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Altered adipose tissue and adipocyte function in the pathogenesis of metabolic syndrome

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Over the past decade, great progress has been made in understanding the complexity of adipose tissue biology and its role in metabolism. This includes new insights into the multiple layers of adipose tissue heterogeneity, not only differences between white and brown adipocytes, but also differences in white adipose tissue at the depot level and even heterogeneity of white adipocytes within a single depot. These inter- and intra-depot differences in adipocytes are developmentally programmed and contribute to the wide range of effects observed in disorders with fat excess (overweight/obesity) or fat loss (lipodystrophy). Recent studies also highlight the underappreciated dynamic nature of adipose tissue, including potential to undergo rapid turnover and dedifferentiation and as a source of stem cells. Finally, we explore the rapidly expanding field of adipose tissue as an endocrine organ, and how adipose tissue communicates with other tissues to regulate systemic metabolism both centrally and peripherally through secretion of adipocyte-derived peptide hormones, inflammatory mediators, signaling lipids, and miRNAs packaged in exosomes. Together these attributes and complexities create a robust, multidimensional signaling network that is central to metabolic homeostasis.

Obesity, i.e., increased adipose tissue mass, is a major driving force in insulin resistance and the pathogenesis of type 2 diabetes (T2D) and metabolic syndrome. Over the past decade it has become clear that this association depends not only on the balance between energy intake and utilization, but also on the balance between white fat, which is the primary site of energy storage, and brown and beige adipose tissue, which are sites for energy expenditure (1, 2). On the other hand, lipodystrophy, i.e., complete or partial loss of body fat, can also be associated with insulin resistance and metabolic syndrome (3). These diametrically opposed states illustrate the complex interaction between body fat and the control of metabolism. In addition, some people appear metabolically healthy despite obesity, and there is growing evidence that this may reflect the fact that white adipose tissue is heterogeneous and that different classes of adipocytes have differing metabolism and ability to communicate with other tissues by secretion of peptides, lipids, and miRNAs, which affect systemic metabolism differently (4–6). In this Review, we will explore these relationships, focusing on some of the newest aspects linking adipose tissue to the control of whole-body metabolism.

Heterogeneity of adipose tissue at multiple levels

Adipose tissue is classically divided based on anatomic location and major cell type constituent (Figure 1A). Histologically, there are three major types of adipose tissue: white adipose tissue (WAT), which represents more than 95% of adipose mass; brown adipose tissue (BAT), which represents 1% to 2% of fat and, in humans, occurs in small collections in the cervical, axillary, and paraspinal regions; and beige/brite adipose tissue, which is difficult to quantitate but represents cells interspersed within WAT that are capable of transforming into brown-like adipocytes following cold exposure or adrenergic stimulation. In contrast to white adipocytes, which have a large unilocular lipid droplet, brown and beige adipocytes have multilocular droplets and high mitochondrial density for dissipation of energy through uncoupled mitochondrial respiration, a feature that could potentially be used to combat obesity (1, 2). In vivo, the abundance of BAT and, to some extent, beige fat can be estimated using PET/CT with 2-deoxy-2-[^{18}F]fluoroglucose (1, 2), xenon-enhanced CT (7), and, in mice, luciferase-based markers (8); however, these techniques all depend on functional aspects of brown and beige fat and do not necessarily represent the actual mass of tissue.

In addition, it is important to keep in mind that adipocytes only make up a portion of the adipose depot and that adipose tissue contains other cell types that contribute to its physiology and pathophysiology, including preadipocytes, mesenchymal stem cells, vascular cells, and inflammatory cells. While there is no specific marker for preadipocytes, studies suggest that these may come from vascular mural cells, pericytes, and/or adventitial fibroblasts and include adipogenic and fibrogenic subtypes (9–11). Fat also contains dipeptidyl peptidase-4–expressing (DPP4$^+$) multipotent progenitors that give rise to committed preadipocytes and CD142$^+$ cells, which have anti-adipogenic properties (12). In addition, a fibroblast population that secretes fibroblast-specific protein-1 (FSP1$^+$ fibroblasts) is important for maintaining the preadipocyte pool (13).

Depot-specific differences between visceral and subcutaneous adipose tissue. Anatomically, WAT is divided into visceral and subcutaneous depots. Accumulation of visceral intra-abdominal

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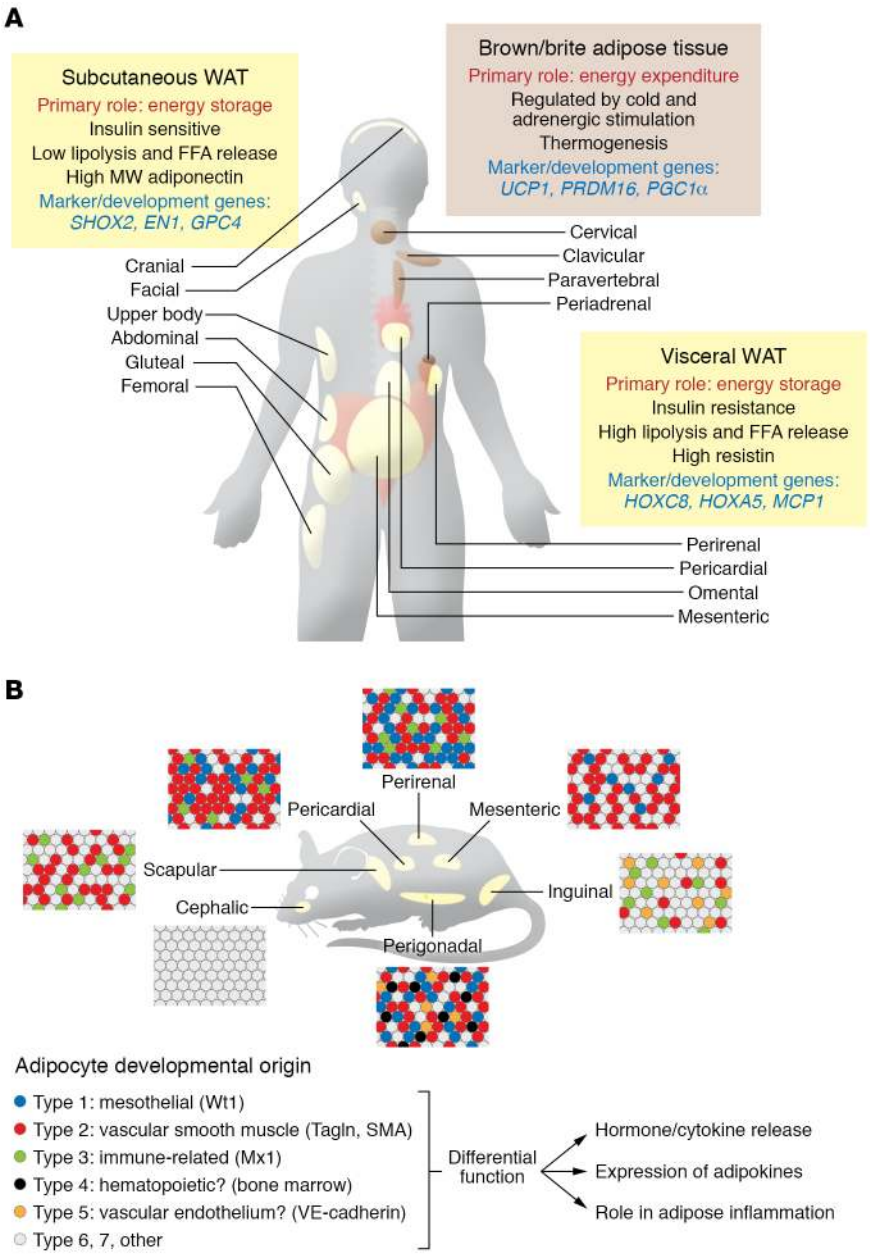

Figure 1. Heterogeneity of adipose tissue at multiple levels. (**A**) Human adipose tissue illustrating the multiple depots of brown and white subcutaneous and visceral fat. The different roles, properties, and marker/development genes of these depots are indicated. (**B**) Heterogeneity of adipose tissue in the mouse, showing different depots of white adipose tissue, each containing a mixture of white adipocytes of different subtypes.

WAT, i.e., central obesity, is associated with insulin resistance and increased risk of metabolic disease, whereas accumulation of subcutaneous WAT, i.e., fat in the hips and flanks, has no adverse effect and may even be protective against metabolic syndrome (14, 15). Indeed, studies have shown lower cardiovascular risk in individuals with subcutaneous obesity, independent of whether they have visceral obesity (16, 17). In rodents, transplantation of subcutaneous WAT improves glucose metabolism, indicating that these depot effects are mediated, at least in part, by cell-autonomous differences, not simply anatomical position (18, 19). Consistent with this, subcutaneous preadipocytes have increased rates of proliferation and lipid accumulation (20, 21), whereas visceral adipocytes have increased rates of lipolysis and increased susceptibility to apoptosis (22, 23). Many of these differences are due to variations in gene expression, including the expression of developmental genes (21, 24–26). Thus, subcutaneous adipocytes/preadipocytes have higher expression of short stature homeobox 2 (Shox2) and glypican-4 (GPC4), which repress lipolysis and insulin sensitivity, respectively (24–27), whereas visceral adipose tissue has higher levels of HoxC8 and HoxA5, which regulate browning and adipogenesis (28, 29).

In addition to subcutaneous and visceral fat, WAT in other depots may have distinct functions and effects on metabolism. White adipocytes within dermal layers are developmentally distinct from subcutaneous WAT (30) and play roles in wound healing, hair development, and pathogen resistance (31). Bone marrow adipose tissue (MAT) is also a distinct depot and includes two distinct subtypes (32): constitutive MAT (cMAT), concentrated in the distal skeletal bones, and regulated MAT (rMAT), which is diffusely distributed in the spine and proximal limb bones and is regulated in response to environmental factors (33, 34). MAT plays important roles in bone metabolism and osteoblastic activity (35). Interestingly, MAT is not depleted in calorically deficient states and may be a major source of circulating adiponectin (36, 37).

Intra-depot heterogeneity in adipose tissue. A growing body of evidence indicates that adipocytes, even within a single fat pad, are heterogeneous in nature both genetically and metabolically (Figure 1B and refs. 38–41). This was initially suggested by a bimodal size distribution of adipocytes in mice with fat-specific ablation of the insulin receptor or hormone-sensitive lipase (HSL) (42, 43). Recent studies using clonal cell analysis and single-cell RNA-Seq further highlight this heterogeneity. Thus, white preadipocytes with low levels of CD9 are more adipogenic, whereas preadipocytes with high CD9 are more profibrotic and proinflammatory (44). By combining clonal analysis and lineage tracing, Lee et al. identified at least three functionally and developmentally distinct subpopulations of white preadipocytes in mice characterized by unique gene expression profiles and high expression of the marker genes Wilms tumor-1 (Wt1), transgelin, and myxovirus-1 (Mx1), termed types 1–3, respectively (45). Likewise, single-cell transcriptomic profiling of human preadipocytes and mesenchymal progenitor cells (46) has identified up to four adipocyte subtypes, including a beige/brite thermogenic subtype and a subtype specialized for leptin secretion.

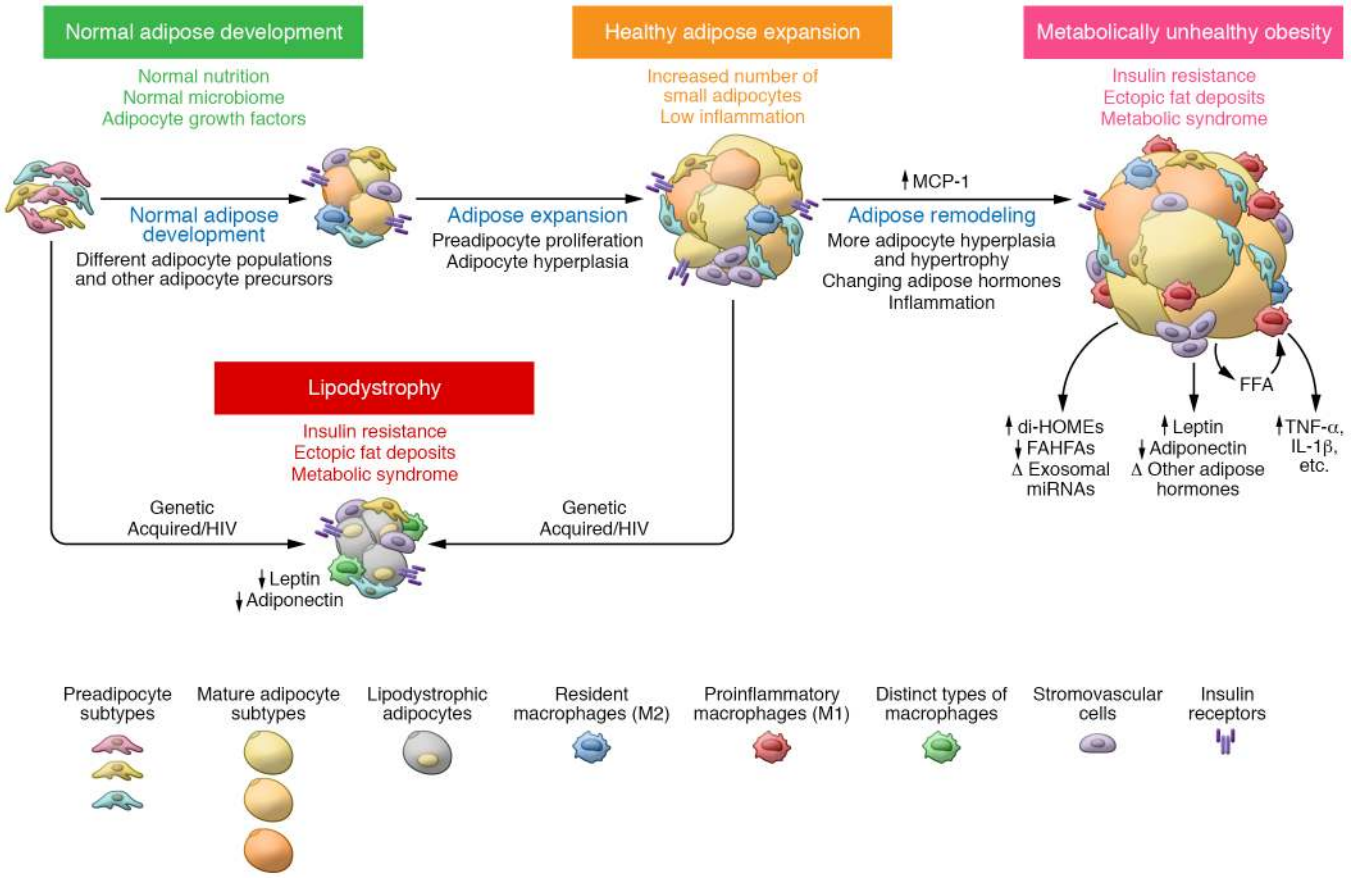

Figure 2. Adipose tissue development and remodeling in health and disease. From left to right, the figure illustrates the conversion of preadipocytes to mature adipocytes followed by adipose expansion due to preadipocyte proliferation and hyperplasia of adipocytes followed by adipocyte hypertrophy, adipose tissue inflammation, and changes in adipocyte hormone leading to insulin resistance. In lipodystrophy this process is also disrupted, leading to insulin resistance.

Lineage tracing has also provided insights into different developmental origins of white adipocytes. Using a tetracycline transactivator under the control of the PPARγ gene locus, Tang et al. demonstrated that preadipocytes can be found within the mural cell compartment of the adipose vasculature (9). A subset of these preadipocytes, marked by smooth muscle actin (SMA), was found to be important in adipose tissue homeostasis later in life (47). Transgelin (also called smooth muscle-22α) is also highly expressed in vascular smooth muscle and pericytes, suggestive of similar mural origin, and marks a subset of adipocytes in all depots (45, 48). Some adipose progenitor cells can be labeled by endothelial-specific VE-cadherin-Cre, and the preadipocyte marker Zfp423 is found in both mural and vascular endothelial precursors, further supporting the idea of a vascular origin of preadipocytes (49).

The visceral mesothelium, which covers internal organs, has been shown to contribute to adipocyte lineages in visceral and cardiac adipose depots. This subpopulation of adipocytes has reduced triglyceride accumulation and highly glycolytic metabolism (45). Mesothelial cells are highly responsive to inflammatory signals and secrete high levels of IL-6 and IL-8 following stimulation (50, 51), suggesting a potential role for mesothelial-derived adipocytes in the inflammatory response in visceral fat.

Most adipose originates from the mesoderm. Lineage tracing using the paraxial mesoderm–specific genes *Meox1*, *Pax3/7*, and *Myf5*, originally thought to give rise only to brown adipocytes and skeletal muscle, also gives rise to subsets of white adipocytes in retroperitoneal and interscapular depots (52, 53). By contrast, lateral plate mesoderm, marked by HoxB6, contributes to posterior and ventral adipose depots, including inguinal, mesenteric, and perigonadal WAT of mice (Figure 2B). Lineage tracing has shown that Prx1-expressing progenitors gives rise to a majority of subcutaneous, but not visceral, adipocytes (54, 55). A subset of visceral white adipocytes may be bone marrow–derived from hematopoietic lineages (56), although this has been challenged (10). Finally, a subset of adipocytes in the face and neck are derived from neural crest progenitors marked by Wnt1 and Sox10 (57, 58), although over time they are replaced by mesodermal-derived adipocytes (59).

Brown and beige adipocytes also display intrinsic heterogeneity and a broad range of thermogenic competency (60–62). Similarly, beige adipocytes demonstrate distinct subpopulations with differences in the expression of regulators of lipid synthesis and oxidation (63). Beige/brite adipocytes may also be derived from different developmental sources, including a vascular smooth muscle origin (64). Lastly, a developmentally distinct type of glycolytic beige fat has been described (65). Molecular characterizations of BAT in adult humans suggest that it may be composed of both conventional brown fat cells and beige/brite adipocytes (61, 62).

Lipodystrophy – clinical evidence of adipocyte heterogeneity

Lipodystrophies encompass a range of genetic and acquired disorders in which the body is unable to produce/maintain adipose tissue, resulting in either partial or generalized loss of fat (66). The effects of absence of adipose tissue on metabolism are strikingly similar to those found in individuals with an excess of adipose tissue, i.e., severe insulin resistance, hypertriglyceridemia, hepatic steatosis, and metabolic syndrome (3, 67), indicating the critical role of maintaining an optimal adipose tissue mass in the regulation of metabolism. One common feature of obesity and lipodystrophy is the diversion of excess calories into formation of ectopic fat in other tissues, including liver, skeletal muscle, and pancreatic β cells. This ectopic fat deposition is thought to directly drive insulin resistance (68, 69). The concept that adipose tissue provides protection against ectopic storage is supported by mouse models overexpressing adiponectin or with knockout of collagen VI, both of which allow for uninhibited expansion of adipose tissue and improved glucose and insulin sensitivity (70, 71). This is also observed in mouse models with genetic or pharmacological inhibition of lipolysis and β-oxidation (72, 73). In addition to lipid storage, the low levels of adiponectin and leptin in patients with lipodystrophy may play important roles in mediating the severe insulin resistance and metabolic complications. Leptin infusion into lipodystrophic patients or mice improves insulin sensitivity and decreases hepatic and circulating triglycerides (74, 75).

The abnormal distributions of adipose tissue seen in partial lipodystrophies support the concept of developmental and functional heterogeneity of adipose tissue. Dunnigan-type familial partial lipodystrophy is characterized by the loss of subcutaneous fat in the extremities and trunk, but an accrual of fat in the visceral and head/neck regions (76, 77). Similarly, patients with mutations in the p85α regulatory subunit of PI3K, which is critical for adipocyte differentiation, are characterized by selective lipoatrophy of subcutaneous and facial fat (78), and patients with Barraquer-Simons syndrome have selective loss of upper body fat (79). Although many of the genes implicated in various forms of partial lipodystrophy, including those encoding PPARγ, CIDEC, perilipin-1, and AKT-2, are known to have critical roles in adipocyte biology, why these lead to loss (or gain) of fat in particular regions remains unknown (80–82). Finally, an acquired form of lipoatrophy associated with increased dorsocervical adipose tissue (buffalo hump) is observed in treated HIV patients and has been attributed to changes in transcription factors and miRNAs involved in differentiation and increased adipocyte apoptosis (83, 84).

Adipose tissue turnover

In terms of mass, WAT is the most variable and dynamic tissue in the body, ranging from less than 2% to more than 70% of body weight. The dramatic increase in fat mass in obesity can occur through adipocyte hypertrophy, i.e., enlargement due to lipid accumulation, and adipocyte hyperplasia, i.e., proliferation/differentiation of preadipocytes resulting in increased numbers of adipocytes (Figure 2 and ref. 14). In general, the total number of fat cells is set during childhood and remains constant through adulthood (85, 86), but may be increased with early-onset obesity and in some depots in adults by overfeeding (87).

Taking advantage of changes in atmospheric ^{14}C, Spalding et al. have shown that in humans approximately 10% of adipocytes are replaced every year, regardless of age or obesity, whereas the half-life of adipocyte triglycerides is only approximately 1.6 years (86). Individuals with hypertrophic obesity tend to produce fewer adipocytes than individuals with hyperplastic obesity (88). While heavy water labeling suggests that adipocyte and triglyceride turnover may be higher (89), studies using multi-isotope imaging mass spectrometry find similar results to the atmospheric ^{14}C studies (90). Likewise, basal adipocyte turnover is very low in rodents, but can be accelerated by high-fat diet (HFD) feeding (91). The effect is depot-specific and higher in visceral versus subcutaneous fat (92). Lineage tracing studies show that adipogenesis increases in visceral fat within 4 weeks of HFD feeding (93). The full capacity for adipose tissue regeneration is observed in models in which adipose tissue is acutely ablated, such as the Fat-AATC mouse (in which apoptosis in adipose tissue is induced by activation of caspase-8) (94) and mice with fat-specific inducible knockout of the insulin receptor and IGF-1R (95). Both lead to rapid fat loss followed by rapid induction of preadipocyte proliferation and differentiation, producing new populations of brown and white adipocytes to restore fat tissues and resolve the metabolic syndrome within 10–30 days. These results suggest the presence of a feedback mechanism that attempts to maintain adipose tissue mass.

Adipocyte dedifferentiation. Recent work suggests that adipocytes can also dedifferentiate back into pluripotent progenitor cells in vivo in both healthy and pathological conditions (96, 97). Lineage tracing has demonstrated that "pink" adipocytes in mouse mammary gland can give rise to mammary epithelial cells during lactation, then revert back to adipocytes during involution (98), although these reports have been challenged by others who find that it is adipocyte progenitors that transition into epithelial cells (99). Adipocyte dedifferentiation has also been linked to some cancers, including breast cancer (100), suggesting the therapeutic potential of PPARγ agonist treatment to revert some breast cancer cells into adipocytes. Dedifferentiated white adipocytes may also represent a source of stem cells to repair cardiac tissue and spinal cord injuries (101, 102). Adipocytes in dermal WAT can revert into myofibroblasts and contribute to wound healing (31).

Adipose tissue as an endocrine organ

Adipocyte hormones. Over the past two decades it has become clear that in addition to their roles in energy storage, adipose tissues are endocrine organs secreting a large number of factors with hormonal, autocrine, and paracrine properties (Figure 3). While a complete review of these adipocyte hormones is beyond the scope of this Review, many of them have important effects on metabolism.

Leptin is a 16-kDa protein produced primarily by white adipocytes that acts on leptin receptors (LEPR/LepR) in the hypothalamus to suppress feeding and increase energy expenditure (103, 104). While LEPR has multiple isoforms, leptin's metabolic actions are mediated by the long-form LepRb, whose cytoplasmic tail associates with the Jak2 tyrosine kinase to mediate intracellular signaling. This engages multiple downstream molecules, including SHP-2 and STAT3, which regulate ERK activation and suppressor of cytokine signaling 3 (SOCS3) as well as PI3K (105). Mice and humans with mutations in leptin or LEPR are massively

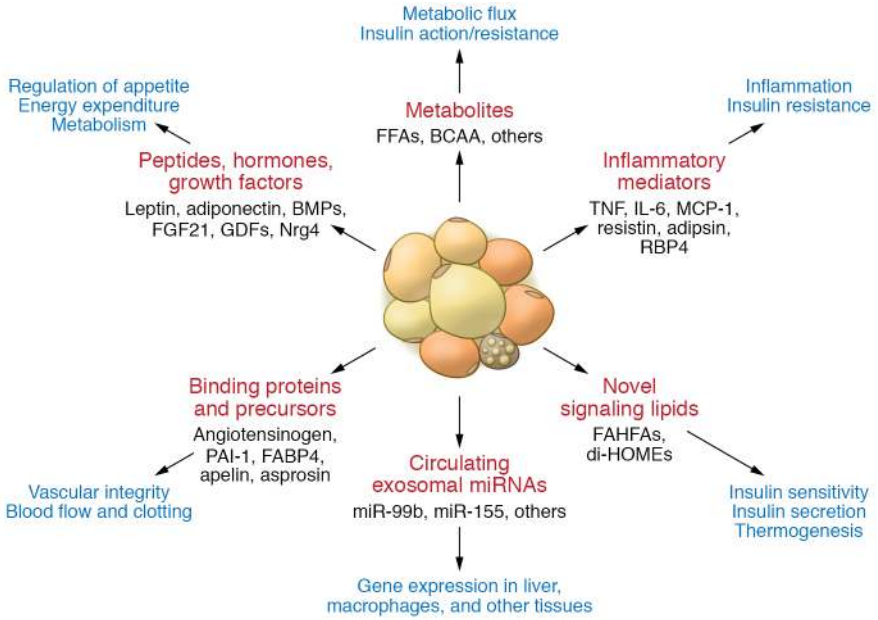

Figure 3. Adipocyte hormones in intertissue communication. The figure illustrates different classes of adipocyte hormones and their varied effects on metabolism and the development of insulin sensitivity or resistance. BCAA, branched-chain amino acids; GDF, growth differentiation factor ; Nrg4, neuroregulin 4.

obese and hyperphagic (106–108). In humans or mice with obesity due to mutations in the leptin gene, treatment with recombinant leptin restores near-normal health. Unfortunately, common forms of human obesity do not respond to leptin, indicating leptin resistance (108, 109). Physiologically, leptin may be most important when its levels are low. In fasting or starvation, low leptin creates a strong stimulus for increased food intake and decreased energy expenditure (110, 111), and leptin replacement during fasting prevents starvation-induced changes in the hypothalamic-pituitary axis through actions on expression of corticotropin-releasing hormone, thyrotropin-releasing hormone, and gonadotropin-releasing hormone (112, 113). Some peripheral tissues also express LEPRs, contributing to leptin effects on bone, immune cells, and angiogenesis. Leptin treatment lowers blood glucose in mouse models of insulin-deficient diabetes, suggesting possible use in type 1 diabetes; however, this has not been shown in humans (114).

Adiponectin is an approximately 30-kDa protein produced in both white and brown adipocytes, with the highest levels in subcutaneous WAT. Paradoxically, adiponectin levels are high when fat mass is low and vice versa. Adiponectin circulates as a range of multimers, from trimers to high–molecular weight (HMW) dodecamers (115, 116). HMW adiponectin appears to account for most of its effects (117). Adiponectin levels are markedly elevated in patients with severe insulin resistance due to anti–insulin receptor antibodies or insulin receptor mutations, suggesting feedback between insulin resistance and adiponectin secretion (118). Adiponectin acts to improve insulin sensitivity through two atypical seven-transmembrane receptors. In muscle, adiponectin acts through AdipoR1 to activate AMPK; in liver, adiponectin acts on both AdipoR1 and AdipoR2 to suppress hepatic glucose output (119, 120). Whether the latter effect occurs through AMPK or increased ceramidase activity is controversial (121, 122). In addition, adiponectin can act in the CNS to stimulate appetite, reduce energy expenditure, and perhaps affect neurodegeneration (123, 124); on endothelial cells, it affects angiogenesis (125, 126).

In addition to leptin and adiponectin, adipose tissue produces a number of other peptide adipocyte hormones linked to insulin resistance and metabolic syndrome. Resistin is an approximately 12-kDa polypeptide. In mice, resistin is produced mainly by visceral WAT and was shown to induce insulin resistance through a mechanism involving SOCS3 activation (127, 128). In humans, resistin is produced mainly by macrophages, and its role in insulin resistance is less clear (129). Retinol-binding protein 4 (RBP4) is also produced by visceral adipocytes and other tissues, especially liver (130, 131). RBP4 can activate promote adipose tissue inflammation, thus contributing to insulin resistance (130, 132). Other peptide adipocyte hormones include apelin, which has three active peptides potentially involved in regulating cardiovascular function (133, 134); omentin, an insulin-sensitizing peptide produced by non-adipocyte cells in adipose depots (135); vaspin, a serine protease inhibitor thought to act as an insulin sensitizer (135); nesfatin-1, a peptide derived from nucleobinding-2 suggested to potentiate glucose-induced insulin secretion from β cells (136); DPP4, the peptidase that degrades GLP-1 (137); and asprosin, a cleavage product of the fibrillin-1 gene, which stimulates hepatic glucose release (138).

Adipose tissue is also a source of multiple growth factors, including FGF21, BMPs, TGF-β, VEGFs, and growth differentiation factors. BMPs such as BMP2, BMP4, BMP7, and BMP8b not only come from fat but also play important roles in fat. BMP2 and BMP4 stimulate white adipocyte differentiation (139, 140), whereas BMP7 is critical for brown adipocyte development (141). BMP4 also plays a role in development and browning of WAT, while BMP8b enhances BAT's response to β_3-adrenergic stimulation (142). VEGF-A, a potent angiogenic factor, is expressed in both white and brown adipocytes (143) and is important in sustaining adequate circulation to adipose tissue (144, 145). Finally, adipose tissue is a site for production of neurotrophic factors such as NGF, Nrg4, and the semaphorins, which play a particularly important role in innervation of BAT.

Adipose tissue and inflammatory crosstalk in insulin resistance

Inflammation in adipose tissue is a characteristic of obesity and is marked by secretion of multiple inflammatory cytokines and proteins of the alternate complement system, as well as infiltration of adipose tissue with macrophages and leukocytes. Evidence for a role of inflammation as a component of T2D dates to the century-old observation that high doses of sodium salicylate reduce blood glucose in people with T2D (146). This occurs through inhibition of the IKKβ/NF-κB pathway and improvement in insulin sensitivity (147, 148). Epidemiologically, T2D is associated with increased levels of markers/mediators of inflammation, including C-reactive protein, IL-6, plasminogen activator inhibitor-1 (PAI-1), and TNF-α (reviewed in ref. 149). TNF-α expression is increased in adipose tissue in rodent models of obesity and diabetes (150), where it induces insulin resistance by impairing insulin receptor and insulin receptor substrate-1 (IRS-1) phosphorylation (151). Neutralizing TNF-α increases peripheral tissue glucose uptake in obese diabetic rats (150). Although one clinical trial showed that targeting TNF-α can reduce hyperglycemia in patients with metabolic syndrome (152), most studies report no beneficial effect of TNF-α antagonism on insulin sensitivity (153, 154), questioning TNF-α's role as the causative link between adipose tissue inflammation and insulin resistance in humans.

In obesity, adipose tissue undergoes remodeling during which macrophages infiltrate the tissue and secrete multiple proinflammatory cytokines. Increased expression of monocyte chemoattractant protein-1 (MCP-1) is seen as early as 3 weeks after HFD feeding in rodents; however, the number of macrophages in WAT does not increase until 10 to 16 weeks later (155), suggesting that adipose tissue inflammation could be an adaptive response to insulin resistance rather than its cause. Indeed, immunocompromised mice develop a degree of insulin resistance similar to that in controls after short-term HFD feeding (156). Supporting the idea that proinflammatory signaling in adipocytes may be required for healthy expansion of visceral WAT, an impaired proinflammatory response in adipocytes can lead to ectopic lipid accumulation and glucose intolerance in mice on HFD (157). It has also been suggested that an ineffective inflammatory response in mesenteric WAT could allow gut microbial–derived antigens to enter the circulation and serve as triggers for systemic inflammation (157).

In addition to increased macrophage number, the polarity of adipose tissue macrophages also changes during obesity progression (158). In obesity, there is an increase in M1 (classically activated) macrophages, while alternatively activated M2 macrophages are reduced. This change is thought to occur through proinflammatory mediators, such as lipopolysaccharide. T cells have also been found in adipose tissue, and their composition changes as obesity progresses, with increased infiltration of $CD8^+$ cytotoxic T cells and decreased presence of regulatory T cells (159, 160). These changes precede macrophage infiltration. Drugs that block the effects of proinflammatory cytokines, such as CCL2 antagonists and IL-1R antagonists, reduce systemic inflammation and improve glycemic control in obese/diabetic rodents (161). Amlexanox, an inhibitor of noncanonical IκB kinases IKKε and TBK1, also shows beneficial effects in both rodents and humans (162, 163).

Emerging evidence suggests that adipose tissue fibrosis also plays a role in the regulation of adipose tissue health (see ref. 164, this issue of the *JCI*). Clinical studies report a link between excess extracellular matrix accumulation in subcutaneous WAT and insulin resistance (165). Importantly, repression of adipose tissue fibrosis by whole-body collagen VI knockout (71) or adipose tissue–specific repression of profibrosis program (166) significantly improves glucose metabolism, suggesting that adipose tissue fibrosis is more than just a morphological marker of dysfunctional fat.

Signaling lipids as adipocyte hormones

The normal physiology of lipid storage as triglycerides and release as free fatty acids (FFA) and glycerol means that adipose tissue is a site of high lipid flux. In addition, adipose tissue may secrete specialized signaling lipid species that mediate communication between adipose tissues and other tissues.

One class are the branched fatty acid esters of hydroxyl fatty acids called branched fatty acid esters of hydroxy fatty acids (FAHFAs) (167). These were discovered to be markedly elevated in mice with Glut4 overexpression in adipose tissue and were associated with the improved metabolic phenotype in these mice (167). FAHFAs may have varying fatty acid composition, including palmitoleic acid, palmitic acid, or oleic acid as the fatty acid moiety, and hydroxyl–palmitic acid or hydroxyl–steric acid as the hydroxyl–fatty acid moiety, creating many isoforms. The effects of palmitic acid-hydroxy-stearic acids (PAHSAs) have been studied in the most detail. Serum PAHSA levels are decreased in insulin-resistant humans and positively correlate with insulin sensitivity (167). Oral gavage of 5-PAHSA and 9-PAHSA reduces blood glucose levels in HFD-fed mice and improves glucose tolerance in both chow- and HFD-fed mice (167). Chronic PAHSA administration in HFD-fed mice improves insulin sensitivity and glucose tolerance (168). Mechanistically, PAHSAs exert their beneficial effects through activating GPR120 and GPR40 (167, 168). Knockdown or blockade of GPR120 reverses the enhanced insulin-stimulated glucose transport in PAHSA-treated adipocytes (167). Blocking GPR40 inhibits PAHSA augmentation of glucose-stimulated insulin secretion from islets (167, 168). Less abundant fatty acids, such as docosahexaenoic acid (DHA), can also be incorporated into novel FAHFAs if provided externally (169). Both human and murine WAT can synthesize several kinds of DHA hydroxyl–linoleic acid (DHAHLA). 13-DHA-HLA demonstrates antiinflammatory properties and reduces LPS-induced macrophage activation (169). Although enzymes responsible for FAHFA synthesis have not been identified, four FAHFA-specific hydrolases, AIG1, ADTRP, CEL, and Ces3/CES1, have been identified (170, 171). These inhibitors could serve as a new class of antidiabetic and antiinflammatory drugs.

A second class of lipid adipocyte hormones are the diHOMEs, products of linoleic acid metabolism, such as 12,13-dihydroxy-9Z-octadecenoic acid (12,13-diHOME). Lynes et al. have shown that 12,13-diHOME is elevated in BAT versus WAT, and its levels in BAT and serum increase upon cold exposure in humans and rodents (172). 12,13-diHOME then acts back on BAT to increase fatty acid uptake, resulting in enhanced cold tolerance (172). Increased release of 12,13-diHOME in BAT has also been observed following exercise, and its actions on skeletal muscle increase fatty acid uptake and oxidation (173). Recently, 12,13-diHOME was also identified in peripheral nervous tissues in response to inflammatory pain (174). Thus, induction of 12,13-diHOME in BAT might be part of a stress response.

Exosomal miRNAs as novel adipocyte "hormones"

miRNAs are small noncoding RNAs of approximately 22 nt produced by all cells of the body (175). miRNAs play important roles in differentiation and function of brown, beige, and white fat (83, 176, 177). In addition, miRNA expression in adipose tissue differs between obese and lean humans (178, 179), and levels of these miRNAs variably correlate with BMI, glycemia, and insulin resistance. The importance of miRNAs in adipose development/function is illustrated by the fact that adipocyte-specific knockout of the miRNA-processing enzyme DICER (ADicerKO) or its partner DGCR8 (ADgcr8KO) in mice produces partial lipodystrophy and insulin resistance (83, 180, 181).

There is growing evidence that fat is a major source of circulating miRNAs and that miRNAs secreted by adipocytes, especially those in extracellular vesicles or exosomes, may participate in intertissue communication and serve as novel adipose hormones. Thus, ADicerKO mice exhibit significant decreases in about half of circulating exosomal miRNAs (6). Circulating exosomal miRNAs are also decreased in humans with genetic or HIV-related lipodystrophy, and in the latter this is associated with a decrease in DICER in adipose tissue (6, 84). These adipose-derived circulating miRNAs can act on other tissues like liver and muscle to modulate mRNA translation and stability (6, 182). An example of an adipose-derived circulating miRNA contributing to the control of metabolic homeostasis is the regulation of liver FGF21 by adipose-derived miR-99b (6). Accordingly, ADicerKO mice have reduced levels of miR-99b in circulating exosomes and upregulation of *Fgf21* mRNA and its 3′-UTR reporter activity in liver (6), which can be partially corrected by administration of exosomes loaded with miR-99b. ADicerKO mice exhibit a wide range of phenotypes reflecting dysfunction in other nonadipose tissues, as well as systemic insulin resistance (83, 181), suggesting that this is a generalized mechanism of intertissue communication.

Since adipose tissue is a major contributor to circulating exosomal miRNAs, it is not surprising that circulating miRNAs are altered in individuals with obesity, lipodystrophy, T2D, and metabolic syndrome, and may contribute to insulin resistance in these diseases (6, 183–187). In obese humans and rodents, there is upregulation of miR-122, miR-142-3p, miR-192, miR-222, and miR-378a and downregulation of miR-138 and miR-221 (188–190). Among these, miR-222 is a negative regulator of insulin sensitivity in adipocytes, where it reduces GLUT4-mediated glucose uptake (191), and hepatocytes, where it targets IRS-1 (192). miR-222 levels increase in blood (193, 194) and fat (195) with obesity (193–195). Circulating miR-222 is both found in exosomes and associated with HDL (196, 197). Mice injected with exosomes containing miR-122 mimetics develop metabolic dysfunction with insulin resistance and dyslipidemia (190). Likewise, miR-155 released in exosomes from adipose tissue macrophages during inflammation has been shown to be transferred to adipocytes, myotubes, or hepatocytes, where it worsens insulin resistance (182).

Adipose-derived exosomal miRNAs may also serve paracrine functions. Thus, miRNA-containing vesicles released from large adipocytes can be transferred to small adipocytes and stimulate lipogenesis and adipocyte hypertrophy (198). Secretion of miRNAs by adipocytes may also be regulated by FFA and H_2O_2 (198), indicating that signals promoting lipid accumulation and insulin resistance may spread from insulin-resistant adipocytes to newly formed adipocytes. Conversely, amelioration of metabolic dysfunction by weight loss may be due in part to changes in circulating miRNAs (199). In addition, miRNAs differentially released in the circulation of obese versus lean subjects may act on the TGF-β pathway, thus providing a link to nonalcoholic fatty liver disease (200, 201). This may be part of a more complex regulatory loop in which TGF-β induces adipocyte secretion of miR-130b, which is then transferred to muscle, where it acts to reduce the expression of PGC-1α, reducing muscle oxidative metabolism (202). Skeletal muscle is also responsive to miR-27a, which is present in adipose-derived exosomes and induces insulin resistance via PPARγ repression (203). Serum levels of miR-27a are positively associated with obesity and insulin resistance in children and in mice with obesity, indicating that miR-27a may be another modulator of obesity-associated insulin resistance (203).

Inflammation in adipose tissue and liver may also be mediated, in part, by circulating adipocyte-derived exosomes. Mice injected with extracellular vesicles from adipose tissue of obese mice develop increased levels of circulating IL-6 and TNF-α and develop insulin resistance (204). This appears to be controlled by miR-155, which can target SOCS1 in macrophages, promote STAT1 signaling, and suppress STAT6 signaling, thereby promoting M1 macrophage polarization (205). Conversely, it has been shown that extracellular vesicles from adipose tissue macrophages of obese mice, which contain miR-155, can induce insulin resistance when administrated to lean mice or incubated in vitro with adipocytes, myocytes, or hepatocytes, and knockout of miR-155 in HFD-fed mice results in improved insulin sensitivity (182). This effect is reversed by transplantation of WT bone marrow, further supporting a role for exosomal miRNAs in adipocyte-macrophage crosstalk (206, 207). Exosomes secreted by adipose-derived stem cells may also contribute to effects on macrophages (208) and vascular integrity in obesity (209, 210). Together these data indicate that adipose tissue is a major contributor to circulating exosomal miRNAs and that adipose-derived exosomes may possess hormone-like functions, communicating with other tissues to coordinate metabolic homeostasis and energy balance. When these systems are perturbed, they may also contribute importantly to the pathophysiology of metabolic diseases.

Targeting adipose tissue to treat metabolic syndrome

From the evidence above, it is clear that targeting adipose tissue and its signaling molecules can provide unique opportunities to better understand the pathophysiology and treatment of obesity, insulin resistance, T2D, and metabolic syndrome. While considerable effort has already been made to target the inflammation in adipose tissue as a component of insulin resistance and some work has been devoted to finding AdipoR agonists, there remains great opportunity to find mimics or antagonists of other adipose hormones. This includes not only the peptide adipose hormones, but also bioactive signaling lipids secreted by white and brown fat. Adipose-secreted exosomal miRNAs might also provide new diagnostics to distinguish metabolically healthy versus metabolically unhealthy obesity and new approaches to deliver miRNAs that target genes in liver and other tissues to regulate metabolic syndrome. Finally, understand-

ing the heterogeneity of adipose tissue — both from the perspective of white, brown, and beige fat and within WAT itself — offers a unique opportunity to develop drugs that can change distribution of adipose tissue as well as shift it from a metabolically unhealthy subtype to a more metabolically healthy subtype. With modern technologies, all of these opportunities are within the reach of reality.

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