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Review

Advances in Adipose Tissue Biology

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Abstract

Adipose tissue has emerged as a central regulator of human physiology, with its dysfunction driving the global rise in obesity-associated diseases, such as type 2 diabetes, cardiovascular and liver diseases, and several cancers. Once thought to be inert, adipocytes are now recognized as dynamic, responsive cells essential for energy homeostasis and interorgan communication, including the brain. Distinct adipose depots support specialized functions across development, sex, and aging. Technologies like single-cell RNA sequencing are unraveling depot-specific mechanisms, with the potential of identifying new therapeutic targets. This review highlights major scientific advancements leading to our current appreciation of the pivotal role of adipose tissue in health and disease. Many key discoveries in this field have been catalyzed by National Institutes of Health funding, particularly through the National Institute of Diabetes, Digestive and Kidney Diseases, now celebrating its 75th anniversary.

Key Words: adipose tissue, obesity, energy homeostasis, depots, type 2 diabetes, adipocytes

Abbreviations: 12,13-diHOME, 12,13-dihydroxy-(9Z)-octadecenoic acid; 12-HEPE, 12-hydroxy-5Z,8Z,10E,14Z,17Z-eicosapentaenoic acid; AR, adrenergic receptor; ASPC, adipose stromal and progenitor cell; BAT, brown adipose tissue; BMI, body mass index; Chrna2, cholinergic receptor nicotinic alpha 2 subunit; EV, extracellular vesicle; FAHFA, Fatty acid esters of hydroxy fatty acid; FGF21, fibroblast growth factor 21; IL-6, interleukin 6; ISM1, isthmin-1; iWAT, inguinal white adipose tissue; MASH, metabolic dysfunction–associated steatohepatitis; MASLD, metabolic dysfunction–associated steatotic liver disease; miRNA, microRNA; NPY, neuropeptide Y; NRG4, neuregulin 4; PKA, protein kinase A; PPAR, peroxisome proliferator-activated receptor; SNS, sympathetic nervous system; Sparcl1, secreted protein acidic and rich in cysteine-like 1; UCP1, uncoupling protein 1; Upd2, unpaired 2; WAT, white adipose tissue.

Essential Points

- Adipose tissue is a pivotal regulator of metabolic homeostasis, and its dysfunction is causally linked to the pathogenesis of obesity-associated comorbidities, including type 2 diabetes, cardiovascular disease, nonalcoholic fatty liver disease, and some cancers
- Recent advances—particularly single-cell and single-nucleus RNA sequencing—have enabled unprecedented resolution of adipose tissue cellular composition in both human and animal models
- Adipocytes orchestrate whole-body homeostasis via the secretion of bioactive molecules that engage in crosstalk with multiple organ systems, including the brain, enabling adaptation to nutritional and environmental stresses
- Adipose tissue exhibits pronounced sex-specific functional and developmental differences, influencing processes such as pregnancy, lactation, and differential aging trajectories

Adipose Tissue Depots and Cellular Composition

Global deaths and disability-adjusted life years associated with abnormal adipose tissue doubled from 1990 to 2017 (1), with increased risk of type 2 diabetes mellitus, ischemic heart disease, asthma, chronic obstructive pulmonary disease,

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and nonalcoholic fatty liver disease. In addition, metabolic dysfunction is associated with cancers of the digestive system, uterus, kidney, and bladder (2). Unraveling how normal adipose tissue function protects against these diseases will not only help address the consequences of obesity but also enable approaches to mitigate other environmental stresses and age-associated disease risks.

Adipose depots are ensembles of cells distributed throughout the body (Fig. 1). Depots are classified primarily by location but also by function. Visceral adipose tissue is stored primarily in the abdominal cavity and around the internal organs and includes mesenteric (attached to the intestines), omental (stomach, spleen to ventral abdomen), retroperitoneal (peritoneum, kidneys and pancreas), perirenal (kidneys), gonadal (ovaries and uterus in females, epididymis and testes in males), and pericardial (heart) (Fig. 1). Subcutaneous adipose tissue is located beneath the skin and includes deep and superficial adipose in the glutes and thigh regions. Brown adipose tissue is located above the clavicle in the supraclavicular and in the subscapular areas. There are many depot-specific functions; for example, subcutaneous adipose tissue is generally regarded as a safer energy storage site, linked to better metabolic health and exhibits greater thermogenic potential. In contrast, visceral adipocytes are associated with a pro-inflammatory profile and an increased risk of metabolic disorders. Importantly, adipocytes are also found intermuscularly and intra-muscularly, in breast tissue, and in yellow bone marrow, where their abundance increases with aging (3). The precise role of adipocytes in other sites in the body is an important unresolved question. It is also important to note that these roles may vary depending on the species. For example, gonadal adipose tissue is not as prominent in humans as it is in some rodents.

The cellular composition of adipose tissue has been revealed in recent years through the application of single-cell and single-nuclei RNA sequencing (4-6). A comprehensive study leveraging both technologies has provided single-cell and single-nuclei RNA transcriptomic data from subcutaneous and visceral depots of both humans and mice under normal conditions and metabolic stress, allowing inter-depot and inter-species comparisons (7). In addition, several recently integrated datasets and knowledge portals are being produced to harmonize the communities' efforts to fully understand the development and function of diverse adipose tissue depots both in humans and animal models (8, 9).

Cells in adipose tissue include adipocytes, adipose stromal and progenitor cells (ASPCs), endothelial cells, pericytes, smooth muscle cells, mesothelial cells, Schwann cells and immune cells including B cells, T cells, NK cells, innate lymphoid cells, dendritic cells, neutrophils, monocytes, macrophages, and mast cells (Fig. 1). The proportion of these cells varies with species, depot, sex, and metabolic state. Cells of adipose tissue interact with each other, ensuring that tissue integrity is maintained under conditions of growth, stress, or injury (10-12). Below we review some of the main findings related to adipose tissue cell types.

Adipocytes

Adipocytes are the defining cell of adipose tissue. They are characterized by specialized lipid droplets capable of storing and releasing free fatty acids, depending on systemic signals. Adipocytes are unique in their ability to efficiently store excess energy as triglycerides in lipid droplets, mobilize these stores during periods of energy demand or in response to cold stress, and regulate systemic energy balance through the secretion of adipokines. This unique combination of metabolic, signaling, and storage capacities positions adipocytes at the center of energy homeostasis in the body.

White adipocytes

White adipocytes are the predominant cell type in most adipose depots, including the subcutaneous, various visceral depots, bone marrow, and the supraclavicular and paravertebral regions (Fig. 1). They are characterized by their large size and the presence of a single, unilocular lipid droplet. This large droplet allows white adipocytes to store energy in the form of triglycerides, which can be mobilized through lipolysis in response to catabolic hormonal signals and cellular energy demands. Under fed conditions, white adipocytes take up lipids from circulating lipoproteins for storage; during fasting, exercise, or cold exposure, they release fatty acids into the circulation to support systemic energy needs. Beyond their role in energy storage and mobilization, white adipocytes also function as endocrine cells, secreting a broad array of hormones and metabolites (13). Key adipokines such as leptin help regulate appetite and metabolic homeostasis. Other secreted factors—including cytokines, chemokines, and angiogenic and neurogenic molecules—extend the influence of adipocytes well beyond energy metabolism.

Brown adipocytes

Brown adipocytes predominate in the interscapular brown adipose tissue of rodents. Brown adipocytes are smaller than white adipocytes and are characterized by multiple small lipid droplets and a high density of mitochondria, in contrast to the single large droplet and few mitochondria seen in unilocular white adipocytes. Their defining feature is the expression of uncoupling protein 1 (UCP1), which dissipates the mitochondrial proton gradient to generate heat instead of ATP (14). Brown adipocytes play a critical role in maintaining core body temperature. In these cells, fatty acids are oxidized by mitochondria to fuel the electron transport chain, and heat is generated through the action of uncoupling protein 1 (UCP1), which accelerates proton leak across the mitochondrial membrane. In adult humans, brown adipocytes are found interspersed within predominantly white adipose depots, including the cervical, supraclavicular, axillary, perirenal, and paravertebral regions. There is ongoing debate as to whether these human brown adipocytes represent classical brown adipocytes or instead correspond to the "beige" adipocyte subtype, described below. Like white adipocytes, emerging evidence highlights the significant secretory role of brown adipocytes. While some brown adipose tissue (BAT)-secreted molecules, termed BATokines, differ in nature from white adipokines or WATokines, they similarly contribute to energy homeostasis, glucose and lipid metabolism, immune responses, and vascular health (15).

Beige adipocytes

Beige adipocytes are typically located in the supraclavicular, paravertebral, and suprarenal regions in humans, and in the inguinal depot in mice, where they are typically interspersed among white adipocytes. Their characteristics are intermediate between white and brown adipocytes, including smaller size,

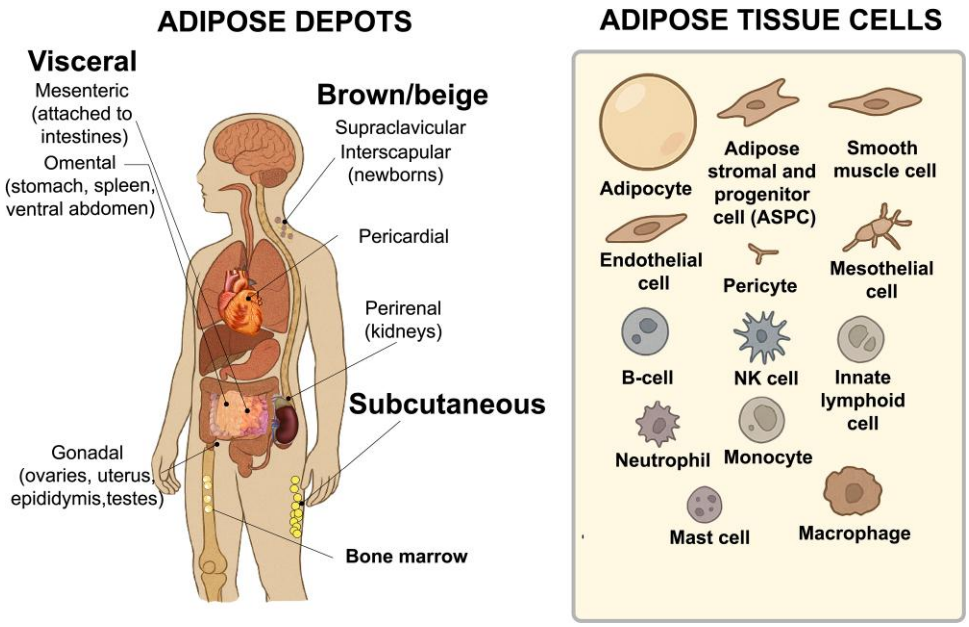

Figure 1. Human adipose tissue depots and cellular composition. The left panel depicts major adipose tissue depots in humans, including subcutaneous, visceral (mesenteric and omental), gonadal, brown, and beige fat. The right panel shows the main cell types residing within adipose tissue depots.

multilocular lipid droplets, higher mitochondrial content, and expression of UCP1. Compared to white adipocytes, beige adipocytes exhibit increased nutrient consumption (16), and their abundance closely correlates with favorable metabolic health (17). A distinctive feature of beige adipocytes is that they are induced in response to chronic stimulation such as persistent cold exposure, exercise, or β-adrenergic signaling (16), but can revert to a white adipocyte–like morphology following removal of stimuli. These beige adipocytes can then induce UCP1 acutely in response to stimuli such as cold (18, 19). This represents a clear example of adipocyte functional and morphological plasticity that allows dynamic adaptation to metabolic status and energy demand. Extensive research in rodent models has examined mechanisms involved in beiging, and evidence for this phenomenon in humans has been observed in pathological states, including severe burn injuries (20) and in patients with catecholamine-secreting tumors such as pheochromocytoma (21) and paraganglioma (22).

The abundance of UCP1-expressing adipocytes decreases with age, obesity, and warming (17, 23). In rodents, whitening of BAT is characterized by reduced thermogenic activity, lower mitochondrial content, and lipid accumulation within brown adipocytes, resulting in a phenotype resembling beige adipocytes (24). It is not yet known whether additional energy-consuming adipocyte subtypes also decline with age or obesity, or other environmental stresses. Understanding the mechanisms underlying age- and obesity-induced decline of different adipocyte subtypes represents a crucial yet largely unexplored frontier in adipose tissue biology.

Other adipocyte subtypes

The high granularity of single-cell RNA sequencing studies has suggested that, beyond UCP1-expressing adipocytes, each adipose depot houses distinct adipocyte subtypes, specialized for lipogenesis, mitochondrial oxidation, thermogenesis, inflammatory signaling, or extracellular matrix remodeling (7, 8). Recent research has also uncovered adipocytes which display UCP1-independent energy-consuming pathways. These include creatine-dependent substrate cycling (25), Ca^{2+} futile cycling (26), and triacylglycerol futile cycling (27). Specialized depots, such as mammary adipose tissue, contain pink adipocytes, critical for lactation (28), while adipocytes within the bone marrow affect hematopoiesis (29) and bone metabolism (30). Another example is the adipocytes within the dermis, which contribute to immune responses, wound healing, hair follicle growth, and thermoregulation (31, 32). The ongoing discovery of these specialized adipocytes and their developmental mechanisms (8) has broadened the traditional view of adipocytes as merely energy reservoirs or thermogenic cells, highlighting their diverse roles in systemic physiology. The identification of specific markers for these cell types and subtypes is enabling the creation of models to probe specific functions and identify their physiological role. In the meantime, one can speculate that adipocyte specialization may allow a more tailored response to the dynamic nutritional needs of distinct tissues and organs.

Adipocyte Stromal Progenitor Cells

A second critical cell component of adipose tissue are ASPCs. These cells, present in adult adipose depots, are of mesenchymal origin and can differentiate into multiple lineages (33), including diverse adipocyte subtypes (34). Single-cell analysis of adipose tissue has pointed to several ASPC subtypes. Some may correspond to different stages of adipocyte differentiation (4, 35), and some may have regulatory functions (5, 36, 37). Alterations in ASPCs have profound consequences on subsequent adipose tissue metabolic function (38). In vitro analysis suggests that maintenance of a multipotent ASPC population is an inherent feature of the human adipose differentiation program (39, 40). Interestingly, experiments involving parabiosis of old and young mice show that ASPCs are among the most responsive cells to aging environments (41), linking adipose tissue development and function to organismal aging (3).

Endothelial Cells

Endothelial cells in adipose tissue are crucial components of the dense vasculature of this tissue, necessary for oxygen and nutrient transport to and from the tissue. The vasculature of adipose tissue is the niche for ASPCs, and transcriptomic analysis has suggested important signaling mechanisms between adipocytes, endothelial cells, and ASPCs (12). Analysis of the unique transcriptomic signatures of endothelial cells from multiple organs reveals that endothelial cells of adipose tissue are distinct from those of brain, lung, and liver, but similar to those of skeletal and cardiac muscle (42).

Macrophages

Macrophages in adipose tissue increase in response to obesity (43), and many new insights into the functional roles of these immune cells have been gained over the past 20 years (44). Multiple distinct populations of adipose tissue macrophages have been identified, with unique tissue distributions, transcriptomes, chromatin landscapes, and functions. A specific population of macrophages identified in both mouse and human adipose tissue are lipid-laden and pro-inflammatory (45, 46). This lipid-laden macrophage population appears to play a major role in lipid homeostasis in obesity. Importantly, obesity-induced changes in immune cell composition persist after weight loss (47, 48), potentially worsening the deleterious effects of subsequent weight re-gain. Future studies are necessary to uncover the roles of additional cells of adipose tissue, including mesothelial and Schwann cells, on adipose tissue biology.

Communication to Adipose Tissue

The roles of adipose tissue in the control of energy homeostasis are regulated and coordinated by other organs and tissues, prominently the brain. Neuronal inputs into adipose tissue are crucial in initiating lipolysis to satisfy systemic energy requirements. Outputs from adipose tissue provide regulatory feedback as well as information on the status of energy storage in adipose tissue. In the sections below, we review neuronal mechanisms that regulate adipose tissue functions.

Insights From Model Organisms

The fundamental architecture of adipose-brain communication is evolutionarily conserved, with studies in model organisms revealing ancient mechanisms (49, 50). In Drosophila, the fat body functions as a nutrient sensor and is a model for vertebrate adipose tissue, orchestrating systemic metabolism through hormone-like factors (51, 52). A central neuropeptide, insulin, is produced by insulin-producing cells (IPCs) located in a neuroendocrine region analogous to the mammalian hypothalamus (53). The fat body remotely regulates insulin release based on nutrient status, ensuring metabolic coordination.

Unpaired 2 (Upd2), an ancient JAK/STAT ligand, mirrors mammalian leptin as a satiety signal and primary adipokine that promotes insulin release in well-fed flies (54) (Fig. 2). Human leptin can functionally substitute for Upd2, highlighting strong evolutionary conservation. While leptin acts in the hypothalamus to stimulate α-MSH release, Upd2 targets insulin-regulating neural circuits (54). Like leptin, Upd2 modulates GABAergic neurons to orchestrate systemic metabolism (54). Its expression and release tightly reflect fat stores (55) and regulate feeding (56), sleep (57), and taste perception (58), linking lipid status to behavior.

Drosophila studies have illuminated cellular mechanisms coupling adipokine secretion to nutrient state. Upd2 modulates GABAergic synapses via cytoskeletal remodeling, offering a model for how leptin may regulate mammalian synapses (59). Both leptin and Upd2 utilize a noncanonical LC3-associated secretory pathway, underscoring a conserved mechanism linking adipokine release to metabolic status (56). These insights demonstrate how comparative models uncover core principles of adipose-brain communication and inform leptin biology.

Additional adipokines enrich this signaling network. Neural Lazarillo (NLaz), a homolog of vertebrate retinol-binding protein 4, regulates neuronal metabolism and insulin sensitivity (60). Growth-blocking peptides, secreted in response to dietary amino acids, act as long-range epidermal growth factor receptor ligands, linking amino acid sensing to insulin secretion and systemic growth (61-63).

Beyond protein signals, lipid signaling also modulates brain-metabolism interactions. Impairment of the enzyme for phosphatidylethanolamine production in Drosophila fat tissue disrupts feeding via altered lipoprotein trafficking, mimicking diet-induced dysfunction (64). Like Drosophila, the *C. elegans* model system offers complementary advantages for uncovering conserved lipid-brain signaling. Despite lacking classical adipose tissue, *C. elegans* stores fat in intestinal cells, which functionally resemble adipocytes. A growing body of work has shown that lysosomal lipid breakdown in these cells generates specific fatty acids—such as dihomo-γ-linolenic acid—that are transported to the nervous system via lipid chaperones like LBP-3. This fat-to-neuron signal activates neuropeptide transcription through the nuclear receptor NHR-49, extending lifespan (65). Other *C. elegans* studies reveal that monounsaturated fatty acids (MUFAs), such as oleic acid, increase both lipid droplet and peroxisome number, and this organelle network is essential for longevity benefits of MUFA-rich diets (66).

In parallel, oxygen-sensing neurons orchestrate lipid metabolism based on environmental oxygen availability, which serves as a proxy for food presence. Since *C. elegans* feeds on oxygen-consuming bacteria, high ambient oxygen typically signals low bacterial (food) density, while low oxygen signals food-rich conditions. This environmental logic is encoded into a reciprocal neural circuit: URX neurons become activated under high oxygen and trigger fat mobilization from the intestine to fuel energy needs during perceived nutrient scarcity. Conversely, under low oxygen conditions, BAG neurons release the neuropeptide FLP-17, which binds the EGL-6 receptor on URX neurons, dampening their tonic activity and preserving fat stores. This dynamic neuropeptide-mediated antagonism enables precise, real-time regulation of lipid metabolism, coupling environmental oxygen cues directly to nutrient sensing and energy conservation (67).

Moreover, dietary restriction studies in *C. elegans* have identified lipid signaling pathways involving NHR-49 and mitochondrial metabolism that critically influence lifespan and metabolic homeostasis (68). These discoveries highlight how *C. elegans* helps delineate conserved fat-brain communication pathways critical for metabolism, longevity, and behavior, particularly through lipid-derived and neuropeptidergic signals. Together, these conserved mechanisms reveal how adipose-derived signals regulate neural and systemic metabolism, highlighting the utility of model organisms in uncovering

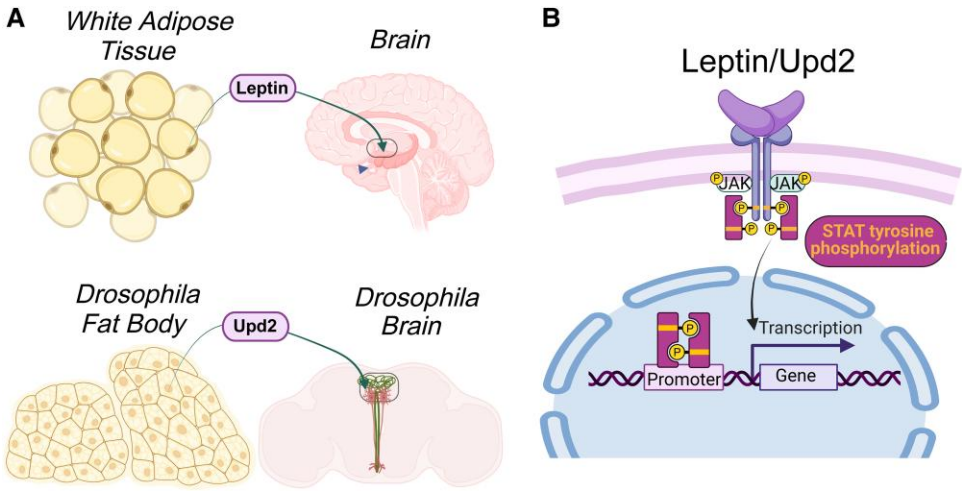

Figure 2. Adipose-brain crosstalk via leptin signaling in mammals and Drosophila. A, Top: In mammals, leptin is secreted by adipocytes and acts on the brain, primarily the hypothalamus, to regulate energy balance and appetite. Bottom: In Drosophila, the fat body serves as the adipose equivalent and communicates with the brain via Unpaired 2 (Upd2), an ancient JAK-STAT ligand that functions as a satiety signal. B, Leptin signals through its receptor (LepR) on target neurons, activating the JAK-STAT pathway and leading to STAT-dependent transcriptional responses that suppress food intake.

fundamental processes and pointing to new therapeutic avenues for metabolic disorders.

Neural and Neurotransmitter Signaling

In mammals, neural outflow to adipose depots is conveyed by the sympathetic nervous system (SNS), which projects outside the brain through relay stations in the spinal cord (preganglionic neurons) and in sympathetic chain ganglia (postganglion neurons) to innervate adipose depots across the body axis (69-72) (Fig. 3). SNS outflow enhances lipolysis and suppresses adipocyte proliferation in white adipose tissues (73-75), while promoting the recruitment of thermogenic adipocytes and fat oxidation to generate heat through nonshivering thermogenesis.

During fasting, exercise, hypoglycemia, or prolonged BAT activation, white adipose tissue (WAT) lipolysis is activated (76). Interestingly, visceral fat depots are mobilized before and to a greater extent than subcutaneous depots during caloric restriction in mice (77-79). A similar phenomenon is also observed in humans (14, 80-82). Brain circuits driving sympathetic outflow to WAT and BAT are recruited or suppressed under different conditions. Sympathetic outflow to BAT is stimulated by cold sensation and signals related to caloric consumption, and conversely it is repressed by warm temperatures or signals related to fasting (14, 76, 83). SNS signals that promote lipolysis in WAT are also activated by exposure to cold, but in contrast to BAT, they are stimulated by fasting and hypoglycemia (6). This bias may be beneficial by providing fatty acids necessary for heat production by thermogenic adipocytes surrounding critical organs and preserving the insulating subcutaneous fat layer that constitutes a further defense against cold (77).

There are also differences in SNS control across different WAT depots. Visceral WAT is more sensitive to SNS signals than subcutaneous WAT, so visceral fat depots are mobilized before and to a greater extent than subcutaneous depots during caloric restriction (71, 72, 74-77). In the context of obesity, impaired lipolysis in visceral depots is closely associated with dyslipidemia (84).

Integration of interoceptive and sensory circuits that provide information about internal and external body states modulate SNS outflow to adipose tissues to match metabolic needs. Neuronal subpopulations in the medial preoptic area integrate information about external temperature from warm- and cold-sensing somatosensory neurons in the skin with signals from thermosensory neurons that detect changes in brain temperature (7). Spinal sensory neurons that innervate BAT and inguinal WAT (iWAT) also provide feedback to central circuits regulating sympathetic drive to the same and to other adipose depots (85).

The mechanism by which sympathetic nerves act on adipose tissue is through the release of norepinephrine along with cotransmitters such as ATP or neuropeptide Y (NPY). At least 2 distinct subpopulations of postganglionic sympathetic neurons innervate BAT: one that wraps around large arterioles and expresses high NPY levels, and another that forms fine fibers within adipocytes in the parenchyma (86-90). Whether molecularly distinct sympathetic neuron subpopulations innervate WAT depots has not been determined, but NPY is broadly expressed (89).

Norepinephrine acts through β1, β2, and β3 adrenergic receptors (ARs) (91-93), which are detected in rodent and primate adipocytes at varying levels (94, 95). Human adipocytes express significantly lower levels of functional β3AR compared to rodents (96, 97), potentially explaining mixed results obtained when targeting of β3AR for obesity and metabolic syndrome (98, 99). α-Adrenergic receptors (α2ARs) are also expressed in adipocytes in a species-dependent manner (100). α2ARs serve inhibitory roles through Gi coupling and adenylyl cyclase inhibition (101). α1ARs sometimes play auxiliary roles (102).

βARs stimulate lipolysis through activation of adenylate cyclase and protein kinase A (PKA), which modulates adipose triglyceride lipase activity by acting on perilipins and CGI-58 (103, 104). β3AR uniquely couples to both Gs and Gi proteins, with the Gi pathway increasing ERK MAPK activity (105), which also contributes to adipocyte lipolysis (106). PKA can also directly phosphorylate and activate mTORC1 in response to various cAMP-elevating agents,

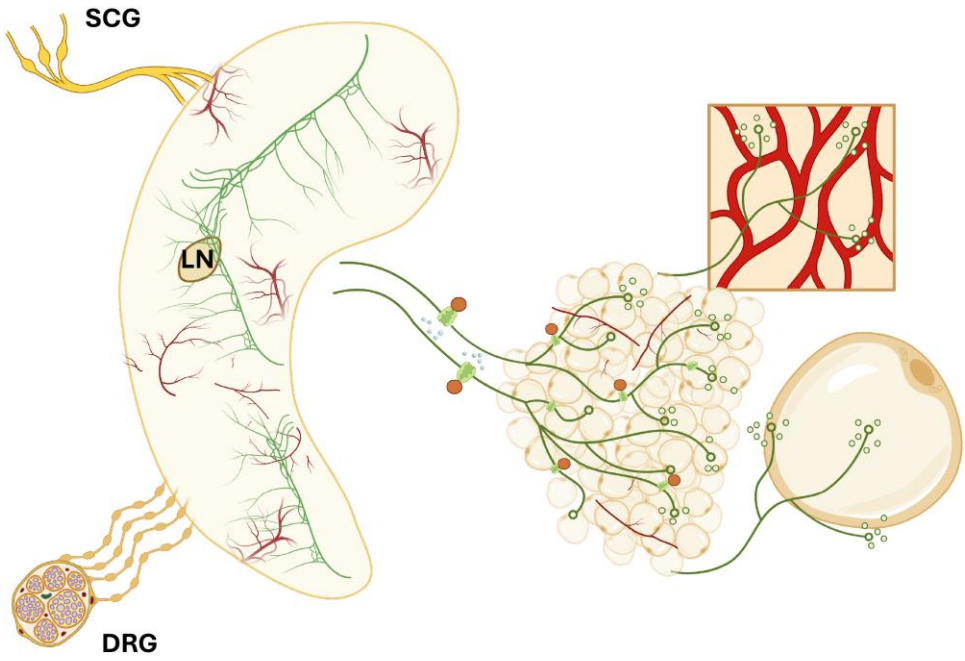

Figure 3. Adipose tissue innervation. Adipose depots are innervated by spinal sensory (dorsal root ganglia; DRG) and sympathetic (SC) axons that release numerous nerve products including neurotransmitters, neuropeptides, and neuromodulators. These axons are varicose, many are myelinated, and they form innervation patterns on and around adipocytes and the stromovascular fraction, as well as neurovascular units on blood and lymphatic vasculature. The lymph nodes (LN) are also densely innervated structures found in adipose depots. Larger nerve bundles entering the tissues tend to be a mix of sensory and sympathetic axons, with one large bundle entering mouse interscapular brown adipose, and several large bundles entering mouse inguinal subcutaneous white adipose tissue.

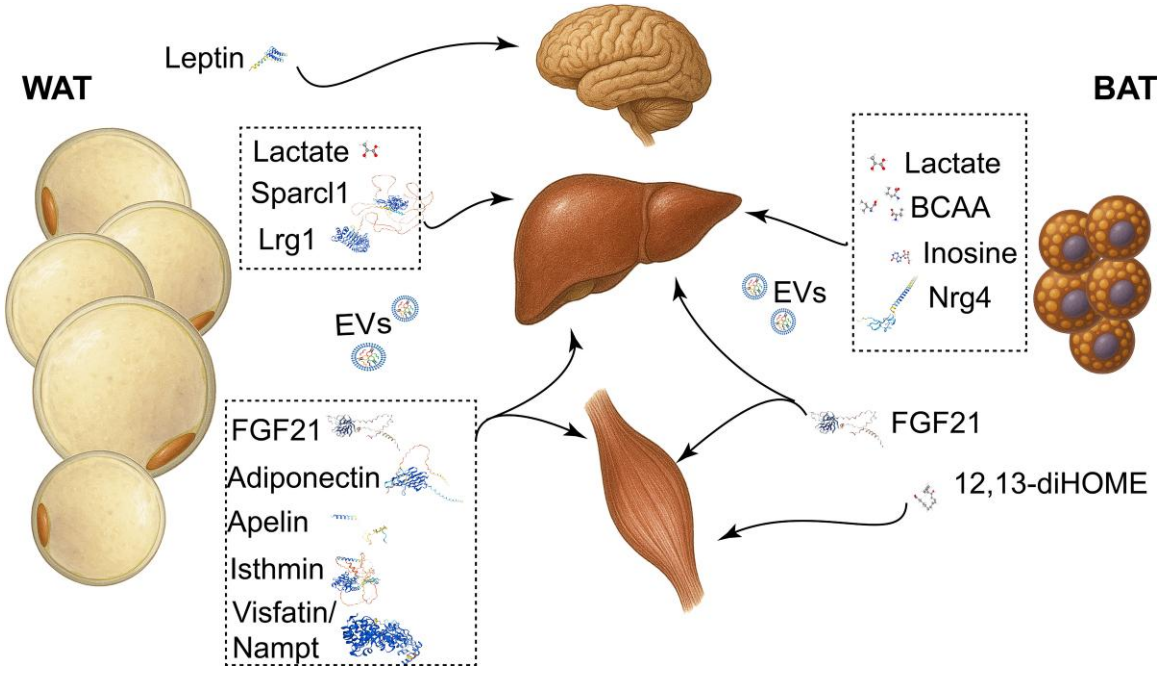

Figure 4. Interorgan communication mediated by white and brown adipocytes. White and brown adipocytes crosstalk with the brain, liver, and/or muscle through a variety of signaling molecules. These include peptides, cytokines, lipokines, and extracellular vesicles carrying proteins, metabolites, and RNAs. These signals coordinate systemic energy balance, metabolism, and inflammation across tissues. White adipose tissue–derived factors regulate insulin resistance, fuel uptake and oxidation, glucose tolerance, insulin secretion, and systemic energy metabolism via actions on brain, liver, or muscle. Brown adipose tissue influences thermogenesis, energy metabolism, and insulin sensitivity through signaling by factors acting on liver, muscle, or both.

including the GLP-1 receptor agonist liraglutide (107, 108). Recent studies have identified downstream substrates of PKA-activated mTORC1 in adipocytes (109, 110) and other tissues (111, 112). The p38 MAPK module is also activated downstream of PKA and controls activation of Ucp1 transcription (113-117).

In addition to neurons, an important role is played by non-neuronal support cells residing within and outside adipose

tissue. For example, Schwann cells, the main neuroglial cells, are responsible for myelination, neurotrophic factor secretion, damaged nerve repair, and maintaining axonal integrity (118). Schwann cell numbers decrease in adipose tissue with obesity, and this decrease may account for the "adipose neuropathy" (118, 119) seen in adipose tissue in multiple models of obesity (120, 121). Neuroimmune cells facilitate bidirectional communication with nerves, with nerve-associated macrophages providing trophic support and neurotransmitter clearance (85, 122).

Cholinergic adipose macrophages (ChAMs), identified in adipose tissue, produce acetylcholine in response to cold exposure (123, 124). Choline acetyltransferase (ChAT), the enzyme responsible for acetylcholine synthesis, is expressed in both murine and human visceral fat and is modulated by obesity (125). Cholinergic signaling is further amplified by fibroblast growth factor 21 (FGF21), forming a feedforward loop (126). This signaling pathway also plays a role in the hypermetabolic response following burn injury (127).

The cholinergic receptor nicotinic alpha 2 subunit (Chrna2) is upregulated in activated beige adipocytes within subcutaneous inguinal white adipose tissue (123, 128), and Chrna2$^+$ beige adipocytes appear to have functional significance in this depot (18). The importance of this pathway is underscored by thermogenic impairments and glucose intolerance observed in adipocyte-specific Chrna2 knockout mice (128). In addition to metabolic effects, non-neuronal cholinergic signaling also contributes to inflammation and immune regulation (129-131). Chrna2 downstream signaling involves classical cAMP-PKA pathways as well as creatine-mediated futile cycling (123, 128, 132, 133). Pharmacological inhibitors of acetylcholine degradation—commonly used to treat neurodegenerative diseases—have been in clinical use for decades (134, 135). These agents may hold therapeutic potential for metabolic disorders by activating beige adipocytes through peripheral cholinergic pathways.

Other factors also impacting adipose tissue in parallel to norepinephrine and acetylcholine include cardiac natriuretic peptides, which function in adipocytes through cGMP and protein kinase G activation (136, 137). These peptides activate lipolysis (138) and thermogenesis through p38 MAPK (137) and mTORC1 activation (123).

Communication From Adipose Tissue

As noted above, adipose tissue is widely distributed throughout the body, with distinct depots performing specialized local roles in immunity, angiogenesis, neurogenesis, and tissue repair. The mechanisms by which adipocytes contribute to these processes remain incompletely understood, but an expanding repertoire of adipocyte-derived secreted factors is being identified. Below, we briefly review the mediators of adipose tissue communication with other organs—including peptide hormones, cytokines, chemokines, lipokines, metabolites, and exosomal microRNAs (Fig. 4). We also summarize current knowledge of the bidirectional interactions between adipose tissue and 3 key metabolic organs—the brain, liver, and skeletal muscle—which are essential for maintaining whole-body metabolic homeostasis.

Mediators

Peptide hormones

Over the past 3 decades, various peptide hormones in addition to leptin, which will be discussed in more detail below, have been identified as produced by adipose tissue. Adiponectin exerts anti-inflammatory, anti-apoptotic, and insulin-sensitizing effects, supporting metabolic processes by reducing hepatic gluconeogenesis, enhancing glucose uptake, and promoting lipid oxidation in various tissues (139). Adipsin, also known as complement factor D, secreted primarily by adipocytes (140), is crucial in the alternative complement pathway. Adipsin influences glucose homeostasis by promoting insulin secretion, and its levels correlate variably with glucose intolerance and obesity-related conditions. FGF21 is an endocrine hormone recognized for its beneficial effects on metabolism. While the liver is considered the primary source of circulating FGF21, several reports reveal that adipose tissue can also produce this peptide hormone. Adipose-specific FGF21-deficient mice show no changes in circulating FGF21 or insulin resistance (141), making the role of adipose tissue–derived FGF21 controversial (142).

Cytokines

Adipose tissue also produces different cytokines or chemokines to regulate systemic metabolism and inflammation. C-X-C motif chemokine ligand 14 (CXCL14) is a chemokine expressed by various immune and epithelial cells with no known receptor (143). Identified as an adipokine produced by BAT, cold increases CXCL14 expression in brown and white adipocytes, while a high-fat diet reduces its expression. CXCL14-deficient mice show impaired thermogenesis and glucose tolerance, while systemic CXCL14 administration enhances BAT thermogenesis, promotes WAT browning, and improves insulin resistance in obese mice (144). Interleukin-6 (IL-6) is a cytokine secreted by both BAT and WAT and nonadipose tissues, such as skeletal muscle, during exercise. In individuals with obesity and diabetes, IL-6 levels are often elevated (145). IL-6 secretion in WAT can be stimulated by pro-inflammatory cytokines and increased lipolysis, potentially contributing to insulin resistance in the liver. IL-6 exhibits both pro-inflammatory and anti-inflammatory properties (146, 147). While IL-6 signaling can offer protection in liver cells and myeloid cells, inhibiting this cytokine in T cells and natural killer cells can enhance insulin sensitivity.

Lipokines

Bioactive lipid mediators, or lipokines, play key roles in metabolism, immunity, and tissue homeostasis (148-150). Several adipose-derived lipokines link fat tissue to systemic metabolism, regulating insulin sensitivity, glucose tolerance, and inflammation (151-153). Fatty acid esters of hydroxy fatty acids (FAHFAs), produced via de novo lipogenesis in adipose tissue, are a notable lipokine class (154). In humans and mice, FAHFA levels in WAT and plasma correlate with insulin sensitivity (155). Palmitic acid hydroxystearic acid (PAHSA), a key FAHFA subgroup, improves glucose tolerance by activating the GPR120 receptor and enhancing glucose uptake in adipocytes (154, 156). PAHSAs also engage GPR40, stimulating GLP-1 and insulin secretion (155).

Beyond WAT, the BAT also contributes to metabolic regulation through lipokine secretion. Upon cold exposure or exercise, BAT produces lipids that enhance fatty acid and glucose metabolism and reduce obesity-related inflammation (152, 157-159). One such lipokine, 12,13-dihydroxy-(9Z)-octadecenoic acid (12,13-diHOME), rises in both humans and mice during cold exposure and exercise (157, 159). It promotes fatty acid uptake

in brown adipocytes and skeletal muscle, supporting thermogenesis and energy metabolism. It also improves cardiac function (160) and enhances endothelial health, reducing atherosclerosis in mice (161). In humans, 12,13-diHOME levels inversely correlate with BMI and insulin resistance, emphasizing its potential in cardiometabolic health (157).

Another BAT-derived lipokine, 12-hydroxy-5Z,8Z,10E, 14Z,17Z-eicosapentaenoic acid (12-HEPE), is induced by cold and β3-adrenergic signaling in mice (152). In humans, it enhances glucose uptake in BAT and muscle via the PI3K-mTOR-Akt-Glut4 pathway. In mice, 12-HEPE reduces atherosclerosis through PPARγ signaling (162) and suppresses skin inflammation by blocking neutrophil migration (163). These findings suggest that 12-HEPE also exerts anti-inflammatory effects beyond its metabolic functions.

Specialized pro-resolving mediators (SPMs) offer an alternative by resolving inflammation and promoting tissue repair with immunosuppressive effects (164). While SPMs were initially linked to immune cells, recent findings demonstrate that BAT also produces maresins. Maresin 2, derived from omega-3 DHA and produced by BAT in response to cold exposure, reduces systemic and hepatic inflammation in obesity (158). Maresin 2 also promotes macrophage efferocytosis, resolving inflammation in obesity, particularly by targeting liver macrophages.

Metabolites

Adenosine is released from BAT during sympathetic stimulation and directly from brown adipocytes. It activates BAT thermogenesis via the A2A receptor. In mice, A2A receptor blockade or deletion impairs thermogenesis, while A2A agonists enhance energy expenditure, underscoring the importance of adenosine-A2A signaling in protecting against diet-induced obesity (165).

Under stress or apoptosis, brown adipocytes release inosine, which boosts energy expenditure in neighboring brown adipocytes and promotes brown preadipocyte differentiation. Elevating extracellular inosine—via diet or inhibition of its transporters—enhances systemic energy expenditure and may counteract obesity (166, 167).

Though lactate's role in skeletal muscle metabolism is well known, BAT is also a major lactate source, producing roughly 4 times more than WAT. During cold exposure or hypoxia, BAT accounts for most glucose uptake. In adipocytes, lactate regulates metabolic plasticity by balancing redox states and modulating key signaling pathways (168, 169).

Histidine, an essential amino acid, activates hypothalamic histaminergic neurons after crossing the blood-brain barrier. Exposure of WAT to blue light increases histidine metabolites in tissue and circulation through an Opsin3 photoreceptor-dependent mechanism. This light-induced histidine signaling enhances BAT innervation and improves adiposity in high-fat diet conditions (170). In addition to histidine, branched-chained amino acids and derived amino acid species are also metabolites which are released from BAT and delivered to the liver, improving hepatic insulin sensitivity (171, 172).

microRNAs

Extracellular vesicles (EVs) are essential mediators of intercellular communication, transporting proteins, lipids, and small RNAs, including microRNAs (miRNAs) (173). Loss of adipocyte-specific Dicer significantly reduces plasma miRNA levels (174), and in lipodystrophy, circulating miRNAs are mainly downregulated, highlighting adipose tissue as a key source of plasma miRNAs (174). Specific miRNAs from adipose tissues exert systemic effects: BAT-derived miR-99b suppresses hepatic FGF21 expression, while WAT-derived miR-27a and miR-130b promote insulin resistance in skeletal muscle (175), and miR-155 from WAT activates M1 macrophages, exacerbating insulin resistance. Additionally, hypertrophic adipocytes release small EVs enriched in lipogenic miRNAs, which enhance lipid accumulation in neighboring smaller adipocytes (176). In obesity, both the content and secretion of WAT-derived EVs are altered, contributing to glucose intolerance and insulin resistance. In contrast, under healthy conditions, WAT-derived EVs support glucose homeostasis (177).

Signaling to the Brain

Leptin's discovery in the 1990s provided the first clear evidence that adipose tissue is a dynamic endocrine organ (178, 179) and transformed our understanding of metabolic regulation (180, 181). Leptin is secreted in proportion to fat mass, binds to its receptor (LepR) in the hypothalamus, and activates the Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway, regulating energy balance and feeding behavior (182-184). Initially considered an anti-obesity hormone, leptin is now recognized as a starvation signal, defending against energy insufficiency by promoting adaptive responses that preserve energy stores and suppress nonessential processes such as reproduction (185, 186). Remarkably, leptin signaling is conserved from fruit flies to humans, highlighting its ancient role in energy homeostasis (54).

In the hypothalamic arcuate nucleus (ARC), leptin acts on distinct neuronal populations to modulate feeding behavior (187, 188; Fig. 2). It reduces inhibitory GABAergic input to pro-opiomelanocortin (POMC) neurons, enhancing anorexigenic signaling while simultaneously inhibiting agouti-related peptide (AgRP) neurons that promote feeding (189, 190). This coordinated response reduces food intake. Clinical studies of individuals with congenital leptin deficiency demonstrate rapid normalization of appetite and body weight with leptin treatment (191, 192). However, in diet-induced obesity, leptin's regulatory capacity falters despite elevated circulating levels—a phenomenon known as leptin resistance (193-195). Mechanistic studies implicate impaired transport across the blood-brain barrier (196-198), chronic hypothalamic inflammation (199), and disruptions in LepR signaling, particularly through the action of suppressor of cytokine signaling 3 (SOCS3) (200).

A more nuanced understanding of body weight regulation has emerged with the 2-system model, suggesting that while decreasing leptin levels signals energy deficit, defending against weight gain may rely on a leptin-independent mechanism (186, 201). Studies in a mouse model of gastric overfeeding show that overfed mice defend their body weight even when leptin levels are fixed at low concentrations (202), highlighting the need to discover new fat-derived signals involved in body weight defense.

Leptin's role extends beyond energy homeostasis to glucose regulation (203). In type 1 diabetes, leptin normalizes blood glucose through an insulin-independent mechanism by acting on GABAergic neurons in the arcuate nucleus, which is aberrantly activated in type 1 diabetes due to energy deprivation (204). Leptin restores nutrient sensing via the AMP-activated

protein kinase (AMPK) pathway, reducing excessive counter-regulatory hormone responses that drive hyperglycemia, offering a novel therapeutic avenue for managing type 1 diabetes (204).

Leptin plays additional roles in the central nervous system (205), contributing to neuroprotection (206) and peripheral nerve repair (10). In the hippocampus, leptin enhances synaptic plasticity, supporting cognitive functions while reducing oxidative stress and preventing neuronal apoptosis (207, 208). In the peripheral nervous system, leptin supports Schwann cells—glial cells essential for nerve repair (10). After nerve injury, Schwann cells express leptin receptors, and their activation by adipocyte-derived leptin triggers mitochondrial oxidative phosphorylation (OxPhos) and enhances myelin autophagy, promoting axonal regrowth and remyelination. This adipo-glial communication axis highlights leptin's role in facilitating peripheral nerve regeneration, particularly in aged or impaired states (10). As research continues to uncover new functions, leptin's therapeutic potential—from metabolic disorders to neuroprotection and nerve repair—becomes increasingly evident.

While leptin is central to adipose-brain signaling, multiple other adipokines and lipids make crucial contributions to this communication network. Adiponectin, the most abundant circulating adipokine, enhances insulin sensitivity and exerts neuroprotective effects (209). Its receptors are expressed in the brain, where adiponectin influences energy metabolism and cognitive function (210-212). Higher adiponectin levels are associated with a reduced risk of neurodegenerative diseases like Alzheimer disease (213).

Lipid-derived signals also play a critical role in regulating neuronal plasticity and inflammation. Free fatty acids act as metabolic substrates and signal molecules in the hypothalamus, but chronic exposure can promote hypothalamic inflammation and impair neuronal function (214). In contrast, specialized pro-resolving mediators (SPMs) such as resolvins and protectins derived from omega-3 fatty acids reduce neuroinflammation (215) and promote neuronal survival, highlighting the complex interplay between lipid metabolism and brain function.

In addition to adipokines and lipids, communication from adipose tissue to the brain is mediated by somatosensory neurons innervation whose soma reside in the dorsal root ganglia. Sensory axons are pseudo-unipolar and send axons in opposite directions to both innervate peripheral target tissues and relay afferent axon potentials to neurons in the dorsal horn of the spinal cord. These spinal sensory axons in adipose may sense local stimuli such as pressure and temperature within adipose depots and relay them via spinal circuits to the brain, while concurrently releasing neuropeptides that modulate the function of the innervated organ.

Sensory projections to adipose depots are largely peptidergic and myelinated. Two classes of sensory fibers exist: large bundles extending along vasculature and thin fibers forming terminals near adipocytes (216-218), many (40%) co-expressing tyrosine hydroxylase (218). In iWAT, specialized sensory nerve endings form around certain tissue surface adipocytes (217). Sensory neuropeptides are expressed in adipose, including calcitonin gene related peptide (CGRP) and substance P (reviewed in (85)).

Sensory stimuli relayed via spinal circuits (also called spinal afferent signals) provide feedback to central circuits regulating sympathetic outflow. Simultaneous tracing of sensory and sympathetic pathways from BAT and iWAT into the brain identified potential nodes of integration in the hypothalamus, midbrain, brainstem, and spinal cord (219, 220). However, the direction of the effect of sensory feedback on sympathetic outflow is debated. Manipulations of TRPV1+ WAT sensory nerves by chemical means produced data supporting a positive feedback loop promoting sympathetic outflow (221-224). Conversely, selective ablation of generic iWAT sensory nerves using viral tools supported a negative feedback role on sympathetic drive in the manipulated fat pad but not others (218).

Signaling to Liver

The interplay between liver and adipose tissue determines many aspects of lipid metabolism. Under conditions of positive energy balance, lipids produced in the liver are exported for storage in adipose tissue, and under fasting or stress, fatty acids released from adipose tissue can accumulate in the liver. Prolonged nutrient overload taxes the capacity of adipose tissue lipid storage, resulting in insufficient lipid clearance and uncontrolled fatty acid release (225). Through these interactions, adipose tissue contributes to the development of metabolic dysfunction–associated fatty liver disease (MASLD), metabolic dysfunction–associated steatohepatitis (MASH) (21), and type 2 diabetes (225, 226).

Lipid flux between liver and adipose tissue is modulated by factors that enhance or decrease lipid utilization. For example, through its actions in the brain leptin promotes fatty acid oxidation and reduces lipid accumulation in liver (227, 228). While leptin receptors are expressed in the liver, the hepatic effects are secondary as liver-specific leptin receptor–KO mice fail to recapitulate the phenotypes of the ob/ob mice (229).

Adiponectin is released at high levels from adipose tissue and enhances hepatic insulin sensitivity and promotes fatty acid oxidation. In obesity, adiponectin levels are reduced, leading to a loss of these protective effects and an increase in insulin resistance and MASLD. The effects of adiponectin are thought to be mediated through the activation of adiponectin receptor 2 (AdipoR2) leading to AMPK and peroxisome proliferator-activated receptor alpha (PPARα) activation (230). However, the physiological effect of hepatocyte adiponectin function using liver-specific adiponectin receptor–KO mice has not been evaluated so the direct contribution of adiponectin on hepatocytes is still unknown.

Neuregulin 4 (NRG4) is released primarily from BAT, and acts on the related Erb-B2 receptor tyrosine kinase 4 (ErbB4) (231). In the liver, NRG4 inhibits de novo lipogenesis and enhances energy expenditure (232). In hepatocyte-specific ErbB4 knockout mice, NRG4 treatment fails to reduce the expression of lipogenic genes including sterol regulatory element-binding protein 1c (SREBP-1c), and does not mitigate hepatic steatosis, suggesting that ErbB4 is necessary for mediating some of NRG4's metabolic effect (232). Reduced circulating NRG4 levels have been observed in MASLD patients (233, 234), highlighting its potential as a biomarker and a potential therapeutic target for metabolic liver diseases.

Isthmin-1 (ISM1) is secreted from adipose tissue. Levels of ISM1 are increased in obese adolescent boys, and circulating ISM1 levels were positively correlated with body mass index (BMI), low-density lipoprotein cholesterol, liver damage markers and homeostatic model assessment for insulin resistance (HOMA-IR) (235). ISM1 increases insulin-independent glucose uptake into adipocytes and skeletal muscle and

induces protein synthesis in muscle and the liver (236, 237). The receptor(s) for ISM1 have not yet been identified, presenting an opportunity to elucidate its organ-specific mechanisms of action.

Two newly identified secreted adipokines, Leucine-rich alpha-2-glycoprotein 1 (LRG1) and secreted protein acidic and rich in cysteine-like 1 (Sparcl1) have been reported to have roles in metabolic syndrome and liver metabolism (238), potentially via pathways involved in inflammation (239). Sparcl1 expression positively correlated with hepatic pathology in MASH patients (240). Functional studies in the same paper indicated that both chronic administration of recombinant Sparcl1 protein and overexpression of Sparcl1 in mice exacerbated hepatic inflammation and liver injury. Conversely, Sparcl1-deficient mice were protected from diet-induced MASH (240). For both LRG1 and Sparcl1, no hepatic signaling or receptor has been identified yet. Further studies are necessary to determine their physiological role and therapeutic potential in energy balance.

Signaling to Muscle

In addition to the long-recognized role of WAT to supply fuel to skeletal muscle in the form of free fatty acids, it is now well established that adipose tissue can communicate with skeletal muscle to control of both muscle and systemic metabolism, and that alterations in this tissue-tissue crosstalk often contribute to metabolic disease. Adipose-muscle crosstalk plays a major role in coordinating energy balance by controlling muscle substrate utilization and insulin sensitivity. Numerous adipokines, metabolites, and EVs have been identified that function in adipose-muscle communication, a few of which will be discussed here. Some of the most prominently studied adipokines in the field, such as leptin, adiponectin, apelin, visfatin, and FGF21, are known to play important roles in regulating skeletal muscle metabolism. Adiponectin, typically considered a beneficial adipokine, increases AMPK in skeletal muscle leading to enhanced glucose uptake, fatty acid oxidation, and improved mitochondrial function (241). Although chronically elevated levels of leptin are known to cause leptin resistance and have deleterious effects, moderate levels of leptin can have beneficial effects on skeletal muscle via stimulation of AMPK and increasing glucose uptake and fatty acid oxidation (242-245). Apelin increases glucose uptake and mitochondrial function (246), and visfatin improves skeletal muscle insulin sensitivity (247).

While there are numerous adipokines that have beneficial effects on skeletal muscle metabolism, obesity can interfere with muscle function through both the downregulation of beneficial adipokines and the upregulation of adipokines that negatively affect skeletal muscle. TNF-α impairs skeletal muscle insulin signaling and promotes inflammation (248, 249), whereas chronically elevated levels of IL-6 are known to contribute to insulin resistance (250). Other adipose-derived factors that affect skeletal muscle include resistin, which interferes with insulin receptor signaling in muscle (251-253), and retinol-binding protein that can negatively affect insulin signaling (254). Another means of tissue communication is EVs originating from adipose tissue. Adipose EVs have been shown to transport specific miRNAs to skeletal muscle, having effects on metabolic and inflammatory pathways. As examples, miR-27a suppresses PPARγ, impairing lipid metabolism and insulin sensitivity in muscle (255), and miR-222 downregulates IRS-1, diminishing insulin signaling (256). Finally, metabolic intermediates can promote fuel-driven signaling between adipose tissue and muscle. In healthy individuals, this communication is beneficial to muscle metabolism and function, whereas excess free fatty acids and/or branched-chain amino acids can lead to high levels of lipid accumulation, mitochondrial dysfunction, and insulin resistance (257, 258).

Alterations in diet, cold exposure, as well as lifestyle changes such as exercise and weight loss all have the potential to restore beneficial adipose signaling, thereby improving skeletal muscle metabolic function (259). One example is palmitoleic acid (C16:1n7), a monounsaturated fatty acid that has been identified as a lipokine. Palmitoleic acid improves insulin action in muscle, reduces fat accumulation, and counteracts some of the metabolic consequences of a high-fat diet (260). Another important exercise-regulated lipokine is 12,13-diHOME (157), which is released from BAT during exercise and cold exposure and communicates with skeletal muscle by increasing fatty acid uptake and oxidation (159). Transforming growth factor-β2 (TGF-β2) is an exercise-induced adipokine that has major effects on skeletal muscle and systemic metabolism. Exercise training increases TGF-β2 in WAT in both mice and humans. TGF-β2 is secreted from WAT in response to exercise and improves glucose tolerance, adaptations due to increased glucose and fatty acid uptake in skeletal muscle (261).

In summary, adipose tissues communicate with skeletal muscle through a complex network of adipokines, EVs, and metabolic intermediates. While healthy adipose tissue supports muscle metabolism and insulin sensitivity, dysfunctional adipose signaling in obesity and metabolic disorders contributes to muscle insulin resistance, inflammation, and impaired function. Exercise, cold exposure, and diet all can reverse some of these deleterious effects on adipose tissue–skeletal muscle communication.

Sex Dimorphism in Adipose Tissue

Energetic demands differ between biological males and females, with sex-specific metabolic traits observed across species. These differences are thought to support reproductive success and survival. Many adipose-associated diseases are highly sexually dimorphic, in that they manifest differently in males vs females. For example, very recent research found that sex differences in how the perivascular adipose tissue responds to a high-fat diet are associated with differences in obesity-associated vascular dysfunction in male vs female mice (262). Human studies similarly found that effects of type 2 diabetes on vascular function differ between men and women (263). While our understanding of sexual dimorphism in adipose tissue is growing, many questions remain regarding how these differences are established genetically and molecularly, and how they evolve across the lifespan.

Sexual dimorphism in adipose tissue is detectable at birth (264), and this is reflected in obesity prevalence across the lifespan. According to 2020 World Health Organization data, obesity is more common among boys (9.43%) than girls (6.96%) aged 5 to 19. However, in adulthood, women exhibit higher obesity rates than men (17.9% vs 13.6%, BMI ≥ 30).

Men and women show marked differences in fat distribution (265) and BAT mass and activity (23, 266), though there are discrepancies between clinical and experimental analyses. For example, while retrospective analysis of clinical scans detected

higher BAT activity in females than in males (267), experimental studies combining scans with fixed or personalized cold exposure—the most sensitive and accurate approach to assess BAT—did not provide clear confirmation of the clinical results (268-270). Such discrepancies may be the result of sex differences in physiological responsiveness and sensitivity to cold temperature. While gonads are the primary source of sex hormones, extra-gonadal organs—including adipose tissue and the brain—also produce small amounts of androgens and estrogens that may act locally in a paracrine fashion (271). Animal studies provide additional insights. In mice and rats, iWAT shows sex-specific structural and functional differences (272, 273). For example, iWAT adipocyte size decreased following exercise in male mice, but not in females (260), and patterns of gene expression changes in exercised rats were distinctly different between male and female mice (261).

Female metabolism undergoes significant shifts during pregnancy and menopause. Notably, during pregnancy and lactation, women develop "pink" adipose tissue, which supports mammary gland development and milk production (274). Women also exhibit higher circulating levels of major adipokines than men (275, 276), with some differences apparent even before puberty (277) and persisting after menopause (278), suggesting hormonal and nonhormonal mechanisms at play.

Beyond hormonal influences, sex chromosomes also directly shape adipose tissue function. Mouse models under high-fat diet conditions reveal thousands of genes differentially expressed between sexes, particularly those related to lipid metabolism and insulin signaling (279, 280). Many of these differences appear independent of circulating sex hormones, pointing to intrinsic sex-specific programming. Consistent with this possibility, mouse models have demonstrated that X chromosome dosage and the presence of a Y chromosome independently affect adipose biology (157, 281). While the specific loci responsible remain unidentified, a small number of transcription factors involved in adipogenesis may drive broader sex-specific gene expression patterns (282).

To directly assess how sex chromosome constitution shapes adipocyte function, models that manipulate sex determination within adipose tissue are required. In Drosophila larvae, which lack mature gonads and secondary sex characteristics, fat storage cells exhibit distinct metabolic gene expression profiles based on whether the male or female sex determination pathway is active—independent of the organism's overall sex (283). Feminizing the sex determination pathway in male fat cells was sufficient to induce female-like fat storage characteristics (283). Interestingly, as in humans, fat distribution patterns in Drosophila reverse with age: male larvae have more body fat than females, but this difference flips in adulthood (284-286).

Future Directions and Impact on Human Disease

The field of adipose tissue biology stands at the threshold of transformative discoveries that will reshape our understanding of metabolic health. Advanced technologies including spatial transcriptomics and single-cell analysis are now uncovering unprecedented insights into the functional diversity of adipose depots. These innovations are addressing long-standing questions, including how gluteofemoral adipose tissue protects against metabolic disease, why bone marrow adipose tissue paradoxically increases during starvation and with aging, how perivascular adipose tissue regulates blood pressure, and the role of perineurial adipose tissue in peripheral nerve function.

We are now equipped to understand the complex adipose tissue microenvironment. By combining spatial transcriptomics with metabolomics, researchers can visualize how adipocytes interact with immune cells, endothelial cells, and nerve cells to influence whole-body metabolism. The identification of adipose stem and progenitor cell (ASPC) subtypes provides critical insight into the factors that determine healthy vs pathological adipose expansion, and their roles in aging and disease progression.

Communication mechanisms between adipocytes and other tissues are being elucidated through computational drug discovery approaches (287) and advanced methods like long-read RNA sequencing that accurately predict protein sequences. These techniques, alongside enhanced peptidomics, are revealing the full spectrum of adipokines—including peptides and micropeptides—with potential as therapeutic targets.

These technological advances are crucial for understanding diseases of adipose tissue. Lipodystrophy syndromes, characterized by adipose tissue deficiency and low levels of adipocyte-derived hormones like leptin, can be genetic or acquired, generalized or partial. Patients develop insulin resistance leading to diabetes, dyslipidemia, steatohepatitis, polycystic ovary syndrome, and premature cardiovascular disease. Understanding the mechanisms underlying these conditions and developing targeted therapies remains a priority for adipose tissue researchers.

Sex differences significantly influence adipose tissue disorders. Polycystic ovary syndrome features hormonally influenced insulin resistance, while lipedema—a disorder of lower body adipose tissue causing mobility impairments and pain—affects almost exclusively females, often triggered by endocrine stressors like pregnancy. Exploring the molecular basis for sex-specific differences in fat distribution and these diseases remains an important goal, as does understanding how environmental factors and dietary patterns influence epigenetic programming of adipose tissue and inherited metabolic risks.

Despite recent technological advances, further acceleration in the field requires developing new in vitro and in vivo model systems. For example, 3D cultures and hybrid tissues are next-generation methods that will increase our understanding of function. These will be essential for discovering underlying mechanisms and conducting efficacy and toxicology studies necessary for therapeutic development.

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