of PAI-1 in mice leads to improved glucose and insulin metabolism [166], and PAI-1 has been found to negatively regulate adipogenesis [167]. IL-6, but not TNF-α, stimulates PAI-1 expression in human adipose tissue [163, 165].

6. Depot-specific effects of adipokines and other signaling molecules

As an endocrine organ, WAT secretes a variety of hormones and cytokines, also known as "adipokines". While another chapter in this book will provide a broader overview of the endocrine functions of AT, we would be remiss if we did not mention the depot-dependent adipokine profile of AT. In addition, we will discuss two recently discovered classes of endocrine signaling molecules derived from adipose tissue: distinct lipid species, known as "lipokines" and circulating microRNAs.

6.1. Adipokines

Adiponectin is an adipokine that has anti-inflammatory and insulin-sensitizing action [168]. The majority of reports suggest that adiponectin secretion is primarily driven by subcutaneous rather than visceral fat, and that adiponectin level are low in obese and insulin resistant patients [97, 169–171]. Inflammatory cytokines reduce adiponectin secretion, especially in the visceral adipose tissue [169]. Not only is reduced adiponectin involved in insulin resistance, but albuminuria, a marker of kidney damage, is related to adiponectin deficiency [172], further extending the protective effects of adiponectin in metabolic health.

Leptin is a satiety hormone primarily secreted by adipocytes that acts on the hypothalamus to decrease food intake and increase energy expenditure, among other functions. As such, mice and humans with mutations of leptin or its receptor exhibit marked obesity [173–175]. Leptin is secreted by adipocytes and levels are positively correlated with the amount of body fat [135, 176]. Secretion of leptin appears to be depot-dependent, with subcutaneous WAT producing greater amounts than visceral WAT [89, 159, 170, 177, 178].

Resistin is a peptide hormone expressed in adipose tissues of both rodents and humans. In rodent, the primary source of resistin are the mature visceral adipocytes, but in humans the visceral fat macrophages are the major contributor of circulating resistin [179–182]. Anti-resistin treatment or loss of resistin signaling improves insulin sensitivity and glucose homeostasis, while recombinant resistin treatment impairs glucose and insulin metabolism [181, 183, 184]. Although the cellular source of resistin is different between humans and mice, macrophage-derived human resistin is also sufficient to exacerbate adipose tissue inflammation and insulin resistance in mice [185].

Visfatin (or pre-B cell colony enhancing factor PBEF) is an adipokine named for the suggestion that it would be predominantly produced and secreted in visceral fat [186]. Visfatin was found to be released predominantly from macrophages rather than from adipocytes in visceral adipose tissue, and plasma visfatin significantly correlates with BMI and body fat [187]. Visfatin has been shown to have endocrine, paracrine, and autocrine action, and may function through binding of the insulin receptor [186].

Retinol binding protein 4 (Rbp4) is a secreted factor from adipocyte tissue that has marked metabolic effects both on liver and skeletal muscle. Ablation of Rbp4 leads to improvements of glucose and insulin metabolism while addition of Rbp4 impairs insulin signaling in muscle [188]. Rbp4 expression is dramatically increased by obesity and insulin resistance in humans, and is much more highly expressed in visceral than subcutaneous adipose tissue [189, 190].

Apelin is an insulin-regulated adipokine expressed in mature adipocytes whose expression is increased in obesity. Apelin appears to be equally expressed in visceral and subcutaneous adipose tissue [191]. Apelin inhibits diet-induced obesity through increasing lymphatic and blood vessel integrity and enhancing brown adipogenesis [192, 193].

6.2. Lipid mediators "lipokines"

Recent studies have determined that specific lipid species communicate from adipose tissue to distal sites, and act as a new class of molecules termed "lipokines". The first lipokine, C16:1n7-palmitoleate, is derived from adipose tissue and regulates gene expression and insulin sensitivity of both muscle and liver [194]. Another class of lipokine, fatty acid esters of hydroxy fatty acids (FAHFAs) are reduced in serum and adipose tissue of insulin-resistant people and high-fat diet-fed mice. Administration of FAHFAs increases insulin-mediated glucose uptake into the liver and skeletal muscle [195, 196]. Finally, a BAT specific lipokine, 12,13-dihydroxy-9Z-octadecenoic acid (12,13-diHOME) has also recently been identified. 12,13-diHOME is a stimulator of BAT activity and its circulating levels are negatively correlated with body-mass index and insulin sensitivity. 12,13-diHOME increases fatty acid uptake into brown adipocytes by promoting the translocation of the FA transporters to the cell membrane [197].

6.3. MicroRNAs

MicroRNAs (miRNAs) are non-coding RNAs that are ~22 nucleotides in length that regulate mRNA translation. Each miRNA can regulate multiple mRNA targets, and each mRNA target can be regulated by multiple miRNAs. Primary miRNAs are transcribed, and cleaved in

a multi-step process by ribonuclease enzymes, including Drosha and Dicer, to form mature miRNAs. The mature miRNAs are then loaded into the RNA-induced silencing complex (RISC), and are directed to the 3′ untranslated region (UTR) of the target mRNAs to modify their translation [198–200].

6.3.1. Circulating MicroRNAs as endocrine signaling molecules

Adipocyte-specific ablation of Dicer (ADicerKO) produces mice with a lipodystrophic phenotype marked by insulin resistance, dyslipidemia, and a reduction in both local and circulating miRNA (packaged within exosomes), suggesting important roles of miRNAs in adipocyte functions [201, 202]. Transplantation of wild-type adipocytes into ADicerKOs leads to improved metabolism. Notably, a depot-specific contribution of adipose tissue to the circulating exosomal miRNA transcriptome was observed. Furthermore, these adipose-derived circulating RNAs can also modify gene expression in other tissues, including the liver [203]. Likewise, exosomal transfer of macrophage-derived miRNAs can control gene expression and metabolism in adipocytes [204, 205]. Thus, like adipokines or lipokines, miRNAs can function as both paracrine and endocrine signals molecule to alter the physiology of distinct target tissues.

6.3.2. Cell autonomous actions of MicroRNAs in WAT

6.3.2.1. MicroRNA regulation of preadipocyte determination and adipogenesis

The formation of adipocytes from mesenchymal stem cells is based on inhibition of other lineages (chondrocyte, osteocyte, and myocyte) and promotion of adipocyte lineage (**Figure 1**). Runt-related transcription factor 2 (Runx2) and bone morphogenetic protein (BMP)-2, both osteogenic factors, are inhibited by adipose tissue expressed miRNAs. Chondrogenesis is controlled by TGF-β, which is regulated by miR-21, a miRNA that is known to be increased in human obesity and type 2 diabetes [206–208]. miR-148 and -124 target adipogenic inhibitors Wnt1 and Sox9, respectively, at the initiation of adipogenesis [200, 209, 210].

After committing to adipocyte lineage, lipid accumulation in differentiating adipocytes is controlled, at least in part by the expression and activity of PPAR and C/EBP proteins. miR-375 suppresses ERK1/2 phosphorylation which allows the activation of PPARγ [211]. miR-143 and -103 are both increased during adipocyte differentiation and have clear roles in lipid accumulation, especially within subcutaneous WAT, as confirmed by both over-expression and inhibition studies [212, 213]. miR-519d inhibition of PPARα reduces fatty acid oxidation and increase lipid storage [214], and reduced adipocyte size in human subjects is correlated with reduced expression of miR-519d [215]. On the other hand, miRNAs that target PPARγ including miR-27 and miR-130 act as anti-adipogenic regulators [216, 217] (**Figure 2A**).

6.3.2.2. MicroRNA regulation of adipocyte metabolism and inflammation

MicroRNAs target all aspects of adipocyte metabolism and a comprehensive examination of these effects is not possible within the confines of this chapter. However, we will briefly discuss how miRNAs directly regulate insulin signaling and modulate the inflammatory response of adipocytes. miRNAs can impair insulin signaling by targeting many of the key

molecules involved, including: effects on insulin receptor, IRS1, and GLUT4 (**Figure 2B**). Insulin receptor stability is partially dependent upon the protein caveolin-1, which itself is a target of miR-103. Inhibition of miR-103 thus increases insulin receptor stability and leads to improved insulin sensitivity [218]. IRS1 is downregulated by miR-139-5 and -144 [219, 220] while insulin-stimulated glucose uptake through GLUT4 is downregulated with high expression of miR-93 and -223 [221, 222] (**Figure 2B**). Macrophage infiltration is directed by expression of chemokine (C-C motif) ligand 2 (CCL2 or MCP-1). CCL2 expression is increased by miR-145, but is reduced by miR-126 and miR-193b [223]. miRNAs also control polarization of classically activated pro-inflammatory (M1) macrophages and alternatively activated anti-inflammatory (M2) macrophages. Increasing miR-223 reduces expression the

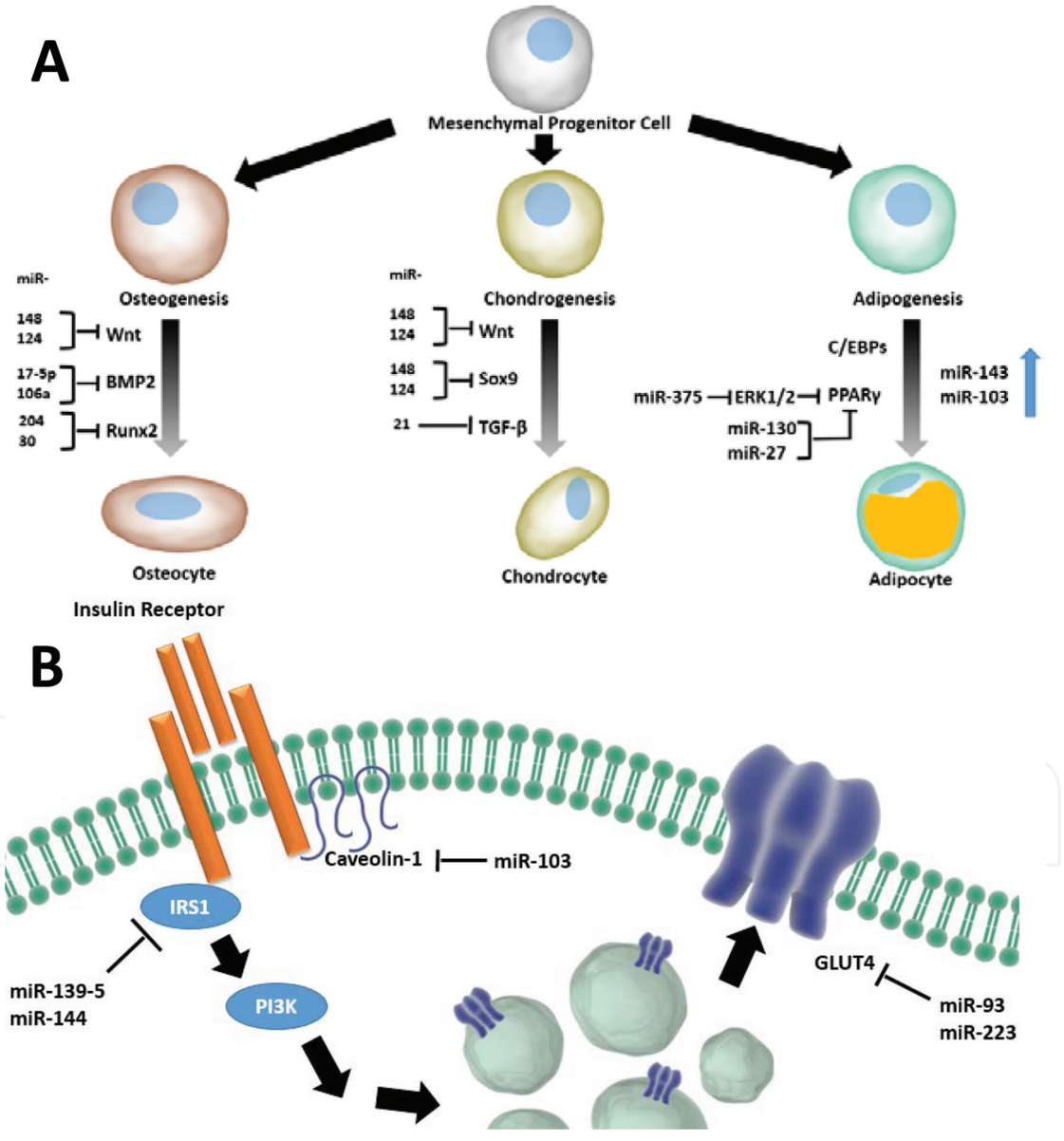

Figure 1. The roles of microRNAs in adipogenesis and insulin signaling. (A) miRNAs play an important role in promoting adipogenesis and inhibiting osteogenesis and chondrogenesis. (B) miRNAs participate in insulin resistance by targeting IRS1, insulin receptor stabilizer (caveolin-1), and GLUT4 expressions.

http://dx.doi.org/10.5772/intechopen.76898

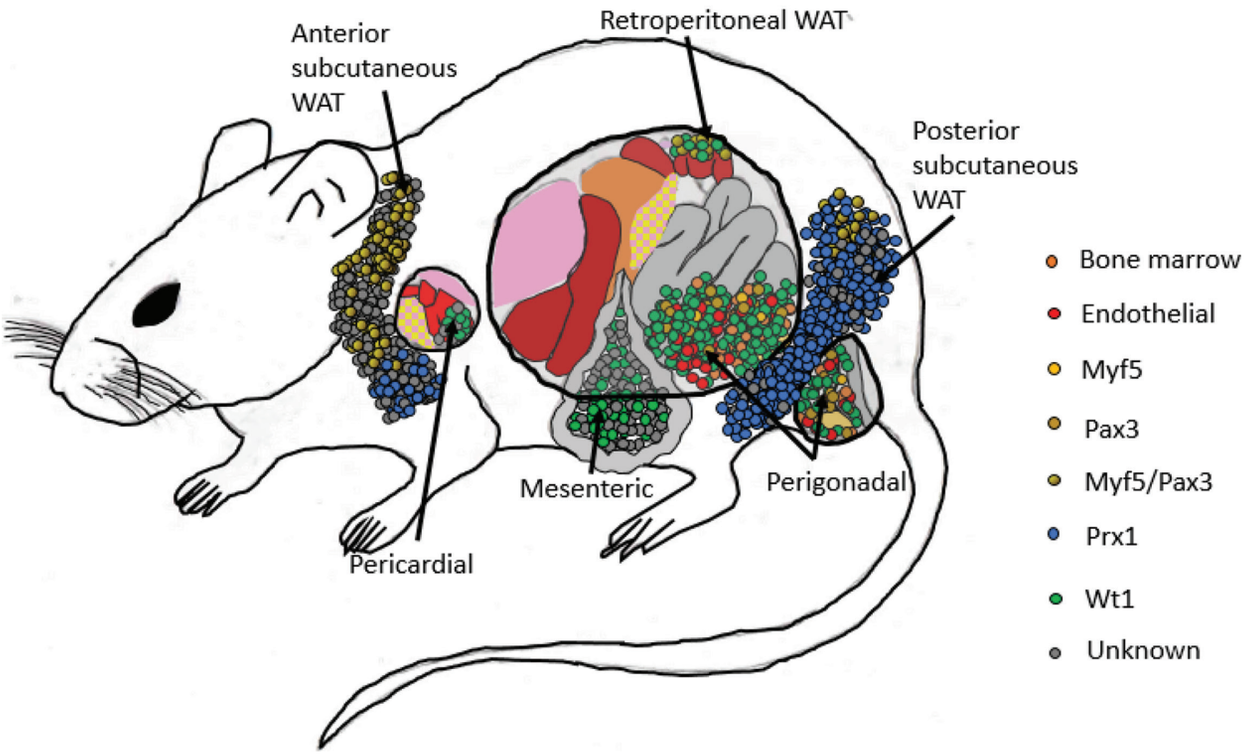

Figure 2. Intra-depot heterogeneity of WAT in mice. Bone marrow-derived adipocytes makes up about 5–10% perigonadal depot without induction of rosiglitazone or high-fat diet. Endothelial cell-derived adipocytes were also found in perigonadal depot. Myf5 and Pax3 share overlapping distribution, mostly in the anterior subcutaneous and retroperitoneal WAT. Prx1-derived pre-adipocytes were mostly found in the posterior subcutaneous WAT (75%), with a small degree in the anterior subcutaneous WAT (15%). Wt1-derived pre-adipocytes were present in only visceral depots including perigonadal (77%), pericardial (66%), retroperitoneum (50%), and mesenteric WAT (28%).

pro-inflammatory factor Pknox1, and leads to switch to M2 macrophages [224, 225]. Taken together, these studies and others demonstrate that miRNAs controls adipose tissue biology and obesity-associated pathologies through autocrine, paracrine, and endocrine actions.

7. Intra-depot heterogeneity of white adipose tissue

In addition to the differences between visceral and subcutaneous adipose tissue, growing evidence suggest that adipocytes, even within a single fat pad, are heterogeneous in nature. This heterogeneity is observable in metabolic measurements of adipocytes. These studies found that glucose uptake, lipogenesis, lipolytic response, lipid accumulation, glycolysis vs. oxidative phosphorylation, and uptake of fatty acids were markedly heterogeneous even within size-matched adipocytes of a single fat depot [226–230]. Similarly, heterogeneity in the lipolytic response of human omental adipocytes to catecholamines was previously described. These differences were at least in part, attributed to the expression of different adrenergic receptors [231]. Furthermore, ablation of hormone-sensitive lipase (HSL) or fat specific ablation of the insulin receptor lead to a polarization of adipocytes into large and small cells, thus unmasking an intrinsic heterogeneity [232, 233].

Lineage tracing analysis has been instrumental in elucidating both inter- and intra-depot heterogeneity, and the developmental origins of adipocyte lineages. In both chicken embryos and mouse embryos, populations of adipocytes in the head and thoracic regions are developmentally derived from neural crest cells [234, 235]. Although some reports suggest that adipocytes can be derived from an endothelial cell lineage both *in vitro* and i*n vivo* [236, 237], other reports dispute this claim [238]. Furthermore, studies indicate that a subset of visceral adipocytes are derived from a hematopoietic origin [239–241]. Another subpopulation of visceral adipocytes are derived from the mesothelial cells [242]. Finally, the myogenic lineage, once thought to only give rise to muscle and brown fat, gives rise to a subpopulation of white adipose tissue as well. This lineage, marked by the expression of myogenic factor 5 (Myf5) and paired box gene 3 (Pax3) give rise to adipocytes predominantly in the dorsal-anterior region, including adipocytes from the anterior subcutaneous and retroperitoneal visceral depot. This adipocyte subpopulation is dynamically distributed and its contribution to fat depots is altered in response to high fat diet and age [243] (**Figure 2**).

8. Conclusions

In summary, WAT is highly heterogeneous endocrine organ. The compartmentalization of adipose tissue into separate depots within the body is due to different developmental origins of the precursor cells. In addition, even within adipose tissue depots, individual adipocytes display developmental, genetic, and functional differences. The inter- and intra-depot heterogeneity of both preadipocytes and mature adipocytes have profound effects on whole-body metabolism, due to cell-autonomous differences in glucose and fatty acid metabolism. This heterogeneity also results in the differential inflammatory response between WAT depots. Furthermore, the differential expression of inflammatory cytokines, adipokines, and novel signaling molecules including lipokines and miRNAs between adipose depots impact the action not only of adipose tissue, but of other target tissues as well. Almost all of these factors are influenced by obesity, diet, gender, and age. Further studies to refine current knowledge on the heterogeneity of WAT may provide unique ways to manipulate physiology and lead new targets in the treatment of obesity and related disorders.

Acknowledgements

This work was supported by start-up funds from Ohio University College of Osteopathic Medicine (KYL), and the American Diabetes Association Junior Faculty Development Award 1-17-JDF-055 (KYL), and the John J Kopchick Fellowship (QL).

Conflict of interest

The authors declare that they have no conflict of interest.

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