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The Heterogeneity of White Adipose Tissue

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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
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]. 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,
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 underlying 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, 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 (cBMAs) and regulated BMA (rBMAs) [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, PPARγ 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 rodents, 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.
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 in 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.

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Conflict of interest

The authors declare that they have no conflict of interest.
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References

[1] Kwok KH, Lam KS, Xu A. Heterogeneity of white adipose tissue: Molecular basis and clinical implications. Experimental & Molecular Medicine. 2016;48:e215

[2] Feldmann HM et al. UCP1 ablation induces obesity and abolishes diet-induced thermogenesis in mice exempt from thermal stress by living at thermoneutrality. Cell Metabolism. 2009;9(2):203-209

[3] Enerback S et al. Mice lacking mitochondrial uncoupling protein are cold-sensitive but not obese. Nature. 1997;387(6628):90-94

[4] Giralt M, Villarroya F. White, brown, beige/brite: Different adipose cells for different functions? Endocrinology. 2013;154(9):2992-3000

[5] Wang QA et al. Tracking adipogenesis during white adipose tissue development, expansion and regeneration. Nature Medicine. 2013;19(10):1338-1344

[6] Vitali A et al. The adipose organ of obesity-prone C57BL/6J mice is composed of mixed white and brown adipocytes. Journal of Lipid Research. 2012;53(4):619-629

[7] Wang H et al. Browning of white adipose tissue with roscovitine induces a distinct population of UCP1(+) adipocytes. Cell Metabolism. 2016;24(6):835-847

[8] Shinoda K et al. Genetic and functional characterization of clonally derived adult human brown adipocytes. Nature Medicine. 2015;21(4):389-394

[9] Wu J et al. Beige adipocytes are a distinct type of thermogenic fat cell in mouse and human. Cell. 2012;150(2):366-376

[10] Saito M et al. High incidence of metabolically active brown adipose tissue in healthy adult humans: Effects of cold exposure and adiposity. Diabetes. 2009;58(7):1526-1531

[11] Virtanen KA et al. Functional brown adipose tissue in healthy adults. The New England Journal of Medicine. 2009;360(15):1518-1525

[12] Cypess AM et al. Identification and importance of brown adipose tissue in adult humans. The New England Journal of Medicine. 2009;360(15):1509-1517
van Marken Lichtenbelt WD et al. Cold-activated brown adipose tissue in healthy men. The New England Journal of Medicine. 2009;360(15):1500-1508

Stephens JM. The fat controller: Adipocyte development. PLoS Biology. 2012;10(11):e1001436

Gastaldelli A et al. Metabolic effects of visceral fat accumulation in type 2 diabetes. The Journal of Clinical Endocrinology and Metabolism. 2002;87(11):5098-5103

Kissebah AH et al. Relation of body fat distribution to metabolic complications of obesity. The Journal of Clinical Endocrinology and Metabolism. 1982;54(2):254-260

Zhang M et al. Associations of different adipose tissue depots with insulin resistance: A systematic review and meta-analysis of observational studies. Scientific Reports. 2015;5:18495

Cinti S. The adipose organ at a glance. Disease Models & Mechanisms. 2012;5(5):588-594

Misra A et al. Relationship of anterior and posterior subcutaneous abdominal fat to insulin sensitivity in nondiabetic men. Obesity Research. 1997;5(2):93-99

Chusyd DE et al. Relationships between rodent white adipose fat pads and human white adipose fat depots. Frontiers in Nutrition. 2016;3:10

Tchkonia T et al. Mechanisms and metabolic implications of regional differences among fat depots. Cell Metabolism. 2013;17(5):644-656

Snijder MB et al. Larger thigh and hip circumferences are associated with better glucose tolerance: The Hoorn study. Obesity Research. 2003;11(1):104-111

Tanko LB et al. Peripheral adiposity exhibits an independent dominant antiatherogenic effect in elderly women. Circulation. 2003;107(12):1626-1631

Kelley DE et al. Subdivisions of subcutaneous abdominal adipose tissue and insulin resistance. American Journal of Physiology. Endocrinology and Metabolism. 2000;278(5):E941-E948

Sackmann-Sala L et al. Heterogeneity among white adipose tissue depots in male C57BL/6J mice. Obesity (Silver Spring). 2012;20(1):101-111

Fernandez Munoz MJ et al. Epicardial adipose tissue is associated with visceral fat, metabolic syndrome, and insulin resistance in menopausal women. Revista Española de Cardiología (English ed.). 2014;67(6):436-441

Iacobellis G et al. Echocardiographic epicardial adipose tissue is related to anthropometric and clinical parameters of metabolic syndrome: A new indicator of cardiovascular risk. The Journal of Clinical Endocrinology and Metabolism. 2003;88(11):5163-5168

Rosito GA et al. Pericardial fat, visceral abdominal fat, cardiovascular disease risk factors, and vascular calcification in a community-based sample: The Framingham Heart Study. Circulation. 2008;117(5):605-613

Meenakshi K et al. Epicardial fat thickness: A surrogate marker of coronary artery disease—Assessment by echocardiography. Indian Heart Journal. 2016;68(3):336-341
[30] Cignarelli M, Lamacchia O. Obesity and kidney disease. Nutrition, Metabolism, and Cardiovascular Diseases. 2007;17(10):757-762
[31] Lamacchia O et al. Para- and perirenal fat thickness is an independent predictor of chronic kidney disease, increased renal resistance index and hyperuricaemia in type-2 diabetic patients. Nephrology, Dialysis, Transplantation. 2011;26(3):892-898
[32] Chughtai HL et al. Renal sinus fat and poor blood pressure control in middle-aged and elderly individuals at risk for cardiovascular events. Hypertension. 2010;56(5):901-906
[33] Ritz E, Koleganova N. Obesity and chronic kidney disease. Seminars in Nephrology. 2009;29(5):504-511
[34] Liu KH et al. Sonographic measurement of mesenteric fat thickness is a good correlate with cardiovascular risk factors: Comparison with subcutaneous and preperitoneal fat thickness, magnetic resonance imaging and anthropometric indexes. International Journal of Obesity and Related Metabolic Disorders. 2003;27(10):1267-1273
[35] Peyrin-Biroulet L et al. Mesenteric fat as a source of C reactive protein and as a target for bacterial translocation in Crohn’s disease. Gut. 2012;61(1):78-85
[36] Wueest S et al. Mesenteric fat lipolysis mediates obesity-associated hepatic Steatosis and insulin resistance. Diabetes. 2016;65(1):140-148
[37] Driskell RR et al. Defining dermal adipose tissue. Experimental Dermatology. 2014;23(9):629-631
[38] Wojciechowicz K et al. Development of the mouse dermal adipose layer occurs independently of subcutaneous adipose tissue and is marked by restricted early expression of FABP4. PLoS One. 2013;8(3):e59811
[39] Kruglikov IL, Scherer PE. Dermal adipocytes and hair cycling: Is spatial heterogeneity a characteristic feature of the dermal adipose tissue depot? Experimental Dermatology. 2016;25(4):258-262
[40] Matsumura H et al. Cones of skin occur where hypertrophic scar occurs. Wound Repair and Regeneration. 2001;9(4):269-277
[41] Marangozi RG et al. Myofibroblasts in murine cutaneous fibrosis originate from adiponectin-positive intradermal progenitors. Arthritis & Rheumatology. 2015;67(4):1062-1073
[42] Desai VD, Hsia HC, Schwarzbauer JE. Reversible modulation of myofibroblast differentiation in adipose-derived mesenchymal stem cells. PLoS One. 2014;9(1):e86865
[43] van den Broek LJ et al. Development, validation and testing of a human tissue engineered hypertrophic scar model. ALTEX. 2012;29(4):389-402
[44] Martins V et al. FIZZ1-induced myofibroblast transdifferentiation from adipocytes and its potential role in dermal fibrosis and lipoatrophy. The American Journal of Pathology. 2015;185(10):2768-2776
[45] Wu M et al. Rosiglitazone abrogates bleomycin-induced scleroderma and blocks profibrotic responses through peroxisome proliferator-activated receptor-gamma. The American Journal of Pathology. 2009;174(2):519-533
Schmidt BA, Horsley V. Intradermal adipocytes mediate fibroblast recruitment during skin wound healing. Development. 2013;140(7):1517-1527

Ohgo S et al. Bleomycin inhibits adipogenesis and accelerates fibrosis in the subcutaneous adipose layer through TGF-beta1. Experimental Dermatology. 2013;22(11):769-771

Festa E et al. Adipocyte lineage cells contribute to the skin stem cell niche to drive hair cycling. Cell. 2011;146(5):761-771

Kruglikov IL, Scherer PE. Skin aging: Are adipocytes the next target? Aging (Albany NY). 2016;8(7):1457-1469

Zhang LJ et al. Innate immunity. Dermal adipocytes protect against invasive Staphylococcus aureus skin infection. Science. 2015;347(6217):67-71

Kasza I et al. Syndecan-1 is required to maintain intradermal fat and prevent cold stress. PLoS Genetics. 2014;10(8):e1004514

Chen J et al. Osx-Cre targets multiple cell types besides osteoblast lineage in postnatal mice. PLoS One. 2014;9(1):e85161

Suchacki KJ, Cawthorn WP, Rosen CJ. Bone marrow adipose tissue: Formation, function and regulation. Current Opinion in Pharmacology. 2016;28:50-56

Scheller EL et al. Region-specific variation in the properties of skeletal adipocytes reveals regulated and constitutive marrow adipose tissues. Nature Communications. 2015;6:7808

Griffith JF et al. A study of bone marrow and subcutaneous fatty acid composition in subjects of varying bone mineral density. Bone. 2009;44(6):1092-1096

Poloni A et al. Molecular and functional characterization of human bone marrow adipocytes. Experimental Hematology. 2013;41(6):558-566 e2

Scheller EL et al. Marrow adipose tissue: Trimming the fat. Trends in Endocrinology and Metabolism. 2016;27(6):392-403

Hardouin P, Rharass T, Lucas S. Bone marrow adipose tissue: To be or not to be a typical adipose tissue? Frontiers in Endocrinology. 2016;7:85

Krings A et al. Bone marrow fat has brown adipose tissue characteristics, which are attenuated with aging and diabetes. Bone. 2012;50(2):546-552

Kajkenova O et al. Increased adipogenesis and myelopoiesis in the bone marrow of SAMP6, a murine model of defective osteoblastogenesis and low turnover osteopenia. Journal of Bone and Mineral Research. 1997;12(11):1772-1779

Justesen J et al. Adipocyte tissue volume in bone marrow is increased with aging and in patients with osteoporosis. Biogerontology. 2001;2(3):165-171

Syed FA et al. Effects of estrogen therapy on bone marrow adipocytes in postmenopausal osteoporotic women. Osteoporosis International. 2008;19(9):1323-1330
[63] Kurabayashi T et al. Effects of a beta 3 adrenergic receptor agonist on bone and bone marrow adipocytes in the tibia and lumbar spine of the ovariectomized rat. Calcified Tissue International. 2001;68(4):248-254

[64] Geer EB et al. Body composition and cardiovascular risk markers after remission of Cushing's disease: A prospective study using whole-body MRI. The Journal of Clinical Endocrinology and Metabolism. 2012;97(5):1702-1711

[65] Li GW et al. The temporal characterization of marrow lipids and adipocytes in a rabbit model of glucocorticoid-induced osteoporosis. Skeletal Radiology. 2013;42(9):1235-1244

[66] Cawthorn WP et al. Expansion of bone marrow adipose tissue during caloric restriction is associated with increased circulating glucocorticoids and not with hypoleptinemia. Endocrinology. 2016;157(2):508-521

[67] Hamrick MW et al. Leptin treatment induces loss of bone marrow adipocytes and increases bone formation in leptin-deficient ob/ob mice. Journal of Bone and Mineral Research. 2005;20(6):994-1001

[68] Bartell SM et al. Central (ICV) leptin injection increases bone formation, bone mineral density, muscle mass, serum IGF-1, and the expression of osteogenic genes in leptin-deficient ob/ob mice. Journal of Bone and Mineral Research. 2011;26(8):1710-1720

[69] Hamrick MW et al. Injections of leptin into rat ventromedial hypothalamus increase adipocyte apoptosis in peripheral fat and in bone marrow. Cell and Tissue Research. 2007;327(1):133-141

[70] Hamrick MW et al. Leptin deficiency produces contrasting phenotypes in bones of the limb and spine. Bone. 2004;34(3):376-383

[71] Halade GV et al. High fat diet-induced animal model of age-associated obesity and osteoporosis. The Journal of Nutritional Biochemistry. 2010;21(12):1162-1169

[72] Doucette CR et al. A high fat diet increases bone marrow adipose tissue (MAT) but does not alter trabecular or cortical bone mass in C57BL/6J mice. Journal of Cellular Physiology. 2015;230(9):2032-2037

[73] Shu L et al. High-fat diet causes bone loss in young mice by promoting osteoclastogenesis through alteration of the bone marrow environment. Calcified Tissue International. 2015;96(4):313-323

[74] Iwaniec UT, Turner RT. Failure to generate bone marrow adipocytes does not protect mice from ovariectomy-induced osteopenia. Bone. 2013;53(1):145-153

[75] Justesen J et al. Mice deficient in 11beta-hydroxysteroid dehydrogenase type 1 lack bone marrow adipocytes, but maintain normal bone formation. Endocrinology. 2004;145(4):1916-1925

[76] Yaturu S, Bryant B, Jain SK. Thiazolidinedione treatment decreases bone mineral density in type 2 diabetic men. Diabetes Care. 2007;30(6):1574-1576
[77] Tornvig L et al. Troglitazone treatment increases bone marrow adipose tissue volume but does not affect trabecular bone volume in mice. Calcified Tissue International. 2001;69(1):46-50

[78] Liu LF et al. Characterization of age-related gene expression profiling in bone marrow and epididymal adipocytes. BMC Genomics. 2011;12:212

[79] Liu LF et al. Age-related modulation of the effects of obesity on gene expression profiles of mouse bone marrow and epididymal adipocytes. PLoS One. 2013;8(8):e72367

[80] Bredella MA et al. Increased bone marrow fat in anorexia nervosa. The Journal of Clinical Endocrinology and Metabolism. 2009;94(6):2129-2136

[81] Cordes C et al. MR-detected changes in liver fat, abdominal fat, and vertebral bone marrow fat after a four-week calorie restriction in obese women. Journal of Magnetic Resonance Imaging. 2015;42(5):1272-1280

[82] Devlin MJ et al. Caloric restriction leads to high marrow adiposity and low bone mass in growing mice. Journal of Bone and Mineral Research. 2010;25(9):2078-2088

[83] Cawthorn WP et al. Bone marrow adipose tissue is an endocrine organ that contributes to increased circulating adiponectin during caloric restriction. Cell Metabolism. 2014;20(2):368-375

[84] Naveiras O et al. Bone-marrow adipocytes as negative regulators of the haematopoietic microenvironment. Nature. 2009;460(7252):259-263

[85] Takeshita S et al. Age-related marrow adipogenesis is linked to increased expression of RANKL. The Journal of Biological Chemistry. 2014;289(24):16699-16710

[86] Yeung DK et al. Osteoporosis is associated with increased marrow fat content and decreased marrow fat unsaturation: A proton MR spectroscopy study. Journal of Magnetic Resonance Imaging. 2005;22(2):279-285

[87] Sanchez-Gurmaches J, Hsiao WY, Guertin DA. Highly selective in vivo labeling of subcutaneous white adipocyte precursors with Prx1-Cre. Stem Cell Reports. 2015;4(4):541-550

[88] Macotela Y et al. Intrinsic differences in adipocyte precursor cells from different white fat depots. Diabetes. 2012;61(7):1691-1699

[89] Vohl MC et al. A survey of genes differentially expressed in subcutaneous and visceral adipose tissue in men. Obesity Research. 2004;12(8):1217-1222

[90] Tchoukalova YD et al. Sex- and depot-dependent differences in adipogenesis in normal-weight humans. Obesity (Silver Spring). 2010;18(10):1875-1880

[91] Tchkonia T et al. Identification of depot-specific human fat cell progenitors through distinct expression profiles and developmental gene patterns. American Journal of Physiology. Endocrinology and Metabolism. 2007;292(1):E298-E307

[92] Tchkonia T et al. Fat depot-specific characteristics are retained in strains derived from single human preadipocytes. Diabetes. 2006;55(9):2571-2578
[93] Tchkonia T et al. Fat depot origin affects adipogenesis in primary cultured and cloned human preadipocytes. American Journal of Physiology. Regulatory, Integrative and Comparative Physiology. 2002;282(5):R1286-R1296

[94] Lefebvre AM et al. Depot-specific differences in adipose tissue gene expression in lean and obese subjects. Diabetes. 1998;47(1):98-103

[95] Tchkonia T et al. Abundance of two human preadipocyte subtypes with distinct capacities for replication, adipogenesis, and apoptosis varies among fat depots. American Journal of Physiology. Endocrinology and Metabolism. 2005;288(1):E267-E277

[96] Kirkland JL, Hollenberg CH, Gillon WS. Two preadipocyte subtypes cloned from human omental fat. Obesity Research. 1993;1(2):87-91

[97] Lafontan M, Girard J. Impact of visceral adipose tissue on liver metabolism. Part I: Heterogeneity of adipose tissue and functional properties of visceral adipose tissue. Diabetes & Metabolism. 2008;34(4 Pt 1):317-327

[98] Arner P et al. Beta-adrenoceptor expression in human fat cells from different regions. The Journal of Clinical Investigation. 1990;86(5):1595-1600

[99] Ostman J et al. Regional differences in the control of lipolysis in human adipose tissue. Metabolism. 1979;28(12):1198-1205

[100] Richelsen B et al. Regional differences in triglyceride breakdown in human adipose tissue: Effects of catecholamines, insulin, and prostaglandin E2. Metabolism. 1991;40(9):990-996

[101] Berman DM et al. Regional differences in adrenoceptor binding and fat cell lipolysis in obese, postmenopausal women. Metabolism. 1998;47(4):467-473

[102] Kirkland JL, Hollenberg CH, Gillon WS. Age, anatomic site, and the replication and differentiation of adipocyte precursors. The American Journal of Physiology. 1990;258(2 Pt 1):C206-C210

[103] Wang H, Kirkland JL, Hollenberg CH. Varying capacities for replication of rat adipocyte precursor clones and adipose tissue growth. The Journal of Clinical Investigation. 1989;83(5):1741-1746

[104] Djian F, Roncari DA, Hollenberg CH. Adipocyte precursor clones vary in capacity for differentiation. Metabolism. 1985;34(9):880-883

[105] Wang Y et al. Comparison of abdominal adiposity and overall obesity in predicting risk of type 2 diabetes among men. The American Journal of Clinical Nutrition. 2005;81(3):555-563

[106] Carey VJ et al. Body fat distribution and risk of non-insulin-dependent diabetes mellitus in women. The Nurses' Health Study. American Journal of Epidemiology. 1997;145(7):614-619

[107] Nicklas BJ et al. Abdominal obesity is an independent risk factor for chronic heart failure in older people. Journal of the American Geriatrics Society. 2006;54(3):413-420
[108] Porter SA et al. Abdominal subcutaneous adipose tissue: A protective fat depot? Diabetes Care. 2009;32(6):1068-1075

[109] Tran TT et al. Beneficial effects of subcutaneous fat transplantation on metabolism. Cell Metabolism. 2008;7(5):410-420

[110] Stanford KI et al. A novel role for subcutaneous adipose tissue in exercise-induced improvements in glucose homeostasis. Diabetes. 2015;64(6):2002-2014

[111] Klein S et al. Absence of an effect of liposuction on insulin action and risk factors for coronary heart disease. The New England Journal of Medicine. 2004;350(25):2549-2557

[112] Gabriely I et al. Removal of visceral fat prevents insulin resistance and glucose intolerance of aging: An adipokine-mediated process? Diabetes. 2002;51(10):2951-2958

[113] Thorne A et al. A pilot study of long-term effects of a novel obesity treatment: Omentectomy in connection with adjustable gastric banding. International Journal of Obesity and Related Metabolic Disorders. 2002;26(2):193-199

[114] Willenborg S et al. CCR2 recruits an inflammatory macrophage subpopulation critical for angiogenesis in tissue repair. Blood. 2012;120(3):613-625

[115] Strissel KJ et al. Adipocyte death, adipose tissue remodeling, and obesity complications. Diabetes. 2007;56(12):2910-2918

[116] Nishimura S et al. Adipogenesis in obesity requires close interplay between differentiating adipocytes, stromal cells, and blood vessels. Diabetes. 2007;56(6):1517-1526

[117] He Q et al. Regulation of HIF-1alpha activity in adipose tissue by obesity-associated factors: Adipogenesis, insulin, and hypoxia. American Journal of Physiology. Endocrinology and Metabolism. 2011;300(5):E877-E885

[118] Rausch ME et al. Obesity in C57BL/6J mice is characterized by adipose tissue hypoxia and cytotoxic T-cell infiltration. International Journal of Obesity. 2008;32(3):451-463

[119] Ye J et al. Hypoxia is a potential risk factor for chronic inflammation and adiponecin reduction in adipose tissue of ob/ob and dietary obese mice. American Journal of Physiology. Endocrinology and Metabolism. 2007;293(4):E1118-E1128

[120] Pasarica M et al. Reduced adipose tissue oxygenation in human obesity: Evidence for rarefaction, macrophage chemotaxis, and inflammation without an angiogenic response. Diabetes. 2008;58(3):718-725

[121] Halberg N et al. Hypoxia-inducible factor 1alpha induces fibrosis and insulin resistance in white adipose tissue. Molecular and Cellular Biology. 2009;29(16):4467-4483

[122] Lee YS et al. Increased adipocyte O2 consumption triggers HIF-1alpha, causing inflammation and insulin resistance in obesity. Cell. 2014;157(6):1339-1352

[123] Sun K et al. Selective inhibition of hypoxia-inducible factor 1alpha ameliorates adipose tissue dysfunction. Molecular and Cellular Biology. 2013;33(5):904-917

[124] Weisberg SP et al. Obesity is associated with macrophage accumulation in adipose tissue. The Journal of Clinical Investigation. 2003;112(12):1796-1808
[125] Takahashi K et al. Adiposity elevates plasma MCP-1 levels leading to the increased CD11b-positive monocytes in mice. The Journal of Biological Chemistry. 2003;278(47):46654-46660

[126] Thomas D, Apovian C. Macrophage functions in lean and obese adipose tissue. Metabolism. 2017;72:120-143

[127] Cinti S et al. Adipocyte death defines macrophage localization and function in adipose tissue of obese mice and humans. Journal of Lipid Research. 2005;46(11):2347-2355

[128] Lumeng CN et al. Aging is associated with an increase in T cells and inflammatory macrophages in visceral adipose tissue. Journal of Immunology. 2011;187(12):6208-6216

[129] Kaplan JL et al. Adipocyte progenitor cells initiate monocyte chemoattractant protein-1-mediated macrophage accumulation in visceral adipose tissue. Molecular Metabolism. 2015;4(11):779-794

[130] Nishimura S et al. CD8+ effector T cells contribute to macrophage recruitment and adipose tissue inflammation in obesity. Nature Medicine. 2009;15(8):914-920

[131] Lee BC et al. Adipose natural killer cells regulate adipose tissue macrophages to promote insulin resistance in obesity. Cell Metabolism. 2016;23(4):685-698

[132] DeFuria J et al. B cells promote inflammation in obesity and type 2 diabetes through regulation of T-cell function and an inflammatory cytokine profile. Proceedings of the National Academy of Sciences of the United States of America. 2013;110(13):5133-8

[133] Poggi M et al. CD40L deficiency ameliorates adipose tissue inflammation and metabolic manifestations of obesity in mice. Arteriosclerosis, Thrombosis, and Vascular Biology. 2011;31(10):2251-2260

[134] Zhu F et al. Adipose tissue-resident regulatory T cells. Advances in Experimental Medicine and Biology. 2017;1011:153-162

[135] Bastard JP et al. Recent advances in the relationship between obesity, inflammation, and insulin resistance. European Cytokine Network. 2006;17(1):4-12

[136] Morin CL et al. Adipose tissue-derived tumor necrosis factor-alpha activity is elevated in older rats. The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences. 1997;52(4):B190-B195

[137] Arner E, Ryden M, Arner P. Tumor necrosis factor alpha and regulation of adipose tissue. The New England Journal of Medicine. 2010;362(12):1151-1153

[138] Bullo M et al. TNFalpha expression of subcutaneous adipose tissue in obese and morbid obese females: Relationship to adipocyte LPL activity and leptin synthesis. International Journal of Obesity and Related Metabolic Disorders. 2002;26(5):652-658

[139] Kern PA et al. The expression of tumor necrosis factor in human adipose tissue. Regulation by obesity, weight loss, and relationship to lipoprotein lipase. The Journal of Clinical Investigation. 1995;95(5):2111-2119

[140] Hotamisligil GS, Shargill NS, Spiegelman BM. Adipose expression of tumor necrosis factor-alpha: Direct role in obesity-linked insulin resistance. Science. 1993;259(5091):87-91
[141] Uysal KT et al. Protection from obesity-induced insulin resistance in mice lacking TNF-alpha function. Nature. 1997;389(6651):610-614

[142] Uysal KT, Wiesbrock SM, Hotamisligil GS. Functional analysis of tumor necrosis factor (TNF) receptors in TNF-alpha-mediated insulin resistance in genetic obesity. Endocrinology. 1998;139(12):4832-4838

[143] Hube F et al. Expression pattern of tumour necrosis factor receptors in subcutaneous and omental human adipose tissue: Role of obesity and non-insulin-dependent diabetes mellitus. European Journal of Clinical Investigation. 1999;29(8):672-678

[144] Mohamed-Ali V et al. Subcutaneous adipose tissue releases interleukin-6, but not tumour necrosis factor-alpha, in vivo. The Journal of Clinical Endocrinology and Metabolism. 1997;82(12):4196-4200

[145] Stanley TL et al. TNF-alpha antagonism with etanercept decreases glucose and increases the proportion of high molecular weight adiponectin in obese subjects with features of the metabolic syndrome. The Journal of Clinical Endocrinology and Metabolism. 2011;96(1):E146-E150

[146] Ofei F et al. Effects of an engineered human anti-TNF-alpha antibody (CDP571) on insulin sensitivity and glycemic control in patients with NIDDM. Diabetes. 1996;45(7):881-885

[147] Williams PM et al. CCAAT/enhancer binding protein expression is rapidly extinguished in TA1 adipocyte cells treated with tumor necrosis factor. Molecular Endocrinology. 1992;6(7):1135-1141

[148] Ishizuka K et al. Chronic tumor necrosis factor-alpha treatment causes insulin resistance via insulin receptor substrate-1 serine phosphorylation and suppressor of cytokine signaling-3 induction in 3T3-L1 adipocytes. Endocrinology. 2007;148(6):2994-3003

[149] Jin D et al. TNF-alpha reduces g0s2 expression and stimulates lipolysis through PPAR-gamma inhibition in 3T3-L1 adipocytes. Cytokine. 2014;69(2):196-205

[150] Ranjit S et al. Regulation of fat specific protein 27 by isoproterenol and TNF-alpha to control lipolysis in murine adipocytes. Journal of Lipid Research. 2011;52(2):221-236

[151] Lien CC et al. Short-term regulation of tumor necrosis factor-alpha-induced lipolysis in 3T3-L1 adipocytes is mediated through the inducible nitric oxide synthase/nitric oxide-dependent pathway. Endocrinology. 2009;150(11):4892-4900

[152] Ryden M et al. Mapping of early signaling events in tumor necrosis factor-alpha-mediated lipolysis in human fat cells. The Journal of Biological Chemistry. 2002;277(2):1085-1091

[153] Kawakami M et al. Human recombinant TNF suppresses lipoprotein lipase activity and stimulates lipolysis in 3T3-L1 cells. Journal of Biochemistry. 1987;101(2):331-338

[154] Niesler CU, Siddle K, Prins JB. Human preadipocytes display a depot-specific susceptibility to apoptosis. Diabetes. 1998;47(8):1365-1368
[155] Fried SK, Zechner R. Cachectin/tumor necrosis factor decreases human adipose tissue lipoprotein lipase mRNA levels, synthesis, and activity. Journal of Lipid Research. 1989;30(12):1917-1923

[156] Bastard JP et al. Elevated levels of interleukin 6 are reduced in serum and subcutaneous adipose tissue of obese women after weight loss. The Journal of Clinical Endocrinology and Metabolism. 2000;85(9):3338-3342

[157] Fried SK, Bunkin DA, Greenberg AS. Omental and subcutaneous adipose tissues of obese subjects release interleukin-6: Depot difference and regulation by glucocorticoid. The Journal of Clinical Endocrinology and Metabolism. 1998;83(3):847-850

[158] Mohamed-Ali V et al. Beta-adrenergic regulation of IL-6 release from adipose tissue: In vivo and in vitro studies. The Journal of Clinical Endocrinology and Metabolism. 2001;86(12):5864-5869

[159] Fontana L et al. Visceral fat adipokine secretion is associated with systemic inflammation in obese humans. Diabetes. 2007;56(4):1010-1013

[160] Meier CA et al. IL-1 receptor antagonist serum levels are increased in human obesity: A possible link to the resistance to leptin? The Journal of Clinical Endocrinology and Metabolism. 2002;87(3):1184-1188

[161] Larsen CM et al. Interleukin-1-receptor antagonist in type 2 diabetes mellitus. The New England Journal of Medicine. 2007;356(15):1517-1526

[162] Andersson N et al. Variants of the interleukin-1 receptor antagonist gene are associated with fat mass in men. International Journal of Obesity. 2009;33(5):525-533

[163] Rega G et al. Inflammatory cytokines interleukin-6 and oncostatin m induce plasminogen activator inhibitor-1 in human adipose tissue. Circulation. 2005;111(15):1938-1945

[164] Bastelica D et al. Stromal cells are the main plasminogen activator inhibitor-1-producing cells in human fat: Evidence of differences between visceral and subcutaneous deposits. Arteriosclerosis, Thrombosis, and Vascular Biology. 2002;22(1):173-178

[165] Alessi MC et al. Production of plasminogen activator inhibitor 1 by human adipose tissue: Possible link between visceral fat accumulation and vascular disease. Diabetes. 1997;46(5):860-867

[166] Ma LJ et al. Prevention of obesity and insulin resistance in mice lacking plasminogen activator inhibitor 1. Diabetes. 2004;53(2):336-346

[167] Liang X et al. Plasminogen activator inhibitor-1 modulates adipocyte differentiation. American Journal of Physiology. Endocrinology and Metabolism. 2006;290(1):E103-E113

[168] Fain JN et al. Comparison of the release of adipokines by adipose tissue, adipose tissue matrix, and adipocytes from visceral and subcutaneous abdominal adipose tissues of obese humans. Endocrinology. 2004;145(5):2273-2282
Lihn AS et al. Lower expression of adiponectin mRNA in visceral adipose tissue in lean and obese subjects. Molecular and Cellular Endocrinology. 2004;219(1-2):9-15

Atzmon G et al. Differential gene expression between visceral and subcutaneous fat depots. Hormone and Metabolic Research. 2002;34(11-12):622-628

Motoshima H et al. Differential regulation of adiponectin secretion from cultured human omental and subcutaneous adipocytes: Effects of insulin and rosiglitazone. The Journal of Clinical Endocrinology and Metabolism. 2002;87(12):5662-5667

Sharma K et al. Adiponectin regulates albuminuria and podocyte function in mice. The Journal of Clinical Investigation. 2008;118(5):1645-1656

Clement K et al. A mutation in the human leptin receptor gene causes obesity and pituitary dysfunction. Nature. 1998;392(6674):398-401

Montague CT et al. Congenital leptin deficiency is associated with severe early-onset obesity in humans. Nature. 1997;387(6636):903-908

Chen H et al. Evidence that the diabetes gene encodes the leptin receptor: Identification of a mutation in the leptin receptor gene in db/db mice. Cell. 1996;84(3):491-495

Zhang Y et al. Positional cloning of the mouse obese gene and its human homologue. Nature. 1994;372(6505):425-432

Montague CT et al. Depot- and sex-specific differences in human leptin mRNA expression: Implications for the control of regional fat distribution. Diabetes. 1997;46(3):342-347

Montague CT et al. Depot-related gene expression in human subcutaneous and omental adipocytes. Diabetes. 1998;47(9):1384-1391

Curat CA et al. Macrophages in human visceral adipose tissue: Increased accumulation in obesity and a source of resistin and visfatin. Diabetologia. 2006;49(4):744-747

Patel L et al. Resistin is expressed in human macrophages and directly regulated by PPAR gamma activators. Biochemical and Biophysical Research Communications. 2003;300(2):472-476

Steppan CM et al. The hormone resistin links obesity to diabetes. Nature. 2001;409(6818):307-312

McTernan PG et al. Increased resistin gene and protein expression in human abdominal adipose tissue. The Journal of Clinical Endocrinology and Metabolism. 2002;87(5):2407

Muse ED et al. Role of resistin in diet-induced hepatic insulin resistance. The Journal of Clinical Investigation. 2004;114(2):232-239

Banerjee RR et al. Regulation of fasted blood glucose by resistin. Science. 2004;303(5661):1195-1198

Qatanani M et al. Macrophage-derived human resistin exacerbates adipose tissue inflammation and insulin resistance in mice. The Journal of Clinical Investigation. 2009;119(3):531-539
[186] Fukuhara A et al. Visfatin: A protein secreted by visceral fat that mimics the effects of insulin. Science. 2005;307(5708):426-430

[187] Berndt J et al. Plasma visfatin concentrations and fat depot-specific mRNA expression in humans. Diabetes. 2005;54(10):2911-2916

[188] Yang Q et al. Serum retinol binding protein 4 contributes to insulin resistance in obesity and type 2 diabetes. Nature. 2005;436(7049):356-362

[189] Kloting N et al. Serum retinol-binding protein is more highly expressed in visceral than in subcutaneous adipose tissue and is a marker of intra-abdominal fat mass. Cell Metabolism. 2007;6(1):79-87

[190] Graham TE et al. Retinol-binding protein 4 and insulin resistance in lean, obese, and diabetic subjects. The New England Journal of Medicine. 2006;354(24):2552-2563

[191] Boucher J et al. Apelin, a newly identified adipokine up-regulated by insulin and obesity. Endocrinology. 2005;146(4):1764-1771

[192] Than A et al. Apelin enhances brown adipogenesis and browning of white adipocytes. The Journal of Biological Chemistry. 2015;290(23):14679-14691

[193] Sawane M et al. Apelin inhibits diet-induced obesity by enhancing lymphatic and blood vessel integrity. Diabetes. 2013;62(6):1970-1980

[194] Cao H et al. Identification of a lipokine, a lipid hormone linking adipose tissue to systemic metabolism. Cell. 2008;134(6):933-944

[195] Syed I et al. Palmitic acid hydroxystearic acids activate GPR40, which is involved in their beneficial effects on glucose homeostasis. Cell Metabolism. 2018;27(2):419-427 e4

[196] Yore MM et al. Discovery of a class of endogenous mammalian lipids with anti-diabetic and anti-inflammatory effects. Cell. 2014;159(2):318-332

[197] Lynes MD et al. The cold-induced lipokine 12,13-diHOME promotes fatty acid transport into brown adipose tissue. Nature Medicine. 2017;23(5):631-637

[198] Brandao BB, Guerra BA, Mori MA. Shortcuts to a functional adipose tissue: The role of small non-coding RNAs. Redox Biology. 2017;12:82-102

[199] Hilton C, Neville MJ, Karpe F. MicroRNAs in adipose tissue: Their role in adipogenesis and obesity. International Journal of Obesity. 2013;37(3):325-332

[200] Icli B, Feinberg MW. MicroRNAs in dysfunctional adipose tissue: Cardiovascular implications. Cardiovascular Research. 2017;113(9):1024-1034

[201] Reis FC et al. Fat-specific dicer deficiency accelerates aging and mitigates several effects of dietary restriction in mice. Aging (Albany NY). 2016;8(6):1201-1222

[202] Mori MA et al. Altered miRNA processing disrupts brown/white adipocyte determination and associates with lipodystrophy. The Journal of Clinical Investigation. 2014;124(8):3339-3351

[203] Thomou T et al. Adipose-derived circulating miRNAs regulate gene expression in other tissues. Nature. 2017;542(7642):450-455
Ying W et al. Adipose tissue macrophage-derived exosomal miRNAs can modulate in vivo and in vitro insulin sensitivity. Cell. 2017;171(2):372-384 e12

Kloeting N et al. MicroRNA expression in human omental and subcutaneous adipose tissue. PLoS One. 2009;4(3):e4699

Kim YJ et al. MicroRNA 21 regulates the proliferation of human adipose tissue-derived mesenchymal stem cells and high-fat diet-induced obesity alters microRNA 21 expression in white adipose tissues. Journal of Cellular Physiology. 2012;227(1):183-193

Kim YJ et al. MiR-21 regulates adipogenic differentiation through the modulation of TGF-beta signaling in mesenchymal stem cells derived from human adipose tissue. Stem Cells. 2009;27(12):3093-3102

Guglielmi V et al. MicroRNA 21 is up-regulated in adipose tissue of obese diabetic subjects. Nutrition and Healthy Aging. 2017;4(2):141-145

Stockl S et al. Sox9 modulates proliferation and expression of osteogenic markers of adipose-derived stem cells (ASC). Cellular Physiology and Biochemistry. 2013;31(4-5):703-717

Wang Y, Sul HS. Pref-1 regulates mesenchymal cell commitment and differentiation through Sox9. Cell Metabolism. 2009;9(3):287-302

Ling HY et al. MicroRNA-375 promotes 3T3-L1 adipocyte differentiation through modulation of extracellular signal-regulated kinase signalling. Clinical and Experimental Pharmacology & Physiology. 2011;38(4):239-246

Esau C et al. MicroRNA-143 regulates adipocyte differentiation. The Journal of Biological Chemistry. 2004;279(50):52361-52365

Xie H, Lim B, Lodish HF. MicroRNAs induced during adipogenesis that accelerate fat cell development are downregulated in obesity. Diabetes. 2009;58(5):1050-1057

Martinelli R et al. miR-519d overexpression is associated with human obesity. Obesity (Silver Spring). 2010;18(11):2170-2176

Nardelli C et al. Changes in the microRNA profile observed in the subcutaneous adipose tissue of obese patients after laparoscopic adjustable gastric banding. Journal of Obesity. 2017;2017:6754734

Lin Q et al. A role of miR-27 in the regulation of adipogenesis. The FEBS Journal. 2009;276(8):2348-2358

Lee EK et al. miR-130 suppresses adipogenesis by inhibiting peroxisome proliferator-activated receptor gamma expression. Molecular and Cellular Biology. 2011;31(4):626-638

Trajkovski M et al. MicroRNAs 103 and 107 regulate insulin sensitivity. Nature. 2011;474(7353):649-653

Karolina DS et al. MicroRNA 144 impairs insulin signaling by inhibiting the expression of insulin receptor substrate 1 in type 2 diabetes mellitus. PLoS One. 2011;6(8):e22839
[220] Mi L et al. MicroRNA-139-5p suppresses 3T3-L1 preadipocyte differentiation through notch and IRS1/PI3K/Akt insulin signaling pathways. Journal of Cellular Biochemistry. 2015;116(7):1195-1204

[221] Chuang TY et al. MicroRNA-223 expression is upregulated in insulin resistant human adipose tissue. Journal of Diabetes Research. 2015;2015:943659

[222] Chen YH et al. miRNA-93 inhibits GLUT4 and is overexpressed in adipose tissue of polycystic ovary syndrome patients and women with insulin resistance. Diabetes. 2013;62(7):2278-2286

[223] Arner E et al. Adipose tissue microRNAs as regulators of CCL2 production in human obesity. Diabetes. 2012;61(8):1986-1993

[224] Zhuang G et al. A novel regulator of macrophage activation: miR-223 in obesity-associated adipose tissue inflammation. Circulation. 2012;125(23):2892-2903

[225] Deiuliis JA et al. Visceral adipose microRNA 223 is upregulated in human and murine obesity and modulates the inflammatory phenotype of macrophages. PLoS One. 2016;11(11):e0165962

[226] Varlamov O et al. Cell-autonomous heterogeneity of nutrient uptake in white adipose tissue of rhesus macaques. Endocrinology. 2015;156(1):80-89

[227] Gliemann J, Vinten J. Lipogenesis and insulin sensitivity of single fat cells. The Journal of Physiology. 1974;236(3):499-516

[228] Salans LB, Dougherty JW. The effect of insulin upon glucose metabolism by adipose cells of different size. Influence of cell lipid and protein content, age, and nutritional state. Journal of Clinical Investigation. 1971;50(7):1399-1410

[229] Katz LS, Geras-Raaka E, Gershengorn MC. Heritability of fat accumulation in white adipocytes. American Journal of Physiology. Endocrinology and Metabolism. 2014;307(3):E335-E344

[230] Lee KY et al. Tbx15 defines a glycolytic subpopulation and white adipocyte heterogeneity. Diabetes. 2017;66(11):2822-2829

[231] Seydoux J et al. Adrenoceptor heterogeneity in human white adipocytes differentiated in culture as assessed by cytosolic free calcium measurements. Cellular Signalling. 1996;8(2):117-122

[232] Wang SP et al. The adipose tissue phenotype of hormone-sensitive lipase deficiency in mice. Obesity Research. 2001;9(2):119-128

[233] Bluher M et al. Intrinsic heterogeneity in adipose tissue of fat-specific insulin receptor knock-out mice is associated with differences in patterns of gene expression. The Journal of Biological Chemistry. 2004;279(30):31891-31901

[234] Le Lievre CS, Le Douarin NM. Mesenchymal derivatives of the neural crest: Analysis of chimaeric quail and chick embryos. Journal of Embryology and Experimental Morphology. 1975;34(1):125-154
[235] Billon N et al. The generation of adipocytes by the neural crest. Development. 2007;134(12):2283-2292

[236] Tran KV et al. The vascular endothelium of the adipose tissue gives rise to both white and brown fat cells. Cell Metabolism. 2012;15(2):222-229

[237] Li H et al. Adipogenic potential of adipose stem cell subpopulations. Plastic and Reconstructive Surgery. 2011;128(3):663-672

[238] Berry R, Rodeheffer MS. Characterization of the adipocyte cellular lineage in vivo. Nature Cell Biology. 2013;15(3):302-308

[239] Crossno JT Jr et al. Rosiglitazone promotes development of a novel adipocyte population from bone marrow-derived circulating progenitor cells. The Journal of Clinical Investigation. 2006;116(12):3220-3228

[240] Majka SM et al. De novo generation of white adipocytes from the myeloid lineage via mesenchymal intermediates is age, adipose depot, and gender specific. Proceedings of the National Academy of Sciences of the United States of America. 2010;107(33):14781-14786

[241] Majka SM et al. Adipose lineage specification of bone marrow-derived myeloid cells. Adipocytes. 2012;1(4):215-229

[242] Chau YY et al. Visceral and subcutaneous fat have different origins and evidence supports a mesothelial source. Nature Cell Biology. 2014;16(4):367-375

[243] Sanchez-Gurmaches J, Guertin DA. Adipocytes arise from multiple lineages that are heterogeneously and dynamically distributed. Nature Communications. 2014;5:4099