

# Advances in Adipose Tissue Biology

Silvia Corvera,<sup>1</sup> Akhila Rajan,<sup>2</sup> Kristy L. Townsend,<sup>3</sup> Farnaz Shamsi,<sup>4,5</sup> Jun Wu,<sup>6</sup> Katrin J. Svensson,<sup>7</sup> Lori M. Zeltser,<sup>8</sup> Sheila Collins,<sup>9</sup> Tânia Reis,<sup>10</sup> Yu-Hua Tseng,<sup>11</sup> and Laurie J. Goodyear<sup>11</sup>

<sup>1</sup>Program in Molecular Medicine, University of Massachusetts Chan Medical School, Worcester, MA 01655, USA

<sup>2</sup>Basic Sciences Division, Fred Hutch, Seattle, WA 98109, USA

<sup>3</sup>Department of Neurological Surgery, The Ohio State University, Columbus, OH 43210, USA

<sup>4</sup>Department of Molecular Pathobiology, New York University, New York, NY 10010, USA

<sup>5</sup>Department of Cell Biology and Medicine, Grossman School of Medicine, New York University, New York, NY 10016, USA

<sup>6</sup>Department of Molecular and Integrative Physiology, University of Michigan Medical School, Ann Arbor, MI 48109, USA

<sup>7</sup>Department of Pathology, Stanford University School of Medicine, Stanford, CA 94304, USA

<sup>8</sup>Naomi Berrie Diabetes Center and Department of Pathology and Cell Biology, Columbia University Irving Medical Center, New York, NY 10032, USA

<sup>9</sup>Division of Cardiovascular Medicine, Department of Medicine, Vanderbilt University Medical Center, Nashville, TN 37232, USA

<sup>10</sup>Division of Endocrinology, Metabolism and Diabetes, Department of Medicine, University of Colorado Anschutz Medical Campus, Aurora, CO 80045, USA

<sup>11</sup>Section on Integrative Physiology and Metabolism, Research Division, Joslin Diabetes Center, Harvard Medical School, Boston, MA 02115, USA

**Correspondence:** Silvia Corvera, MD, Program in Molecular Medicine, University of Massachusetts Chan Medical School, 55 N Lake Ave, Worcester, MA 01655, USA. Email: [Silvia.Corvera@umassmed.edu](mailto:Silvia.Corvera@umassmed.edu).

## 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; Chrn2, 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,

Received: 4 April 2025. Corrected and Typeset: 10 October 2025

© The Author(s) 2025. Published by Oxford University Press on behalf of the Endocrine Society. All rights reserved. For commercial re-use, please contact [reprints@oup.com](mailto:reprints@oup.com) for reprints and translation rights for reprints. All other permissions can be obtained through our RightsLink service via the Permissions link on the article page on our site—for further information please contact [journals.permissions@oup.com](mailto:journals.permissions@oup.com). See the journal About page for additional terms.

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 inter-muscularly 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

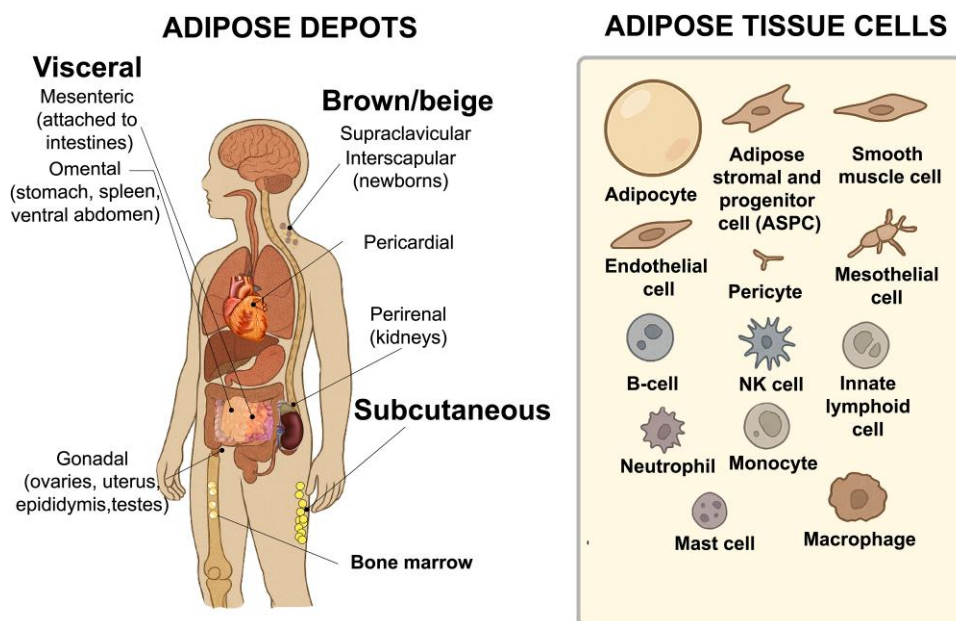
White adipocytes are the predominant cell type in most adipose depots, including the subcutaneous, various visceral depots, bone marrow, and the supraclavicular and paravertebral regions (Fig. 1). They are characterized by their large size and the presence of a single, unilocular lipid droplet. This 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  $\beta$ -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),  $\text{Ca}^{2+}$  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 ASCs, and transcriptomic analysis has suggested important signaling mechanisms between adipocytes, endothelial cells, and ASCs (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  $\alpha$ -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.

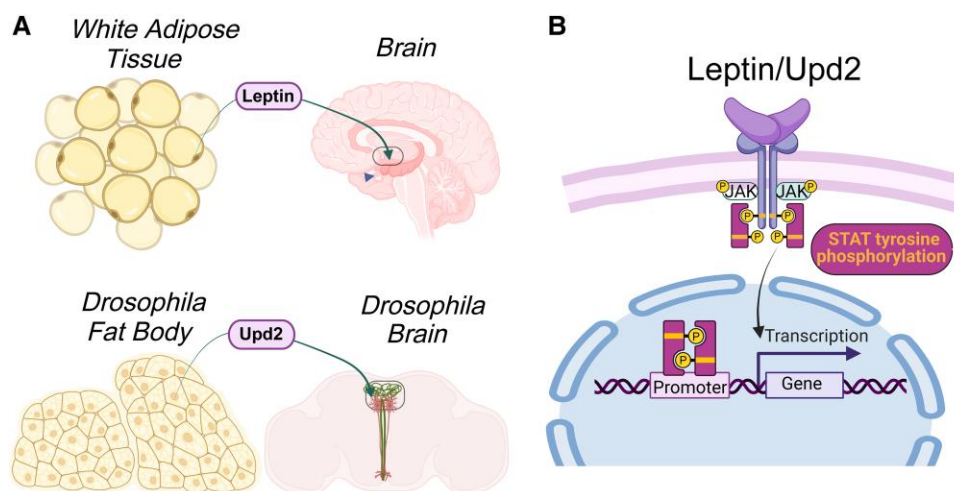
*Drosophila* studies have illuminated cellular mechanisms coupling adipokine secretion to nutrient state. Upd2 modulates GABAergic synapses via cytoskeletal remodeling, offering a model for how leptin may regulate mammalian synapses (59). Both leptin and Upd2 utilize a noncanonical LC3-associated secretory 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- $\gamma$ -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 (postganglionic 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 non-shivering 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).

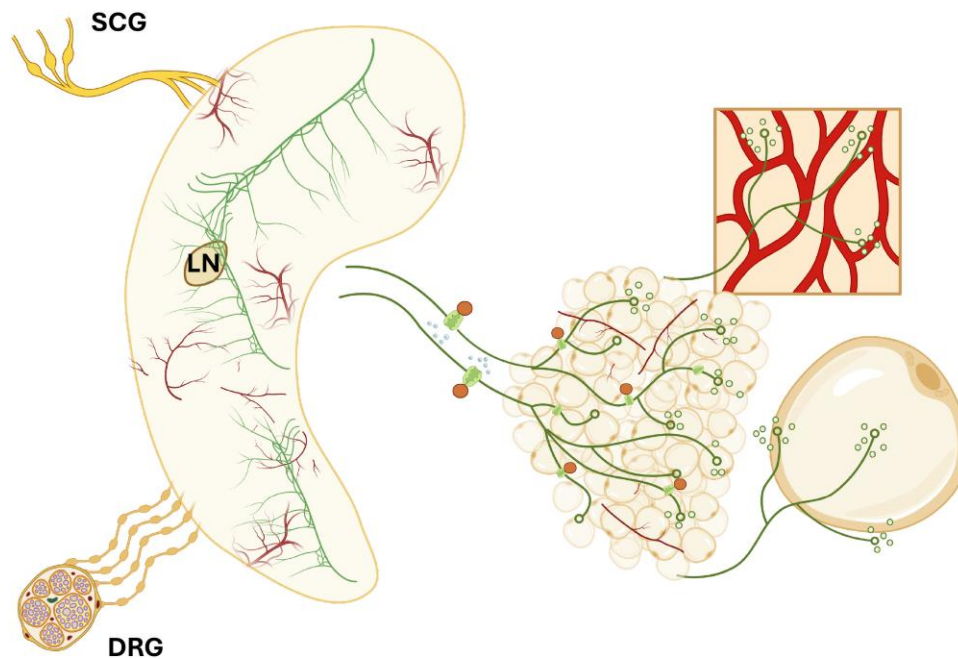
There are also differences in SNS control across different WAT depots. Visceral WAT is more sensitive to SNS signals than subcutaneous WAT, so visceral fat depots are mobilized before and to a greater extent than subcutaneous depots during caloric restriction (71, 72, 74–77). In the context of obesity,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

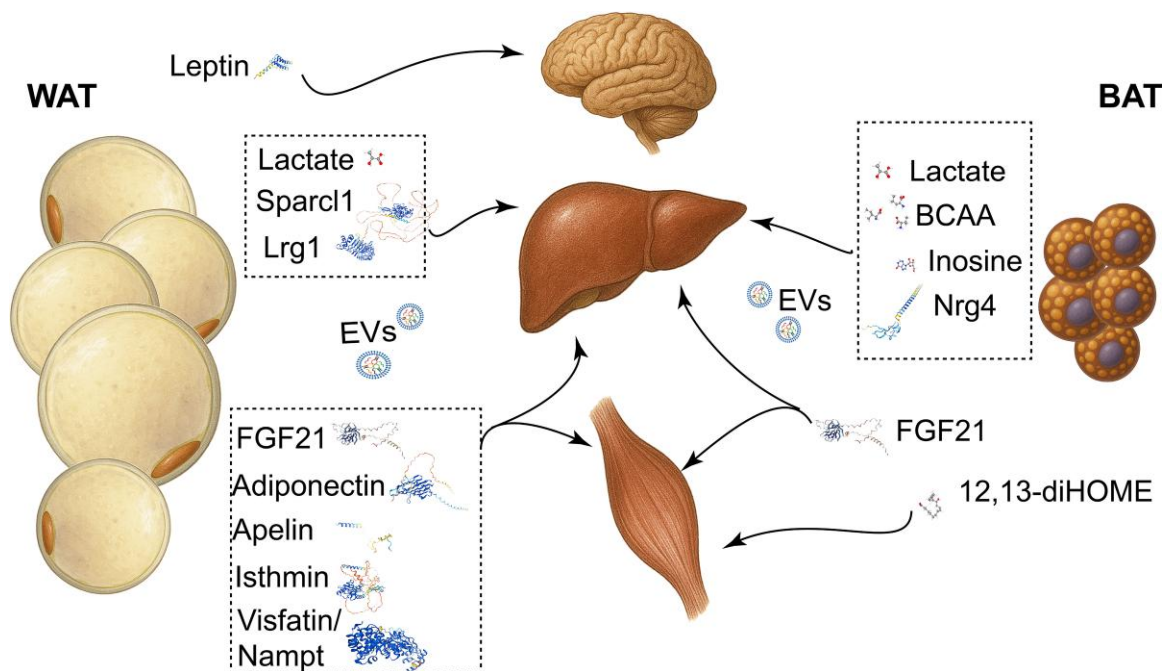
The mechanism by which sympathetic nerves act on adipose tissue is through the release of norepinephrine along with cotransmitters such as ATP or neuropeptide Y (NPY). At least 2 distinct subpopulations of postganglionic sympathetic neurons innervate BAT: one that wraps around large arterioles and expresses 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  $\beta_1$ ,  $\beta_2$ , and  $\beta_3$  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  $\beta_3$ AR compared to rodents (96, 97), potentially explaining mixed results obtained when targeting of  $\beta_3$ AR for obesity and metabolic syndrome (98, 99).  $\alpha$ -Adrenergic receptors ( $\alpha_2$ ARs) are also expressed in adipocytes in a species-dependent manner (100).  $\alpha_2$ ARs serve inhibitory roles through Gi coupling and adenylyl cyclase inhibition (101).  $\alpha_1$ ARs sometimes play auxiliary roles (102).

$\beta$ ARs stimulate lipolysis through activation of adenylyl cyclase and protein kinase A (PKA), which modulates adipose triglyceride lipase activity by acting on perilipins and CGI-58 (103, 104).  $\beta_3$ AR 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*<sup>+</sup> 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  $\beta$ 3-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 PPAR $\gamma$  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 (PPAR $\alpha$ ) 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 ErbB2 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- $\alpha$  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 PPAR $\gamma$ , 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- $\beta$ 2 (TGF- $\beta$ 2) is an exercise-induced adipokine that has major effects on skeletal muscle and systemic metabolism. Exercise training increases TGF- $\beta$ 2 in WAT in both mice and humans. TGF- $\beta$ 2 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  $\geq$  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 longstanding 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.

## Acknowledgments

The authors were supported by NIH R0DK1123028 and NIH R01DK137403 (S.C.); NIH R35GM124593 (A.R.); NIH R01DK136724 and American Heart Association Career Development Award 24CDA1271852 (F.S.); NIH R01DK125260, P30DK116074, and American Heart Association 23IPA1042031 (K.J.S.); NIH DP1DK139570 (T.R.); NIH R01DK099511, R01DK112283 and P30DK036836 (L.J.G.); NIH R01DK125094, P01AG032959, R56DK140355, Chan Zuckerberg Initiative (L.M.Z.).

## Disclosures

The authors declare no competing interests.

## References

1. Dai H, Alsallhe TA, Chalhaf N, Riccò M, Bragazzi NL, Wu J. The global burden of disease attributable to high body mass index in

- 195 countries and territories, 1990-2017: an analysis of the Global Burden of Disease Study. *PLoS Med.* 2020;17(7):e1003198.
2. Larsson SC, Burgess S. Causal role of high body mass index in multiple chronic diseases: a systematic review and meta-analysis of Mendelian randomization studies. *BMC Med.* 2021;19(1):320.
3. Nguyen TT, Corvera S. Adipose tissue as a linchpin of organismal ageing. *Nat Metab.* 2024;6(5):793-807.
4. Merrick D, Sakers A, Irgebay Z, et al. Identification of a mesenchymal progenitor cell hierarchy in adipose tissue. *Science.* 2019;364(6438):eaav2501.
5. Schwalie PC, Dong H, Zachara M, et al. A stromal cell population that inhibits adipogenesis in mammalian fat depots. *Nature.* 2018;559(7712):103-108.
6. Vijay J, Gauthier MF, Biswell RL, et al. Single-cell analysis of human adipose tissue identifies depot and disease specific cell types. *Nat Metab.* 2020;2(1):97-109.
7. Emont MP, Jacobs C, Essene AL, et al. A single-cell atlas of human and mouse white adipose tissue. *Nature.* 2022;603(7903):926-933.
8. Lazarescu O, Ziv-Agam M, Haim Y, et al. Human subcutaneous and visceral adipocyte atlases uncover classical and nonclassical adipocytes and depot-specific patterns. *Nat Genet.* 2025;57(2):413-426.
9. Zhong J, Zareifi D, Weinbrenner S, et al. A knowledge portal integrating clinical and experimental data from human adipose tissue. *Cell Metab.* 2025;37(3):566-569.
10. Sundaram VK, Schutza V, Schroter NH, et al. Adipo-glial signaling mediates metabolic adaptation in peripheral nerve regeneration. *Cell Metab.* 2023;35(12):2136-2152.e9.
11. Shamsi F, Zheng R, Ho LL, Chen K, Tseng YH. Comprehensive analysis of intercellular communication in the thermogenic adipose niche. *Commun Biol.* 2023;6(1):761.
12. Corvera S, Solivan-Rivera J, Yang Loureiro Z. Angiogenesis in adipose tissue and obesity. *Angiogenesis.* 2022;25(4):439-453.
13. Navarro-Perez J, Vidal-Puig A, Carobbio S. Recent developments in adipose tissue-secreted factors and their target organs. *Curr Opin Genet Dev.* 2023;80:102046.
14. Cannon B, Nedergaard J. Brown adipose tissue: function and physiological significance. *Physiol Rev.* 2004;84(1):277-359.
15. Shamsi F, Wang CH, Tseng YH. The evolving view of thermogenic adipocytes—ontogeny, niche and function. *Nat Rev Endocrinol.* 2021;17(12):726-744.
16. Wu J, Bostrom P, Sparks LM, et al. Beige adipocytes are a distinct type of thermogenic fat cell in mouse and human. *Cell.* 2012;150(2):366-376.
17. Becher T, Palanisamy S, Kramer DJ, et al. Brown adipose tissue is associated with cardiometabolic health. *Nat Med.* 2021;27(1):58-65.
18. Zhu K, Liu S, Huang Y, Zhang B, Houssein N, Wu J. Chrna2-driven CRE is expressed in beige adipocytes. *Endocrinology.* 2024;166(1):bqae153.
19. Shao M, Wang QA, Song A, et al. Cellular origins of beige fat cells revisited. *Diabetes.* 2019;68(10):1874-1885.
20. Sidossis LS, Porter C, Saraf MK, et al. Browning of subcutaneous white adipose tissue in humans after severe adrenergic stress. *Cell Metab.* 2015;22(2):219-227.
21. Vergnes L, Davies GR, Lin JY, et al. Adipocyte browning and higher mitochondrial function in periadrenal but not SC fat in pheochromocytoma. *J Clin Endocrinol Metab.* 2016;101(11):4440-4448.
22. Søndergaard E, Gormsen LC, Christensen MH, et al. Chronic adrenergic stimulation induces brown adipose tissue differentiation in visceral adipose tissue. *Diabet Med.* 2015;32(2):e4-e8.
23. Cypess AM, Lehman S, Williams G, et al. Identification and importance of brown adipose tissue in adult humans. *N Engl J Med.* 2009;360(15):1509-1517.
24. Pfannenberger C, Werner MK, Ripkens S, et al. Impact of age on the relationships of brown adipose tissue with sex and adiposity in humans. *Diabetes.* 2010;59(7):1789-1793.
25. Kazak L, Chouchani ET, Jedrychowski MP, et al. A creatine-driven substrate cycle enhances energy expenditure and thermogenesis in beige fat. *Cell.* 2015;163(3):643-655.
26. Ikeda K, Kang Q, Yoneshiro T, et al. UCP1-independent signaling involving SERCA2b-mediated calcium cycling regulates beige fat thermogenesis and systemic glucose homeostasis. *Nat Med.* 2017;23(12):1454-1465.
27. Oeckl J, Janovska P, Adamcova K, et al. Loss of UCP1 function augments recruitment of futile lipid cycling for thermogenesis in murine brown fat. *Mol Metab.* 2022;61:101499.
28. Cinti S. Pink adipocytes. *Trends Endocrinol Metab.* 2018;29(9):651-666.
29. Zhou BO, Yu H, Yue R, et al. Bone marrow adipocytes promote the regeneration of stem cells and haematopoiesis by secreting SCF. *Nat Cell Biol.* 2017;19(8):891-903.
30. Li Z, Bagchi DP, Zhu J, et al. Constitutive bone marrow adipocytes suppress local bone formation. *JCI Insight.* 2022;7(21):e160915.
31. Zhang LJ, Guerrero-Juarez CF, Hata T, et al. Innate immunity. Dermal adipocytes protect against invasive *Staphylococcus aureus* skin infection. *Science.* 2015;347(6217):67-71.
32. Kruglikov IL, Scherer PE. Dermal adipocytes: from irrelevance to metabolic targets? *Trends Endocrinol Metab.* 2016;27(1):1-10.
33. Zuk PA, Zhu M, Ashjian P, et al. Human adipose tissue is a source of multipotent stem cells. *Mol Biol Cell.* 2002;13(12):4279-4295.
34. Min SY, Desai A, Yang Z, et al. Diverse repertoire of human adipocyte subtypes develops from transcriptionally distinct mesenchymal progenitor cells. *Proc Natl Acad Sci U S A.* 2019;116(36):17970-17979.
35. Stefkovich M, Traynor S, Cheng L, Merrick D, Seale P. Dpp4+ interstitial progenitor cells contribute to basal and high fat diet-induced adipogenesis. *Mol Metab.* 2021;54:101357.
36. Dong H, Sun W, Shen Y, et al. Identification of a regulatory pathway inhibiting adipogenesis via RSPO2. *Nat Metab.* 2022;4(1):90-105.
37. Zachara M, Rainer PY, Hashimi H, et al. Mammalian adipogenesis regulator (Areg) cells use retinoic acid signalling to be non- and anti-adipogenic in age-dependent manner. *EMBO J.* 2022;41(18):e108206.
38. Zhang Q, Shan B, Guo L, et al. Distinct functional properties of murine perinatal and adult adipose progenitor subpopulations. *Nat Metab.* 2022;4(8):1055-1070.
39. Yang Loureiro Z, Joyce S, DeSouza T, et al. Wnt signaling preserves progenitor cell multipotency during adipose tissue development. *Nat Metab.* 2023;5(6):1014-1028.
40. Palani NP, Horvath C, Timshel PN, et al. Adipogenic and SWAT cells separate from a common progenitor in human brown and white adipose depots. *Nat Metab.* 2023;5(6):996-1013.
41. Palovics R, Keller A, Schaum N, et al. Molecular hallmarks of heterochronic parabiosis at single-cell resolution. *Nature.* 2022;603(7900):309-314.
42. Paik DT, Tian L, Williams IM, et al. Single-cell RNA sequencing unveils unique transcriptomic signatures of organ-specific endothelial cells. *Circulation.* 2020;142(19):1848-1862.
43. Weisberg SP, McCann D, Desai M, Rosenbaum M, Leibel RL, Ferrante AW Jr. Obesity is associated with macrophage accumulation in adipose tissue. *J Clin Invest.* 2003;112(12):1796-1808.
44. Chavakis T, Alexaki VI, Ferrante AW Jr. Macrophage function in adipose tissue homeostasis and metabolic inflammation. *Nat Immunol.* 2023;24(5):757-766.
45. Jaitin DA, Adlung L, Thaïss CA, et al. Lipid-associated macrophages control metabolic homeostasis in a Trem2-dependent manner. *Cell.* 2019;178(3):686-698.e14.
46. Hill DA, Lim HW, Kim YH, et al. Distinct macrophage populations direct inflammatory versus physiological changes in adipose tissue. *Proc Natl Acad Sci U S A.* 2018;115(22):E5096-E5105.

47. Zamarron BF, Porsche CE, Luan D, *et al.* Weight regain in formerly obese mice hastens development of hepatic steatosis due to impaired adipose tissue function. *Obesity (Silver Spring)*. 2020;28(6):1086-1097.
48. Cottam MA, Caslin HL, Winn NC, Hasty AH. Multiomics reveals persistence of obesity-associated immune cell phenotypes in adipose tissue during weight loss and weight regain in mice. *Nat Commun*. 2022;13(1):2950.
49. Kim SK, Tsao DD, Suh GSB, Miguel-Aliaga I. Discovering signaling mechanisms governing metabolism and metabolic diseases with *Drosophila*. *Cell Metab*. 2021;33(7):1279-1292.
50. Droujinine IA, Perrimon N. Interorgan communication pathways in physiology: focus on *Drosophila*. *Annu Rev Genet*. 2016;50(1):539-570.
51. Colombani J, Raisin S, Pantalacci S, Radimerski T, Montagne J, Leopold P. A nutrient sensor mechanism controls *Drosophila* growth. *Cell*. 2003;114(6):739-749.
52. Geminard C, Rulifson EJ, Leopold P. Remote control of insulin secretion by fat cells in *Drosophila*. *Cell Metab*. 2009;10(3):199-207.
53. Rulifson EJ, Kim SK, Nusse R. Ablation of insulin-producing neurons in flies: growth and diabetic phenotypes. *Science*. 2002;296(5570):1118-1120.
54. Rajan A, Perrimon N. *Drosophila* cytokine unpaired 2 regulates physiological homeostasis by remotely controlling insulin secretion. *Cell*. 2012;151(1):123-137.
55. Rajan A, Housden BE, Wirtz-Peitz F, Holderbaum L, Perrimon N. A mechanism coupling systemic energy sensing to adipokine secretion. *Dev Cell*. 2017;43(1):83-98.e6.
56. Madan A, Kelly KP, Bahk P, *et al.* Atg8/LC3 controls systemic nutrient surplus signaling in flies and humans. *Curr Biol*. 2024;34(15):3327-3341.e9.
57. Ertekin D, Kirszenblat L, Faville R, van Swinderen B. Down-regulation of a cytokine secreted from peripheral fat bodies improves visual attention while reducing sleep in *Drosophila*. *PLoS Biol*. 2020;18(8):e3000548.
58. Zhao Y, Johansson E, Duan J, Han Z, Alenius M. Fat- and sugar-induced signals regulate sweet and fat taste perception in *Drosophila*. *Cell Rep*. 2023;42(11):113387.
59. Brent AE, Rajan A. Insulin and leptin/Upd2 exert opposing influences on synapse number in fat-sensing neurons. *Cell Metab*. 2020;32(5):786-800.e7.
60. Pasco MY, Léopold P. High sugar-induced insulin resistance in *Drosophila* relies on the lipocalin neural lazarlillo. *PLoS One*. 2012;7(5):e36583.
61. Meschi E, Léopold P, Delanoue R. An EGF-responsive neural circuit couples insulin secretion with nutrition in *Drosophila*. *Dev Cell*. 2019;48(1):76-86.e5.
62. Koyama T, Mirth CK. Growth-blocking peptides as nutrition-sensitive signals for insulin secretion and body size regulation. *PLoS Biol*. 2016;14(2):e1002392.
63. Meschi E, Delanoue R. Adipokine and fat body in flies: connecting organs. *Mol Cell Endocrinol*. 2021;533:111339.
64. Kelly KP, Alassaf M, Sullivan CE, *et al.* Fat body phospholipid state dictates hunger-driven feeding behavior. *eLife*. 2022;11:e80282.
65. Savini M, Folick A, Lee YT, *et al.* Lysosome lipid signalling from the periphery to neurons regulates longevity. *Nat Cell Biol*. 2022;24(6):906-916.
66. Papsdorf K, Miklas JW, Hosseini A, *et al.* Lipid droplets and peroxisomes are co-regulated to drive lifespan extension in response to mono-unsaturated fatty acids. *Nat Cell Biol*. 2023;25(5):672-684.
67. Hussey R, Littlejohn NK, Witham E, *et al.* Oxygen-sensing neurons reciprocally regulate peripheral lipid metabolism via neuropeptide signaling in *Caenorhabditis elegans*. *PLoS Genet*. 2018;14(3):e1007305.
68. Imanikia S, Sheng M, Castro C, Griffin JL, Taylor RC. XBP-1 re-models lipid metabolism to extend longevity. *Cell Rep*. 2019;28(3):581-589.e4.
69. Strack AM, Sawyer WB, Hughes JH, Platt KB, Loewy AD. A general pattern of CNS innervation of the sympathetic outflow demonstrated by transneuronal pseudorabies viral infections. *Brain Res*. 1989;491(1):156-162.
70. Cano G, Passerin AM, Schiltz JC, Card JP, Morrison SF, Sved AF. Anatomical substrates for the central control of sympathetic outflow to interscapular adipose tissue during cold exposure. *J Comp Neurol*. 2003;460(3):303-326.
71. Oldfield BJ, Giles ME, Watson A, Anderson C, Colvill LM, McKinley MJ. The neurochemical characterisation of hypothalamic pathways projecting polysynaptically to brown adipose tissue in the rat. *Neuroscience*. 2002;110(3):515-526.
72. Nguyen NL, Barr CL, Ryu V, Cao Q, Xue B, Bartness TJ. Separate and shared sympathetic outflow to white and brown fat coordinately regulates thermoregulation and beige adipocyte recruitment. *Am J Physiol Regul Integr Comp Physiol*. 2017;312(1):R132-R145.
73. Bartness TJ, Bamshad M. Innervation of mammalian white adipose tissue: implications for the regulation of total body fat. *Am J Physiol*. 1998;275(5):R1399-R1411.
74. Foster MT, Bartness TJ. Sympathetic but not sensory denervation stimulates white adipocyte proliferation. *Am J Physiol Regul Integr Comp Physiol*. 2006;291(6):R1630-R1637.
75. Dodt C, Lonnroth P, Wellhoner JP, Fehm HL, Elam M. Sympathetic control of white adipose tissue in lean and obese humans. *Acta Physiol Scand*. 2003;177(3):351-357.
76. Brito NA, Brito MN, Bartness TJ. Differential sympathetic drive to adipose tissues after food deprivation, cold exposure or glucoprivation. *Am J Physiol Regul Integr Comp Physiol*. 2008;294(5):R1445-R1452.
77. Bartness TJ, Hamilton JM, Wade GN, Goldman BD. Regional differences in fat pad responses to short days in Siberian hamsters. *Am J Physiol*. 1989;257(6):R1533-R1540.
78. Youngstrom TG, Bartness TJ. Catecholaminergic innervation of white adipose tissue in Siberian hamsters. *Am J Physiol*. 1995;268(3):R744-R751.
79. Sipe LM, Yang C, Ephrem J, Garren E, Hirsh J, Deppmann CD. Differential sympathetic outflow to adipose depots is required for visceral fat loss in response to calorie restriction. *Nutr Diabetes*. 2017;7(4):e260.
80. Krotkiewski M. Can body fat patterning be changed? *Acta Med Scand Suppl*. 1987;222:213-223.
81. Chaston TB, Dixon JB. Factors associated with percent change in visceral versus subcutaneous abdominal fat during weight loss: findings from a systematic review. *Int J Obes (Lond)*. 2008;32(4):619-628.
82. Li Y, Bujo H, Takahashi K, *et al.* Visceral fat: higher responsiveness of fat mass and gene expression to calorie restriction than subcutaneous fat. *Exp Biol Med (Maywood)*. 2003;228(10):1118-1123.
83. Morrison SF, Madden CJ, Tupone D. Central neural regulation of brown adipose tissue thermogenesis and energy expenditure. *Cell Metab*. 2014;19(5):741-756.
84. Hoffstedt J, Arner E, Wahrenberg H, *et al.* Regional impact of adipose tissue morphology on the metabolic profile in morbid obesity. *Diabetologia*. 2010;53(12):2496-2503.
85. Mishra G, Townsend KL. The metabolic and functional roles of sensory nerves in adipose tissues. *Nat Metab*. 2023;5(9):1461-1474.
86. Cannon B, Nedergaard J, Lundberg JM, Hökfelt T, Terenius L, Goldstein M. Neuropeptide tyrosine (NPY) is co-stored with noradrenaline in vascular but not in parenchymal sympathetic nerves of brown adipose tissue. *Exp Cell Res*. 1986;164(2):546-550.
87. De Matteis R, Ricquier D, Cinti S. TH-, NPY-, SP-, and CGRP-immunoreactive nerves in interscapular brown adipose

- tissue of adult rats acclimated at different temperatures: an immunohistochemical study. *J Neurocytol.* 1998;27(12):877-886.
88. Huesing C, Zhang R, Gummadi S, *et al.* Organization of sympathetic innervation of interscapular brown adipose tissue in the mouse. *J Comp Neurol.* 2022;530(9):1363-1378.
  89. Kumari R, Pascalau R, Wang H, *et al.* Sympathetic NPY controls glucose homeostasis, cold tolerance, and cardiovascular functions in mice. *Cell Rep.* 2024;43(2):113674.
  90. Zhu Y, Yao L, Gallo-Ferraz AL, *et al.* Sympathetic neuropeptide Y protects from obesity by sustaining thermogenic fat. *Nature.* 2024;634(8032):243-250.
  91. Emorine LJ, Marullo S, Briend-Sutren MM, *et al.* Molecular characterization of the human beta 3-adrenergic receptor. *Science.* 1989;245(4922):1118-1121.
  92. Granneman JG, Lahners KN, Chaudhry A. Molecular cloning and expression of the rat beta 3-adrenergic receptor. *Mol Pharmacol.* 1991;40(6):895-899.
  93. Nahmias C, Blin N, Elalouf JM, Mattei MG, Strosberg AD, Emorine LJ. Molecular characterization of the mouse beta 3-adrenergic receptor: relationship with the atypical receptor of adipocytes. *EMBO J.* 1991;10(12):3721-3727.
  94. Langin D, Portillo MP, Saulnier-Blache J-S, Lafontan M. Coexistence of three b-adrenoceptor subtypes in white fat cells of various mammalian species. *Eur J Pharm.* 1991;199(3):291-301.
  95. Collins S, Daniel KW, Rohlfes EM, Ramkumar V, Taylor IL, Gettys TW. Impaired expression and functional activity of the  $\beta_3$ - and  $\beta_1$ -adrenergic receptors in adipose tissue of congenitally obese (C57BL/6J ob/ob) mice. *Mol Endocrinol.* 1994;8(4):518-527.
  96. Barbe P, Millet L, Galitzky J, Lafontan M, Berlan M. In situ assessment of the role of the beta 1-, beta 2- and beta 3-adrenoceptors in the control of lipolysis and nutritive blood flow in human subcutaneous adipose tissue. *Br J Pharmacol.* 1996;117(5):907-913.
  97. Tavernier G, Barbe P, Galitzky J, *et al.* Expression of beta3-adrenoceptors with low lipolytic action in human subcutaneous white adipocytes. *J Lipid Res.* 1996;37(1):87-97.
  98. Arch JR. Challenges in beta(3)-adrenoceptor agonist drug development. *Ther Adv Endocrinol Metab.* 2011;2(2):59-64.
  99. Cero C, Lea HJ, Zhu KY, Shamsi F, Tseng YH, Cypess AM. beta3-adrenergic receptors regulate human brown/beige adipocyte lipolysis and thermogenesis. *JCI Insight.* 2021;6(11):e139160.
  100. Lafontan M, Berlan M, Carpenne C. Fat cell adrenoceptors: inter- and intraspecific differences and hormone regulation. *Int J Obes.* 1985;9(Suppl 1):117-127.
  101. Langin D. Adipose tissue lipolysis as a metabolic pathway to define pharmacological strategies against obesity and the metabolic syndrome. *Pharmacol Res.* 2006;53(6):482-491.
  102. Zhao J, Cannon B, Nedergaard J.  $\alpha_1$ -adrenergic stimulation potentiates the thermogenic action of  $\beta_3$ -adrenoreceptor-generated cAMP in brown fat cells. *J Biol Chem.* 1997;272(52):32847-32856.
  103. Zechner R, Madeo F, Kratky D. Cytosolic lipolysis and lipophagy: two sides of the same coin. *Nat Rev Mol Cell Biol.* 2017;18(11):671-684.
  104. Grabner GF, Xie H, Schweiger M, Zechner R. Lipolysis: cellular mechanisms for lipid mobilization from fat stores. *Nat Metab.* 2021;3(11):1445-1465.
  105. Soeder KS, Snedden SK, Cao W, *et al.* The  $\beta_3$ -adrenergic receptor activates mitogen-activated protein kinase in adipocytes through a Gi-dependent mechanism. *J Biol Chem.* 1999;274(17):12017-12022.
  106. Robidoux J, Kumar N, Daniel KW, *et al.* Maximal beta3-adrenergic regulation of lipolysis involves src and epidermal growth factor receptor-dependent ERK1/2 activation. *J Biol Chem.* 2006;281(49):37794-37802.
  107. Liu D, Bordicchia M, Zhang C, *et al.* Activation of mTORC1 is essential for  $\beta$ -adrenergic stimulation of adipose browning. *J Clin Invest.* 2016;126(5):1704-1716.
  108. Le TDV, Liu D, Besing GK, *et al.* Glucagon-like peptide-1 receptor activation stimulates PKA-mediated phosphorylation of Raptor and this contributes to the weight loss effect of liraglutide. *eLife.* 2023;12:e80944.
  109. Crowder MK, Shrestha S, Cartailier JP, Collins S. Protein kinase D1 (Prkd1) deletion in brown adipose tissue leads to altered myogenic gene expression after cold exposure, while thermogenesis remains intact. *Physiol Rep.* 2023;11(4):e15576.
  110. Shi F, de Fatima Silva F, Liu D, *et al.* Salt-inducible kinase inhibition promotes the adipocyte thermogenic program and adipose tissue browning. *Mol Metab.* 2023;74:101753.
  111. Blancaquert S, Wang L, Paternot S, *et al.* cAMP-dependent activation of mammalian target of rapamycin (mTOR) in thyroid cells. Implication in mitogenesis and activation of CDK4. *Mol Endocrinol.* 2010;24(7):1453-1468.
  112. de Joussineau C, Sahut-Barnola I, Tissier F, *et al.* mTOR pathway is activated by PKA in adrenocortical cells and participates in vivo to apoptosis resistance in primary pigmented nodular adrenocortical disease (PPNAD). *Hum Mol Genet.* 2014;23(20):5418-5428.
  113. Cao W, Daniel KW, Robidoux J, *et al.* P38 mitogen-activated protein kinase is the central regulator of cyclic AMP-dependent transcription of the brown fat uncoupling protein 1 gene. *Mol Cell Biol.* 2004;24(7):3057-3067.
  114. Cao W, Medvedev AV, Daniel KW, Collins S.  $\beta$ -Adrenergic activation of p38 MAP kinase in adipocytes: cAMP induction of the uncoupling protein-1 (UCP1) gene requires p38 MAP kinase. *J Biol Chem.* 2001;276(29):27077-27082.
  115. Cao WH, Madden CJ, Morrison SF. Inhibition of brown adipose tissue thermogenesis by neurons in the ventrolateral medulla and in the nucleus tractus solitarius. *Am J Physiol Regul Integr Comp Physiol.* 2010;299(1):R277-R290.
  116. Collins S, Cao W, Robidoux J. Learning new tricks from old dogs: beta-adrenergic receptors teach new lessons on firing up adipose tissue metabolism. *Mol Endocrinol.* 2004;18(9):2123-2131.
  117. Robidoux J, Cao W, Quan H, *et al.* Selective activation of mitogen-activated protein (MAP) kinase kinase 3 and p38alpha MAP kinase is essential for cyclic AMP-dependent UCP1 expression in adipocytes. *Mol Cell Biol.* 2005;25(13):5466-5479.
  118. Willows JW, Gunsch G, Paradie E, *et al.* Schwann cells contribute to demyelinating diabetic neuropathy and nerve terminal structures in white adipose tissue. *iScience.* 2023;26(3):106189.
  119. Blaszkiewicz M, Willows JW, Dubois AL, *et al.* Neuropathy and neural plasticity in the subcutaneous white adipose depot. *PLoS One.* 2019;14(9):e0221766.
  120. Cardoso F, Klein Wolterink RGJ, Godinho-Silva C, *et al.* Neuro-mesenchymal units control ILC2 and obesity via a brain-adipose circuit. *Nature.* 2021;597(7876):410-414.
  121. Wang P, Loh KH, Wu M, *et al.* A leptin-BDNF pathway regulating sympathetic innervation of adipose tissue. *Nature.* 2020;583(7818):839-844.
  122. Willows JW, Blaszkiewicz M, Townsend KL. The sympathetic innervation of adipose tissues: regulation, functions, and plasticity. *Compr Physiol.* 2023;13(3):4985-5021.
  123. Jun H, Yu H, Gong J, *et al.* An immune-beige adipocyte communication via nicotinic acetylcholine receptor signaling. *Nat Med.* 2018;24(6):814-822.
  124. Knights AJ, Liu S, Ma Y, *et al.* Acetylcholine-synthesizing macrophages in subcutaneous fat are regulated by beta(2) -adrenergic signaling. *EMBO J.* 2021;40(24):e106061.
  125. Severi I, Perugini J, Ruocco C, *et al.* Activation of a non-neuronal cholinergic system in visceral white adipose tissue of obese mice and humans. *Mol Metab.* 2024;79:101862.
  126. Meng W, Xiao T, Liang X, *et al.* The miR-182-5p/FGF21/acetylcholine axis mediates the crosstalk between adipocytes and macrophages to promote beige fat thermogenesis. *JCI Insight.* 2021;6(17):e150249.

127. Knuth CM, Barayan D, Lee JH, *et al.* Subcutaneous white adipose tissue independently regulates burn-induced hypermetabolism via immune-adipose crosstalk. *Cell Rep.* 2024;43(1):113584.
128. Jun H, Ma Y, Chen Y, *et al.* Adrenergic-independent signaling via CHRNA2 regulates beige fat activation. *Dev Cell.* 2020;54(1):106-116.e5.
129. Ma Y, Jun H, Wu J. Immune cell cholinergic signaling in adipose thermoregulation and immunometabolism. *Trends Immunol.* 2022;43(9):718-727.
130. Malin SG, Shavva VS, Tarnawski L, Olofsson PS. Functions of acetylcholine-producing lymphocytes in immunobiology. *Curr Opin Neurobiol.* 2020;62:115-121.
131. Chavan SS, Pavlov VA, Tracey KJ. Mechanisms and therapeutic relevance of neuro-immune communication. *Immunity.* 2017;46(6):927-942.
132. Chen Y, Ikeda K, Yoneshiro T, *et al.* Thermal stress induces glycolytic beige fat formation via a myogenic state. *Nature.* 2019;565(7738):180-185.
133. Ma Y, Liu S, Jun H, Wu J. CHRNA2: a new paradigm in beige thermoregulation and metabolism. *Trends Cell Biol.* 2022;32(6):479-489.
134. Roberson ED, Mucke L. 100 years and counting: prospects for defeating Alzheimer's disease. *Science.* 2006;314(5800):781-784.
135. Vaz M, Silvestre S. Alzheimer's disease: recent treatment strategies. *Eur J Pharmacol.* 2020;887:173554.
136. Collins S. A heart-adipose tissue connection in the regulation of energy metabolism. *Nat Rev Endocrinol.* 2014;10(3):157-163.
137. Bordicchia M, Liu D, Amri EZ, *et al.* Cardiac natriuretic peptides act via p38 MAPK to induce the brown fat thermogenic program in mouse and human adipocytes. *J Clin Invest.* 2012;122(3):1022-1036.
138. Sengenès C, Berlan M, De Glisezinski I, Lafontan M, Galitzky J. Natriuretic peptides: a new lipolytic pathway in human adipocytes. *FASEB J.* 2000;14(10):1345-1351.
139. Xourafa G, Korbacher M, Roden M. Inter-organ crosstalk during development and progression of type 2 diabetes mellitus. *Nat Rev Endocrinol.* 2024;20(1):27-49.
140. Wu X, Hutson I, Akk AM, *et al.* Contribution of adipose-derived factor D/Adipsin to complement alternative pathway activation: lessons from lipodystrophy. *J Immunol.* 2018;200(8):2786-2797.
141. Markan KR, Naber MC, Ameka MK, *et al.* Circulating FGF21 is liver derived and enhances glucose uptake during refeeding and overfeeding. *Diabetes.* 2014;63(12):4057-4063.
142. BonDurant LD, Ameka M, Naber MC, *et al.* FGF21 regulates metabolism through adipose-dependent and -independent mechanisms. *Cell Metab.* 2017;25(4):935-944.e4.
143. Lu J, Chatterjee M, Schmid H, Beck S, Gawaz M. CXCL14 as an emerging immune and inflammatory modulator. *J Inflamm (Lond).* 2016;13(1):1.
144. Cereijo R, Gavalda-Navarro A, Cairo M, *et al.* CXCL14, a brown adipokine that mediates brown-fat-to-macrophage communication in the thermogenic adaptation. *Cell Metab.* 2018;28(5):750-763.e6.
145. Mohamed-Ali V, Goodrick S, Rawesh A, *et al.* Subcutaneous adipose tissue releases interleukin-6, but not tumor necrosis factor- $\alpha$ , in vivo. *J Clin Endocrinol Metab.* 1997;82(12):4196-4200.
146. Theurich S, Tsaousidou E, Hanssen R, *et al.* IL-6/Stat3-dependent induction of a distinct, obesity-associated NK cell subpopulation deteriorates energy and glucose homeostasis. *Cell Metab.* 2017;26(1):171-184.e6.
147. Wunderlich FT, Strohle P, Konner AC, *et al.* Interleukin-6 signaling in liver-parenchymal cells suppresses hepatic inflammation and improves systemic insulin action. *Cell Metab.* 2010;12(3):237-249.
148. Dennis EA, Norris PC. Eicosanoid storm in infection and inflammation. *Nat Rev Immunol.* 2015;15(8):511-523.
149. Chiurchiù V, Leuti A, Maccarrone M. Bioactive lipids and chronic inflammation: managing the fire within. *Front Immunol.* 2018;9:38.
150. Yilmaz M, Claiborn KC, Hotamisligil GS. De novo lipogenesis products and endogenous lipokines. *Diabetes.* 2016;65(7):1800-1807.
151. Hernández-Saavedra D, Stanford KI. The regulation of lipokines by environmental factors. *Nutrients.* 2019;11(10):2422.
152. Leiria LO, Wang CH, Lynes MD, *et al.* 12-lipoxygenase regulates cold adaptation and glucose metabolism by producing the omega-3 lipid 12-HEPE from brown fat. *Cell Metab.* 2019;30(4):768-783.e7.
153. Tsuji T, Tseng YH. Adipose tissue-derived lipokines in metabolism. *Curr Opin Genet Dev.* 2023;81:102089.
154. Yore MM, Syed I, Moraes-Vieira PM, *et al.* Discovery of a class of endogenous mammalian lipids with anti-diabetic and anti-inflammatory effects. *Cell.* 2014;159(2):318-332.
155. Hammarstedt A, Syed I, Vijayakumar A, *et al.* Adipose tissue dysfunction is associated with low levels of the novel palmitic acid hydroxystearic acids. *Sci Rep.* 2018;8(1):15757.
156. Vijayakumar A, Aryal P, Wen J, *et al.* Absence of carbohydrate response element binding protein in adipocytes causes systemic insulin resistance and impairs glucose transport. *Cell Rep.* 2017;21(4):1021-1035.
157. Lynes MD, Leiria LO, Lundh M, *et al.* The cold-induced lipokine 12,13-diHOME promotes fatty acid transport into brown adipose tissue. *Nat Med.* 2017;23(5):631-637.
158. Sugimoto S, Mena HA, Sansbury BE, *et al.* Brown adipose tissue-derived Mar2 contributes to cold-induced resolution of inflammation. *Cell Metab.* 2022;4(6):775-790.
159. Stanford KI, Lynes MD, Takahashi H, *et al.* 12,13-diHOME: an exercise-induced lipokine that increases skeletal muscle fatty acid uptake. *Cell Metab.* 2018;27(5):1111-1120.e3.
160. Pinckard KM, Shettigar VK, Wright KR, *et al.* A novel endocrine role for the BAT-released lipokine 12,13-diHOME to mediate cardiac function. *Circulation.* 2021;143(2):145-159.
161. Park K, Li Q, Lynes MD, *et al.* Endothelial cells induced progenitors into brown fat to reduce atherosclerosis. *Circ Res.* 2022;131(2):168-183.
162. Nagatake T, Shibata Y, Morimoto S, *et al.* 12-Hydroxyeicosapentaenoic acid inhibits foam cell formation and ameliorates high-fat diet-induced pathology of atherosclerosis in mice. *Sci Rep.* 2021;11(1):10426.
163. Saika A, Nagatake T, Hirata SI, *et al.* Omega3 fatty acid metabolite, 12-hydroxyeicosapentaenoic acid, alleviates contact hypersensitivity by downregulation of CXCL1 and CXCL2 gene expression in keratinocytes via retinoid X receptor  $\alpha$ . *FASEB J.* 2021;35(4):e21354.
164. Serhan CN, Gupta SK, Perretti M, *et al.* The Atlas of Inflammation Resolution (AIR). *Mol Aspects Med.* 2020;74:100894.
165. Gnad T, Scheibler S, von Kugelgen I, *et al.* Adenosine activates brown adipose tissue and recruits beige adipocytes via A2A receptors. *Nature.* 2014;516(7531):395-399.
166. Niemann B, Haufs-Brusberg S, Puetz L, *et al.* Apoptotic brown adipocytes enhance energy expenditure via extracellular inosine. *Nature.* 2022;609(7926):361-368.
167. Pfeifer A, Mikhael M, Niemann B. Inosine: novel activator of brown adipose tissue and energy homeostasis. *Trends Cell Biol.* 2024;34(1):72-82.
168. Weir G, Ramage LE, Akyol M, *et al.* Substantial metabolic activity of human brown adipose tissue during warm conditions and cold-induced lipolysis of local triglycerides. *Cell Metab.* 2018;27(6):1348-1355.e4.
169. Lagarde D, Jeanson Y, Portais JC, *et al.* Lactate fluxes and plasticity of adipose tissues: a redox perspective. *Front Physiol.* 2021;12:689747.
170. Tsuji T, Tolstikov V, Zhang Y, *et al.* Light-responsive adipose-hypothalamus axis controls metabolic regulation. *Nat Commun.* 2024;15(1):6768.
171. Verkerke ARP, Wang D, Yoshida N, *et al.* BCAA-nitrogen flux in brown fat controls metabolic health independent of thermogenesis. *Cell.* 2024;187(10):2359-2374.e18.

172. Yoneshiro T, Wang Q, Tajima K, *et al.* BCAA catabolism in brown fat controls energy homeostasis through SLC25A44. *Nature*. 2019;572(7771):614-619.
173. Th  ry M, Th  ry C. Communication by extracellular vesicles: where we are and where we need to go. *Cell*. 2016;164(6):1226-1232.
174. Thomou T, Mori MA, Dreyfuss JM, *et al.* Adipose-derived circulating miRNAs regulate gene expression in other tissues. *Nature*. 2017;542(7642):450-455.
175. Mori MA, Ludwig RG, Garcia-Martin R, Brandao BB, Kahn CR. Extracellular miRNAs: from biomarkers to mediators of physiology and disease. *Cell Metab*. 2019;30(4):656-673.
176. M  ller G, Schneider M, Biemer-Daub G, Wied S. Microvesicles released from rat adipocytes and harboring glycosylphosphatidylinositol-anchored proteins transfer RNA stimulating lipid synthesis. *Cell Signal*. 2011;23(7):1207-1223.
177. Deng ZB, Poliakov A, Hardy RW, *et al.* Adipose tissue exosome-like vesicles mediate activation of macrophage-induced insulin resistance. *Diabetes*. 2009;58(11):2498-2505.
178. Zhang Y, Proenca R, Maffei M, Barone M, Leopold L, Friedman JM. Positional cloning of the mouse obese gene and its human homologue. *Nature*. 1994;372(6505):425-432.
179. Halaas JL, Gajiwala KS, Maffei M, *et al.* Weight-reducing effects of the plasma protein encoded by the obese gene. *Science*. 1995;269(5223):543-546.
180. Flier JS. Starvation in the midst of plenty: reflections on the history and biology of insulin and leptin. *Endocr Rev*. 2019;40(1):1-16.
181. Farooqi IS, O'Rahilly S. Leptin: a pivotal regulator of human energy homeostasis. *Am J Clin Nutr*. 2009;89(3):980S-984S.
182. Buettner C, Poci   A, Muse ED, Etgen AM, Myers MG Jr, Rossetti L. Critical role of STAT3 in leptin's metabolic actions. *Cell Metab*. 2006;4(1):49-60.
183. Vaisse C, Halaas JL, Horvath CM, Darnell JE Jr, Stoffel M, Friedman JM. Leptin activation of Stat3 in the hypothalamus of wild-type and ob/ob mice but not db/db mice. *Nat Genet*. 1996;14(1):95-97.
184. Hill JW, Elmquist JK, Elias CF. Hypothalamic pathways linking energy balance and reproduction. *Am J Physiol-Endocrinol Metab*. 2008;294(5):E827-E832.
185. Ahima RS, Prabakaran D, Mantzoros C, *et al.* Role of leptin in the neuroendocrine response to fasting. *Nature*. 1996;382(6588):250-252.
186. Flier JS, Maratos-Flier E. Leptin's physiologic role: does the emperor of energy balance have no clothes? *Cell Metab*. 2017;26(1):24-26.
187. Morton GJ, Cummings DE, Baskin DG, Barsh GS, Schwartz MW. Central nervous system control of food intake and body weight. *Nature*. 2006;443(7109):289-295.
188. Flak JN, Myers MG Jr. CNS mechanisms of leptin action. *Mol Endocrinol*. 2016;30(1):3-12.
189. Vong L, Ye C, Yang Z, Choi B, Chua S Jr, Lowell BB. Leptin action on GABAergic neurons prevents obesity and reduces inhibitory tone to POMC neurons. *Neuron*. 2011;71(1):142-154.
190. Kong D, Tong Q, Ye C, *et al.* GABAergic RIP-Cre neurons in the arcuate nucleus selectively regulate energy expenditure. *Cell*. 2012;151(3):645-657.
191. Montague CT, Farooqi IS, Whitehead JP, *et al.* Congenital leptin deficiency is associated with severe early-onset obesity in humans. *Nature*. 1997;387(6636):903-908.
192. Farooqi IS, Matarese G, Lord GM, *et al.* Beneficial effects of leptin on obesity, T cell hyporesponsiveness, and neuroendocrine/metabolic dysfunction of human congenital leptin deficiency. *J Clin Invest*. 2002;110(8):1093-1103.
193. Myers MG Jr, Leibel RL, Seeley RJ, Schwartz MW. Obesity and leptin resistance: distinguishing cause from effect. *Trends Endocrinol Metab*. 2010;21(11):643-651.
194. Frederich RC, Hamann A, Anderson S, Lollmann B, Lowell BB, Flier JS. Leptin levels reflect body lipid content in mice: evidence for diet-induced resistance to leptin action. *Nat Med*. 1995;1(12):1311-1314.
195. Knight ZA, Hannan KS, Greenberg ML, Friedman JM. Hyperleptinemia is required for the development of leptin resistance. *PLoS One*. 2010;5(6):e11376.
196. Caro JF, Kolaczynski JW, Nyce MR, *et al.* Decreased cerebrospinal-fluid/serum leptin ratio in obesity: a possible mechanism for leptin resistance. *Lancet*. 1996;348(9021):159-161.
197. Banks WA. Blood-brain barrier and energy balance. *Obesity (Silver Spring)*. 2006;14(S8):234S-237S.
198. Banks WA, Farr SA, Morley JE. The effects of high fat diets on the blood-brain barrier transport of leptin: failure or adaptation? *Physiol Behav*. 2006;88(3):244-248.
199. Munzberg H, Flier JS, Bjorbaek C. Region-specific leptin resistance within the hypothalamus of diet-induced obese mice. *Endocrinology*. 2004;145(11):4880-4889.
200. Bjorbaek C, Elmquist JK, Frantz JD, Shoelson SE, Flier JS. Identification of SOCS-3 as a potential mediator of central leptin resistance. *Mol Cell*. 1998;1(4):619-625.
201. Ravussin Y, Leibel RL, Ferrante AW Jr. A missing link in body weight homeostasis: the catabolic signal of the overfed state. *Cell Metab*. 2014;20(4):565-572.
202. Ravussin Y, Edwin E, Gallop M, *et al.* Evidence for a non-leptin system that defends against weight gain in overfeeding. *Cell Metab*. 2018;28(2):289-299.e5.
203. Morton GJ, Schwartz MW. Leptin and the central nervous system control of glucose metabolism. *Physiol Rev*. 2011;91(2):389-411.
204. Fan S, Xu Y, Lu Y, *et al.* A neural basis for brain leptin action on reducing type 1 diabetic hyperglycemia. *Nat Commun*. 2021;12(1):2662.
205. Harvey J. Leptin: a multifaceted hormone in the central nervous system. *Mol Neurobiol*. 2003;28(3):245-258.
206. Signore AP, Zhang F, Weng Z, Gao Y, Chen J. Leptin neuroprotection in the CNS: mechanisms and therapeutic potentials. *J Neurochem*. 2008;106(5):1977-1990.
207. Shanley LJ, Irving AJ, Harvey J. Leptin enhances NMDA receptor function and modulates hippocampal synaptic plasticity. *J Neurosci*. 2001;21(24):RC186.
208. Durakoglugil M, Irving AJ, Harvey J. Leptin induces a novel form of NMDA receptor-dependent long-term depression. *J Neurochem*. 2005;95(2):396-405.
209. Yamauchi T, Kamon J, Ito Y, *et al.* Cloning of adiponectin receptors that mediate antidiabetic metabolic effects. *Nature*. 2003;423(6941):762-769.
210. Yamauchi T, Nio Y, Maki T, *et al.* Targeted disruption of AdipoR1 and AdipoR2 causes abrogation of adiponectin binding and metabolic actions. *Nat Med*. 2007;13(3):332-339.
211. Kubota N, Yano W, Kubota T, *et al.* Adiponectin stimulates AMP-activated protein kinase in the hypothalamus and increases food intake. *Cell Metab*. 2007;6(1):55-68.
212. Kadowaki T, Yamauchi T, Kubota N. The physiological and pathophysiological role of adiponectin and adiponectin receptors in the peripheral tissues and CNS. *FEBS Lett*. 2008;582(1):74-80.
213. Chen R, Shu Y, Zeng Y. Links between adiponectin and dementia: from risk factors to pathophysiology. *Front Aging Neurosci*. 2020;11:356.
214. Dragano NR, Monfort-Pires M, Velloso LA. Mechanisms mediating the actions of fatty acids in the hypothalamus. *Neuroscience*. 2020;447:15-27.
215. Basil MC, Levy BD. Specialized pro-resolving mediators: endogenous regulators of infection and inflammation. *Nat Rev Immunol*. 2016;16(1):51-67.
216. Makwana K, Chodavarapu H, Morones N, *et al.* Sensory neurons expressing calcitonin gene-related peptide alpha regulate adaptive thermogenesis and diet-induced obesity. *Mol Metab*. 2021;45:101161.
217. Willows JW, Blaszkiewicz M, Lamore A, *et al.* Visualization and analysis of whole depot adipose tissue neural innervation. *iScience*. 2021;24(10):103127.

218. Wang Y, Leung VH, Zhang Y, *et al.* The role of somatosensory innervation of adipose tissues. *Nature*. 2022;609(7927):569-574.
219. Ryu V, Garretson JT, Liu Y, Vaughan CH, Bartness TJ. Brown adipose tissue has sympathetic-sensory feedback circuits. *J Neurosci*. 2015;35(5):2181-2190.
220. Ryu V, Watts AG, Xue B, Bartness TJ. Bidirectional crosstalk between the sensory and sympathetic motor systems innervating brown and white adipose tissue in male Siberian hamsters. *Am J Physiol Regul Integr Comp Physiol*. 2017;312(3):R324-R337.
221. Osaka T, Kobayashi A, Namba Y, *et al.* Temperature- and capsaicin-sensitive nerve fibers in brown adipose tissue attenuate thermogenesis in the rat. *Pflügers Arch*. 1998;437(1):36-42.
222. Vaughan CH, Bartness TJ. Anterograde transneuronal viral tract tracing reveals central sensory circuits from brown fat and sensory denervation alters its thermogenic responses. *Am J Physiol Regul Integr Comp Physiol*. 2012;302(9):R1049-R1058.
223. Shi Z, Chen WW, Xiong XQ, *et al.* Sympathetic activation by chemical stimulation of white adipose tissues in rats. *J Appl Physiol* (1985). 2012;112(6):1008-1014.
224. Nguyen NLT, Xue B, Bartness TJ. Sensory denervation of inguinal white fat modifies sympathetic outflow to white and brown fat in Siberian hamsters. *Physiol Behav*. 2018;190:28-33.
225. Fabbri E, Mohammed BS, Magkos F, Korenblat KM, Patterson BW, Klein S. Alterations in adipose tissue and hepatic lipid kinetics in obese men and women with nonalcoholic fatty liver disease. *Gastroenterology*. 2008;134(2):424-431.
226. Smith GI, Shankaran M, Yoshino M, *et al.* Insulin resistance drives hepatic de novo lipogenesis in nonalcoholic fatty liver disease. *J Clin Invest*. 2020;130(3):1453-1460.
227. Huang W, Dedousis N, Bandi A, Lopaschuk GD, O'Doherty RM. Liver triglyceride secretion and lipid oxidative metabolism are rapidly altered by leptin in vivo. *Endocrinology*. 2006;147(3):1480-1487.
228. Hackl MT, Fürnsinn C, Schuh CM, *et al.* Brain leptin reduces liver lipids by increasing hepatic triglyceride secretion and lowering lipogenesis. *Nat Commun*. 2019;10(1):2717.
229. Mittenbühler MJ, Sprenger H-G, Gruber S, *et al.* Hepatic leptin receptor expression can partially compensate for IL-6R $\alpha$  deficiency in DEN-induced hepatocellular carcinoma. *Mol Metabol*. 2018;17:122-133.
230. Tomita K, Oike Y, Teratani T, *et al.* Hepatic AdipoR2 signaling plays a protective role against progression of nonalcoholic steatohepatitis in mice. *Hepatology (Baltimore, Md)*. 2008;48(2):458-473.
231. Harari D, Tzahar E, Romano J, *et al.* Neuregulin-4: a novel growth factor that acts through the ErbB-4 receptor tyrosine kinase. *Oncogene*. 1999;18(17):2681-2689.
232. Wang G-X, Zhao X-Y, Meng Z-X, *et al.* The brown fat-enriched secreted factor Nrg4 preserves metabolic homeostasis through attenuation of hepatic lipogenesis. *Nat Med*. 2014;20(12):1436-1443.
233. Tutunchi H, Mobasser M, Aghamohammadzadeh N, Hooshyar J, Naeini F, Najafipour F. Serum neuregulin 4 (NRG-4) level and non-alcoholic fatty liver disease (NAFLD): a case-control study. *Int J Clin Pract*. 2021;75(10):e14555.
234. Cai C, Lin M, Xu Y, Li X, Yang S, Zhang H. Association of circulating neuregulin 4 with metabolic syndrome in obese adults: a cross-sectional study. *BMC Med*. 2016;14(1):165.
235. Lei X, Chen H, Xu Y, *et al.* Serum isthmin-1 is a potential biomarker for metabolic dysfunction associated fatty liver disease in patients with metabolic syndrome and type 2 diabetes mellitus. *BMJ Open Diabetes Res Care*. 2024;12(5):e004514.
236. Zhao M, Banhos Danneskiold-Samsøe N, Ulicna L, *et al.* Phosphoproteomic mapping reveals distinct signaling actions and activation of muscle protein synthesis by Isthmin-1. *eLife*. 2022;11:e80014.
237. Jiang Z, Zhao M, Voilquin L, *et al.* Isthmin-1 is an adipokine that promotes glucose uptake and improves glucose tolerance and hepatic steatosis. *Cell Metab*. 2021;33(9):1836-1852.e11.
238. He S, Ryu J, Liu J, *et al.* LRG1 is an adipokine that mediates obesity-induced hepatosteatosis and insulin resistance. *J Clin Invest*. 2021;131(24):e148545.
239. Choi CHJ, Barr W, Zaman S, *et al.* LRG1 is an adipokine that promotes insulin sensitivity and suppresses inflammation. *eLife*. 2022;11:e81559.
240. Liu B, Xiang L, Ji J, *et al.* Sparcl1 promotes nonalcoholic steatohepatitis progression in mice through upregulation of CCL2. *J Clin Invest*. 2021;131(20):e144801.
241. Yamauchi T, Kamon J, Minokoshi Y, *et al.* Adiponectin stimulates glucose utilization and fatty-acid oxidation by activating AMP-activated protein kinase. *Nat Med*. 2002;8(11):1288-1295.
242. Haque MS, Minokoshi Y, Hamai M, Iwai M, Horiuchi M, Shimazu T. Role of the sympathetic nervous system and insulin in enhancing glucose uptake in peripheral tissues after intrahypothalamic injection of leptin in rats. *Diabetes*. 1999;48(9):1706-1712.
243. Kamohara S, Burcelin R, Halaas JL, Friedman JM, Charron MJ. Acute stimulation of glucose metabolism in mice by leptin treatment. *Nature*. 1997;389(6649):374-377.
244. Minokoshi Y, Kim YB, Peroni OD, *et al.* Leptin stimulates fatty-acid oxidation by activating AMP-activated protein kinase. *Nature*. 2002;415(6869):339-343.
245. Muoio DM, Dohn GL, Fiedorek FT Jr, Tapscott EB, Coleman RA. Leptin directly alters lipid partitioning in skeletal muscle. *Diabetes*. 1997;46(8):1360-1363.
246. Attané C, Foussal C, Le Gonidec S, *et al.* Apelin treatment increases complete Fatty Acid oxidation, mitochondrial oxidative capacity, and biogenesis in muscle of insulin-resistant mice. *Diabetes*. 2012;61(2):310-320.
247. Sun Q, Li L, Li R, *et al.* Overexpression of visfatin/PBEF/Nampt alters whole-body insulin sensitivity and lipid profile in rats. *Ann Med*. 2009;41(4):311-320.
248. de Alvaro C, Teruel T, Hernandez R, Lorenzo M. Tumor necrosis factor alpha produces insulin resistance in skeletal muscle by activation of inhibitor kappaB kinase in a p38 MAPK-dependent manner. *J Biol Chem*. 2004;279(17):17070-17078.
249. Plomgaard P, Bouzakri K, Krogh-Madsen R, Mittendorfer B, Zierath JR, Pedersen BK. Tumor necrosis factor-alpha induces skeletal muscle insulin resistance in healthy human subjects via inhibition of Akt substrate 160 phosphorylation. *Diabetes*. 2005;54(10):2939-2945.
250. Mauer J, Chaurasia B, Goldau J, *et al.* Signaling by IL-6 promotes alternative activation of macrophages to limit endotoxemia and obesity-associated resistance to insulin. *Nat Immunol*. 2014;15(5):423-430.
251. Jiang Y, Lu L, Hu Y, *et al.* Resistin induces hypertension and insulin resistance in mice via a TLR4-dependent pathway. *Sci Rep*. 2016;6(1):22193.
252. Muse ED, Obici S, Bhanot S, *et al.* Role of resistin in diet-induced hepatic insulin resistance. *J Clin Invest*. 2004;114(2):232-239.
253. Steppan CM, Bailey ST, Bhat S, *et al.* The hormone resistin links obesity to diabetes. *Nature*. 2001;409(6818):307-312.
254. Yang Q, Graham TE, Mody N, *et al.* Serum retinol binding protein 4 contributes to insulin resistance in obesity and type 2 diabetes. *Nature*. 2005;436(7049):356-362.
255. Yu Y, Du H, Wei S, *et al.* Adipocyte-derived exosomal MiR-27a induces insulin resistance in skeletal muscle through repression of PPAR $\gamma$ . *Theranostics*. 2018;8(8):2171-2188.
256. Li D, Song H, Shuo L, *et al.* Gonadal white adipose tissue-derived exosomal MiR-222 promotes obesity-associated insulin resistance. *Aging (Albany NY)*. 2020;12(22):22719-22743.
257. Mann G, Mora S, Madu G, Adegoke OAJ. Branched-chain amino acids: catabolism in skeletal muscle and implications for muscle and whole-body metabolism. *Front Physiol*. 2021;12:702826.
258. Szendroedi J, Yoshimura T, Phielix E, *et al.* Role of diacylglycerol activation of PKC $\theta$  in lipid-induced muscle insulin resistance in humans. *Proc Natl Acad Sci U S A*. 2014;111(26):9597-9602.

259. Babaei P, Hoseini R. Exercise training modulates adipokine dysregulations in metabolic syndrome. *Sports Med Health Sci*. 2022;4(1):18-28.
260. Frigolet ME, Gutiérrez-Aguilar R. The role of the novel lipokine palmitoleic acid in health and disease. *Adv Nutr (Bethesda, Md)*. 2017;8(1):173s-181s.
261. Takahashi H, Alves CRR, Stanford KI, *et al*. TGF- $\beta$ 2 is an exercise-induced adipokine that regulates glucose and fatty acid metabolism. *Nat Metab*. 2019;1(2):291-303.
262. Ivatt L, Paul M, Miguelez-Crespo A, *et al*. Obesity-induced mesenteric PVAT remodelling is sexually dimorphic, but not driven by ovarian hormones: Short title: Obesity induces sex-specific responses in mesenteric PVAT. *Cardiovasc Diabetol*. 2025;24(1):39.
263. Dushay J, Rickers ES, Wang E, *et al*. Effects of age and sex on systemic inflammation and cardiometabolic function in individuals with type 2 diabetes. *J Am Heart Assoc*. 2025;14(3):e037863.
264. Gale C, Logan KM, Jeffries S, *et al*. Sexual dimorphism in relation to adipose tissue and intrahepatic lipid deposition in early infancy. *Int J Obes (Lond)*. 2015;39(4):629-632.
265. Palmer BF, Clegg DJ. The sexual dimorphism of obesity. *Mol Cell Endocrinol*. 2015;402:113-119.
266. Rodriguez-Cuenca S, Pujol E, Justo R, *et al*. Sex-dependent thermogenesis, differences in mitochondrial morphology and function, and adrenergic response in brown adipose tissue. *J Biol Chem*. 2002;277(45):42958-42963.
267. Shao X, Chen Y, Shao X, Wang S, Wang S, Wang Y. Gender differences in brown adipose tissue-related brain functional networks: an 18F-FDG-PET study. *Nucl Med Commun*. 2020;41(6):526-532.
268. Matsushita M, Yoneshiro T, Aita S, Kameya T, Sugie H, Saito M. Impact of brown adipose tissue on body fatness and glucose metabolism in healthy humans. *Int J Obes (Lond)*. 2014;38(6):812-817.
269. Herz CT, Kulterer OC, Prager M, *et al*. Sex differences in brown adipose tissue activity and cold-induced thermogenesis. *Mol Cell Endocrinol*. 2021;534:111365.
270. Brychta RJ, McGehee S, Huang S, *et al*. The thermoneutral zone in women takes an "Arctic" shift compared to men. *Proc Natl Acad Sci U S A*. 2024;121(19):e2311116121.
271. Waraich RS, Mauvais-Jarvis F. Paracrine and intracrine contributions of androgens and estrogens to adipose tissue biology: physiopathological aspects. *Horm Mol Biol Clin Investig*. 2013;14(2):49-55.
272. Nigro P, Middelbeek RJW, Alves CRR, *et al*. Exercise training promotes sex-specific adaptations in mouse inguinal white adipose tissue. *Diabetes*. 2021;70(6):1250-1264.
273. Many GM, Sanford JA, Sagendorf TJ, *et al*. Sexual dimorphism and the multi-omic response to exercise training in rat subcutaneous white adipose tissue. *Nat Metab*. 2024;6(5):963-979.
274. Fève B, Cinti S, Beaupère C, *et al*. Pink adipose tissue: a paradigm of adipose tissue plasticity. *Ann Endocrinol (Paris)*. 2024;85(3):248-251.
275. Considine RV, Sinha MK, Heiman ML, *et al*. Serum immunoreactive-leptin concentrations in normal-weight and obese humans. *N Engl J Med*. 1996;334(5):292-295.
276. Nishizawa H, Shimomura I, Kishida K, *et al*. Androgens decrease plasma adiponectin, an insulin-sensitizing adipocyte-derived protein. *Diabetes*. 2002;51(9):2734-2741.
277. Nagy TR, Gower BA, Trowbridge CA, Dezenberg C, Shewchuk RM, Goran MI. Effects of gender, ethnicity, body composition, and fat distribution on serum leptin concentrations in children. *J Clin Endocrinol Metab*. 1997;82(7):2148-2152.
278. Rosenbaum M, Nicolson M, Hirsch J, *et al*. Effects of gender, body composition, and menopause on plasma concentrations of leptin. *J Clin Endocrinol Metab*. 1996;81(9):3424-3427.
279. Yang X, Schadt EE, Wang S, *et al*. Tissue-specific expression and regulation of sexually dimorphic genes in mice. *Genome Res*. 2006;16(8):995-1004.
280. Grove KL, Fried SK, Greenberg AS, Xiao XQ, Clegg DJ. A microarray analysis of sexual dimorphism of adipose tissues in high-fat-diet-induced obese mice. *Int J Obes (Lond)*. 2010;34(6):989-1000.
281. Chen X, McClusky R, Chen J, *et al*. The number of x chromosomes causes sex differences in adiposity in mice. *PLoS Genet*. 2012;8(5):e1002709.
282. Anderson WD, Soh JY, Innis SE, *et al*. Sex differences in human adipose tissue gene expression and genetic regulation involve adipogenesis. *Genome Res*. 2020;30(10):1379-1392.
283. Diaz AV, Stephenson D, Nemkov T, D'Alessandro A, Reis T. Spenito-dependent metabolic sexual dimorphism intrinsic to fat storage cells. *Genetics*. 2023;225(3):iyad164.
284. Rideout EJ, Narsaiya MS, Grewal SS. The sex determination gene transformer regulates male-female differences in *Drosophila* body size. *PLoS Genet*. 2015;11(12):e1005683.
285. Sieber MH, Spradling AC. Steroid signaling establishes a female metabolic state and regulates SREBP to control oocyte lipid accumulation. *Curr Biol*. 2015;25(8):993-1004.
286. Bednarova A, Tomcala A, Mochanova M, Kodrik D, Krishnan N. Disruption of adipokinetic hormone mediated energy homeostasis has subtle effects on physiology, behavior and lipid status during aging in *Drosophila*. *Front Physiol*. 2018;9:949.
287. Coassolo L, Danneskiold-Samsøe NB, Nguyen Q, *et al*. Prohormone cleavage prediction uncovers a non-incretin anti-obesity peptide. *Nature*. 2025;641(8061):192-201.