The metabolic effects of adipose tissue as an endocrine organ

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Why this topic is important

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Aims of this lecture

- Endocrine effects of WAT
- Immunomodulatory effects of WAT expansion
- Significance of BAT
- Importance of limiting visceral WAT expansion
- Strategies to increase BAT

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Contents

- Adipose tissue anatomy and distribution and types
- Adipose tissue functions
- Adipose tissue innervation
- WAT vs. brown adipose tissue vs. beige adipose tissue
- WAT: Adipose tissue inflammation
- WAT: Pathogenesis of insulin resistance and metabolic syndrome
- How diet modulates inflammation in adipose tissue
- Browning strategies

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Adipose tissue

- Adipose tissue, distributed throughout the body, is capable of expanding to accommodate excess energy.

- Two major types of adipose tissue: WAT and BAT.

- Anatomically, WAT comprises two major depots, **subcutaneous adipose tissue** and **visceral adipose tissue** around internal organs.

- VAT- concentrated in the abdominal cavity-further subdivided into mesenteric, omental, perirenal, and peritoneal depots.

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- Key physiological functions of WAT :**insulation** and **energy storage**.

- In obesity, excess VAT is closely linked to metabolic complications, such as **Insulin Resistance** and **Type 2 diabetes** .

- Mesenteric and omental adipose tissues- particularly important for hepatic insulin resistance and steatosis as liver is directly exposed to adipokines via the portal vein.

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Review

Adipose tissue heterogeneity: Implication of depot differences in adipose tissue for obesity complications

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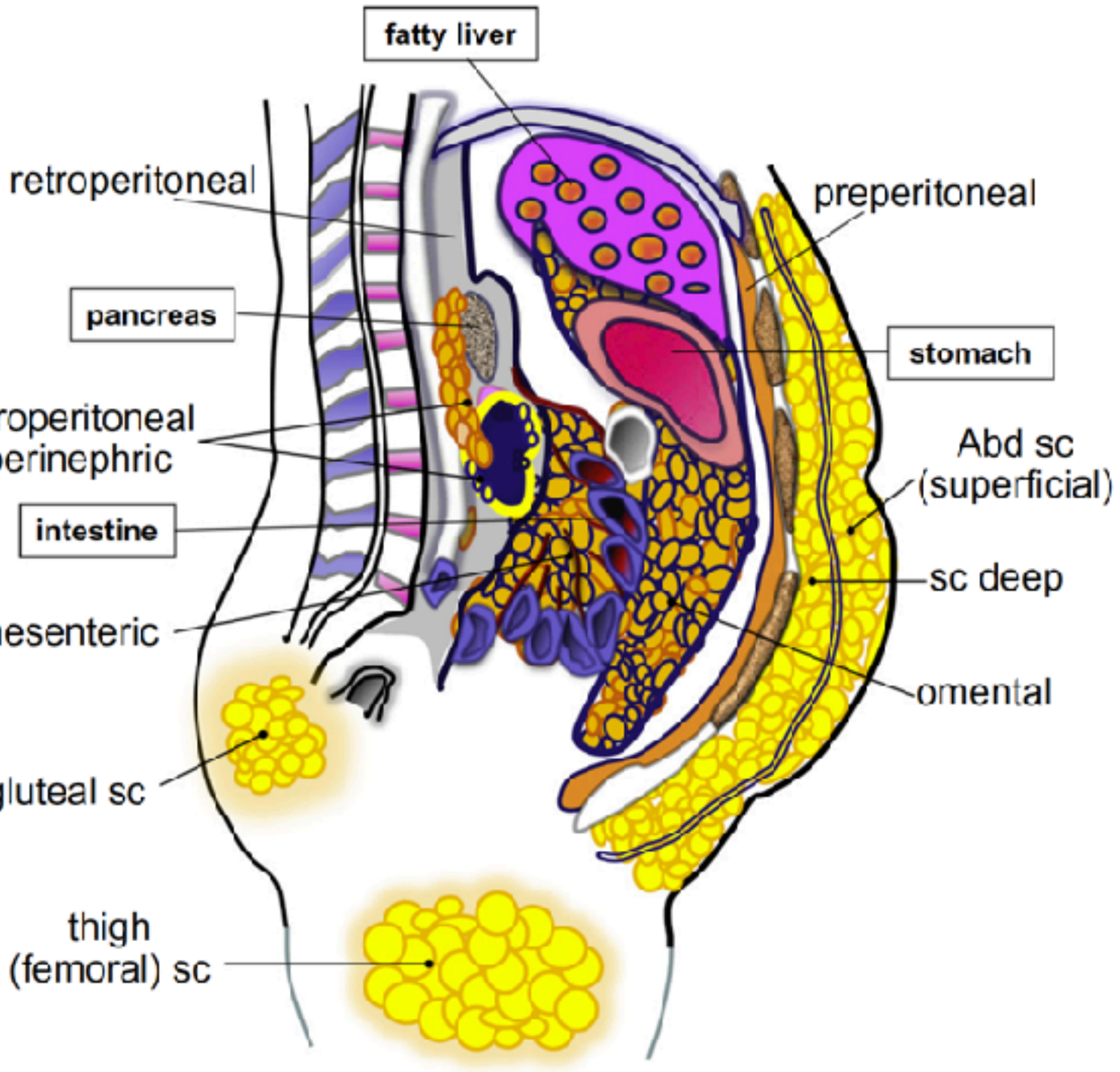

JCI The Journal of Clinical Investigation

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

C. Ronald Kahn, … , Guoxiao Wang, Kevin Y. Lee

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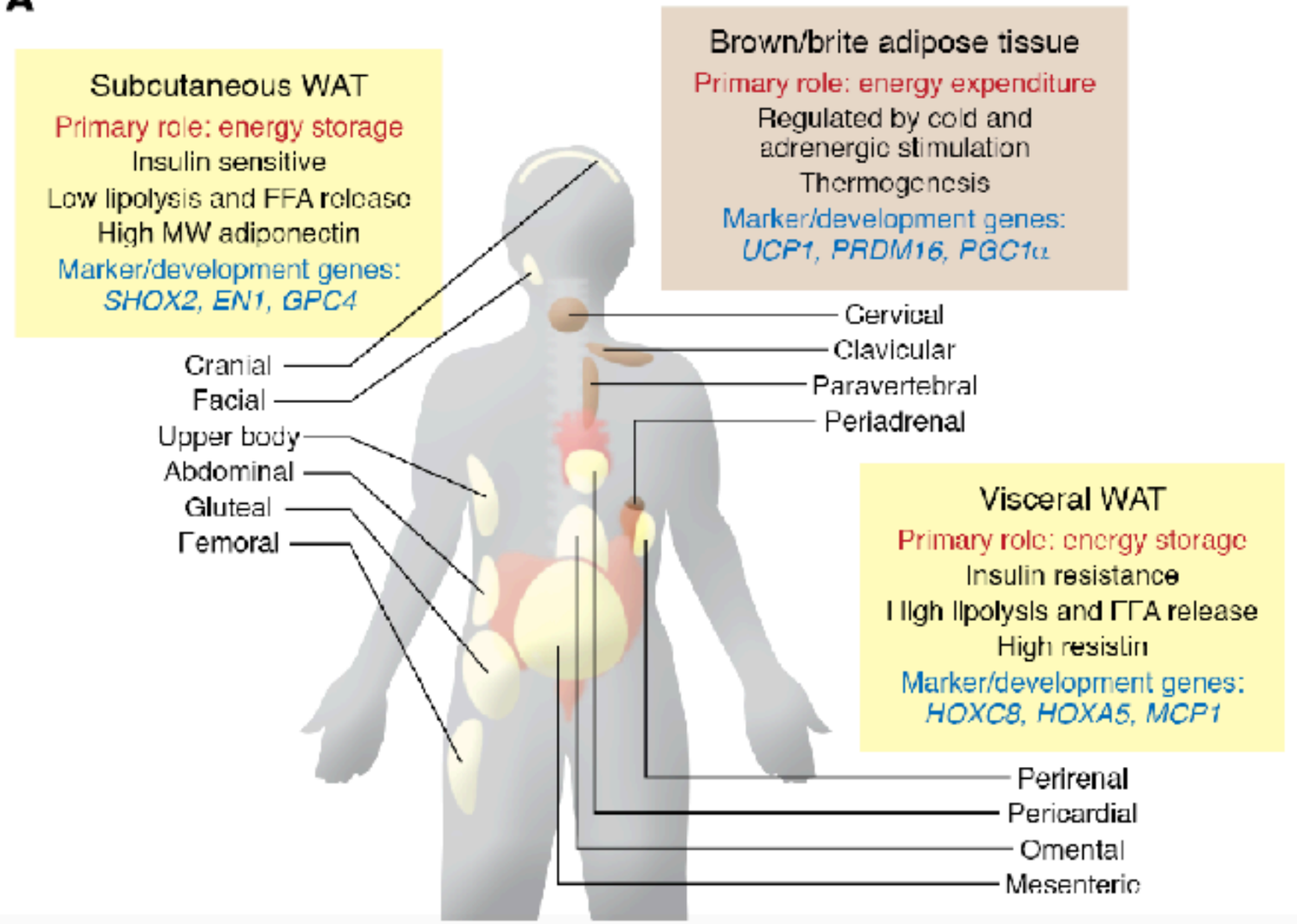

frontiers in Endocrinology

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Adipose Tissue Remodeling: Its Role in Energy Metabolism and Metabolic Disorders

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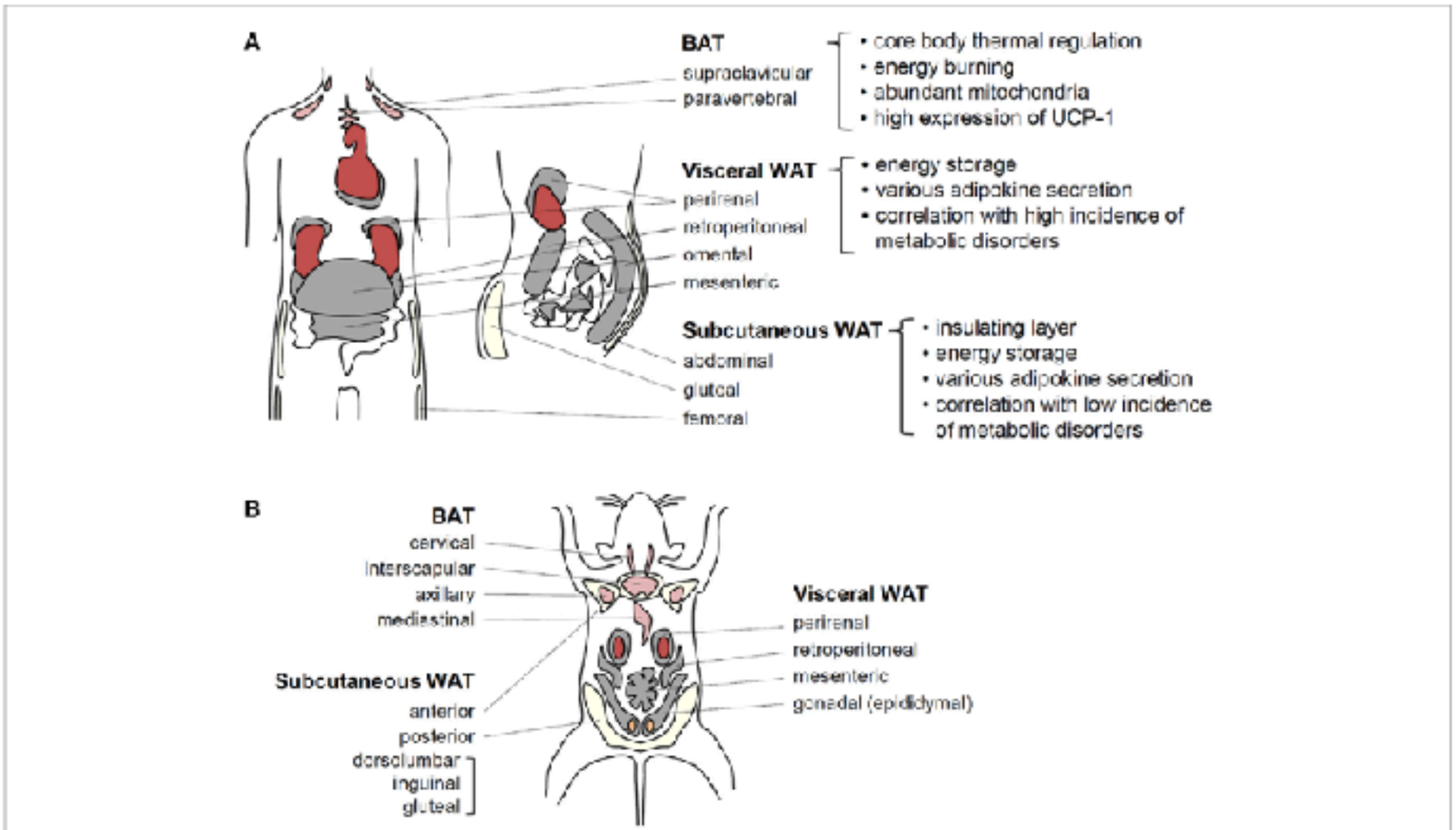

FIGURE 1 | Adipose tissue functions in energy homeostasis and thermal regulation. **(A)** In humans, BAT localized around the shoulders and ribs contributes to heat generation. Brown adipocytes exhibit abundant mitochondria and UCP-1 expression related to thermogenesis. It has recently been speculated that BAT efficiency for fat-burning could be harnessed to reduce obesity. Visceral WAT (VAT) and subcutaneous WAT (SAT) possesses considerable capacities for energy storage. VAT surrounds intra-abdominal organs, whereas SAT spreads throughout the body beneath the skin. These fat tissues secrete various adipokines to regulate energy homeostasis. VAT is more strongly associated with obesity-induced metabolic disorders than SAT. **(B)** In adult mice, BAT is well developed and easily observed compared with that in adult humans. Among WAT depots within the abdominal cavity, the paired gonadal depots located around the ovaries in females and the testes in males are studied as a model of VAT. However, these depots do not exist in humans. The paired inguinal depots in the anterior to the upper part of the hind limbs are representative SATs in mice.

Types of adipose tissue

	WHITE ADIPOSE TISSUE	BROWN ADIPOSE TISSUE	BEIGE ADIPOSE TISSUE
Localization	• Subcutaneous • Intra-abdominal • Epicardial • Gonadal	• Interscapular • Paravertebral • Perirenal • Cervical • Supraclavicular	Emerges in white adipose tissue depots with appropriate stimuli
Morphology	Spherical	Elliptical and smaller than white	Spherical
Cell composition	• Single lipid droplet • Few mitochondria • Flattened peripheral nucleus • Little endoplasmic reticulum	• Multiple small lipid droplets • Large number of mitochondria • Oval central nucleus	• Unilocular morphology but small lipid droplets after stimulation • Mitochondria appear after stimulation
Function	Storing energy	• Expending energy and heat production (non-shivering thermogenesis)	Thermogenic potential
Uncoupling protein	Undetectable	Positive	Positive after stimulation

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El Hadi H, Di Vincenzo A, Vettor R and Rossato M (2019) Food Ingredients Involved in White-to-Brown Adipose Tissue Conversion and in Calorie Burning. Front. Physiol. 9:1954. doi: 10.3389/fphys.2018.01954

Types of adipose tissue

- WAT 95% adipose mass
- BAT 1-2%
- Beige adipose difficult to quantify

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- Brown color of BAT - attributed to high mitochondrial density, critical for heat generation and lipid oxidation.
- Though BAT in humans is mainly limited to neonates and is gradually replaced by WAT with aging, studies have shown that BAT is viable and functional in human adults.

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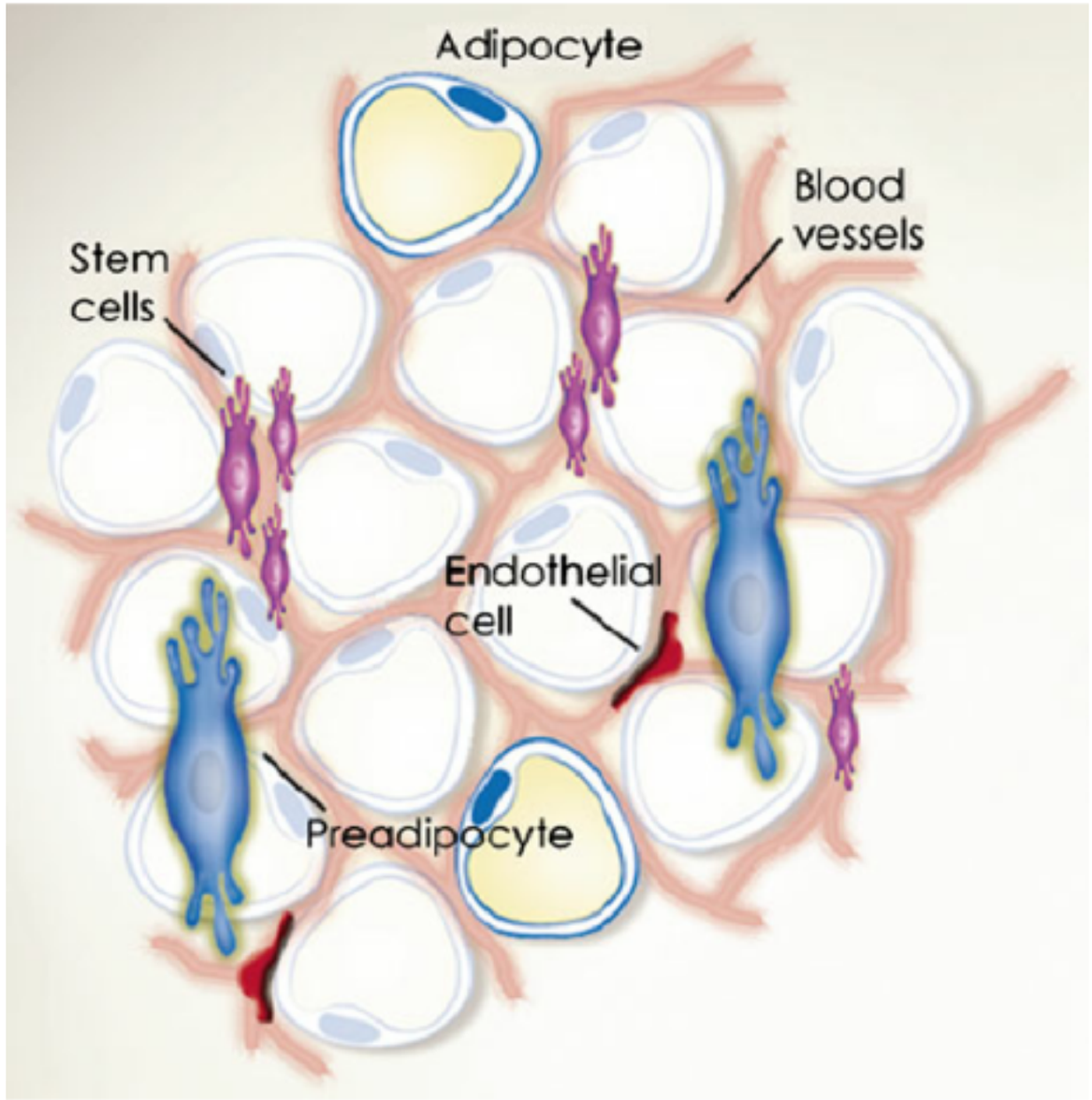
Adipose tissue histology



- Adipose tissue comprises mature adipocytes, preadipocytes, endothelial cells, fibroblasts, mast cells, and immune-system cells.

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Mechanisms of obesity-induced inflammation and insulin resistance: insights into the emerging role of nutritional strategies

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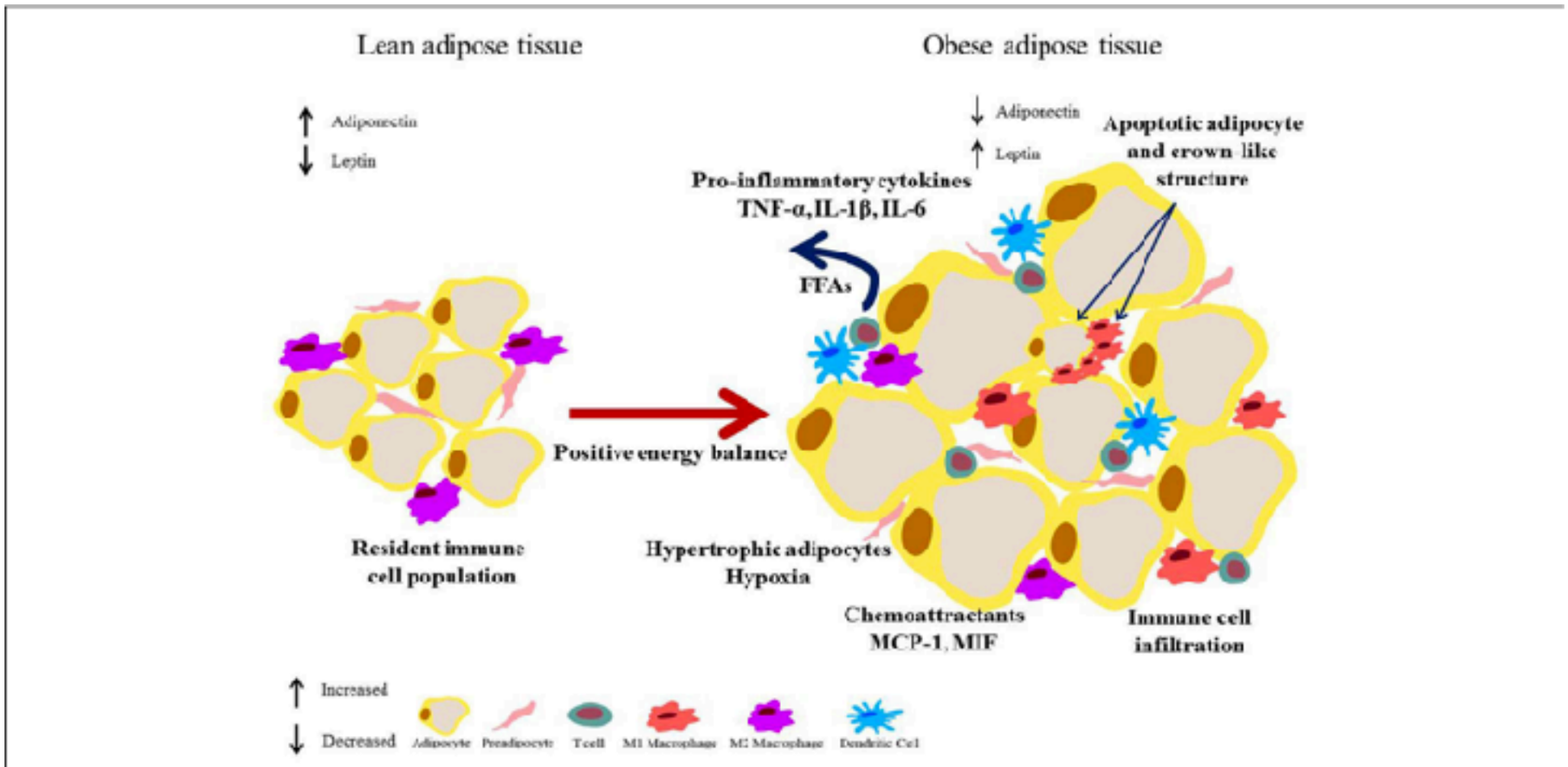

FIGURE 2 | Obese adipose tissue expansion – resultant inflammation and metabolic dysregulation. Excess energy leads to adipose expansion with hypertrophic adipocytes that secrete chemoattractants such as MCP-1, drawing immune cells into the tissue. Secretion of pro-inflammatory mediators such as TNF-α, IL-1β, and IL-6 by adipocytes, pre-adipocytes, and infiltrating immune cells results in polarization of macrophages to a pro-inflammatory M1 phenotype, and drive an inflammatory T cell population. Augmented lipolysis leads to increased levels of FFAs. This environment negatively impacts on the insulin signaling pathway and a state of insulin resistance results. Additionally hypertrophic adipocytes are also linked with hypoxia.

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Mechanisms of obesity-induced inflammation and insulin resistance: insights into the emerging role of nutritional strategies

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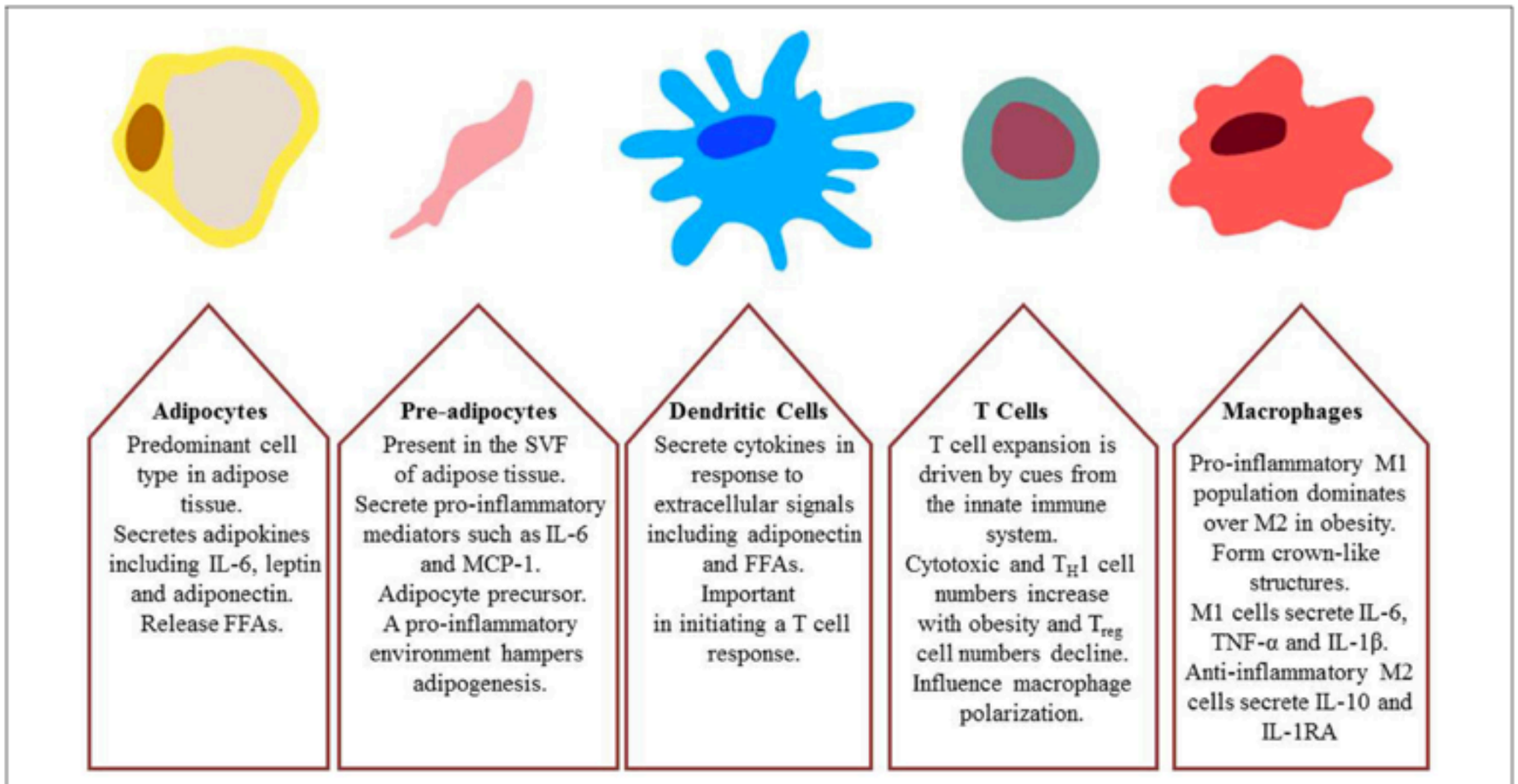

FIGURE 3 | Major cell types involved in obesity-induced inflammation and insulin resistance; adipocytes, pre-adipocytes, dendritic cells, T cells, and macrophages.

Adipose tissue functions

- Specialised energy storage organ
- Endocrine function: regulating energy homeostasis
- Thermal regulator

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Adipose tissue

- Adipose tissues secrete various hormones, cytokines, and metabolites (termed as adipokines) that control systemic energy balance by regulating appetitive signals from the central nerve system as well as metabolic activity in peripheral tissues.

- In response to changes in the nutritional status, the adipose tissue undergoes dynamic remodeling, including quantitative and qualitative alterations in adipose tissue-resident cells

- Anatomic location significant.

- Cell type is significant.

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Adipose tissue innervation

- Adipocytes modulate whole body metabolism through secretion of endocrine and paracrine factors that modulate local immune cell cytokine secretion, endothelium blood flow and neuronal signaling to the brain.

- Adipocytes, immune cells and endothelial cells within adipose tissues secrete factors such as leptin, TNFα and VEGF that regulate local sensory nerve fibers.

- Adipocyte lipid metabolism communicates with local sensory nerve fibers, sending signals to the CNS, and conversely, sensory nerve fibers secrete factors that may regulate adipocytes and other adipose cells.

- Increased lipolysis in white adipose tissue in response to sympathetic activation can cause sensory nerve fibers to regulate the metabolic activity of distant brown adipose tissue depots.

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Molecular pathways linking adipose innervation to insulin sensitivity in obesity and type 2 diabetes

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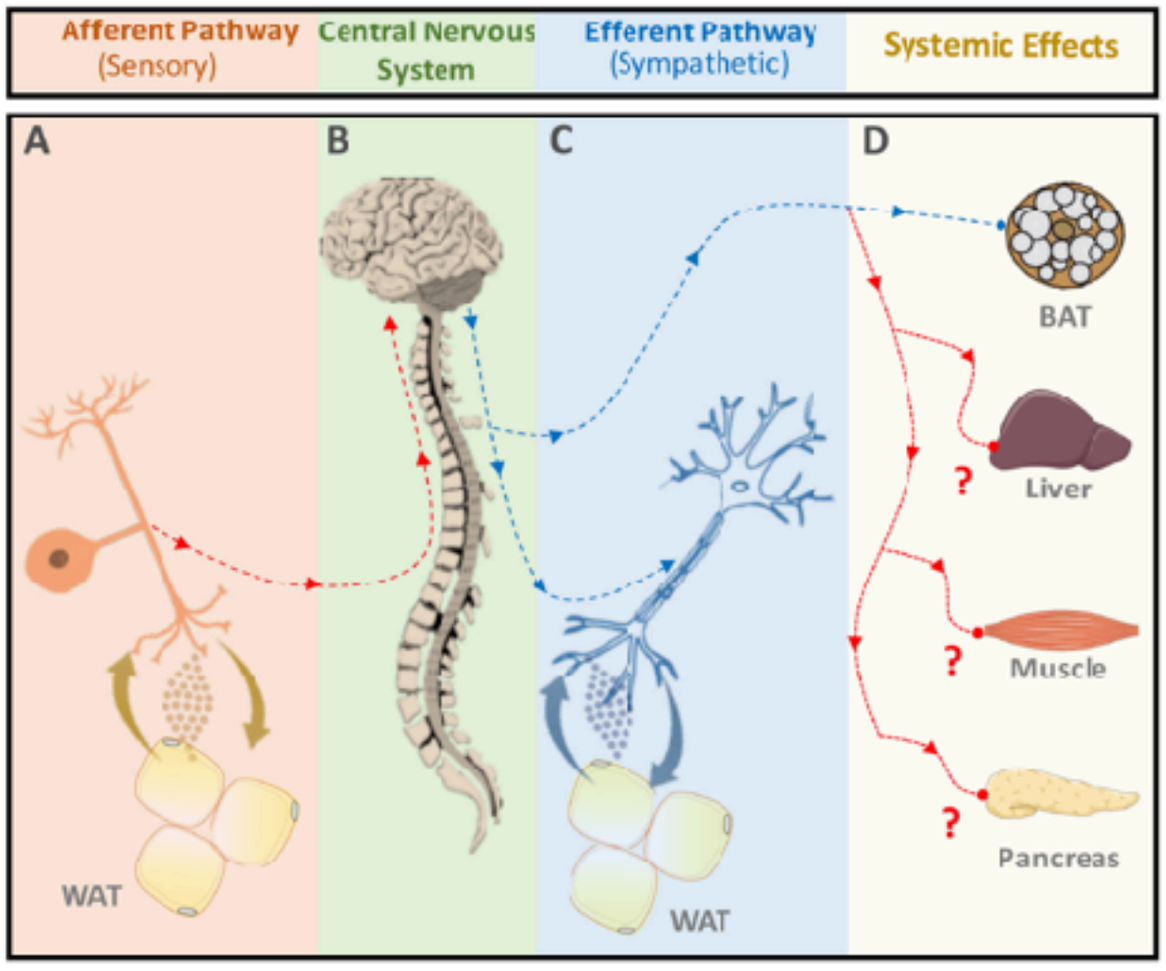

Figure 2: Adipose Signaling to Local Nerve Fibers Regulates Systemic Metabolism.
(A) Sensory nerves relay information from the white adipose tissue (WAT) microenvironment to the central nervous system. **(B)** The central nervous system (CNS) integrates adipose tissue signals to orchestrate a response to the adipose tissue microenvironment. The CNS conveys its response via sympathetic outflow back into the periphery. **(C)** The sympathetic nerve innervating WAT releases signaling factors that influence the adipose tissue microenvironment. **(D)** The autonomic nervous system also affects other metabolic organs in order to promote whole-body homeostasis. Whether adipose metabolic cues are conveyed to CNS to control sympathetic outflow into liver, muscle and pancreas (represented in red lines) is still unknown. Thus, the adipose tissue microenvironment may have a role in regulating systemic metabolism through signaling to local nerve fibers. The depicted cartoon illustrates a general concept. The scale in which the diagrams were drawn is not anatomically accurate.

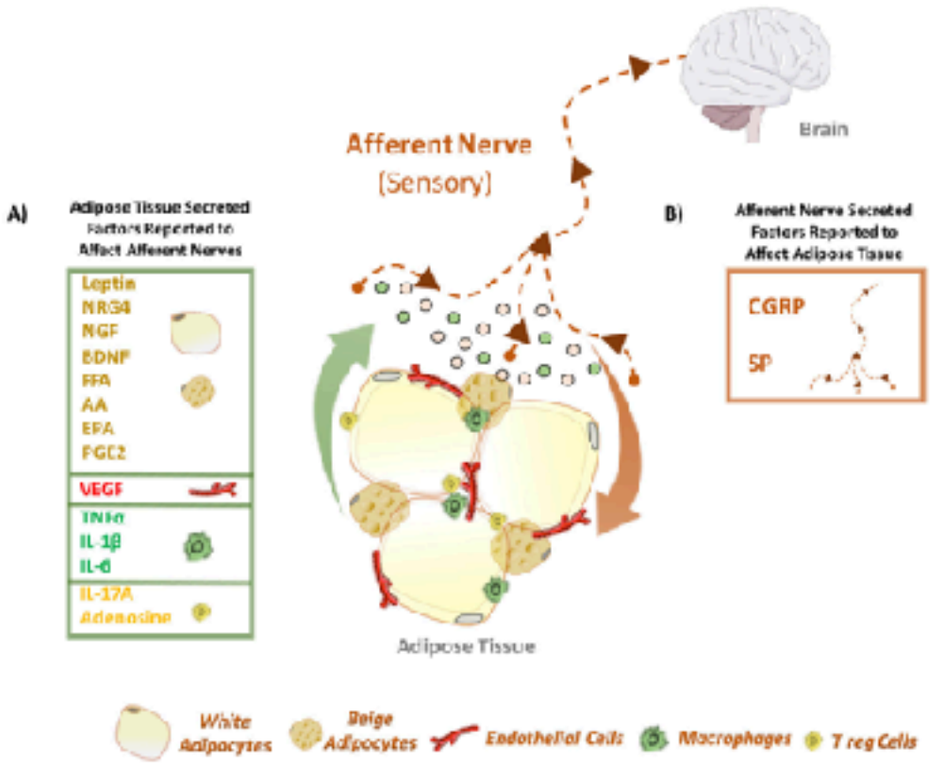

Figure 3: Adipose Tissue-Sensory Nerve Crosstalk.
(A) Adipose tissue resident cells release molecular mediators that can act on the afferent neuronal pathway and invoke a central response to the tissue microenvironment. The principle component of adipose tissue, the adipocyte, can release various neuro-active and neurotrophic peptides, such as leptin, neuregulin-4 (NRG4), nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), free fatty acids (FFA), arachidonic acid (AA) and eicosanoids, such as eicosapentaenoic acid (EPA) and prostaglandin-E2 (PGE2), that act on surrounding cells, including sensory nerve fibers. Endothelial cells, comprising the vasculature of adipose tissue, secrete vascular endothelial growth factor (VEGF) that can promote nerve sprouting and sensory hypersensitization upon interaction with the VEGF receptor family (VEGFR). Cytokines secreted from macrophages, such as tumor necrosis factor alpha (TNFα), interleukin-1 beta (IL-1β) and interleukin-6 (IL-6), may act directly on the sensory nerve itself, or indirectly through their pro-inflammatory effects within the adipose tissue microenvironment. Anti-inflammatory cytokines, such as interleukin-17A (IL-17A) and adenosine, originating from alternatively-activated macrophages and various lymphocytes, including regulatory T-cells (Tregs), can act similarly. **(B)** Conversely, signaling from the sensory nerve terminals to cells within adipose tissue has the potential to modulate adipocyte functions. Upon stimulation, the sensory nerve can release calcitonin

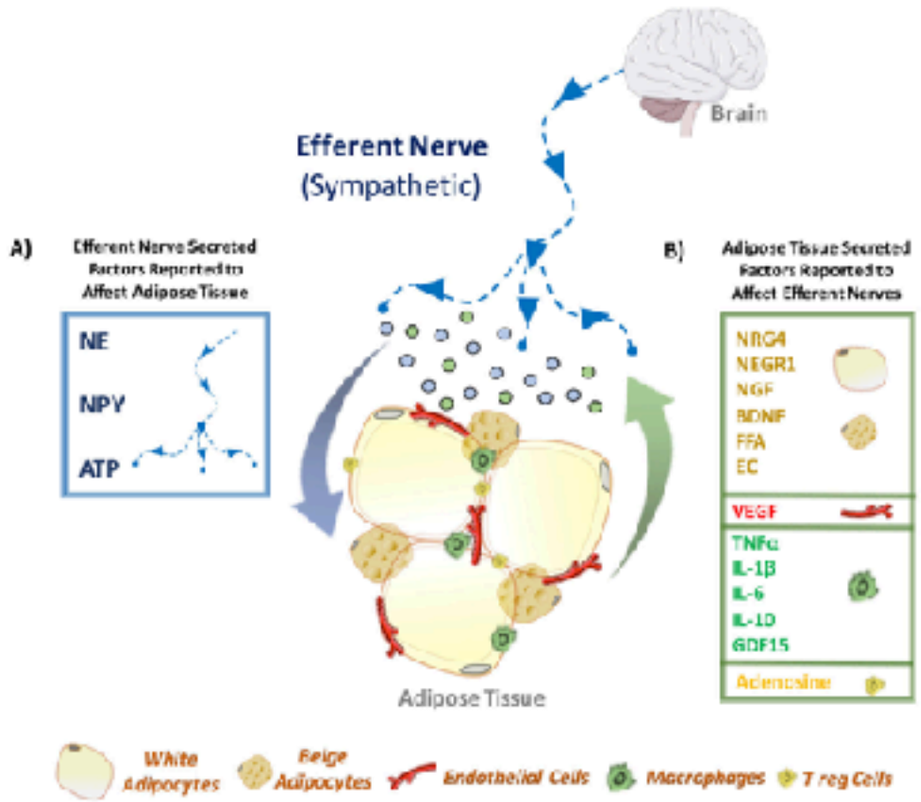

Figure 5: Adipose Tissue-Sympathetic Nerve Crosstalk.
(A) Efferent nerve fibers are known to regulate adipose tissue functions through secretion of bioactive factors. Among them are catecholamine (norepinephrine), neuropeptide Y (NPY) and adenosine triphosphate (ATP). The central nervous system stimulates sympathetic outflow to adipose tissue, triggering the secretion of norepinephrine, NPY or ATP (represented by blue dots). These sympathetic-derived secreted factors, through the activation of their respective receptors, affect not only adipocytes, but also other adipose resident cells, such as endothelial cells, macrophages and lymphocytes. **(B)** In turn, the stimulated adipose cells also produce a number of secreted bioactive factors that communicate with adipose sympathetic fibers. For instance, multilocular beige adipocytes - induced via sympathetic norepinephrine and/or adenosine molecules - produce the neurotrophic factor neuregulin-4 (NRG4), which is known to promote neurite outgrowth. Additionally, white adipocytes have been shown to synthesize several factors with neurotrophic activity that may enhance sympathetic innervation of adipose tissue. Among these factors are the neuronal growth regulator 1 (NEGR1), nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), free fatty acids (FFA) and endocannabinoids (EC). The vascular endothelial growth factor (VEGF) secreted by endothelial cells and

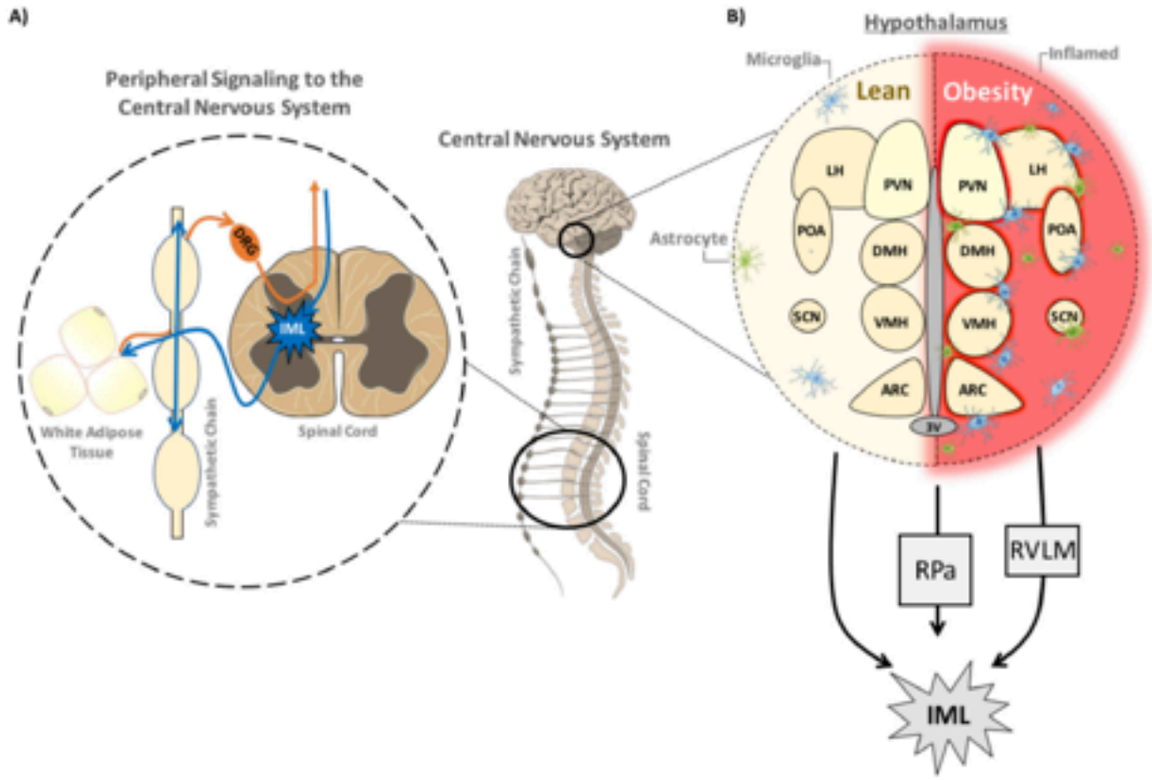

Figure 4: Central Integration of Adipose Signals and Obesity-mediated Dysregulation.

(A) Afferent sensory nerve fibers innervating white adipose tissue depots arise from dorsal root ganglia (DRG) proximal to the spinal cord. The DRG also projects to the brain via the dorsal horn of the spinal cord, relaying sensory information from the periphery to the central nervous system for integration. **(B)** The hypothalamus is a primary area for metabolic regulation in the central nervous system, influencing thermogenesis and food intake, as well as other critical homeostatic functions throughout the body. Projections into the preoptic area (POA), as well as resident temperature-sensitive neurons, relay critical thermoregulatory information to the dorsomedial hypothalamic nucleus (DMH), a core component of the orexinergic system and thermoregulatory function of the hypothalamus. The paraventricular hypothalamus (PVN), which is proximal to the third ventricle (3V), is involved food intake, thermoregulation and neuroendocrine functions through projections to the pituitary. The arcuate nucleus (ARC), along with the ventromedial nucleus of the hypothalamus (VMH) and lateral hypothalamus (LH), are also involved in appetitive behavior and food reward. The suprachiasmatic nucleus (SCN) is a critical area for regulating circadian rhythm. All of these centers play direct or indirect roles in influencing hypothalamic thermogenic regulation. Hypothalamic inflammation has been linked to metabolic dysregulation and obesity-related insulin resistance through excessive gliosis, leading to neuronal damage, particularly noted within arcuate nucleus. The hypothalamus sends sympathetic projections to periphery either directly through the intermediolateral nucleus of the spinal cord (IML), or via relay through the raphe pallidus nucleus (RPa) or the rostral ventrolateral medulla (RVLM) to the IML. The IML houses the preganglionic neurons responsible for synapsing onto the catecholaminergic postganglionic sympathetic fibers innervating the target tissues.

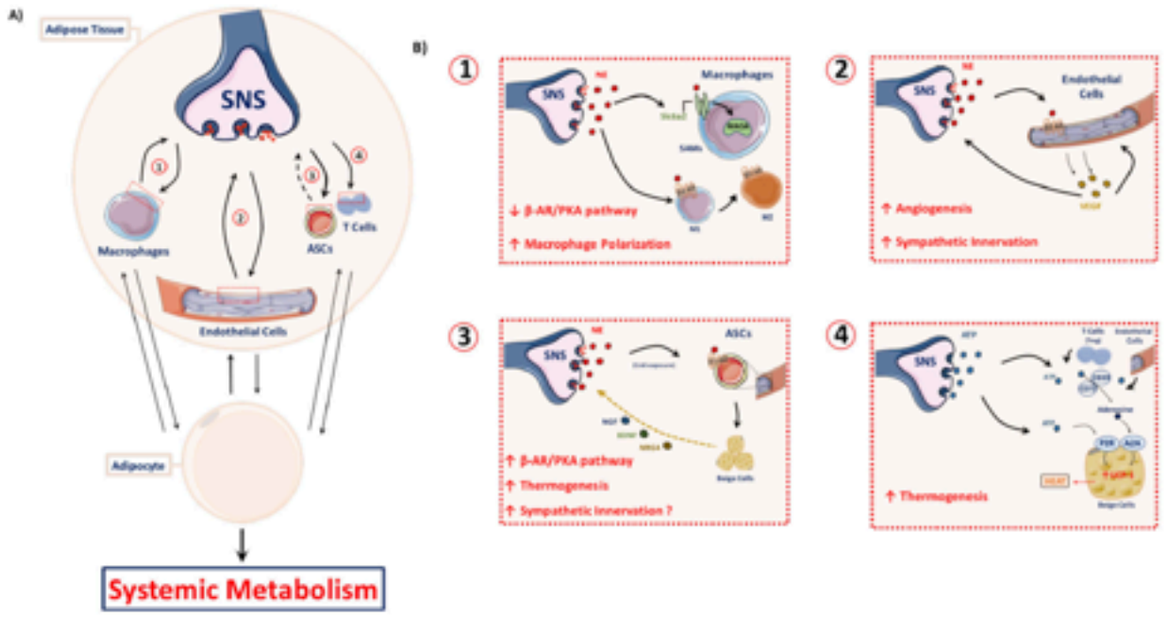

Figure 6: Integrating peripheral signals in adipose tissue.
(A) Much like the integration of adipose signals within the brain, neuro-adipose signal integration also occurs within the periphery. Examples include modulation of the adipose tissue microenvironment via interaction with immune cell populations, endothelial cells, and adipose stem cells (ASCs). Responses of adipose tissue to sympathetic nervous system (SNS) cues allows for the rapid adaptation and remodeling that is required to maintain systemic metabolic homeostasis. **(B)** Sympathetic nerve fibers engage in unique interactions with adipose tissue cell populations. **(1)** Norepinephrine (NE) release from sympathetic terminals leads to adipose macrophage polarization from a proinflammatory (M1) to an anti-inflammatory, alternatively-activated (M2) profile. Sympathetic neuron-associated macrophages (SAMs) localize around sympathetic synapses and take up secreted NE through the solute carrier family 6 member 2 (Slc6a2) NE transporter. Monoamine oxidase A (MAOA) catalyzes the degradation of NE within the SAMs. **(2)** NE release from sympathetic nerve endings stimulates the β2 adrenergic receptor (β2AR) of the endothelial cells of the vasculature, leading to vascular endothelial growth factor (VEGF) secretion from the endothelium. VEGF stimulates angiogenesis and neurite outgrowth, driving increased irrigation and innervation of the adipose tissue. **(3)** Adipose-derived stem cell (ASCs) β1 adrenergic receptor (β1AR) activation by sympathetic NE drives beige adipocyte differentiation. These beige adipocytes have an enhanced thermogenic capacity relative to white adipocytes and a brown-like adipokine expression profile, which may include neurotrophic factors such as nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF) and neuregulin-4 (NRG4). These factors can drive increased sympathetic innervation and arborization. **(4)** The sympathetic cotransmitter adenosine triphosphate (ATP) is cleaved by regulatory T-cells (Tregs) into adenosine via CD73 and CD39-mediated degradation to create the anti-inflammatory "purinergic halo" surrounding the Tregs. The adenosine interacts with the adenosine A2A receptor to drive beige adipocyte thermogenesis through mitochondrial uncoupling protein 1 (UCP1) upregulation. Sympathetic-derived ATP

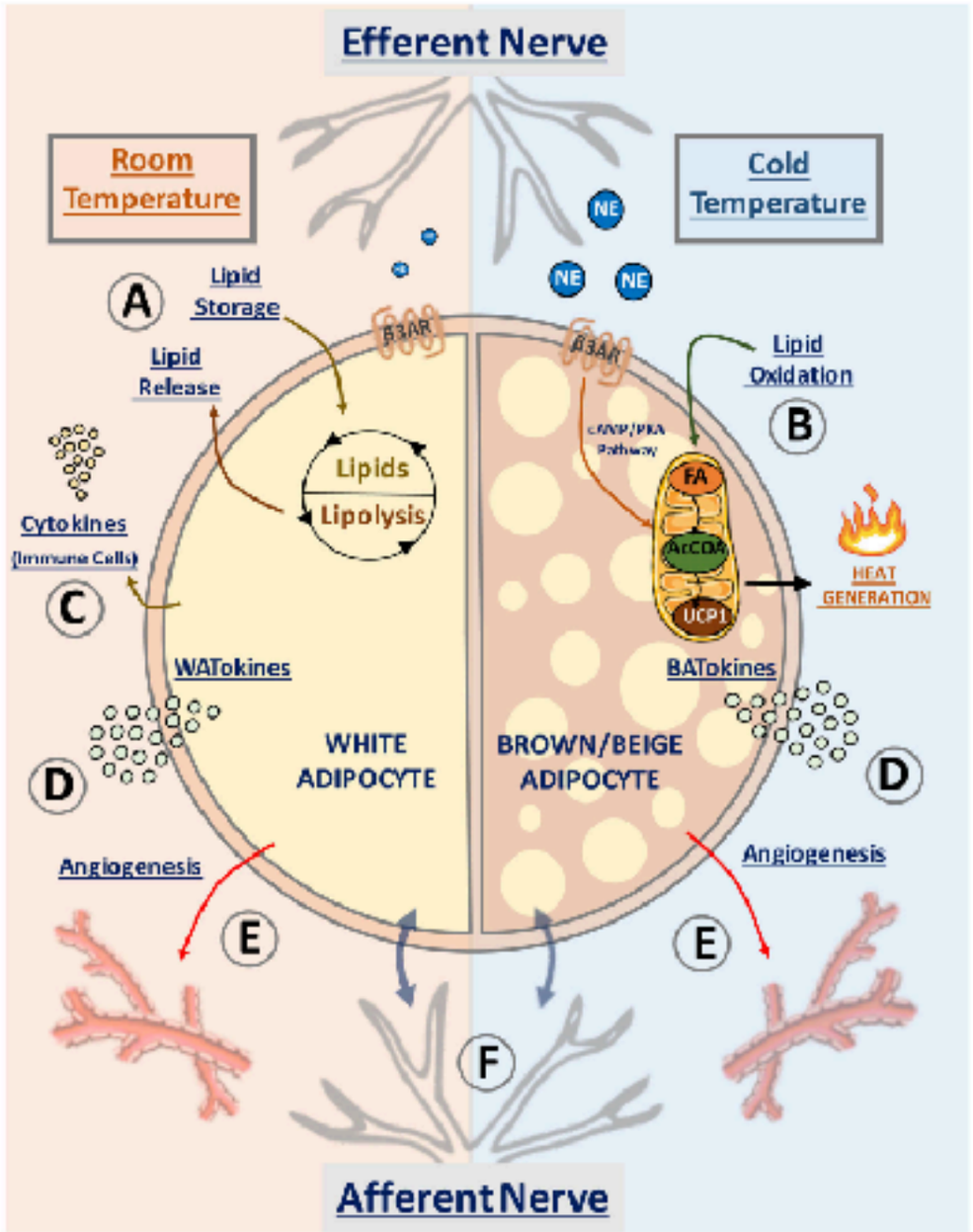

Figure 1: Proposed mechanisms whereby adipose tissue controls systemic insulin sensitivity. Depicted are pathways in white adipocytes (left semicircle) and beige/brown adipocytes (right semicircle) that have been proposed to affect whole body insulin sensitivity and systemic metabolism. At room temperature (22°C) and above, most of WAT is composed of white adipocytes (left), while at low temperature (6°C) brown/beige adipocytes appear in WAT (right). (**A**) White adipocytes promote fatty acid esterification into triglycerides for storage, sequestering fat away from liver and skeletal muscle to prevent "lipotoxicity". (**B**) Sustained release of norepinephrine (NE) by adipose efferent nerves activates β3-adrenergic (β3AR) receptor and induces "beige" adipocyte formation within white adipose tissue. Beige adipocytes display increased mitochondrial density and high capacity for fatty acid (FA) oxidation into acetyl-CoA (AcCOA) which fuels heat production via mitochondrial uncoupling protein-1 (UCP1) within the electron transport chain. (**C**) White adipocytes upregulate resident immune cells in obesity, releasing cytokines into the circulation. (**D**)

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REVIEW

Adipokines: biological functions and metabolically healthy obese profile

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Abstract: Adipose tissue is an extremely active organ, and plays a fundamental role in the genesis of comorbidities associated with obesity. Since the discovery of leptin, an important focus has been assigned to adipose tissue as a key organ in the pathogenesis of metabolic disorders. The influence on the genesis of comorbidities associated with obesity is directly related to the pattern of adipokine secretion, the bioactive molecules produced on adipose tissue. The imbalance of adipokines consequent to the expansion of adipose tissue has been implicated in the development of the low-grade chronic inflammation seen in obesity. Adipokines act in a paracrine, autocrine, and endocrine fashion, influencing cytokine and chemokine secretions and hormonal and growth factors, as well as interfering with actions of insulin and lipid and glucose metabolism. The main adipokines include leptin, adiponectin, resistin, tumor-necrosis factor, interleukin 6, chemokine (C–C motif) ligand 2, interleukin 10, and transforming growth factor-β. The imbalance between pro- and anti-inflammatory adipokines on adipose tissue results in insulin resistance and the development of metabolic syndrome, type 2 diabetes, and cardiovascular disease. However, not all obese individuals develop these comorbidities or metabolic changes. Metabolically normal obese or metabolically healthy obese individuals have been the focus of research because of their absence of comorbidities. The profile of adipokines in adipose tissue of these individuals can be protective for the development of insulin resistance and metabolic disorders. This review emphasizes the roles of adipokines, the signaling pathways involved in the pathogenesis of inflammation and insulin resistance, and the profile found in metabolically healthy obese individuals.

Keywords: adipokines, adipose tissue, obesity, metabolically healthy obese

Introduction

For a long time, adipose tissue was considered a deposit of energy. Nowadays, it is well known that the key role of adipose tissue in metabolism is as an endocrine organ responsible for the secretion of bioactive molecules termed "adipokines."[1] Adipokines have hormone function, act as growth factors that modulate insulin resistance, and act on the fat and glucose metabolism and participate in pro and anti-inflammatory responses.[2,3] Deregulated adipokine expression caused by excessive adiposity and adipocyte dysfunction seen in obesity has been linked to the pathogenesis of several diseases through altered immune responses.[1]

Adipose tissue comprises mature adipocytes, preadipocytes, endothelial cells, fibroblasts, mast cells, and immune-system cells.[4] Adipose tissue is not a uniform organ, and secretes different patterns of adipokines, depending on its location.[5] Changes in specific adipokine profile lead to metabolic disturbances that play a central role in the

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Main adipokines and their functions

Table 1 Main adipokines and their functions

Adipokine	Main functions	Changes in obese individuals compared to eutrophic individuals
Leptin	Food-intake control and increased energy expenditure[18]	↑ expression and secretion (adipocytes)[15] Leptin resistance and hyperleptinemia[19] Inflammatory cell activation[15]
Adiponectin	↑ insulin sensitivity ↑ fatty acid oxidation ↓ free fatty acid uptake ↓ glucose secretion in the liver ↑ glucose uptake (adipose tissue) ↑ adipogenesis (adipose tissue) ↑ glucose metabolism ↑ free fatty acid oxidation (muscle)[5,28] Anti-inflammatory, antiatherogenic, and anticiabetic actions[6,24]	↓ expression and secretion (adipose tissue) ↓ serum levels[20,28]
Resistin	↑ insulin resistance ↑ secretion of proinflammatory cytokines ↑ adhesion molecules[40,45]	↑ serum levels (mice)[39] Controversial results in humans[41,42]
TNF	↓ insulin signaling[54] ↑ lipolysis in adipose tissue[55] ↑ inflammation[33]	↑ expression and secretion in adipose tissue[2]
IL-6	↓ insulin signaling ↓ metabolic actions, insulin-mediated (liver) ↑ release of free fatty acids (adipose tissue)[3]	Increased expression and secretion in adipose tissue, increased serum levels[31]
CCL2	↑ macrophage infiltration ↑ inflammation (adipose tissue)[70,85]	↑ serum levels ↑ expression in adipose tissue[70]
IL-10	↓ macrophage activity ↓ proinflammatory cytokine synthesis[79]	↑ serum levels in obese ↓ levels in metabolic syndrome (women)[83]
TGFβ	↓ growth and activation of immune cells ↓ macrophage activation ↓ T- and B-cell activation[87]	Expression correlates positively with obesity in animal models and humans[93]

Abbreviations: TNF, tumor-necrosis factor; IL, interleukin; CCL, chemokine (C–C motif) ligand; TGF, transforming growth factor.

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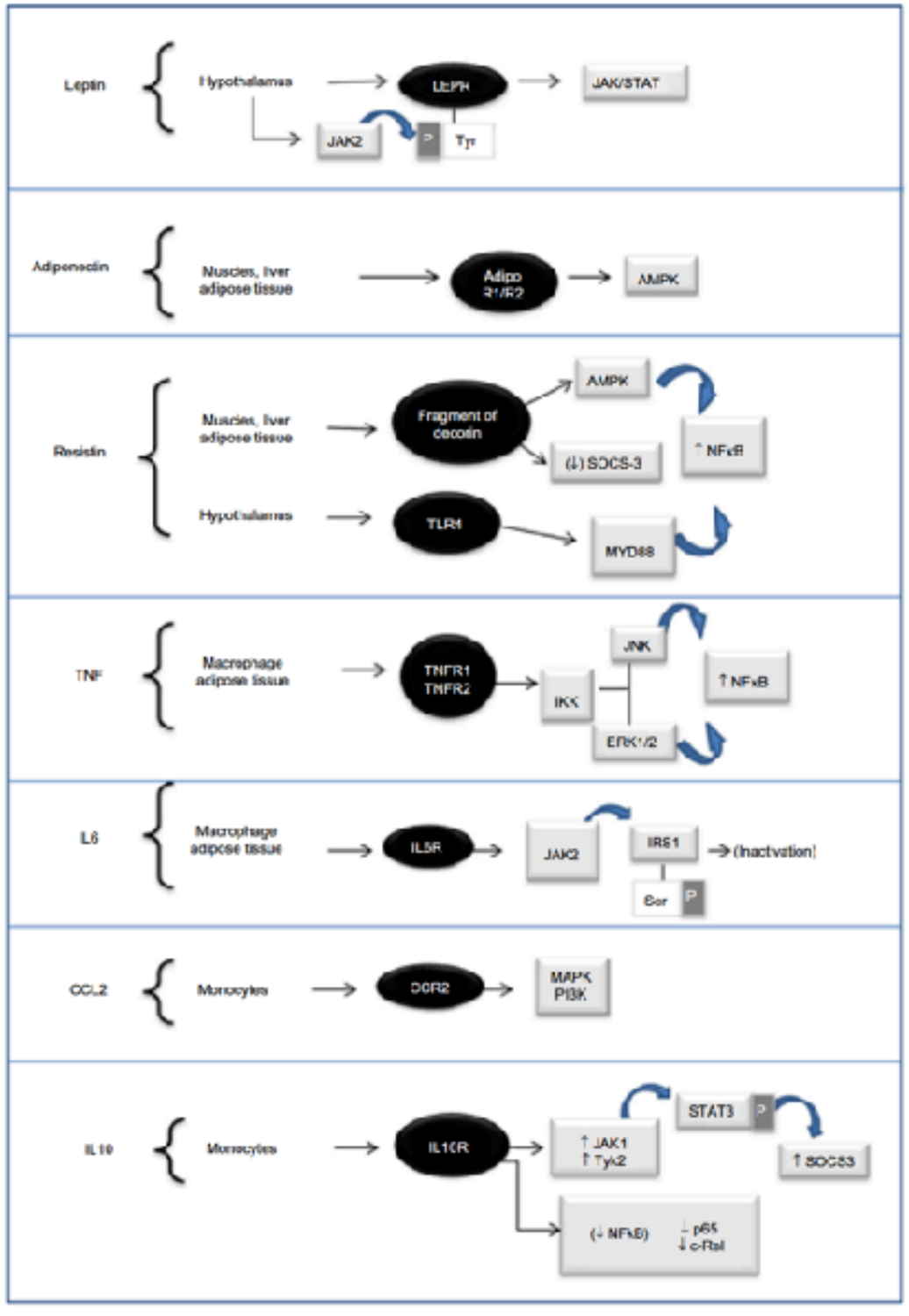

Figure 1 Mechanisms of actions of adipokines.

Notes: Leptin binds to its receptor, LEPR, in the hypothalamus and other organs, resulting in the activation of the (JAK)/signal transducer and activator of transcription (STAT) pathway. JAK2 with LEPR phosphorylates LEPR tyrosine residues. Phosphorylated LEPR in turn phosphorylates members of the STAT family that translocate to the nucleus, regulating genetic transcription. Adiponectin binds to its AdipoR1 or AdipoR2 receptors in muscle, liver, and adipose tissue, increasing the activity of adenosine monophosphate kinase (AMPK; AdipoR1) or peroxisome proliferator-activated receptor (PPAR)-α (AdipoR2). The action of adiponectin occurs through the binding of its receptors with APPL1 (adaptor protein, phosphotyrosine binding domain, PH domain, and leucine zipper-containing protein 1). The anti-inflammatory and antiatherogenic effects are due to inhibition of macrophage differentiation in foam cells, as well as inhibition of vascular monocyte adhesion and smooth-muscle cell proliferation and remodeling. Adiponectin also reduces the inflammatory response by inhibiting the tumor necrosis factor (TNF)-induced activation of nuclear factor (NF)-κB. The resistin receptor is now appears to be a fragment of cecorin, lacking the glycosaminoglycan-binding site. Resistin also binds to Toll-like receptor (TLR)-4, activating pro-inflammatory pathways in the hypothalamus. The main target organs of resistin action are the liver, adipose tissue, and muscles. In rodents, resistin inhibits AMPK in liver and muscle, activates inflammatory cytokines by activating the NFκB pathway, and activates suppressors of cytokine signaling (SOCS)-3, a recognized inhibitor of insulin signaling in adipose and other tissues. TNF binds to its receptors TNFR1 (p60) and TNFR2 (p80) and their soluble forms (sTNFR1 and sTNFR2). The binding to the receptors in adipose tissue and macrophages activates c-Jun N-terminal kinase (JNK), IκB kinase (IKK), and mitogen-activated protein kinase (MAPKs; including extracellular signal-regulated kinase [ERK-1/2]) and NFκB. IL-6 binding to its chemokine receptor (CCR)-2 receptor in monocytes activates the MAPK/phosphatidylinositol-4,5-biphosphate 3-kinase (PI3K) pathway, which induces cytoskeleton modification. The IL-10 receptor (IL-10R) consists of two α- (IL-10Rα) and two β- (IL-10Rβ)-molecules. IL-10Rα has a high affinity binding to the ligand, and is responsible for signal transduction, while IL-10Rβ contributes only to the signaling process. It triggers the activation of JAK1 and Tyk2, resulting in phosphorylation of STAT3 and in induction of STAT3-dependent genes, including SOCS3. It also increases levels of anti-inflammatory cytokines, such as IL-1 receptor antagonist (RA), and suppresses p65 and the c-Rel subunit of NFκB.

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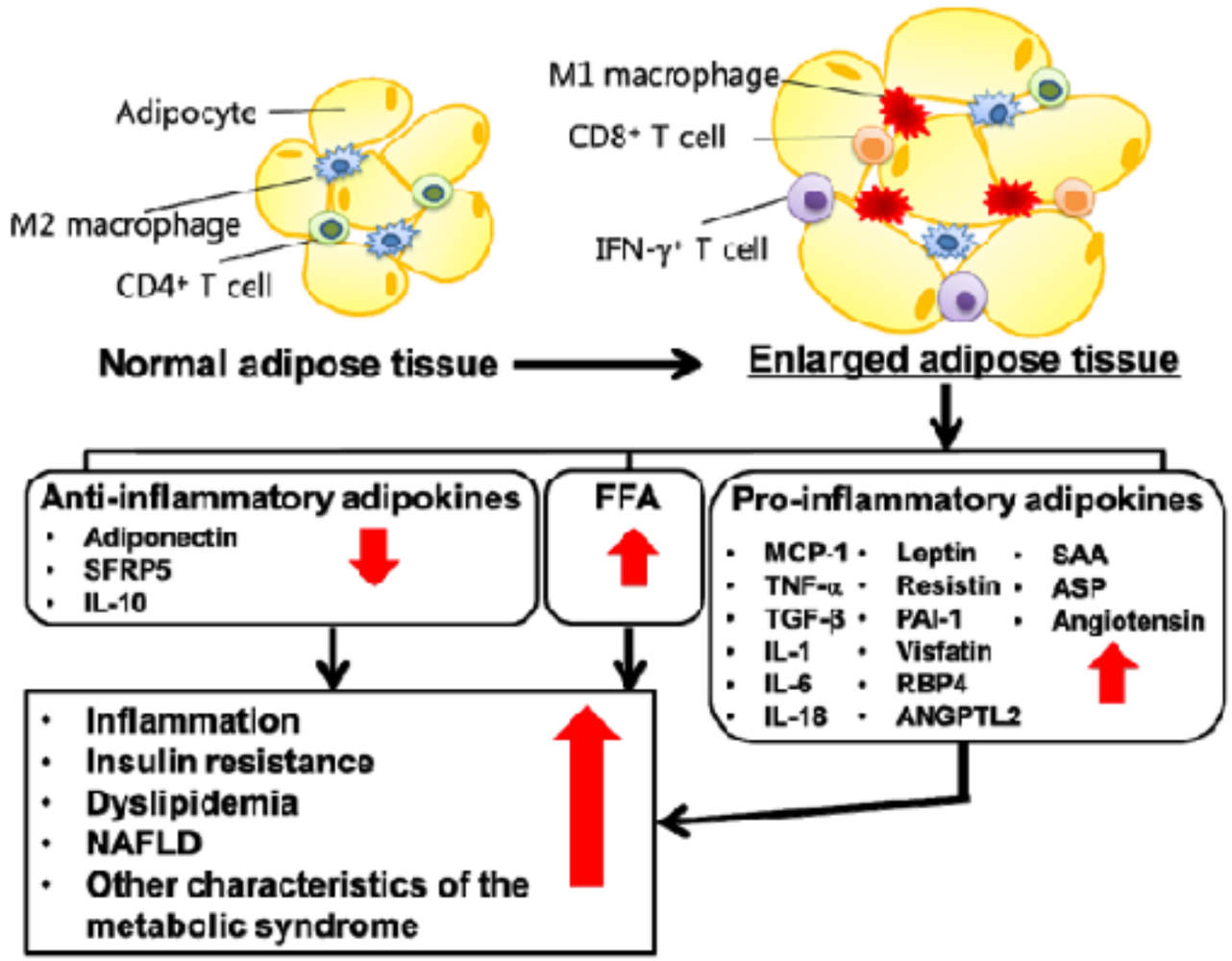
Review

Obesity and Its Metabolic Complications: The Role of Adipokines and the Relationship between Obesity, Inflammation, Insulin Resistance, Dyslipidemia and Nonalcoholic Fatty Liver Disease

Un Ju Jung and Myung-Sook Choi *



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Hindawi

Review Article

Adipose Tissue and Adrenal Glands: Novel Pathophysiological Mechanisms and Clinical Applications

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- Mineralocorticoid/adipose interactions
- Glucocortivcoid adipose interactions
- Adrenal androgens and adipose tissue
- Adipose tissue and adrenal medulla
- Adipocytokine effects on adrenal function
- Leptin adrenal interactions
- Adiponectin adrenal interactions

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WAT

- White adipose tissue is unique in its plasticity, it can adapt quickly to nutrient deprivation and hyper-nutrition alike.

- The flexibility of WAT is largely due to the hypertrophic and hyperplastic changes in adipocytes. WAT plasticity has an important role in determining metabolic health

- Metabolically active tissue : regulates the storage and release of lipids.

- Free fatty acids-major fuel source during times of energy scarcity and high energy demands.

- Dysregulated fatty acid release contributes to dyslipidemia —> ectopic fat deposition into various organs.

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Why does adipose tissue contains immune cells?

Endocrine CONNECTIONS | M Keuper | Inflammatory control of adipocyte bioenergetics | 8:6 | R105–R121

REVIEW

On the role of macrophages in the control of adipocyte energy metabolism

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Immunology
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IMMUNOLOGY REVIEW ARTICLE

Properties and functions of adipose tissue macrophages in obesity

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Summary

The expansion of adipose tissue (AT) in obesity is accompanied by the accumulation of immune cells that contribute to a state of low-grade, chronic inflammation and dysregulated metabolism. Adipose tissue macrophages (ATMs) represent the most abundant class of leukocytes in AT and are involved in the regulation of several regulatory physiological processes, such as tissue remodeling and insulin sensitivity. With progressive obesity, ATMs are key mediators of meta-inflammation, insulin resistance and impairment of adipocyte function. While macrophage recruitment from blood monocytes is a critical component of the generation of AT inflammation, new studies have revealed a role for ATM proliferation in the early stages of obesity and in sustaining AT inflammation. In addition, studies have revealed a more complex range of macrophage activation states than the previous M1/M2 model, and the existence of different macrophage profiles between human and animal models. This review will summarize the current understanding of the regulatory mechanisms of ATM function in relation to obesity, type 2 diabetes, depot of origin, and to other leukocytes such as AT dendritic cells, with hopes of emphasizing the regulatory nodes that can potentially be targeted to prevent and treat obesity-related metabolic disorders.

Keywords: adipose tissue; inflammation; insulin resistance; macrophages; MMe; obesity.

Introduction

The incidence of obesity and associated co-morbidities [type 2 diabetes (DM), liver and cardiovascular diseases, and certain forms of cancer] remains on the rise.[1] Obesity results from a chronic imbalance between caloric intake and energy expenditure that is characterized as a low-grade, chronic inflammatory disease that contributes to metabolic dysfunction and insulin resistance (IR).[2] Although the molecular basis underpinning this inflammation is not fully understood, there is consensus that macrophage activation in adipose tissue (AT) precedes the development of IR and contributes to a pro-inflammatory state.[3,4] Therefore, deciphering macrophage biology and pathophysiology in the obese setting remains a unique challenge to the field of immunology and metabolism research. Transcriptional profiling has advanced the understanding of the plasticity of macrophages suggesting a complex cellular programming in response to stress signals,[5] and has emphasized the concept that macrophages can quickly adopt unique properties depending on microenvironmental cues.[6] Nevertheless, the mechanisms underpinning the specialized transcriptional and signaling profiles in macrophages during obesity-induced AT inflammation are not fully resolved. In this review, we will summarize what is known about adipose tissue macrophage (ATM) biology in the setting of obesity and metabolic disease in a rapidly moving field of investigation.

ATM-driven inflammation links obesity to IR

Obesity is characterized by a chronic low-grade inflammation that is causally implicated in the development of IR. IR is a central mechanism in obesity-associated diseases, such as DM and metabolic syndrome. It is defined as the decline to a normal physiological response to insulin, resulting in a reduction in glucose disposal as well as failure to suppress lipolysis and hepatic glucose production, and occurs prominently in AT. Numerous studies support the role of ATMs and derived inflammatory mediators in the impairment of insulin signaling

ATMΦ

- ATMΦ numerically dominant type of immune cells in WAT. Obesity enhances MΦ numbers —> obesity-related immune imbalances.

- ATMΦ -:distinct roles and beneficial effects on WAT homeostasis eg. healthy lipid storage.

- Dynamic cells -adapt quickly in phenotype and metabolism to changing environments eg. fasting and over nutrition.

- Stimulate healthy lipid storage thus prevent adverse ectopic lipid storage(e.g. hepatic steatosis).

- Anti- and pro-inflammatory signals may be involved in maintaining WAT homeostasis.

- Protective role - anti-inflammatory and clearing dead adipocytes.

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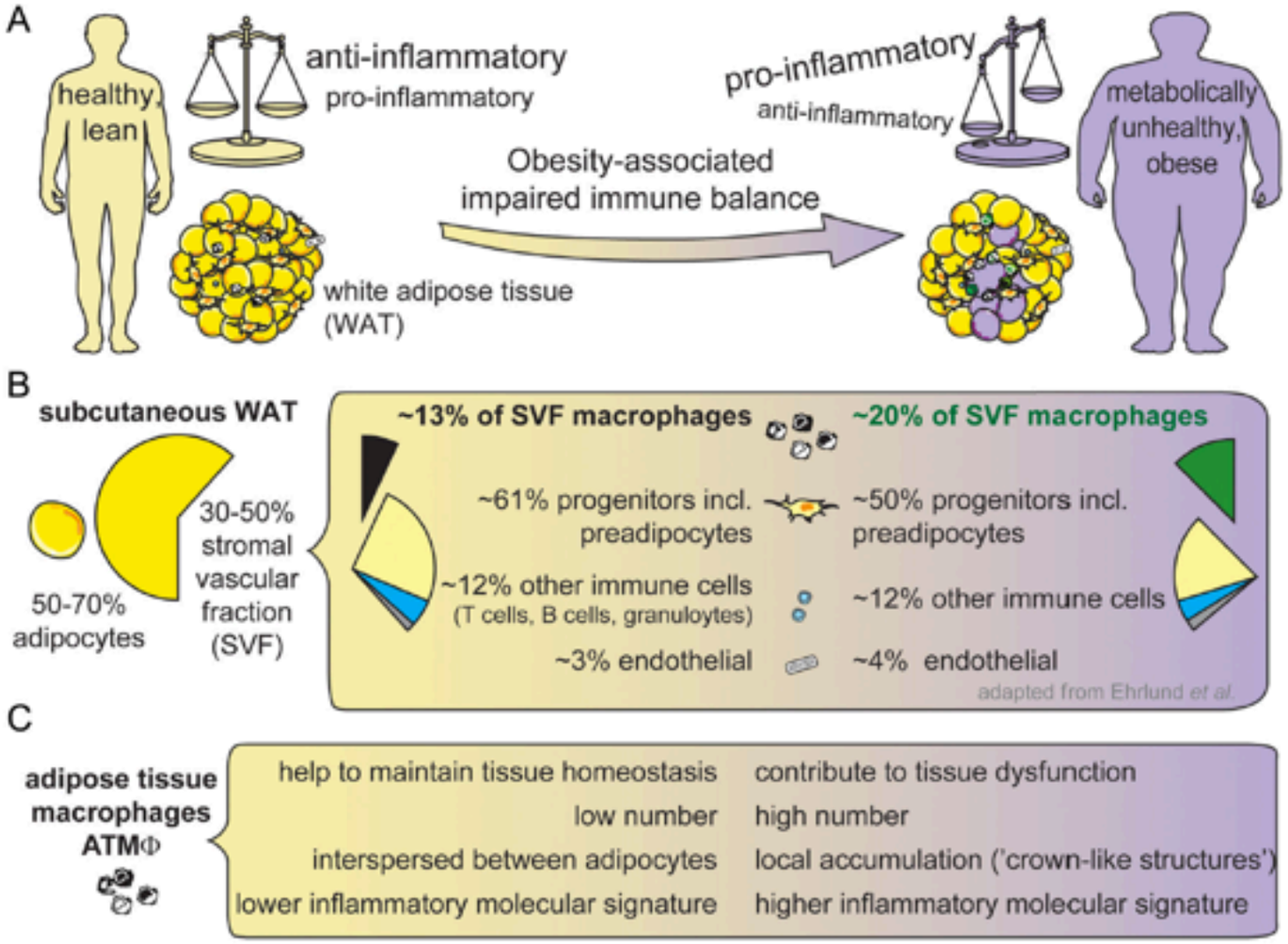

Figure 1

Obesity-associated impaired immune balance in white adipose tissue. (A) Obesity is associated with an impaired immune balance toward pro-inflammatory in WAT. All fat depots are affected, but mostly the viscWAT. (B) ATMΦ amount is low in lean scWAT (~13% of SVF). However, MΦ are numerically the dominant type of immune cells representing half of the immune cells. MΦ increase in obese WAT, for example in human scWAT from 13 to 20% of the SVF (36). (C) The roles of ATMΦ in lean (left) and obese (right) WAT. The number of MΦ is low and they are interspersed between adipocytes in WAT of lean subjects, contrasting the higher number and local accumulation of MΦ in crown-like structures during obesity, which is fostered by proliferation, high immigration and low emigration. The low inflammatory profile (surface markers, cytokine expression and secretion, e.g. IL4, IL10) in lean subjects transforms into higher inflammatory status (e.g. TNFα, IL6, IL1β) during obesity.

Macrophage subtypes

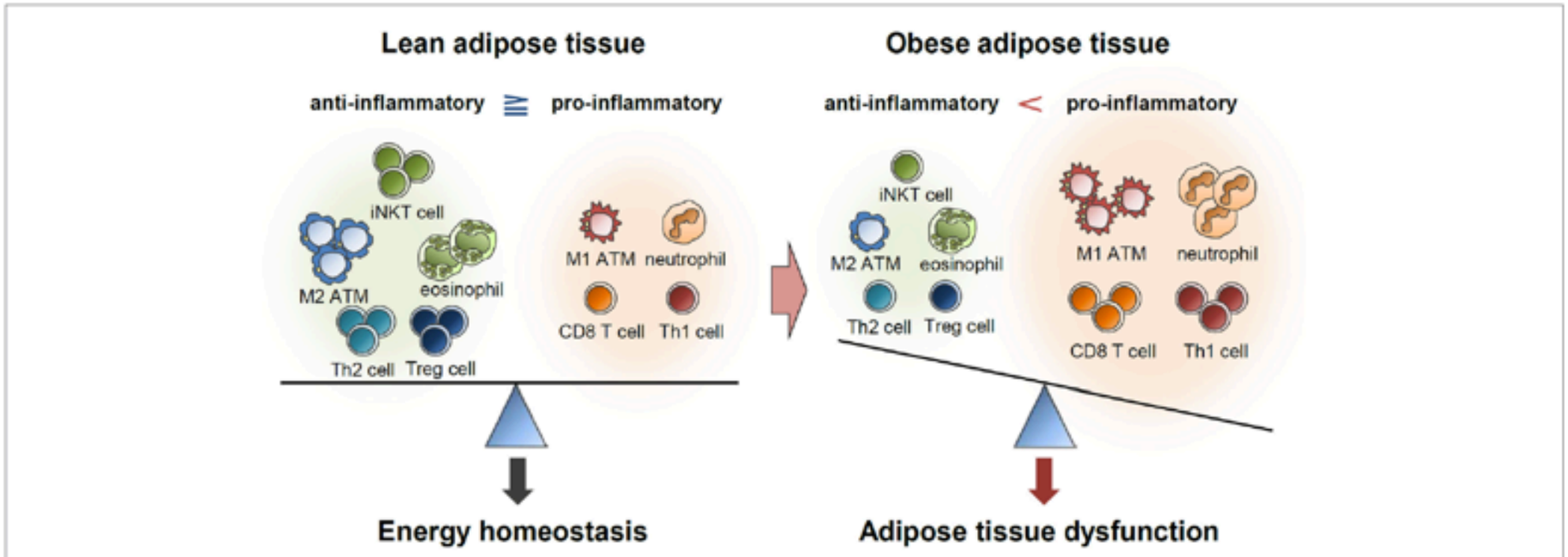

FIGURE 4 | Balance of immune responses in the regulation of adipose tissue function. Lean adipose tissue harbors various anti-inflammatory immune cells, such as eosinophils, M2 macrophages, Th2 cells, iNKT cells, and Treg cells. These immune cells help in maintaining insulin sensitivity and store extra energy in the form of TGs. In obese adipose tissue, the numbers of pro-inflammatory immune cells, including neutrophils, M1 macrophages, mast cells, Th1 cells, and CD8 T cells, are greatly elevated. Simultaneously reduced number of anti-inflammatory immune cells accelerates pro-inflammatory response and adipose tissue dysfunction.

Endocrine CONNECTIONS | M Keuper | Inflammatory control of adipocyte bioenergetics | 8:6 | R105–R121

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Adipose tissue and inflammation

- Dysregulation of a homeostatic mechanism may arise from and result in the overproduction or underproduction of potent signaling molecules.

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How does dysregulation occur?

- In humans, SAT develops during **weeks 14–24 of fetal gestation** through **hyperplasia**.

- During the **first year after birth**, **adipocyte hyperplasia and hypertrophy** both occur. Adipocyte number then appears to **remain stable until adolescence**, when hyperplasia occurs once again.

- Very little is known about the developmental period of VAT except that it is rarely formed before birth and that the total amount of VAT remains small until adolescence.

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- In obese humans, both **SAT** and **VAT** masses- markedly increased.

- **Childhood obesity :** WAT mass expansion is accompanied by **adipocyte hyperplasia**.

- **Adult humans :** increase in WAT mass (that triggers metabolic disorder-primarily due to adipocyte hypertrophy

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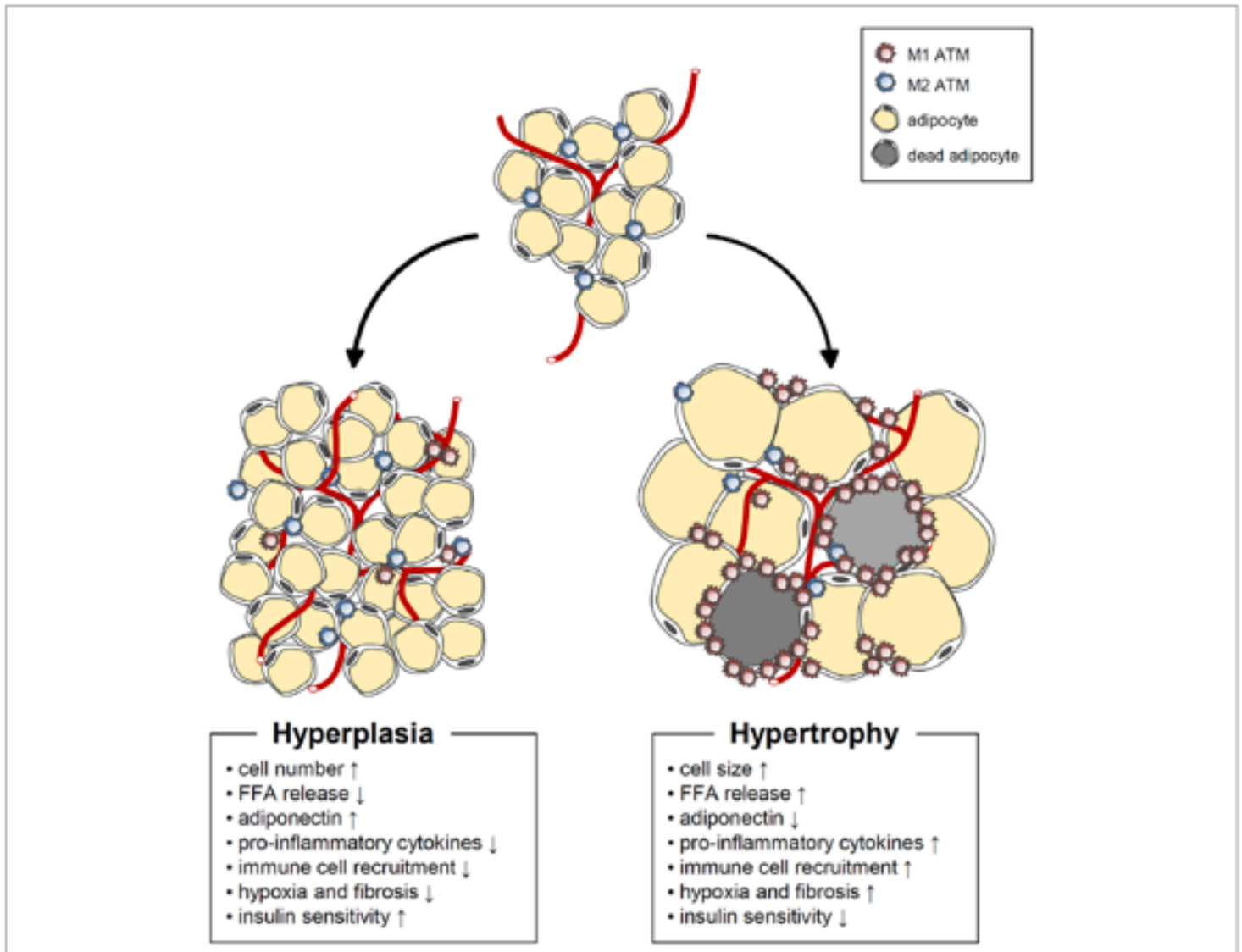

FIGURE 2 | Characteristics of hypertrophic and hyperplasic adipocytes. In obesity, adipose tissue expansion occurs by two different mechanisms. Hypertrophic adipose expansion through increased adipocyte size is associated with such harmful phenomena as increased basal fatty acids release, pro-inflammatory cytokine release, immune cell recruitment, hypoxia, fibrosis, decreased adiponectin, and impaired insulin sensitivity. On the other hand, hyperplasic adipose expansion though increased adipocyte number is linked to beneficial phenomena, such as increased adiponectin, decreased basal fatty acids release, pro-inflammatory cytokine release, immune cell recruitment, hypoxia, fibrosis, and improved insulin sensitivity.

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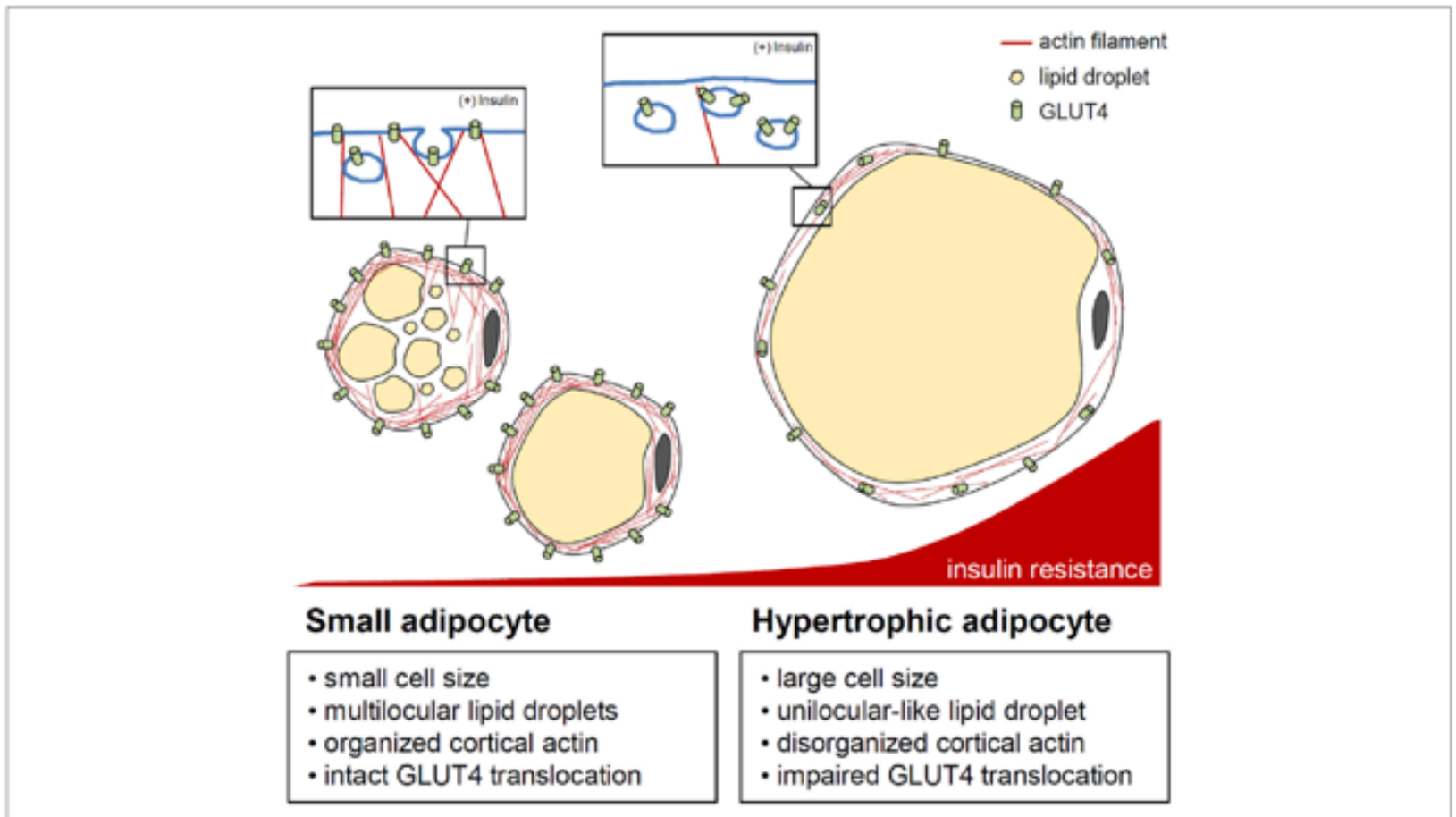

FIGURE 3 | Actin cytoskeleton and insulin-stimulated GLUT4 translocation control in adipocytes. In adipocytes, cytosolic and cortical actin organization is involved in GLUT4 storing vesicle (GSV) transport by insulin stimulation. When adipocytes are hypertrophied, enlarged unilocular lipid droplets and expanded cell volume may impede cortical actin dynamics, resulting in improper/deficient translocation of GSVs. This indicates the importance of the adipocyte cytoskeleton in the regulation of adipocyte glucose metabolism in response to insulin.

Hypertrophic adipocytes

- **First:** Hypertrophic adipocytes show **necrotic** abnormalities. Increase in dead adipocytes in obesity proposed to **impede adipose tissue function** and **induce inflammation**.

- **Second:** Hypertrophic adipocytes -increased expression and secretion of pro-inflammatory cytokines.

Raised pro-inflammatory cytokines

serine phosphorylation of insulin receptor substrate-1

development of insulin resistance.

In addition, pro- inflammatory cytokines recruit more immune cells.

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- **Third:** adipocyte hypertrophy induces local adipose tissue hypoxia because of a relative deficiency of vasculature. Hypoxia results in expression of angiogenic factors upregulation of inflammatory associated genes.

- HIF alpha accelerates adipose tissue fibrosis and augments the local inflammatory response in the obese adipose tissue

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- **Basal lipolysis is elevated** in hypertrophic adipocytes increasing the **leakage of free fatty acids.** Large amounts of FFAs released from the obese adipose tissue are **taken up by other tissues, such as the liver and muscle**, which can cause **ectopic lipid accumulation and lipotoxicity.**

- Saturated fatty acids (palmitic or stearic acids) , activate TLR4 signaling cascade (plays an essential role in innate immunity), leading to chronic inflammation as well as insulin resistance.

- Adipocyte hyper-trophy also impairs insulin-dependent glucose uptake because of a defect in GLUT4 trafficking.

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Macrophages in obesity

- Suggested that **M1 macrophages phagocytize dead adipocytes** and **M2 macrophages reconstruct ECM** and **resolve the activation of M1 macrophages** after removal of dead adipocytes.

- tight regulation of phagocytosis and tissue repair.

- In obesity, balance between M1 and M2 ATMs shifted by increase in M1 macrophage number. This may interrupt the normal process of dead cell clearance, whereas further stimulating a pro-inflammatory response.

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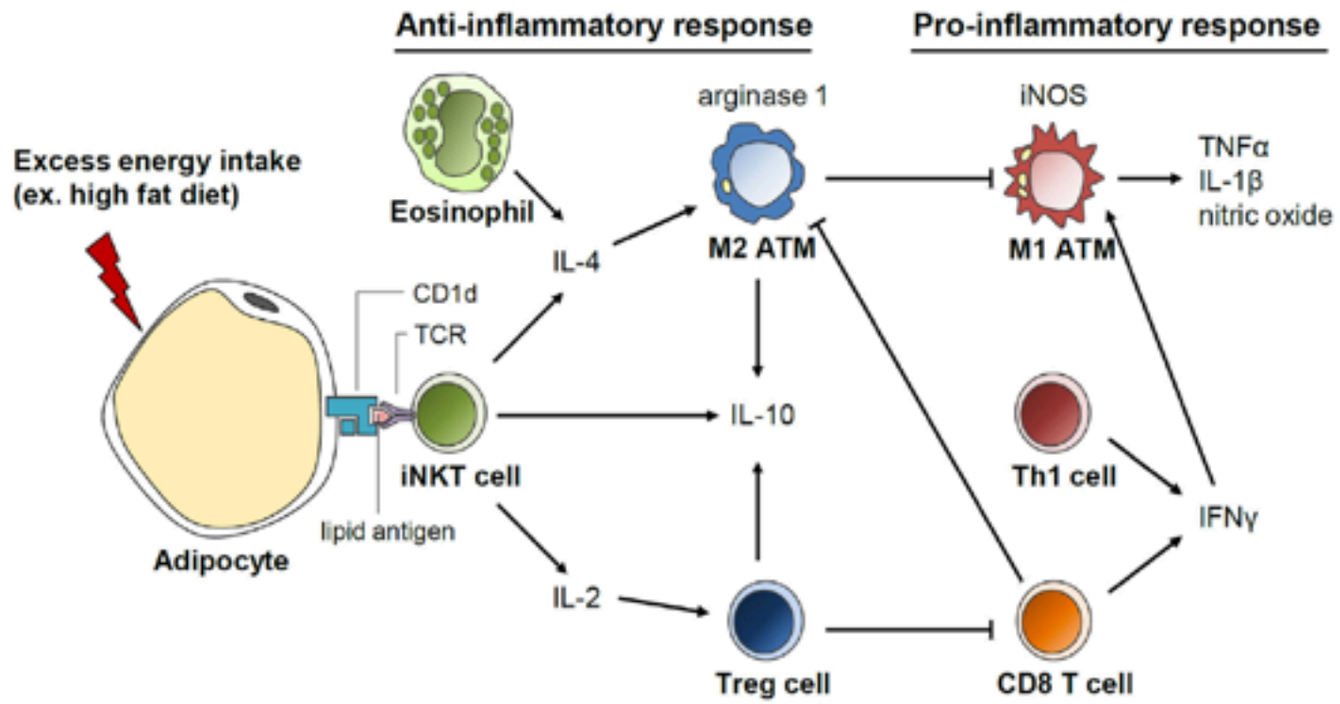

FIGURE 5 | Invariant natural killer T (iNKT) cell-mediated regulation of anti-inflammatory response in the adipose tissue. Adipocytes secrete various inflammation-inducing factors including FFAs upon excess energy intake, such as HFD. In addition, antigen presentation by CD1d on adipocytes could activate iNKT cells, which rapidly secrete great quantities of cytokines, such as IL-4, IL-2, and IL-10. IL-4 produced by iNKT cells induces macrophage polarization into M2 type and arginase expression. IL-2 secretion by iNKT cells promotes Treg cell function in the adipose tissue. Activation of anti-inflammatory responses mediated by iNKT cells could play a crucial role in the suppression of excessive pro-inflammatory response in the adipose tissue upon HFD.

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Obesity, Inflammation, and Insulin Resistance

Steven Shoelson, MD, PhD

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Weight gain and obesity are major risk factors for conditions and diseases ranging from insulin resistance and type 2 diabetes mellitus to atherosclerosis and the sequelae of nonalcoholic fatty liver disease. A chronic, subacute state of inflammation often accompanies the accumulation of excess lipid in adipose tissue and liver (hepatic steatosis), evidenced by changes in both inflammatory cells and biochemical markers of inflammation. These changes can be seen in the involved tissues and systemically, in terms of elevated circulating levels of inflammatory markers. The link between obesity and inflammation has therefore raised the important question of whether obesity-induced inflammation plays a pathogenic role in the development and progression of these disorders. We review the rapidly expanding body of animal and clinical data that support potential roles for inflammation in the pathogenesis of insulin resistance and type 2 diabetes mellitus.

Mammals have evolved mechanisms to store energy during periods of plenty, which helps to guarantee survival during periods of drought and famine. Excess nutrient is stored as triglyceride, primarily in the adipose tissue but in other tissues as well. In addition to the beneficial effects of nutrient storage, however, the long-term storage of excessive amounts of lipid can have a negative impact on health, especially under conditions of longer life span and decreased physical activity. The adverse health consequences of weight gain and obesity are especially prominent following prolonged periods of positive energy balance and may be most pronounced when foods are energy dense because of high proportions of simple carbohydrates and saturated fats, such as occurs today in developed Western societies. As a consequence of sustained overnutrition, obesity has become epidemic in industrialized countries and is increasingly common in developing countries worldwide. The prevalence rates are continuing to rise, most rapidly in developing countries, and obesity is occurring in all groups at younger ages. The World Health Organization estimates that globally there are >1 billion overweight adults, 300 million of whom are obese.[1] Since 1980, obesity rates have risen more than 3-fold in some areas of North America, the United Kingdom, Eastern Europe, the Middle East, the Pacific Islands, Australasia, and China. Very worrisome are the concurrent and parallel increases in the prevalence of pathologic conditions associated with obesity, which include type 2 diabetes mellitus (T2D), cardiovascular disease (CVD), hypertension, hypercholesterolemia, hypertriglyceridemia, nonalcoholic fatty liver disease (NAFLD), arthritis, asthma, and certain forms of cancer. We review the growing evidence that supports the hypothesis that a subacute state of chronic inflammation associated with obesity provides a molecular link to some of these pathologic conditions.

Adipose Tissue

In addition to containing adipocytes, adipose tissue is well vascularized and innervated and contains a connective tissue matrix and numerous immune cells including macrophages.[2,3] White adipose tissue (WAT) is most familiar as the type of fat in which triglyceride is stored and from which lipids are mobilized for systemic utilization when other tissues require energy. WAT is often subdivided into subcutaneous and abdominal depots, whose physiologies may be distinguished and whose roles in pathology may also be distinct. This is contrasted with brown adipose tissue, whose main function is thought to be nonshivering thermogenesis, a pro-

Abbreviations used in this paper: CRP, C-reactive protein; CVD, cardiovascular disease; FFA, free fatty acids; HFD, high-fat diet; IKKβ, inhibitor of NK-kB kinase β; IL-6, interleukin-6; IRS-1, insulin receptor substrate-1; JNK, c-Jun NH2-terminal kinase; MCP-1, monocyte chemoattractant protein-1; NAFLD, nonalcoholic fatty liver disease; PAI-1, plasminogen activator inhibitor-1; PPARγ, peroxisome proliferator-activated receptor-γ; SAA, serum amyloid A; TNF-α, tumor necrosis factor-α; TZD, thiazolidinedione; T2D, type 2 diabetes mellitus.

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JCI The Journal of Clinical Investigation

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

C. Ronald Kahn, … , Guoxiao Wang, Kevin Y. Lee

J Clin Invest. 2019;129(10):3990-4000. https://doi.org/10.1172/JCI129187.

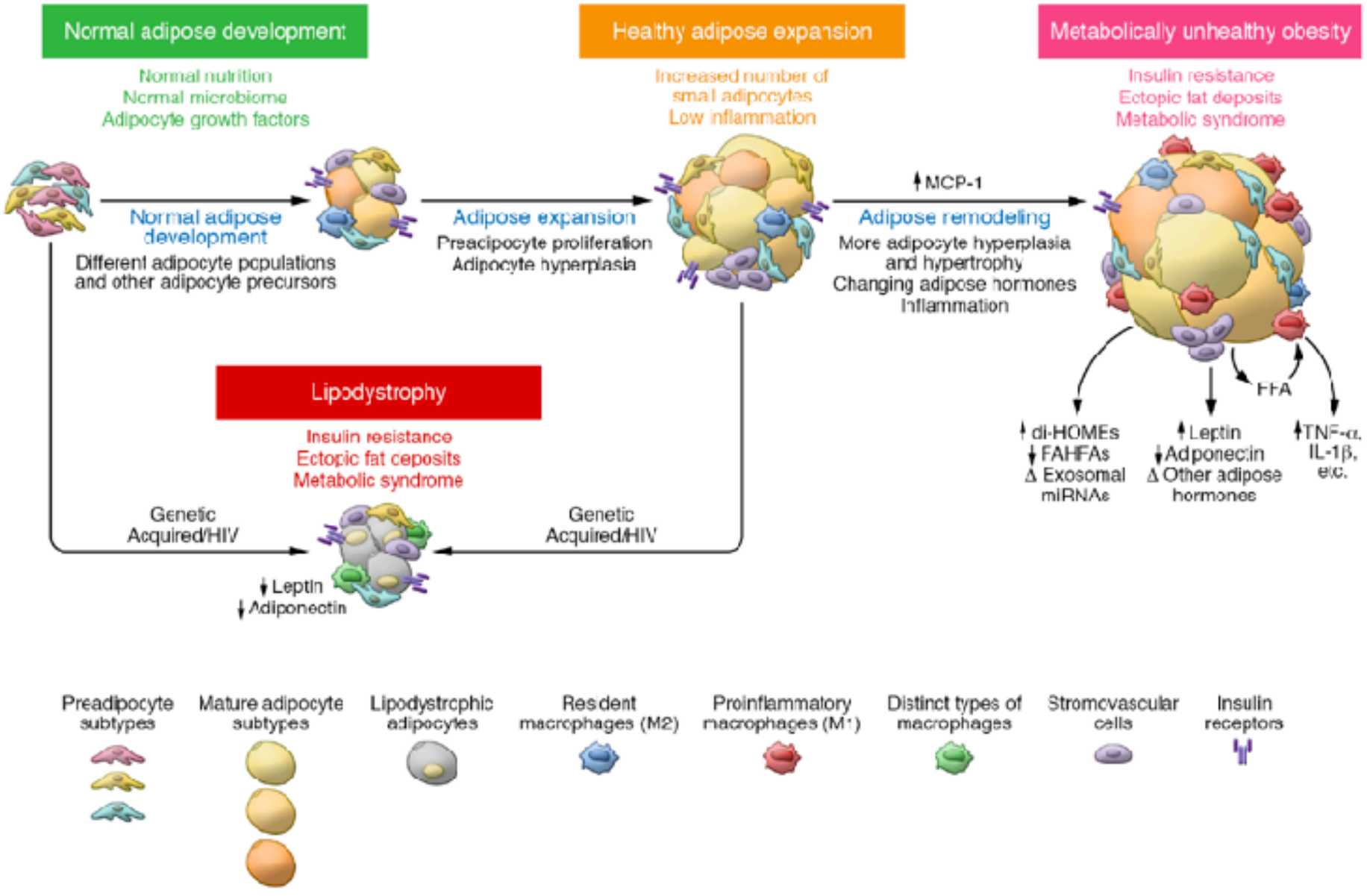

Figure 2. Adipose tissue development and remodeling in health and disease. From left to right, the figure illustrates the conversion of preadipocytes to mature adipocytes followed by adipose expansion due to preadipocyte proliferation and hyperplasia of adipocytes followed by adipocyte hypertrophy, adipose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

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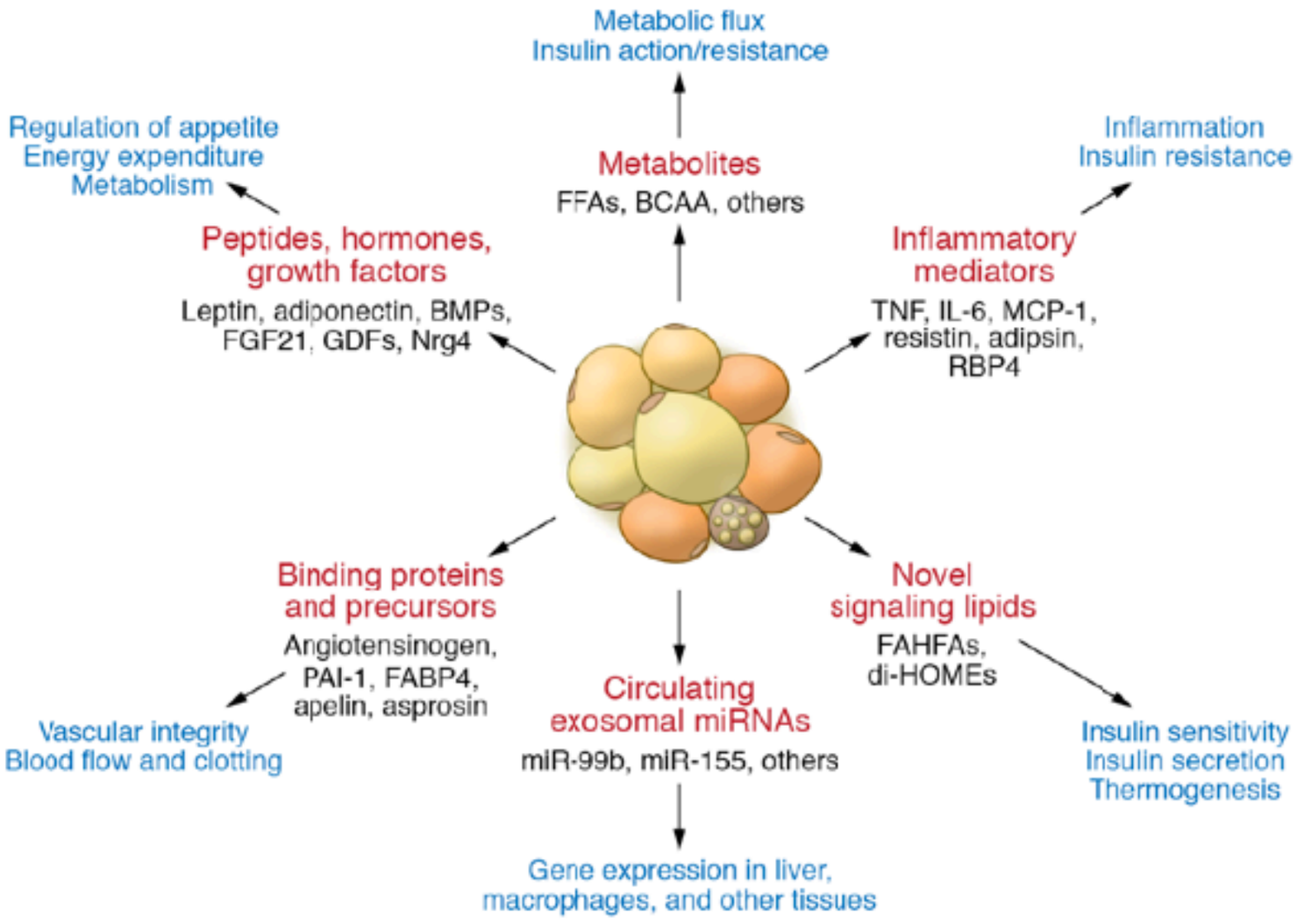

Figure 3. Adipocyte hormones in intertissue communication. The figure illustrates different classes of adipocyte hormones and their varied effects on metabolism and the development of insulin sensitivity or resistance. BCAA, branched-chain amino acids; GDF, growth differentiation factor ; Nrg4, neuroregulin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

Pro-inflammatory cytokine action on Insulin Receptor

- In the IR state, **proinflammatory cytokines** activate several **serine kinases.** These kinases have been shown to **inhibit insulin action** by promoting the **phosphorylation of serine residues of the insulin signaling pathway**, including serine phosphorylation of insulin receptor substrate-1(IRS-1).

- In contrast with **tyrosine phosphorylation of IRS-1** in the **insulin sensitive state**, serine phosphorylation impairs normal insulin signaling.

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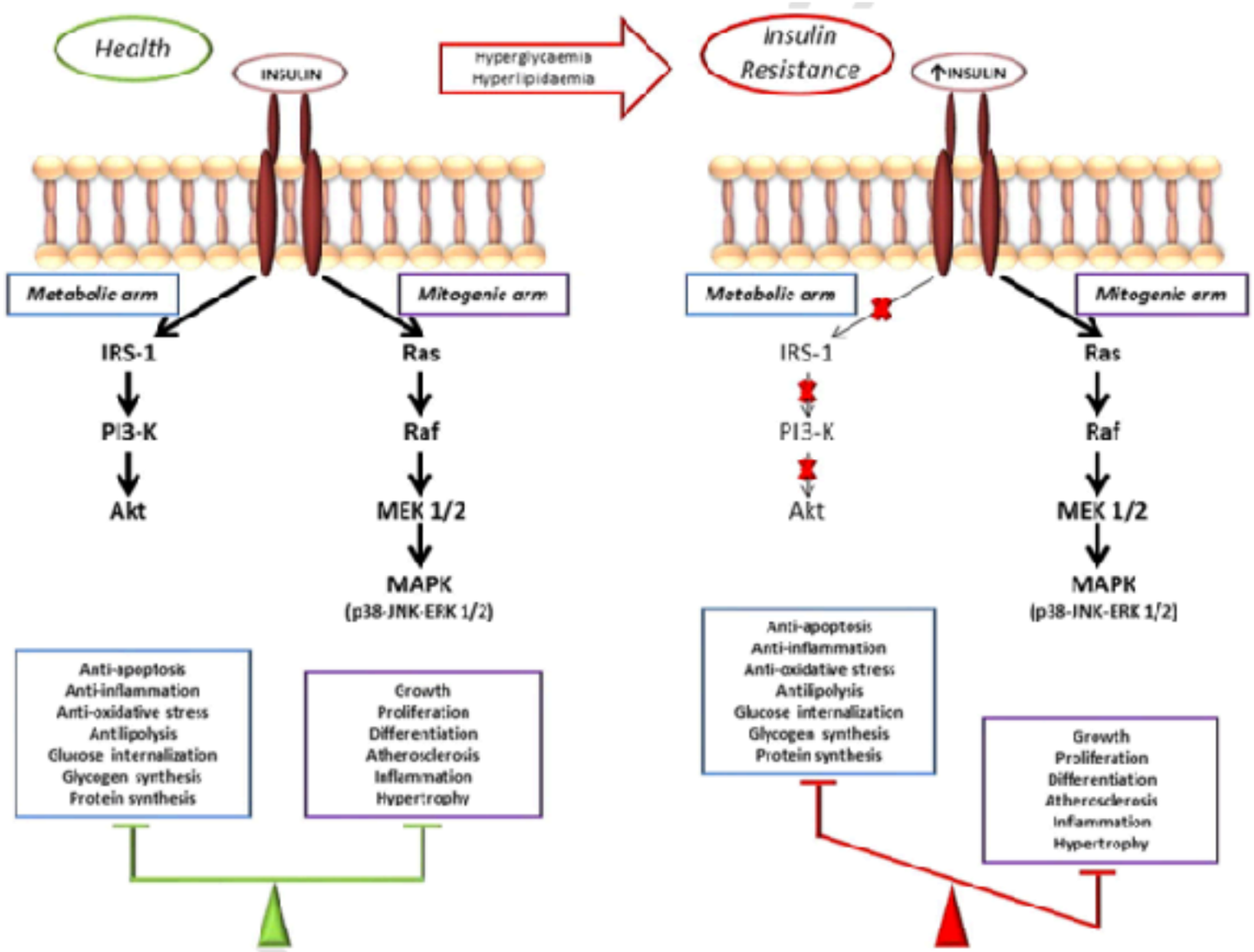

Fig. 1. The insulin signaling pathway and its impairment in insulin resistance. Activation of the insulin receptor results in parallel and balanced insulin signaling to the PI3K-Akt pathway (metabolic arm) and the Ras-MAPK pathway (mitogenic arm), thus promoting cardiovascular and endothelial growth, cell metabolism and healthy vascular function (left panel). "Metabolic" effects refer to glucose transport, glycogen and protein synthesis, protection from apoptosis, oxidative stress and inflammation and inhibition of lipolysis; on the other hand, non-metabolic, proliferative, mitogenic, pro-inflammatory and pro-atherogenic effects of insulin are mediated by the activation of Ras, Raf and MAPK. Insulin resistance, mainly caused by hyperglycemia and hyperlipidemia, is characterized by a specific impairment in PI3K-dependent signaling and consequent compensatory hyperinsulinemia to maintain englycemia. This leads to excessive stimulation of the unaffected mitogenic arm, contributing to cardiovascular and endothelial injury and dysfunction (right panel). ERK, extracellular receptor kinase; IRS-1, insulin substrate receptor-1; JNK, c-jun N-terminal kinase; MAPK, mitogen-activated protein kinase; MEK, mitogen-activated protein kinase/extracellular receptor kinase; p38, p38 mitogen-activated protein kinase; PI3-K, phosphatidylinositol (PI)3-kinase.

PKB/Akt and MAPK/ERK phosphorylation is highly induced by inositols: Novel potential insights in endothelial dysfunction in preeclampsia; Rossella D'Oriaa, Luigi Laviola et. al

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Mechanisms of obesity-induced inflammation and insulin resistance: insights into the emerging role of nutritional strategies

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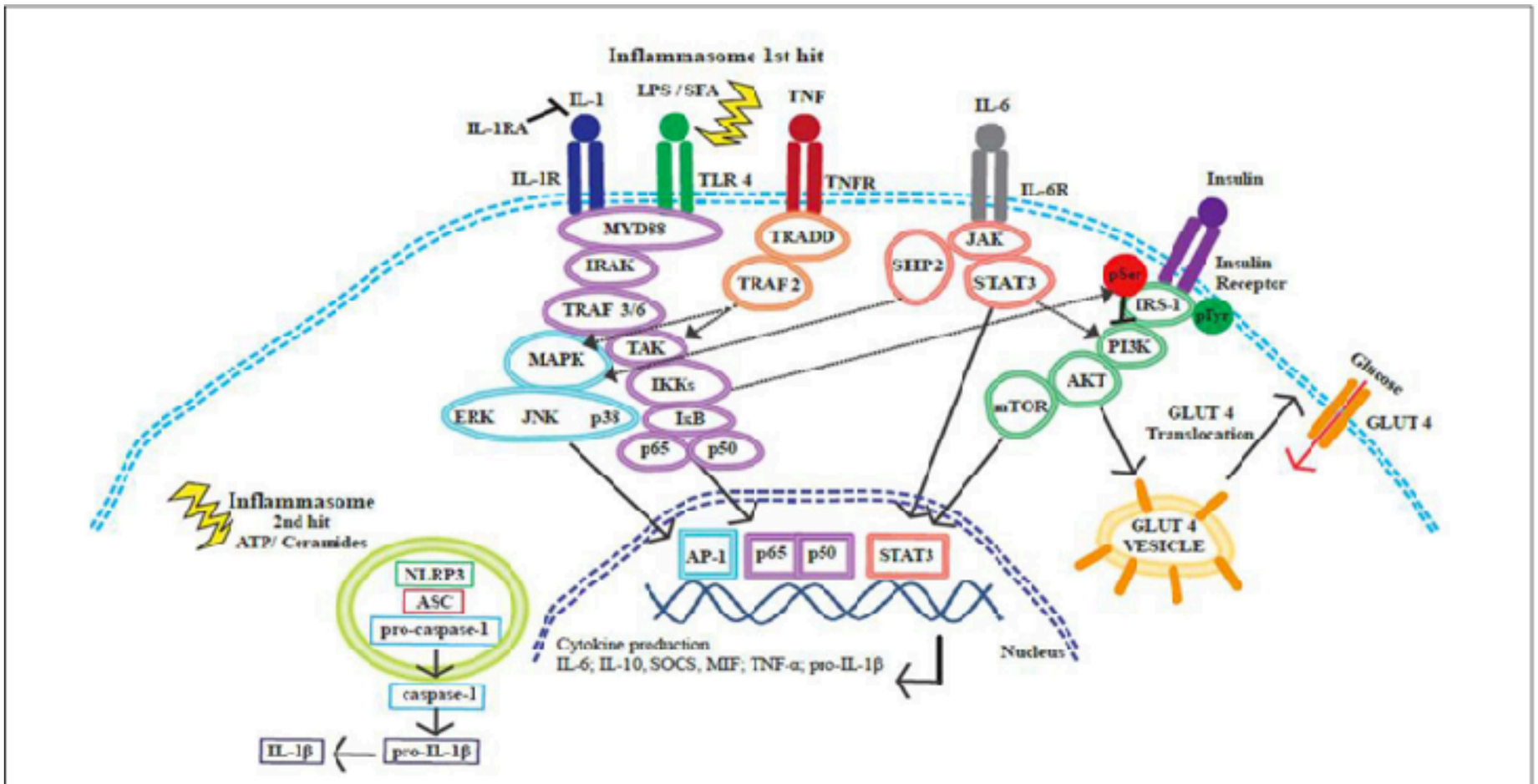

FIGURE 4 | Cross-talk between insulin and inflammatory signaling pathways. Inflammatory signaling pathways activated by SFA or by pro-inflammatory cytokines IL-1β, IL-6, and TNF-α initiate a cascade of events that promote the release of further inflammatory mediators. These signaling events converge at the NF-κB and MAPK pathways, resulting in the translocation of transcription factors to the nucleus, transcriptional activation, and cytokine production. The inflammasome is activated through a two-hit process; with obesity the first hit occurs when TLR4 is activated by SFAs and this results in pro-IL-1β production, ATP or ceramides then provide the second hit. The NLRP3 inflammasome acts on pro-caspase-1 causing the release of caspase-1; caspase-1 then acts upon pro-IL-1β cleaving this precursor to the active IL-1β form. Insulin signaling promotes glucose uptake by promoting the translocation of GLUT4 to the cell surface plasma membrane. Inflammatory signaling pathways can alter the phosphorylation status of IRS-1. IRS-1 is crucial in the insulin signaling pathway, tyrosine phosphorylation is asscciated with an insulin sensitive state. IKKβ and JNK can promote serine phosphorylation of IRS-1 and this phosphorylation state is linked to insulin resistance and reduced glucose uptake.

The Journal of Clinical Investigation

Insulin sensitivity: modulation by nutrients and inflammation

Simon Schenk, … , Maziyar Saberi, Jerrold M. Olefsky

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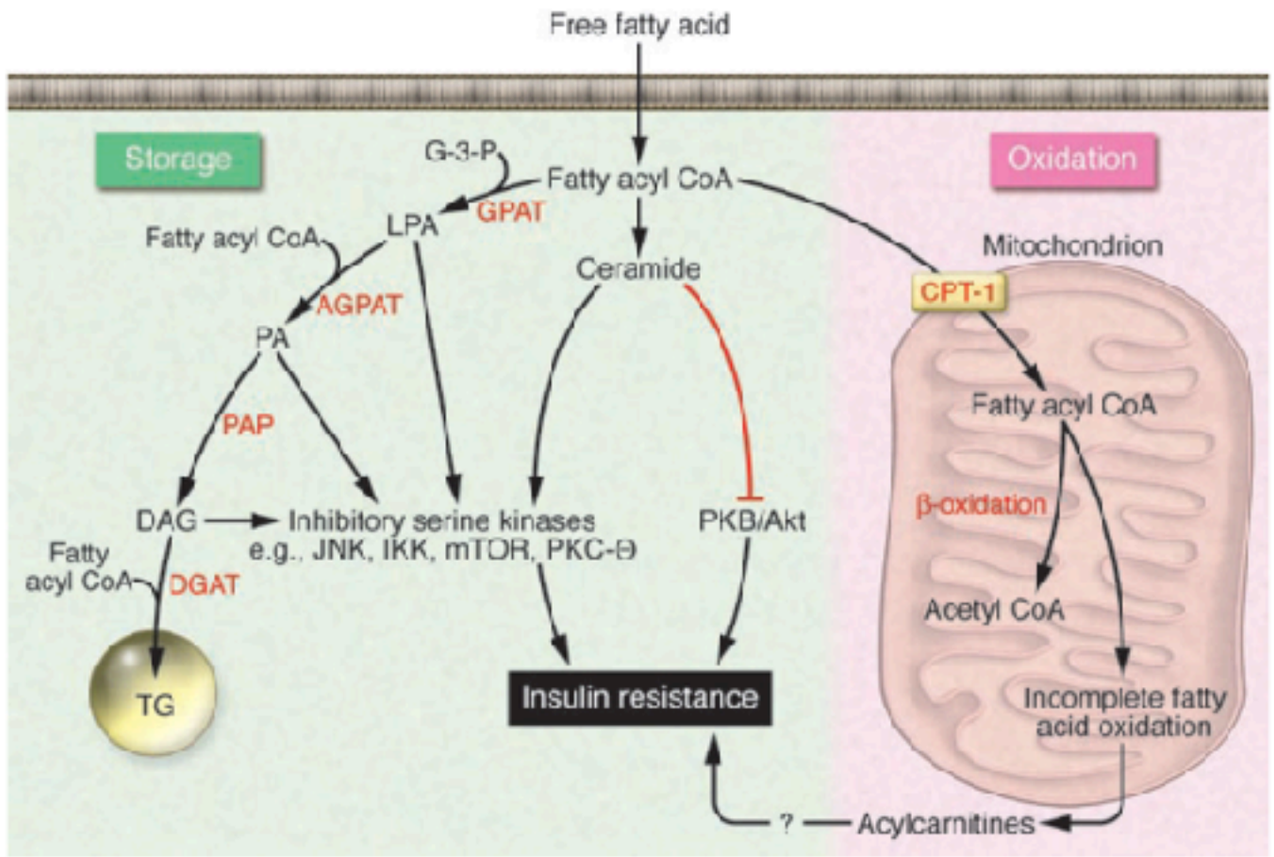

Figure 1

Fatty acid metabolism and insulin action in skeletal muscle or liver. Obesity results in an increased flux of free fatty acids into the circulation and uptake by the myocyte or hepatocyte. Activated fatty acids (i.e., fatty acyl-CoAs) are "metabolized" primarily via one of two pathways, oxidation or storage. When fatty acid flux exceeds the ability of these pathways to dispose of fatty acyl-CoAs, intermediaries of fatty acid metabolism (e.g., DAG, PA, LPA, ceramide) accumulate. In turn, these fatty acid intermediates can activate a number of different serine kinases that can negatively regulate insulin action. Ceramide can also impair insulin action through interactions with PKB/Akt. An inability to completely oxidize fatty acids through β-oxidation, which leads to an accumulation of acylcarnitines, has also been hypothesized to cause insulin resistance, although the precise mechanisms leading to insulin resistance are, to date, unknown. AGPAT, acylglycerol-3-phosphate acyltransferase; PAP, PA phosphohydrolase.

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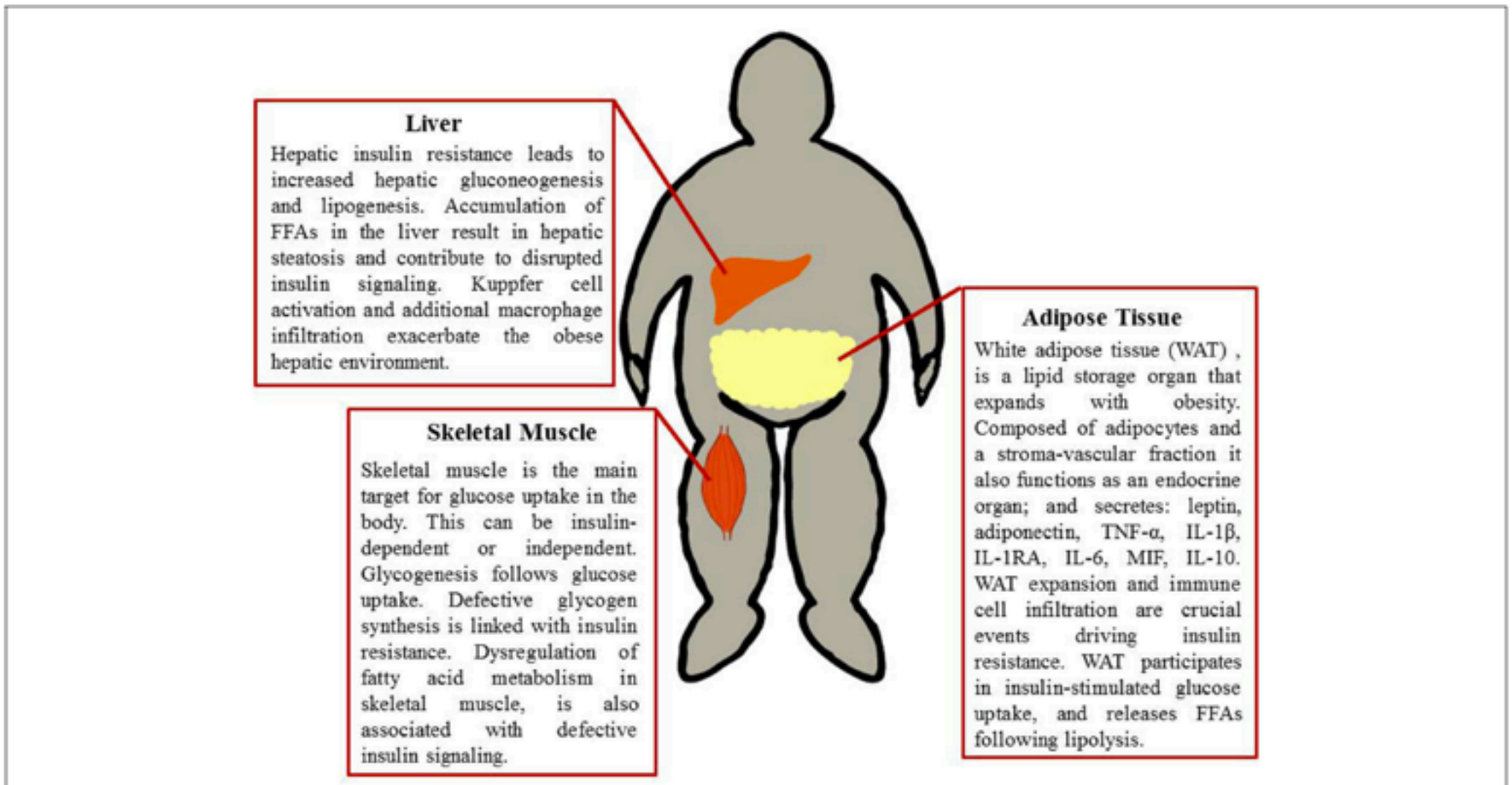

FIGURE 1 | Metabolic tissues implicated in obesity-induced insulin resistance. Adipose tissue, liver, and skeletal muscle are involved in glucose uptake, glucose production, and glucose processing. These tissues therefore are paramount in obesity and the progression of insulin resistance. A combination of defective fatty acid storage and metabolism together with immune cell infiltration and a pro-inflammatory tissue milieu result in dysregulation of insulin signaling.

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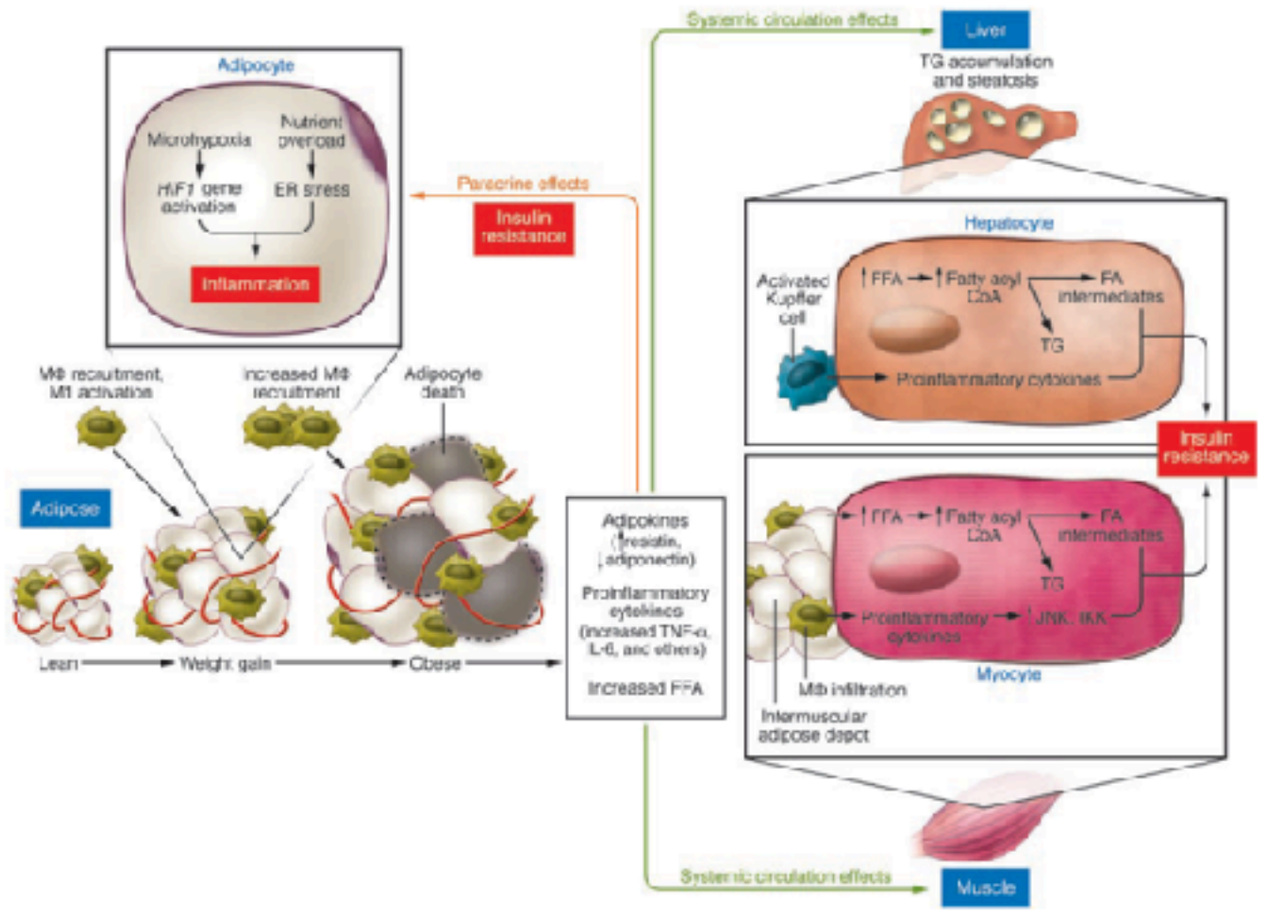

Figure 2
Obesity, tissue inflammation, and insulin resistance. Nutrient excess, weight gain, and ensuing obesity result in expansion of adipose tissue mass and adipocyte size. With this expansion, total free fatty acid release into the circulation is increased and oxygen delivery to the adipocyte is decreased. The combination of microhypoxia and nutrient excess leads to induction of HIF-1 and the downstream target genes as well as ER stress within the adipocyte. This can lead to the eventual death of the adipocyte as well as a characteristic inflammatory response. The inflammatory response includes increased production and release of proinflammatory cytokines/chemokines and the recruitment of bone marrow–derived macrophages (Mø). These macrophages are of the M1 activation/polarization state and are highly inflammatory in nature. Once recruited, these macrophages release proinflammatory cytokines, which work in a paracrine manner to activate the intracellular proinflammatory pathways (e.g., JNK and IKK) in neighboring cells and possibly through endocrine mechanisms in distal tissues. In a feed-forward cycle, activation of macrophages promotes the recruitment and infiltration of additional macrophages into adipose tissue. This results in cell autonomous insulin resistance in adipocytes and liver, exacerbation of the inflammatory state, and systemic insulin resistance. With obesity, there is also increased fat accumulation within skeletal muscle, and these intermuscular fat depots becomes infiltrated with proinflammatory macrophages, which may cause paracrine-like insulin resistance in skeletal muscle. In parallel with these inflammation-related changes, alterations in fatty acid metabolism can lead to the accumulation of fatty acid intermediates with the liver and skeletal muscle, which can cause insulin resistance via mechanisms outlined in Figure 1. In addition, fatty acids can serve as ligands to broadly activate inflammatory pathways in Kupffer cells and ATMs (e.g., via TLR2/TLR4 signaling pathways).

Metabolically healthy Obese

- 20–30% of obese adults **do not** express the adverse metabolic phenotype typically associated with obesity.

- MHO have high levels of insulin sensitivity but may not display symptoms of hypertension, dyslipidemia, or chronic inflammation and have significantly smaller omental adipocytes than metabolically unhealthy individuals.

- In contrast, MONW, raised insulin, TAG, FFA, low HDL

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Brown adipose tissue

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Significance of beige and brown fat

- Unlike WAT, BAT functions prominently in **thermoregulation** through **lipid oxidation-mediated heat generation**.

- Although both BAT and muscles harbor high levels of mitochondria, BAT is **specialized for heat generation** rather than for ATP synthesis by high expression of mitochondrial uncoupling protein 1 **(UCP-1).**

- The adipose tissues express high levels of **β-adrenergic receptors** that mediate cold-induced lipolysis

- **After cold exposure**,large amounts of lipids from **WAT flow into BAT**. Concurrently, β-adrenergic signaling in BAT activates the expression of peroxisome proliferator- activated receptor γ coactivator 1α which stimulates the expression of UCP-1 and mitochondrial genes.

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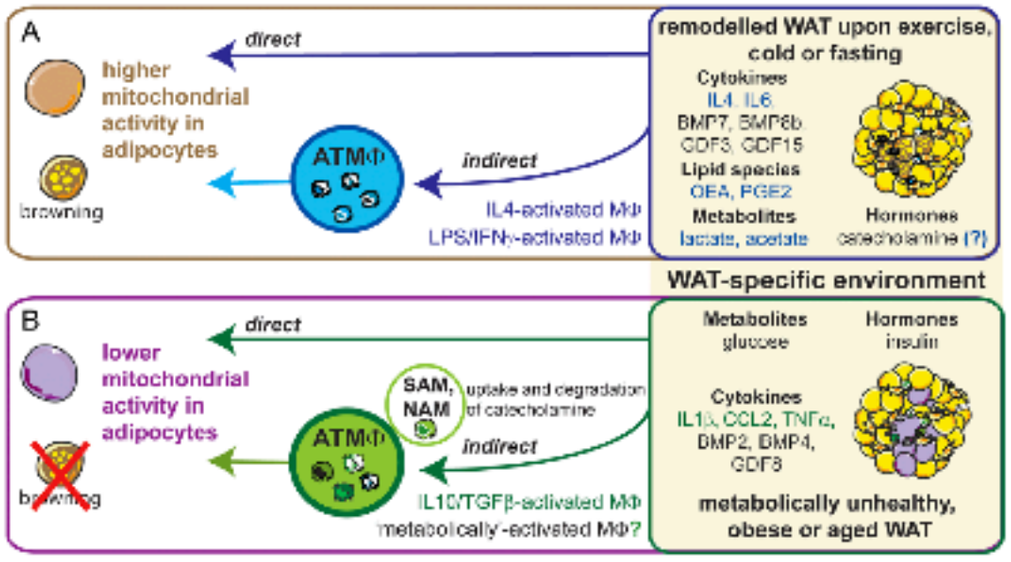

Figure 4
Control of adipocyte energy metabolism. In the WAT-specific environment (yellow background), multiple cytokines/chemokines, metabolites, lipid species and hormones from diverse cell types within WAT and/or circulation can exert either positive (upper box, A) or negative (lower box, B) effects on WAT metabolism. These factors control mitochondrial function of (pre-)adipocytes either directly and/or indirectly by first affecting the ATMΦ secretion profile. Notably, the composition of released factors depends on MΦ activation (known for factors written in blue/green). Depending on the TGFβ superfamily (BMP's and GDF's), WAT metabolism is either promoted or suppressed. A recently identified but controversially discussed mechanism of MΦ invoked browning and enhanced WAT metabolism is the secretion of catecholamine by IL4-activated MΦ during cold and exercise (upper box, A). On the contrary, NAMs/SAMs (lower box, B), which represent MΦ in close proximity of neurons/axons, may reduce local catecholamine levels and thus suppress mitochondrial function of adipocytes with age and obesity.

Endocrine CONNECTIONS | M Keuper | Inflammatory control of adipocyte bioenergetics | 8:6 | R105–R121

REVIEW

On the role of macrophages in the control of adipocyte energy metabolism

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Strategies to increase brown fat

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Adiponectin Changes in Relation to the Macronutrient Composition of a Weight-Loss Diet

Suzanne S. Summer[1], Bonnie J. Brehm[2], Stephen C. Benoit[3] and David A. D'Alessio[4]

Table 1 Baseline characteristics of study participants

	Cohort 1		Cohort 2		Combined cohorts	
	Low-fat ($n = 20$)	Low-carbohydrate ($n = 22$)	Low-fat ($n = 19$)	Low-carbohydrate ($n = 20$)	Low-fat ($n = 39$)	Low-carbohydrate ($n = 42$)
Age, years	42.6 (±1.9)	43.5 (±1.5)	40.2 (±3.2)	44.3 (±2.4)	41.9 (±1.8)	44.5 (±1.4)
Race	7 (35%)	4 (18%)	2 (11%)	5 (25%)	9 (23%)	9 (21%)
Height (m)	1.7 (±0.01)	1.7 (±0.01)	1.6 (±0.01)	1.7 (±0.01)	1.6 (±0.01)	1.7 (±0.01)
Weight (kg)	92.3 (±1.3)	91.2 (±1.3)	90.2 (±2.0)	90.6 (±2.4)	91.3 (±1.2)	90.9 (±1.4)
BMI (kg/m^2)	34.0 (±0.4)	33.1 (±0.4)	33.4 (±0.5)	32.8 (±0.6)	33.8 (±0.4)	33.2 (±0.4)
Body fat (kg)	37.8 (±0.6)	37.3 (±1.0)	36.7 (±0.8)	37.9 (±1.3)	37.3 (±0.5)	37.6 (±0.8)
LBM (kg)	51.0 (±1.1)	50.4 (±1.3)	50.4 (±1.4)	49.6 (±1.2)	50.7 (±0.9)	50.0 (±0.9)
Serum adiponectin (mcg/ml)	9.8 (±1.7)	9.9 (±1.0)	8.7 (±0.8)	10.1 (±0.9)	9.20 (±1.0)	10.0 (±0.7)
FPG (mg/dl)	92.8 (±1.9)	95.4 (±2.3)	89.9 (±2.6)	89.6 (±3.8)	91.4 (±1.6)	92.7 (±2.2)

All subjects are female. Values are mean ± s.e.m, except for the variable race, which is presented as number and percent of subjects who were African American. All other subjects were white.
FPG, fasting plasma glucose; LBM, lean body mass.

Table 2 Mean daily intake of macronutrients: baseline vs. postintervention

	Low-fat ($n = 39$)		Low-carbohydrate ($n = 42$)	
	Baseline	Postintervention	Baseline	Postintervention
Total energy (kcal)	1,948.6 (±87.9)	1,342.2 (±63.0)[a]	1,873.8 (±97.8)	1,404.6 (±81.8)[a]
Carbohydrate (g)	250.1 (±17.5)	170.3 (±10.7)[a]	221.8 (±13.8)	95.1 (±11.7)[a,b]
Portion of energy intake	50%	50%	48%	27%
Fat (g)	79.1 (±5.0)	46.3 (±3.4)[a]	75.5 (±4.8)	75.6 (±5.4)[b]
Portion of energy intake	36%	31%	36%	49%
Protein (g)	71.7 (±3.1)	61.8 (±3.4)[c]	74.0 (±3.9)	81.7 (±4.8)[b]
Portion of energy intake	14%	19%	16%	24%

Values are means ± s.e.m.
[a]$P < 0.001$ compared to baseline. [b]$P < 0.001$, difference between groups. [c]$P < 0.05$ compared to baseline. [d]$P < 0.01$, difference between groups.

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Adiponectin Changes in Relation to the Macronutrient Composition of a Weight-Loss Diet

Suzanne S. Summer[1], Bonnie J. Brehm[2], Stephen C. Benoit[3] and David A. D'Alessio[4]

Table 3 Body weight and body fat: baseline vs. postintervention

	Low-fat (n = 39)		Low-carbohydrate (n = 42)	
	Baseline	Postintervention	Baseline	Postintervention
Body weight (kg)	91.3 (±1.2)	86.3 (±1.4)[a]	90.9 (±1.4)	81.8 (±1.4)[a,b]
Body fat (kg)	37.3 (±0.5)	34.7 (±1.4)[a]	37.6 (±0.8)	32.1 (±0.9)[a,b]

Values are mean ± s.e.m.
[a]$P < 0.001$ compared to baseline. [b]$P < 0.05$, difference between groups.

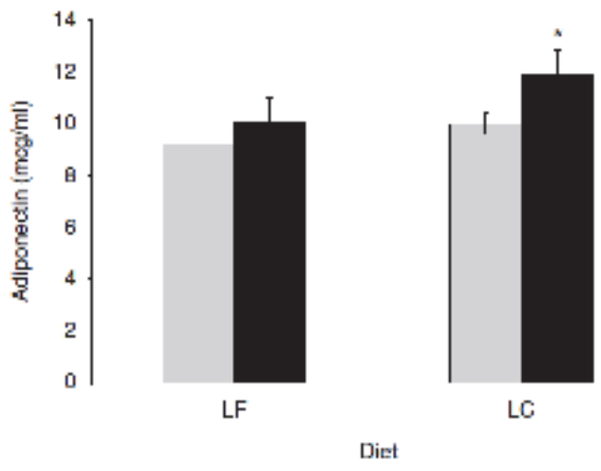

Figure 2 Changes in serum adiponectin, by diet. Data are presented as means ± s.e. *$P < 0.01$ as compared to baseline. Gray bars, baseline; black bars, postintervention.

Food Ingredients Involved in White-to-Brown Adipose Tissue Conversion and in Calorie Burning

*Hamza El Hadi, Angelo Di Vincenzo, Roberto Vettor and Marco Rossato**

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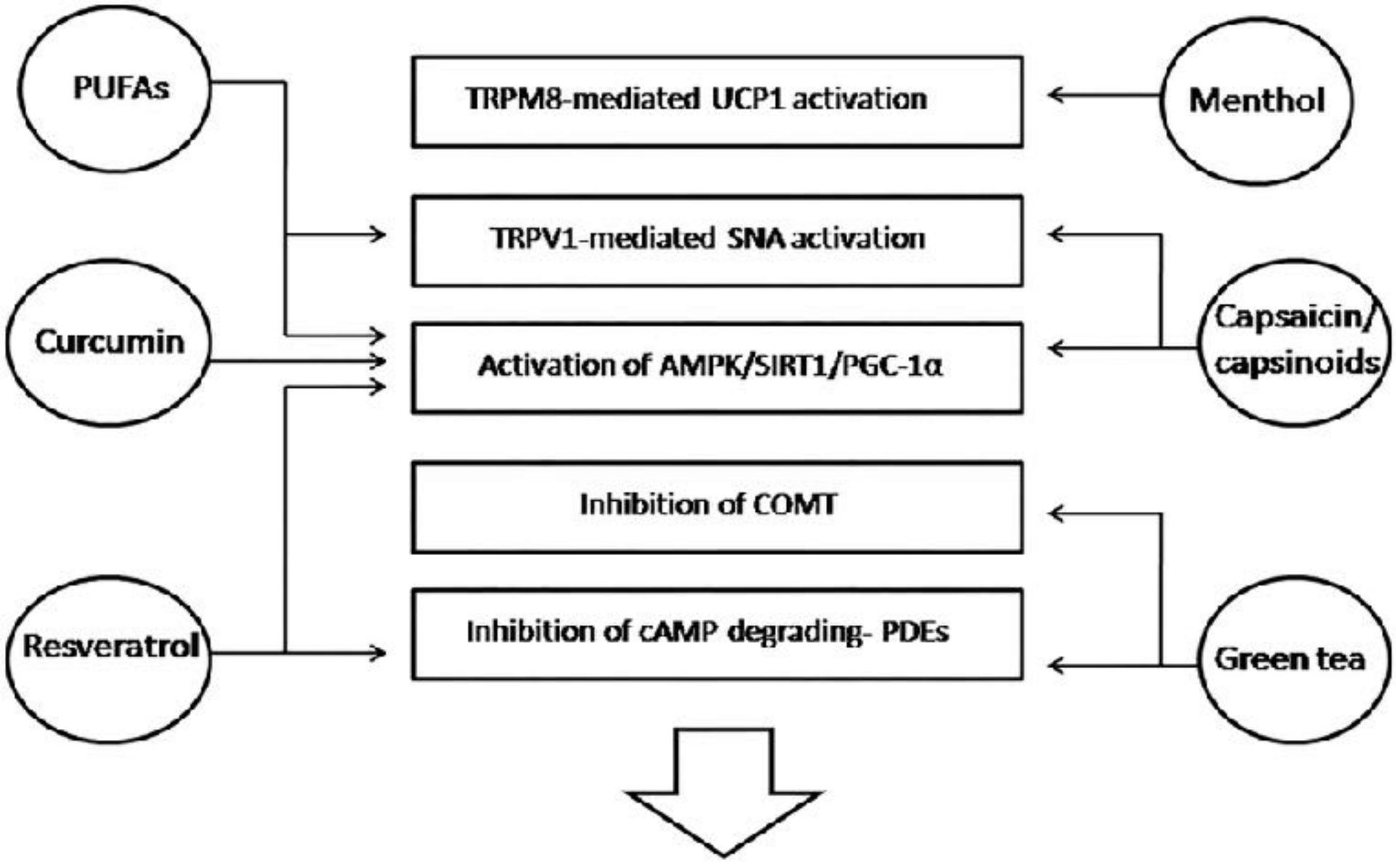

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Food Ingredients Involved in White-to-Brown Adipose Tissue Conversion and in Calorie Burning

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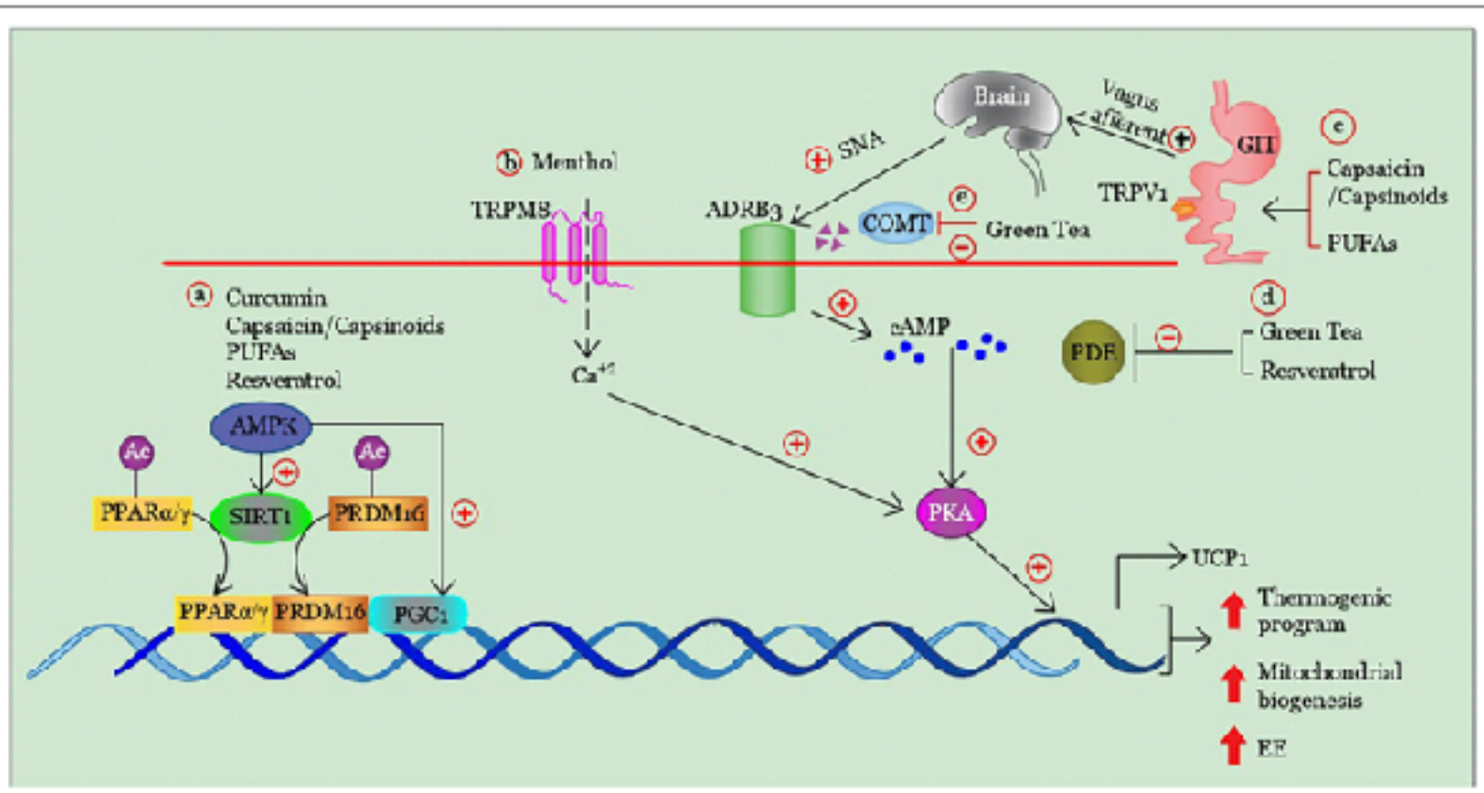

FIGURE 3 | Summary of the mechanisms involved in the stimulation of brown adipogenesis, mitochondrial biogenesis and energy expenditure by some dietary molecules. **(a)** The direct and/ or indirect (via AMPK) activation of SIRT1 induces deacetylation and interaction of key transcription factors promoting brown and beige adipogenesis as PPARα/γ and PRDM16. The PPAR/PRDM16 complex is also able to bind and activate PGC1α, another cofactor specifically expressed in brown and beige adipocytes that stimulates the transcription of several genes involved in thermogenesis and mitochondrial biogenesis. Similarly, AMPK can also directly enhance PGC1α activity by phosphorylation, thus increasing mitochondrial biogenesis. **(b)** TRPM8 activation in brown adipocytes enhances the expression of thermogenic genes via Ca^{2+}-dependent PKA signaling pathway. **(c)** Activation TRPV1 receptors in GII, and consequent stimulation of the vagal afferent pathways leads to activation of neurons within the ventromedial hypothalamus. This mechanism of action induces a cold independent adrenergic response that mediates brown adipogenesis. The adrenergic stimulation in brown adipocytes can be also promoted by the reduction of degradation of **(d)** cAMP and **(e)** norepinephrine through direct inhibition of PDEs and COMT activity, respectively. TRPM8, transient receptor potential cation channel melastatin 8; UCP1, uncoupling protein 1; TRPV1, transient receptor potential vanilloid 1; SNA, sympathetic nerve activity; AMPK, adenosine monophosphate-activated protein kinase; SIRT1, sirtuin-1; PGC 1α, peroxisome proliferator activated receptor gamma coactivator 1 alpha; COMT, catechol O methyl transferase; cAMP, cyclic adenosine monophosphate; PDEs, phosphodiesterases; PUFAs, polyunsaturated fatty acids; Ac, acetyl group; cAMP, cyclic adenosine monophosphate; EE, energy expenditure; PPARα/γ peroxisome proliferator-activated receptor alpha/gamma; PKA, protein kinase A, PRDM16; PR-domain containing 16, (+), stimulation; (–), inhibition; ↑, increase.

Open
ORIGINAL ARTICLE

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www.nature.com/cr

Intermittent fasting promotes adipose thermogenesis and metabolic homeostasis via VEGF-mediated alternative activation of macrophage

Kyoung-Han Kim[1, 12, *], Yun Hye Kim[2, *], Joe Eun Son[1], Ju Hee Lee[2, 3], Sarah Kim[2], Min Seon Choe[1], Joon Ho Moon[2], Jian Zhong[2], Kiya Fu[2], Florine Lenglin[2], Jeong-Ah Yoo[2], Philip J Bilan[4], Amira Klip[4], Andras Nagy[5, 6], Jae-Ryong Kim[7], Jin Gyoon Park[8], Samer MI Hussein[9], Kyung-Oh Doh[10], Chi-chung Hui[11], Hoon-Ki Sung[2, 3]

"In this study, we establish a new IF regimen to investigate the impact of IF under isocaloric conditions and demonstrate that IF improves glucose homeostasis and prevents diet-induced metabolic dysfunction without caloric intake reduction. Mechanistically, we found that WAT is pivotal for mediating IF-induced metabolic benefits via browning of WAT through adipose-VEGF-mediated alternative activation of adipose macrophage (M2 macrophage). Our study unveils a novel mechanism by which IF promotes whole-body homeostasis through browning of WAT by VEGF-mediated macrophage switching."

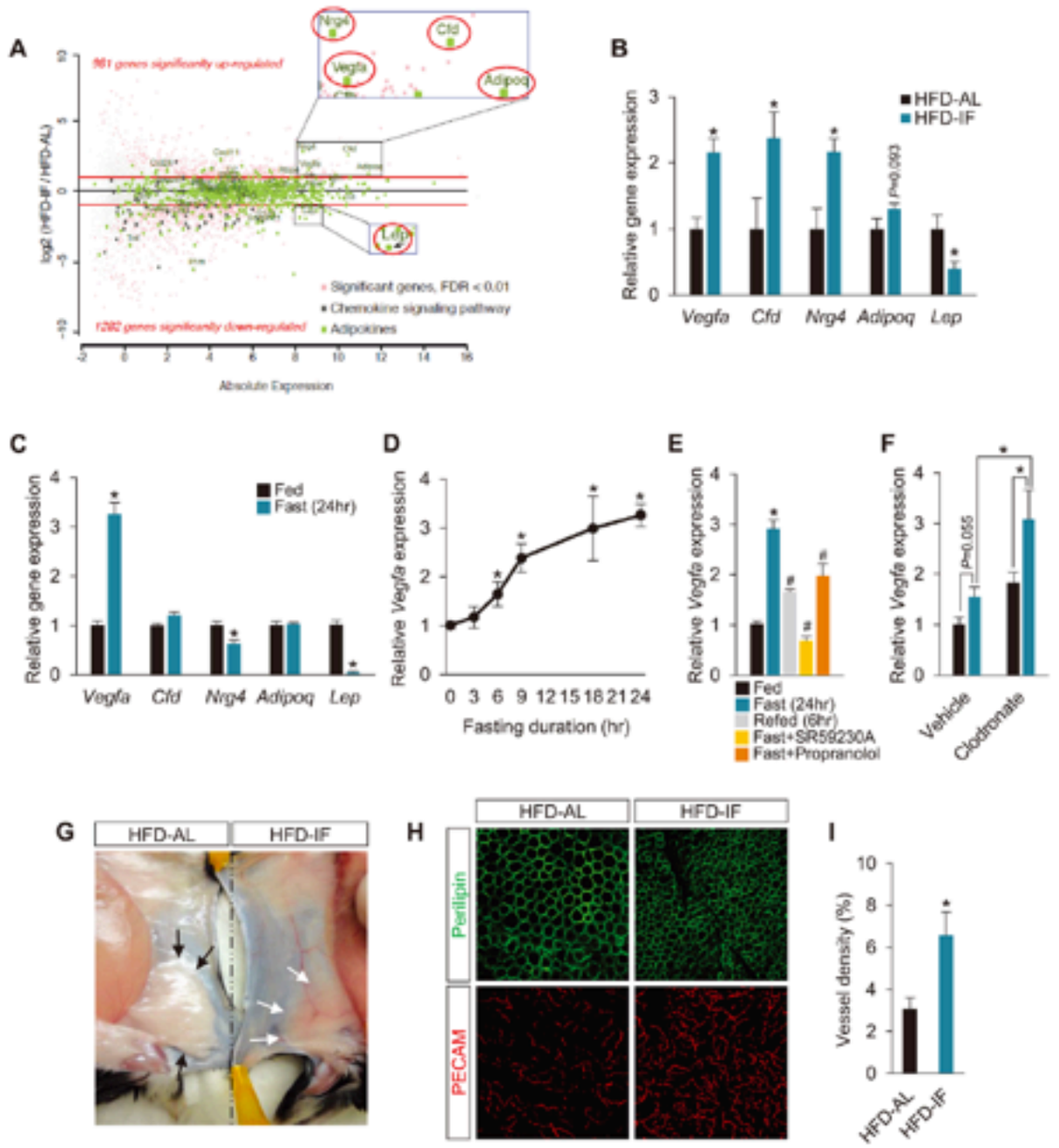

Figure 3 Fasting induces adipose-VEGF expression. **(A)** MA plot highlighting significantly altered mRNA expression of adipose-derived factors in PWAT of HFD-IF mice, compared to that of HFD-AL mice. *Vegfa*, *Cfd*, *Nrg4*, *Adipoq*, and *Lep* encode vascular endothelial growth factor, adipsin, neuregulin 4, adiponectin, and leptin, respectively. **(B)** qPCR validation of adipose-derived factors in PWAT (HFD, AL/IF; $n = 6/8$). **(C)** mRNA expression levels of *Vegfa*, *Cfd*, *Nrg4*, *Adipoq*, and *Lep* in PWAT at feeding and 24 h of fasting ($n = 5$ per group). **(D)** *Vegfa* mRNA expression in PWAT at different fasting durations ($n = 5$-6 per group). **(E)** *Vegfa* mRNA expression in PWAT at feeding, 24 h of fasting, 6 h of refeeding, fasting with β3-AR antagonist, SR59230A (5 mg/kg, i.p.), and fasting with non-specific β-AR antagonist, Propranolol (5 mg/kg, i.p.; $n = 5$ per group). **(F)** *Vegfa* mRNA expression in PWAT at feeding and 24 h of fasting with treatments of vehicle or clodronate ($n = 5$). **(G)** A representative macroscopic image illustrating increased vascularization in IWAT of HFD-IF mice, compared to HFD-AL mice. Black and white arrows indicate IWAT of HFD-AL and HFD-IF mice, respectively. **(H)** Representative microscopic images of adipocytes and blood vessels, visualized with perilipin and PECAM-1 antibodies, respectively, in whole-mount PWAT. **(I)** Quantification of vessel densities in PWAT. Data are mean ± SEM; one- or two-way ANOVA with Student-Newman-Keuls *post hoc* analysis and two-tailed unpaired Student's *t*-test; $^{*}P < 0.05$ vs HFD-AL or Fed. $^{\#}P < 0.05$ vs Fast (24 h).

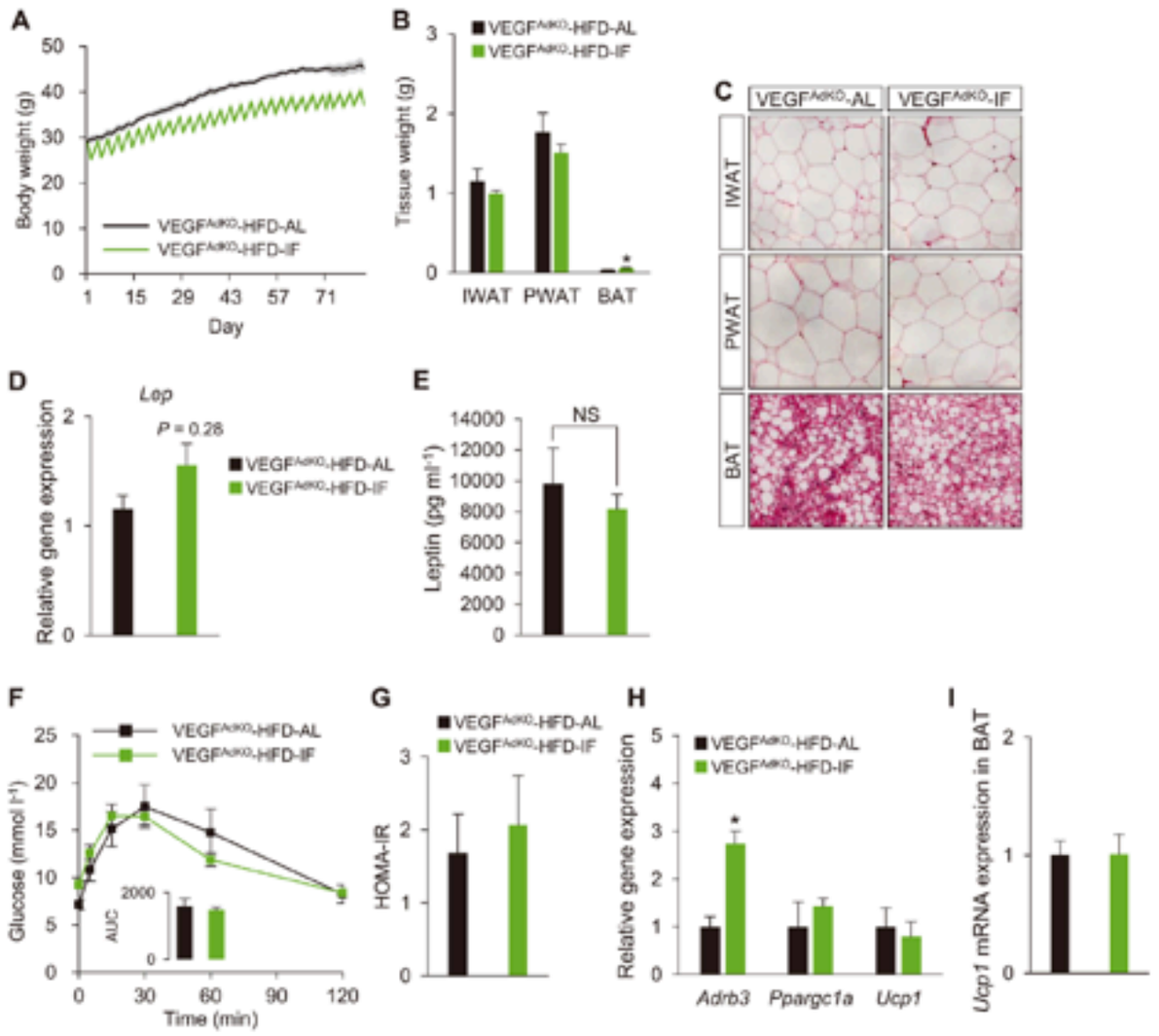

Figure 4 Adipose-VEGF is required for IF-mediated metabolic benefits. **(A)** Body weight measurements of *aP2-Cre;Vegfa*$^{flox/flox}$ mice (VEGF^{AdKO}) subjected to AL and IF under HFD feeding (VEGF^{AdKO}-HFD, AL/IF: $n = 5/6$). **(B)** Tissue weight of IWAT, PWAT, and BAT in VEGF^{AdKO}-HFD-AL and -IF mice. **(C)** H&E-stained sections of IWAT, PWAT, and BAT show no noticeable differences between VEGF^{AdKO}-HFD-AL and -IF mice. **(D)** *Lep* mRNA expression of PWAT in VEGF^{AdKO}-HFD mice. **(E)** Plasma leptin levels. **(F)** GTT in VEGF^{AdKO}-HFD mice. **(G)** HOMA-IR in VEGF^{AdKO}-HFD mice. **(H)** Gene expression analysis revealed that IF increased sympathetic activation (*Adrb3*), but did not affect brown/beige adipocyte maker expression (i.e., *Ucp1*) in PWAT of VEGF^{AdKO} mice. **(I)** No changes in *Ucp1* expression in BAT of VEGF^{AdKO} mice upon IF. Data are mean ± SEM; two-tailed unpaired Student's *t*-test; $^*P < 0.05$ vs VEGF^{AdKO}-HFD-AL. Lep, leptin.

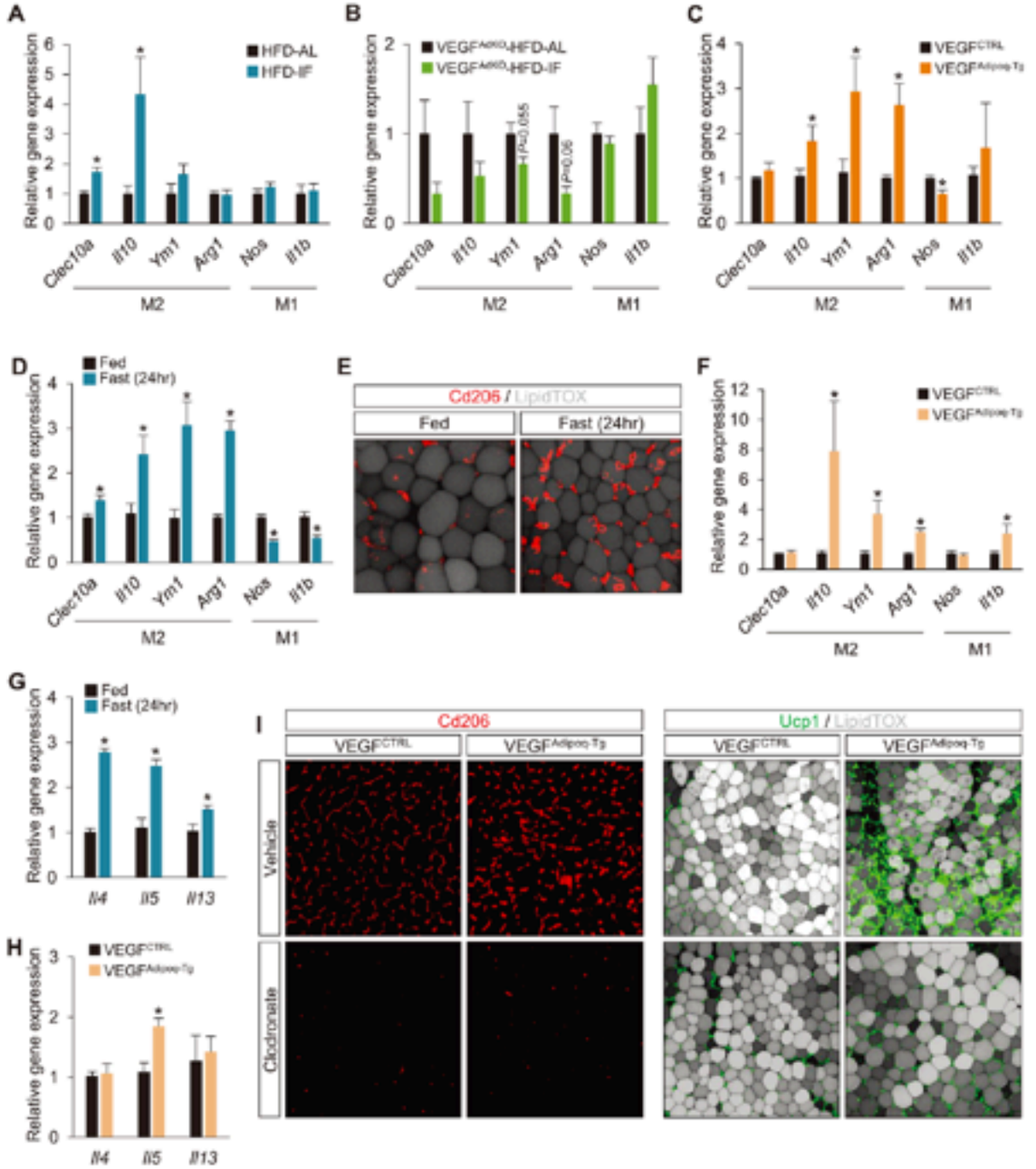

Figure 6 Fasting and adipose-VEGF induce alternative activation of macrophage. **(A)** M1/M2 macrophage marker gene expression analysis in HFD-AL and -IF mice. **(B)** M1/M2 macrophage marker gene expression in $VEGF^{AdKO}$-HFD-AL and -IF mice. **(C)** M1/M2 macrophage marker gene expression after intermittent adipose-VEGF upregulation in $VEGF^{Adipoq\text{-}Tg}$ mice. **(D)** M1/M2 macrophage marker gene expression analysis in fed and fasted (24 h) mice. **(E)** Representative images of M2 marker Cd206-stained cells in whole-mount PWAT of fed and fasted (24 h) mice. **(F)** M1/M2 macrophage marker gene expression analysis after acute adipose-VEGF upregulation in $VEGF^{Adipoq\text{-}Tg}$ mice. **(G)** Type 2 cytokine gene expression in fed and fasted (24 h) mice. **(H)** Type 2 cytokine gene expression after acute adipose-VEGF upregulation (48 h) in $VEGF^{Adipoq\text{-}Tg}$ mice. **(I)** Representative images of M2 macrophages and Ucp1 expression in WAT after acute adipose-VEGF upregulation in $VEGF^{Adipoq\text{-}Tg}$ mice with treatments of vehicle or clodronate. Values are mean ± SEM (post HFD-AL: $n = 7$ and post HFD-IF; $n = 9$); two-tailed unpaired Student's *t*-test; $^*P < 0.05$ vs HFD-AL, $VEGF^{AdKO}$-HFD-AL, $VEGF^{CTRL}$ or fed mice. See also Supplementary information, Figure S7.

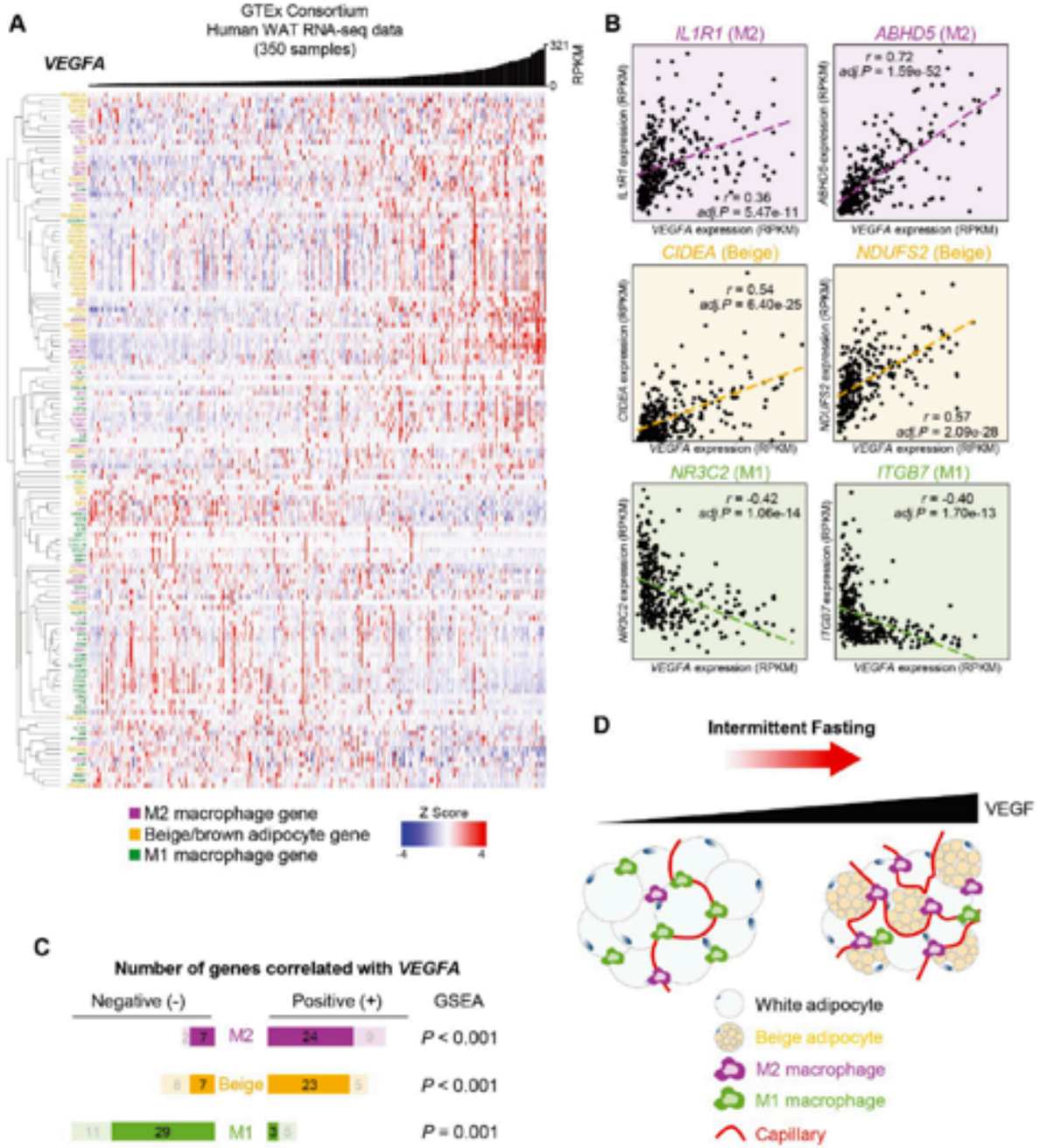

Figure 7 VEGF expression in human WAT correlates with M2 macrophage and WAT browning. **(A)** A correlation heatmap of *VEGFA* gene with unsupervised hierarchical clustering of M1/M2 macrophages- and beige/brown adipocyte-associated genes in human WAT. A histogram of *VEGFA* gene expression level (RPKM) is shown on the top of the heatmap. **(B)** Representative scatter plots showing correlation of *VEGFA* with *IL1R1* & *ABHD5* (M2), *CIDEA* & *NUDFS2* (beige), and *NR3C2* & *ITGB7* (M1) genes. **(C)** Summary of *VEGFA* correlation with M2, beige, and M1-associated genes. Permutation *P*-values with the GSEA are shown. **(D)** Schematic model of IF-mediated VEGF expression underlying adipose thermogenesis and M2 macrophage polarization. GSEA, gene set enrichment analysis.

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Nutrition & Metabolism

RESEARCH Open Access

Plasticity of adipose tissue in response to fasting and refeeding in male mice

Hao-Neng Tang[1,2], Chen-Yi Tang[1], Xiao-Fei Man[1], Shu-Wen Tan[1], Yue Guo[1], Jun Tang[1], Ci-La Zhou[1] and Hou-De Zhou[1*]

"fasting induced preferential mobilization of lipids from the mesenteric adipose tissue depot, whereas refeeding induced preferential restoration of adipose tissue from the inguinal depot. These findings confirmed that long-term fasting and refeeding could lead to a reduction of the'metabolically harmful' visceral adipose tissue, as well as highlighting the role of plasticity of adipose organs on different anatomical sites of adipose tissue when subject to environmental changes."

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Summary

- Adipose tissue is a **central metabolic organ** in the regulation of **whole-body energy homeostasis**.

- WAT is a key energy reservoir for other organs and brown adipose tissue accumulates lipids for cold-induced adaptive thermogenesis. Adipose tissues secrete various **hormones, cytokines, and adipokines** that control systemic energy balance by regulating **appetitive signals from the central nerve system** as well as **metabolic activity in peripheral tissues.**

- Changes in the nutritional status result in dynamic remodeling of adipose tissue.

- Changes in the number and size of the adipocytes affect the microenvironment of expanded fat tissues, accompanied by alterations in adipokine secretion, adipocyte death, local hypoxia, and fatty acid fluxes.

- Stromal vascular cells in the adipose tissue, including immune cells, are involved in numerous adaptive processes, such as dead adipocyte clearance, adipogenesis, and angiogenesis, all of which are **dysregulated** in obese adipose tissue remodeling.

- Chronic overnutrition triggers uncontrolled inflammatory responses, leading to systemic low-grade inflammation and metabolic disorders, such as insulin resistance.

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