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Review

How Adipocytes Orchestrate Inflammation Within Adipose Tissue?

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Abstract

Adipose tissue is far more than a passive reservoir for surplus energy: it is an active metabolic and endocrine organ that senses nutrient availability and orchestrates systemic energy balance. When caloric intake chronically exceeds expenditure, adipocytes become engorged with lipids and exposed to metabolic, mechanical, and hypoxic stress. To adapt, they initiate a fibro-inflammatory response that may be protective in the short term. As this response becomes chronic, adipocytes lose their metabolic flexibility, acquire a maladaptive fibro-inflammatory phenotype, and contribute to the cascade of inflammation, insulin resistance, and metabolic disease that characterizes obesity. In this review, we dissect the cellular and molecular cues that trigger fibro-inflammation, from nutrient excess and mitochondrial stress to hypoxia and immunometabolic rewiring, and highlight how these processes reshape adipocyte identity and tissue homeostasis.

Keywords: adipocyte; obesity; fibro-inflammation

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1. Introduction:

Formerly viewed as a passive, merely an inert reservoir of energy, white adipose tissue (WAT) has now been recognized as a metabolically and immunologically dynamic organ. Although adipocytes occupy 90–95% of tissue volume, they represent only ~20% of total cells. The remaining cells form the stroma vascular fraction (SVF) harboring a rich diversity of immune cells, accounting for up to 60% of SVF cells in obesity [1–4]. These include distinct populations of macrophage and monocyte subsets, B and T lymphocytes, neutrophils, eosinophils, basophils, mast cells, dendritic cells, natural killer cells, and

innate lymphoid cells [2,3,5,6]. Each type occupies specialized anatomical niches that sustain their survival and shape their functional programming [5,7]. Adipocytes critically integrate environmental cues and orchestrate the local immune response through the active secretion of a broad repertoire of cytokines and hormones, collectively referred to as adipokines [8–10]. They also shed extracellular vesicles (EVs) that act as potent messengers across tissues and organs, shaping the inflammatory landscape far beyond adipose depots [9]. Interestingly, a recent study suggests that they are capable of antigen presentation, directly modulating T cell responses [11] (Figure 1).

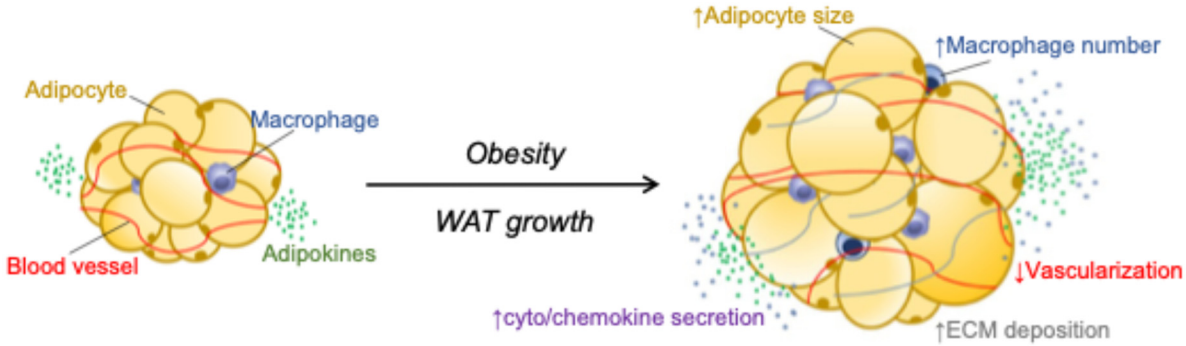

Figure 1. Remodeling of the adipose niche in obesity. With increasing body mass index (BMI), white adipose tissue (WAT) undergoes extensive remodeling. In lean states, WAT maintains a balanced immune landscape composed predominantly of resident macrophages, eosinophils, and regulatory T cells (Tregs), supporting healthy adipocyte function and tissue homeostasis. Chronic overnutrition disrupts this equilibrium: adipocytes enlarge, adipokine secretion becomes aberrant, and the stromal compartment is overtaken by pro-inflammatory immune cells, including pro-inflammatory macrophages, mast cells, and diverse effector T-cell subsets. In parallel, excessive extracellular matrix deposition leads to progressive fibrosis, which stiffens the tissue, restricts adipocyte expandability, and amplifies inflammation. Together, these alterations transform WAT into a dysfunctional, highly inflammatory, and fibrotic environment characteristic of obesity.

This intimate crosstalk takes on pathological significance in obesity, as adipocytes become active drivers of inflammation. This, in turn, promotes the recruitment and activation of immune cells, pushing the tissue into a state of chronic, low-grade inflammation. This so-called "meta-inflammatory" state underpins adipocyte dysfunction and local insulin resistance, propagates systemic insulin resistance, and accelerates the development of type 2 diabetes mellitus (T2DM) [3,12]. A strong correlation between inflammatory burden and the degree of insulin resistance has positioned inflammation as a pivotal driver of metabolic disease [3,13–18]. Experimental models reinforce this concept: targeted depletion of pro-inflammatory immune subsets or blockade of chemokine and cytokine signaling consistently protects adipocyte function and improves insulin sensitivity [3,13,19–22]. Yet the primary trigger that ignites this inflammatory cascade remains poorly defined. Alterations in fatty acid homeostasis, extracellular matrix (ECM) remodeling, mechanical stress, hypoxia, oxidative and endoplasmic reticulum stress, mitochondrial dysfunction and associated quality control processes, as well as direct disruption of insulin signaling, have all been implicated [3,19,23] (Figures 1 and 2). However, the causal hierarchy linking these events to metabolic decline remains unresolved [24].

Although adipose tissue inflammation is traditionally viewed as preceding adipocyte dysfunction, recent findings in both mice and humans indicate that it may instead arise after the onset of insulin resistance [21,25–27]. Moreover, inflammation has been observed to persist within WAT even after significant weight loss and improved glycemic control [28,29]. These observations raise the possibility that inflammation in metabolic tissues may not solely act as a trigger of insulin resistance, but may also participate in serving adaptive

roles, preserving WAT plasticity, supporting extracellular matrix remodeling, promoting angiogenesis, and enabling adipogenesis [30–32]. Indeed, acute inflammatory signaling is essential for normal adipose tissue function, orchestrating tissue remodeling that allows excess lipids to be safely stored through the generation of new, healthy adipocytes. By contrast, failure of adipose tissue to properly sense and respond to inflammatory cues constrains tissue expansion and predisposes to metabolic dysfunction [31–33].

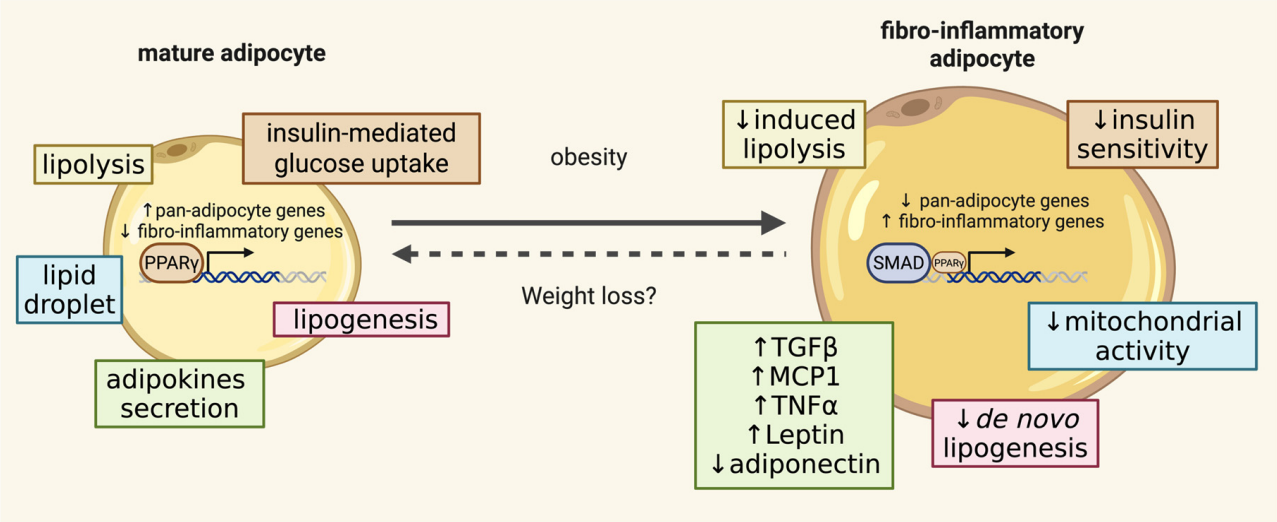

Figure 2. Obesity profoundly alters adipocyte biology. Enlarged adipocytes undergo profound functional decline. They display reduced sensitivity to hormonal and nutrient cues, impaired insulin-stimulated glucose uptake, decreased de novo lipogenesis, blunted hormonally induced lipolysis, and markedly diminished adiponectin secretion. In parallel, hypertrophic adipocytes secrete elevated levels of cytokines and chemokines, fostering immune-cell recruitment and establishing a chronic inflammatory milieu within the tissue. These cellular defects are compounded by substantial remodeling of the extracellular matrix (ECM). In obese WAT, the ECM becomes abnormally stiff, a defining hallmark of adipose pathology. Elevated stiffness correlates strongly with insulin resistance, impaired glucose metabolism, and heightened inflammation, likely because it restricts the adaptive remodeling required for healthy tissue expansion. Created in BioRender. Lec, S. (2026) https://BioRender.com/kthl9nn. (accessed on 2 January 2025).

Thus, WAT inflammation may represent a double-edged sword: maladaptive when chronic and excessive, yet potentially beneficial when engaged in controlled remodeling processes. Deciphering this paradox is essential, not only to resolve the causal interplay between inflammation and insulin resistance, but also to harness immunometabolic pathways as therapeutic targets in obesity and type 2 diabetes. This review explores the immune identities of adipocytes and preadipocytes, and their roles in regulating immune homeostasis within WAT under both physiological and pathological conditions.

2. Adipocyte Heterogeneity and Shifts in Cellular Identity During Obesity

Inflamed WAT in obesity includes aberrant lipid storage, impaired insulin responsiveness, and progressive tissue fibrosis. Considerable attention has been directed toward alterations in the stromal composition during overnutrition. Particularly, the emergence of fibro-inflammatory progenitor populations [4,34–37] and the infiltration of pro-inflammatory immune cells within the epididymal depot both reduce the proportion of adipocytes from ~30% in lean states to only about ~10% following high-fat diet (HFD) feeding [38] (Figures 1 and 2). Yet despite decades of study, the true phenotype of mature adipocytes in obesity remains incompletely defined. This gap stems largely from the technical diffi-

culty of purifying mature adipocytes, which are fragile, buoyant, and prone to rupture. Classic approaches, such as the Rodbell method, lack the precision required to isolate uncontaminated adipocyte populations [39]. To overcome the problem of cellular heterogeneity within intact tissues, several specialized isolation strategies have been developed. Laser-capture microdissection can harvest highly pure populations of rare cells [40], but it demands substantial expertise, costly instrumentation, and suffers from extremely low throughput. Fluorescence-activated cell sorting (FACS) offers another route when unique surface markers or Cre-dependent fluorescent reporters are available. However, the enzymatic dissociation required for FACS can itself distort cellular state [41]. To address these challenges, the team of Evan Rosen introduced NuTRAP (Nuclear tagging and Translating Ribosome Affinity Purification), a transgenic mouse system enabling the simultaneous isolation of cell-type–specific translating mRNA and chromatin from complex tissues [42]. Using NuTRAP, they define the transcriptional and epigenomic signatures of distinct adipocyte populations in vivo, revealing substantial divergence from whole-tissue profiles and from commonly used in vitro adipocyte cell lines [42]. Additionally, emerging technologies, including single-cell RNA sequencing and spatial transcriptomics, are now illuminating, with unprecedented precision, how adipocytes respond to the metabolic stresses of obesity [38,43–47].

Beyond compositional alterations, adipocytes undergo a profound transcriptional reprogramming toward a fibro-inflammatory identity (Figure 2). Comparative transcriptomics analyses between lean and obese mature adipocytes reveal a robust upregulation of pro-inflammatory cytokines, lysosomal program and stress-response genes, and ECM components, collectively driving chronic inflammation [38,42,44] (Figures 1 and 2). This maladaptive remodeling, involving a shift in cellular identity, curtails adipogenic renewal and constrains healthy WAT expansion [33,35]. Such loss of identity carries systemic consequences. Decades of work, dating back to the 1970s, have demonstrated that larger adipocytes are intrinsically less insulin-responsive than their smaller counterparts [48,49]. They exhibit reduced insulin-stimulated glucose uptake (via GLUT4) and diminished suppression of fat breakdown (lipolysis) [48–50]. The resulting fatty-acid spillover promotes ectopic lipid deposition in the liver, skeletal muscle, kidneys, and vasculature, driving lipotoxicity, altered glucose metabolism, and systemic insulin resistance. As hypertrophic adipocytes also lose their capacity to store fatty acids efficiently, WAT becomes a net contributor to circulating lipids [51–53].

Spatial transcriptomics of human subcutaneous WAT has profoundly reshaped our understanding of adipocyte heterogeneity [43]. Only a restricted subset of adipocytes remains insulin-responsive, and the abundance of this subset correlates tightly with whole-body insulin sensitivity. Thus, metabolic health may depend on a privileged minority of functionally preserved adipocytes rather than the average state of the tissue. Spatial analyses revealed striking micro-organizations: pro-inflammatory adipocytes cluster into self-reinforcing neighborhoods that may serve as localized hubs of chronic inflammation [43,54]. Moreover, adipocyte size correlates with leptin (LEP) expression only within the Adipo^{LEP} cluster, suggesting a potential size-dependent leptin feedback loop with central energy regulation [43]. Conversely, the Adipo^{SAA} cluster expresses high levels of *RBP4* and *SAA1/2* [43], potent pro-inflammatory effectors, positioning this population as an inflammatory amplifier [55–57]. These findings support a view of obese WAT as a patchwork of spatially organized endocrine and inflammatory adipocyte niches, not a uniform depot of lipid-storing cells.

At the molecular core of this reprogramming lies the reduction in PPARγ activity. PPARγ is a nuclear hormone receptor and the master transcriptional regulator of adipocyte biology, controlling not only adipocyte differentiation but also the long-term survival

and metabolic activity of mature adipocytes [58–63]. Under nutritional stress, its activity is markedly reduced in WAT [64–67]. Genome-wide binding analyses show that PPARγ occupancy is globally diminished in adipocytes from HFD-fed mice, with most sites downregulated [38]. These lost sites cluster at genes critical for adipokine secretion, insulin signaling, and lipid handling, precisely the pathways whose dysregulation defines the obese state. Whether this decline in binding reflects reduced PPARγ protein abundance, altered ligand availability, or cofactor dysregulation remains unresolved [38]. Mechanistically, PPARγ exerts potent anti-inflammatory effects beyond canonical transcriptional activation, directly repressing pro-inflammatory signaling by interfering with NF-κB, AP-1, and STAT pathways [68–70]. Collectively, these findings position the fibro-inflammatory transcriptional switch and collapse of PPARγ-driven networks as a pivotal nexus linking adipocyte dysfunction to the systemic pathogenesis of obesity and metabolic disease [38] (Figure 2).

3. What Drives the Inflammatory Program in Adipocytes in Obesity?

When caloric intake persistently exceeds energy expenditure, the brain–adipocyte feedback axis collapses under metabolic overload. Chronic hyperinsulinemia, hyperleptinemia, and alterations in catecholaminergic signaling drive persistent adipocyte expansion, pushing cells until their structural and metabolic limits [71–74]. Although the notion of a structural limit for adipocyte lipid storage has gained little mechanistic basis in experimental studies, it is generally accepted that beyond this threshold, anabolic force becomes deleterious, and the adipocyte shifts from storage to stress, from growth to inflammation [3]. Multiple stressors converge at this inflection point: mechanical strain, oxidative and ER stress, yet hypoxia emerges as the earliest and most potent trigger [3]. As adipocytes enlarge, oxygen diffusion lags behind cellular demand, creating micro zones of hypoxia within expanding WAT. The transcription factor HIF-1α, normally degraded via prolyl hydroxylase–mediated hydroxylation, stabilizes and activates a hypoxic gene program that drives angiogenesis, macrophage recruitment, oxidative stress, and fibrosis [75,76]. Genetic models confirm its causal role: adipocyte-specific HIF-1α knockout mice are protected from obesity-induced inflammation and systemic insulin resistance [77]. Importantly, hypoxia is not merely a downstream consequence of obesity; it arises early. Within days of overnutrition, adipocyte respiration becomes uncoupled, oxygen consumption surges, and local hypoxia develops, coinciding with early WAT inflammation [77,78]. Saturated fatty acids activate *adenine nucleotide translocase 2* (ANT2 encoded by the *SLC25A5* gene), a mitochondrial exchanger for ADP/ATP across cytoplasm and mitochondria, promoting proton leak and inefficient oxidative phosphorylation [77]. The paradox: more oxygen consumed, less ATP produced, generating a stress signal powerful enough to ignite inflammation. Simultaneously, excess fatty acid influx stimulates ANT2, the mitochondrial ADP/ATP carrier, escalating oxygen demand and fibrotic remodeling. Deletion of ANT2 reduces oxygen consumption while preserving mitochondrial integrity, shielding WAT from hypoxia-driven inflammation and fibrosis [79]. Collectively, these findings identify hypoxia as the molecular spark that transforms adipocytes from passive energy reservoirs into active instigators of inflammation, collapsing local oxygen homeostasis and destabilizing systemic metabolism (Figure 3).

This mitochondria-driven hypoxic state is accompanied by profound metabolic reprogramming in mature adipocytes. It is now well established that metabolism and gene expression are tightly interconnected: intermediary metabolites serve as substrates for chromatin-modifying enzymes and transcriptional regulators [80]. Among these metabolic regulators, glutamine has recently emerged as a pivotal immunometabolic node linking obesity to adipocyte inflammation. In adipocytes, glutamine depletion increases UDP-

GlcNAc and enhances O-GlcNAcylation of chromatin-bound proteins near inflammatory loci, thereby reinforcing transcription of pro-inflammatory genes [81,82]. In obesity, glutamine availability declines while glutaminase (GLS) activity rises, accelerating glutamine catabolism to glutamate, a metabolic shift that amplifies inflammatory signaling [83]. Crucially, HIF-1α directly upregulates GLS, establishing a mechanistic bridge between hypoxia-induced mitochondrial stress and glutamine-driven inflammatory reprogramming [84]. Elevated GLS activity enhances glutamate synthesis and its export via the cystine/glutamate antiporter xCT (Slc7a11). This glutamate-rich microenvironment, in turn, activates hypoxia-induced CXCL12, which recruits natural killer (NK) cells. NK cells respond by producing interferon-γ (IFN-γ) via mGluR5 activation triggered by extracellular glutamate. IFN-γ then reinforces xCT and CXCL12 expression in adipocytes, creating a self-perpetuating adipocyte-NK cell feedback loop that sustains macrophage activation and metabolic dysfunction [84] (Figure 4).

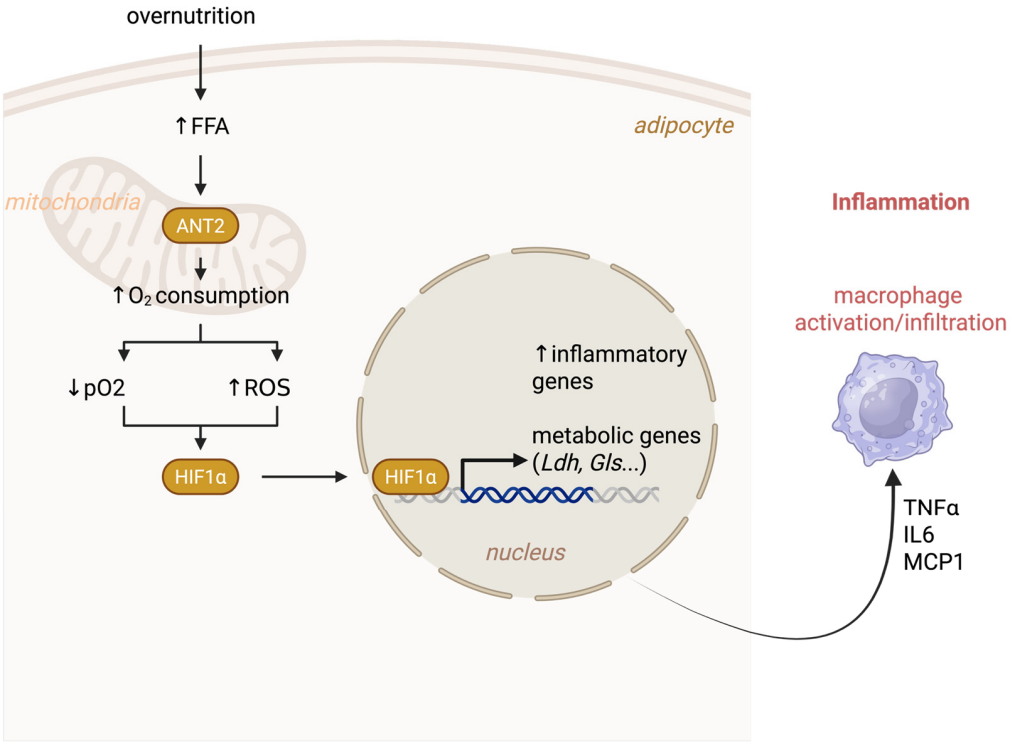

Figure 3. Mitochondrial Uncoupling and Hypoxia as Core Drivers of Adipocyte Dysfunction in Obesity. In lean adipose tissue, adipocytes are well oxygenated by the surrounding vasculature, allowing efficient coupled mitochondrial respiration. Protons are pumped from the mitochondrial matrix into the intermembrane space, generating the membrane potential required for ATP synthesis. Under these conditions, the adenine nucleotide translocase ANT2 remains minimally active, limiting proton leak and maintaining tightly coupled respiration—a metabolic state that preserves normal insulin sensitivity. In obesity, however, ANT2 activity increases, driving proton leak back into the mitochondrial matrix. This shift enhances uncoupled respiration, reduces mitochondrial membrane potential, and elevates oxygen demand despite a progressively inadequate oxygen supply. The resulting local hypoxia activates HIF1α, which in turn induces fibro-inflammatory gene programs and promotes metabolic reprogramming. Although initially adaptive, chronic activation of this pathway compromises adipocyte plasticity and accelerates tissue dysfunction. The persistent mismatch between oxygen availability and oxygen consumption triggers mitochondrial stress and fosters a fibro-inflammatory environment, ultimately contributing to insulin resistance, a defining feature of metabolic dysfunction in obese adipose tissue. FFA, free fatty acids; pO_2, partial pressure of oxygen;

HIF-1α, hypoxia-inducible factor 1 alpha; ROS, reactive oxygen species; ANT2, adenine nucleotide translocase 2; LDH, lactate dehydrogenase; GLS, glutaminase; TNFα, tumor necrosis factor alpha; IL-6, interleukin 6; MCP-1, monocyte chemoattractant protein 1 (CCL2). Created in BioRender. Lec, S. (2026) https://BioRender.com/mzxbcnh. (accessed on 2 January 2025).

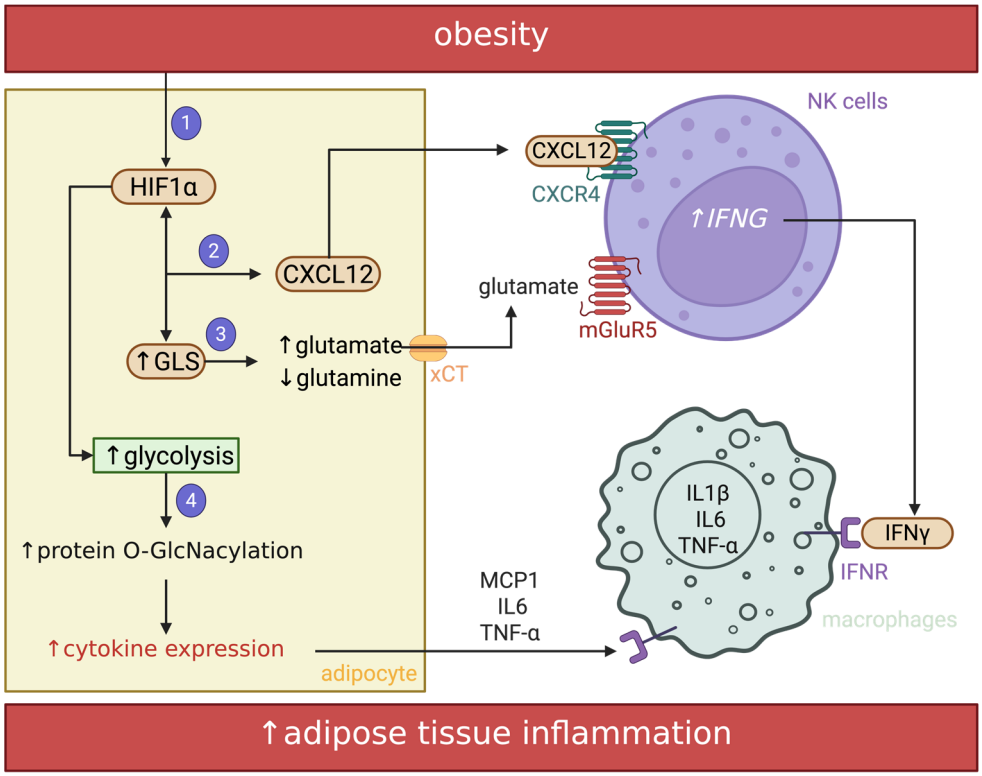

Figure 4. Metabolic circuit driving adipocyte inflammation. Nutrient overload induces local hypoxia in adipose tissue, leading to activation of HIF-1α (**1**) and the acquisition of a fibro-inflammatory adipocyte phenotype. This state is characterized by the overexpression of inflammatory genes, including CXCL12, which is secreted by adipocytes and binds to its receptor CXCR4 expressed on NK cells, thereby promoting IFN-γ production (**2**). Concomitantly, adipocytes undergo metabolic reprogramming marked by increased expression of glutaminase (GLS), enhancing glutamine hydrolysis to glutamate. Glutamate is then exported via the xCT transporter and activates NK cells through mGluR5, further stimulating IFN-γ production (**3**). IFN-γ subsequently promotes macrophage activation and the secretion of pro-inflammatory mediators. In parallel, glutamine depletion in adipocytes, together with increased glycolysis, leads to elevated protein O-GlcNAcylation, which enhances inflammatory gene expression. As a result, adipocytes secrete pro-inflammatory cytokines that further activate immune cells (**4**). Together, these pathways illustrate that adipocytes are not merely passive targets but are key active drivers of inflammation within adipose tissue. HIF-1α, hypoxia-inducible factor 1 alpha; CXCL12, C–X–C motif chemokine ligand 12; CXCR4, C–X–C chemokine receptor 4; NK cells, natural killer cells; IFN-γ, interferon gamma; GLS, glutaminase; xCT, cystine/glutamate antiporter (SLC7A11); mGluR5, metabotropic glutamate receptor 5; O-GlcNAcylation, O-linked β-N-acetylglucosamine modification; IL-6, interleukin 6; TNFα, tumor necrosis factor alpha; IL-1β, interleukin 1 beta. Created in BioRender. Lec, S. (2026) https://BioRender.com/mclp3ar. (accessed on 2 January 2025).

Hypoxic adipocytes also undergo a glycolytic shift, increasing lactate production to sustain ATP generation. Remarkably, adipocytes release substantial amounts of lactate even under normoxic conditions [85,86]. This "Warburg-like" metabolic adaptation persists in insulin-resistant adipocytes, suggesting that lactate production is a core feature of adipocyte metabolism rather than a byproduct of glucose overflow [85,86]. Functionally, lactate acts as a signaling metabolite. Adipocyte-derived lactate stabilizes HIF-1α in macrophages

by directly competing with α-ketoglutarate for binding to prolyl hydroxylase domain-containing 2 (PHD2), thereby promoting IL-1β expression. Accordingly, *Ldha* deletion, which blocks pyruvate-to-lactate conversion, confers protection against obesity-induced insulin resistance and inflammation, concomitantly reducing macrophages and IL-1β production in WAT [87]. Thus, lactate serves as a paracrine amplifier of inflammation linking adipocyte metabolism to immune cell activation (Figure 4).

Other studies have uncovered additional bioenergetic nodes in this inflammatory cascade. Phosphocreatine metabolism, traditionally regarded as a cellular energy buffer, emerges as a key determinant of adipocyte function. Creatine kinase B (CKB) catalyzes the reversible conversion of creatine to phosphocreatine, thereby maintaining the ATP/ADP ratio. In obesity, phosphocreatine turnover is disturbed, and CKB deficiency elevates ATP/ADP ratios and provokes adipose inflammation, identifying CKB as a gatekeeper of metabolic homeostasis [88]. Mechanistically, ER stress represses *CKB* transcription through the XBP1s–DNMT3A axis, promoting promoter methylation and reduced *CKB* gene expression [89]. Perturbation of this pathway upregulates pro-inflammatory cytokines such as CCL2 (MCP1), thereby integrating ER stress, creatine metabolism, and inflammatory signaling in white adipocytes [88–90] (Figure 4).

Downstream of metabolic reprogramming, the hypoxic adipocyte actively reshapes its microenvironment. HIF-1α activation in hypertrophic adipocytes drives excessive production of ECM components, particularly collagens I, IV, and VI, contributing to fibrosis and tissue stiffening [34,91,92]. What initially serves as an adaptive attempt to reinforce tissue integrity quickly degenerates into pathology: ECM accumulation is believed to restrict adipocyte expansion, perpetuating a vicious cycle of mechanical compression, local hypoxia, and chronic inflammation [93]. Functional studies reinforce this causal relationship. Collagen VI deletion in mice markedly reduces adipose inflammation and enhances insulin sensitivity despite persistent hypertrophy [94], whereas its excessive pericellular deposition fosters macrophage infiltration and crown-like structure (CLS) formation. Similarly, in humans, collagen VI upregulation correlates tightly with inflammation, insulin resistance, and metabolic dysregulation [95]. As fibrosis stiffens the adipose matrix, mechanical constraint itself becomes an inflammatory cue. Compression of hypertrophic adipocytes distorts mechano-transduction, disrupts insulin signaling, stimulates adipokine secretion, and perturbs lipid handling [23,96]. Remarkably, ex vivo compression alone recapitulates the inflammatory phenotype, demonstrating that mechanical load is sufficient to convert adipocytes into pro-inflammatory effectors [96] (Figure 4).

Together, these insights redefine adipocytes as active architects of their own inflammatory niche. By coupling hypoxic signaling to ECM remodeling and mechano-transduction, the adipocyte transforms from a passive energy reservoir into a dynamic inflammatory hub, orchestrating the metabolic, mitochondrial, and mechanical stress responses that drive systemic disease.

4. Adipokines: Direct Modulators of the Immune Status Within White Adipose Tissue

Since its initial identification in the 1980s by the Spiegelman lab, Adipsin emerged as the first characterized adipokine [97,98]. Adipokines, proteins secreted by adipocytes into the bloodstream, play key roles in regulating metabolic and immune functions. Subsequent studies revealed that Adipsin is identical to Complement Factor D (CFD), a crucial component in the alternative pathway of the complement system [99]. While most complement components are synthesized by hepatocytes, macrophages, or endothelial cells, Adipsin is almost exclusively produced by WAT under the control of PPARγ activation [60,100]. In experimental models, Adipsin-deficient mice (*Adipsin*$^{-/-}$) fed a high-fat diet gained

less weight than wild-type counterparts, exhibiting reduced inflammation in WAT, fewer macrophage CLS, and diminished mast cell numbers [101]. However, despite lower adiposity, these mice developed impaired glucose tolerance after 16 weeks of HFD feeding without changes in insulin sensitivity [101]. The cause of this glucose intolerance was linked to defective pancreatic β-cell function and reduced insulin secretion. Strikingly, restoring Adipsin levels in *db*/*db* mice using a recombinant adenoviral vector improved fasting blood glucose levels and glucose tolerance, an effect likely mediated by the protein C3a. This body of research underscores the complex role of Adipsin in both inflammation and glucose homeostasis. Although its complete in vivo function remains unclear, recent findings suggest that Adipsin also supports insulin secretion by pancreatic β-cells and protects these cells from apoptosis [101,102].

In 1993, TNFα was identified as a key pro-inflammatory cytokine produced by WAT, particularly in the context of obesity [103]. Early studies suggested adipocytes contributed to its production, but it is now clear that adipocytes are not the major source of TNFα. Instead, the predominant producers are macrophages and other immune cells within the stromal vascular fraction (SVF), which markedly expand in obese WAT. These immune-cell–derived TNFα signals act on neighboring adipocytes to amplify inflammation, impair insulin signaling, and reinforce metabolic dysfunction [104–106]. TNFα plays a critical role in impairing insulin signaling by suppressing key components such as the insulin receptor, insulin receptor substrate 1 (IRS-1), and GLUT4, thereby reducing insulin-stimulated glucose uptake in adipocytes and other insulin-sensitive tissues [107–109]. Additionally, in WAT, TNFα promotes the expression of genes involved in endoplasmic reticulum and oxidative stress responses, contributing to mitochondrial dysfunction and chronic inflammation [110]. Notably, TNFα signaling through TNF receptor 1 (TNFR1) can trigger pro-apoptotic pathways, leading to caspase-8 and caspase-3 activation, adipocyte cell death, and further exacerbation of adipose tissue inflammation [111]. Studies in animal models have demonstrated improved insulin sensitivity following TNFα neutralization, underscoring its pivotal role in metabolic dysfunction associated with obesity [103,112,113]. A similar upregulation of TNFα in WAT has been observed in humans with obesity, suggesting a direct link between higher TNFα levels, increased adiposity, and insulin resistance [113]. However, clinical trials using TNFα blocking antibodies in insulin-resistant humans have been disappointing, as single injections failed to elicit improvements in metabolic and clinical markers of insulin resistance [114–116].

One of the most significant advancements in understanding the role of WAT in regulating immunometabolism was the identification of the genetic forms of obesity and related syndromes [117]. In 1994, Friedman and collaborators discovered the *ob* gene, which encodes leptin, a cytokine-like hormone named from the Greek word “leptos,” which means “thin” [118]. Leptin is “exclusively” secreted by adipocytes [118]. Mutations in the *ob* gene result in a lack of leptin production, leading to excessive eating, weight gain, and disruptions in fertility and thermoregulation [118–120]. Exogenous Leptin administration can correct these symptoms in *ob*/*ob* mice [120,121]. Likewise, in *ob*/*ob* mice, leptin treatment also reduces food intake and causes significant weight loss in humans with leptin gene mutations [121–125]. However, individuals with common forms of obesity typically exhibit elevated plasma leptin levels compared to lean controls, reflecting a state of leptin resistance [126,127]. Recent studies by Scherer and colleagues revealed that elevated leptin levels can contribute to metabolic disorders [128]. Conversely, partial reduction in circulating leptin in obesity can restore leptin sensitivity in the hypothalamus, leading to reduced weight gain and enhanced insulin sensitivity [128]. Beyond its metabolic functions, leptin exerts a broad immunomodulatory effect [129]. Leptin deficiency increases susceptibility to severe responses to lipopolysaccharide (LPS) or TNFα, although this effect

can be partially alleviated by leptin treatment [130]. In leptin-deficient mice, macrophages exhibit impaired phagocytosis and altered cytokine production [131,132]. Leptin treatment of CD4+ T cells enhances the production of pro-inflammatory cytokines originating from T helper 1 (Th1), such as interferon gamma (IFN-γ) and IL-2, and suppresses production of the T helper 2 (Th2) cytokine, IL-4 [133]. Additionally, activated CD4+ T cells from T cell-specific leptin receptor knockout mice produce markedly less IFN-γ compared to wild-type counterparts [134]. These findings collectively suggest that leptin drives pro-inflammatory cytokine production in CD4+ T cells. Furthermore, leptin facilitates the differentiation of pro-inflammatory CD4+ Th1 cells. These data reinforce the dual metabolic and immune roles of leptin (Figure 5).

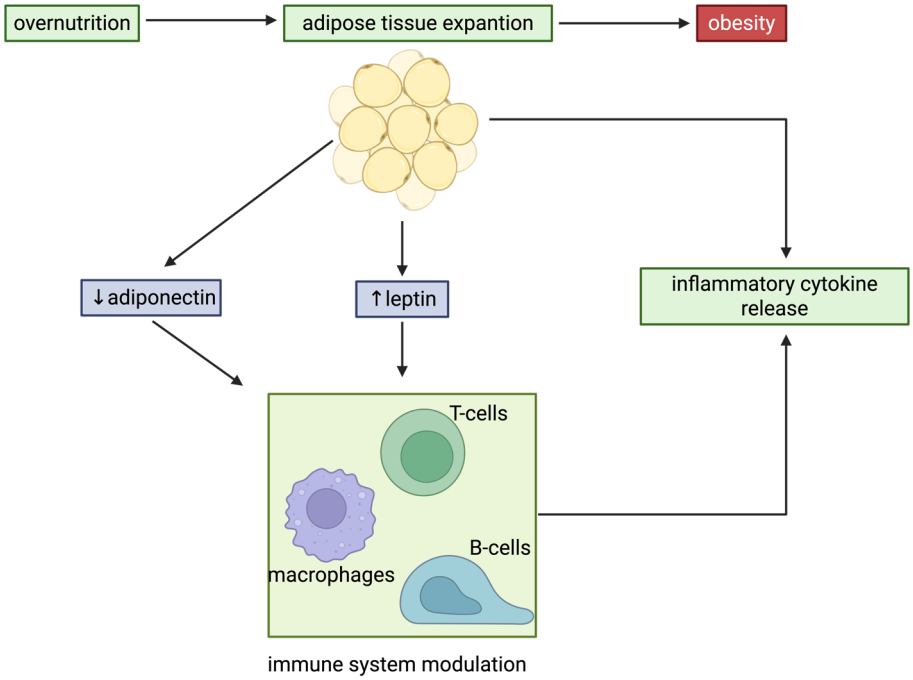

Figure 5. Leptin-driven immune inflammation during adipose tissue expansion. Overnutrition promotes adipose tissue expansion, leading to increased leptin expression and secretion by adipocytes. Adipocyte-derived leptin stimulates pro-inflammatory cytokine production by both innate and adaptive immune cells, thereby creating an inflammatory milieu that contributes to systemic metabolic dysregulation. In parallel, adipocyte secretion of adiponectin, an adipokine with anti-inflammatory properties, is reduced. Created in BioRender. Lec, S. (2026) https://BioRender.com/88e0jzr. (accessed on 2 January 2025).

In contrast to leptin, adiponectin is an essential adipokine that is markedly reduced in obesity and exhibits anti-inflammatory effects and insulin-sensitizing effects [135–139]. Produced almost exclusively by mature adipocytes, adiponectin plays a central role in modulating inflammation and metabolism [139]. In *ob*/*ob* mice that overexpress adiponectin, there is an enhanced capacity for subcutaneous WAT expansion, which is associated with attenuated inflammation and reduced ectopic lipid accumulation in the liver and skeletal muscle [140]. These metabolic improvements lead to improved insulin sensitivity despite the increased WAT mass [140]. Within the innate immune system, adiponectin primarily affects macrophages by promoting anti-inflammatory M2-like polarization and decreasing the abundance of pro-inflammatory M1-like macrophages [141]. Additionally, adiponectin reduces neutrophil phagocytic capacity, promotes neutrophil survival, and limits the production of interferon γ (IFNγ) and interleukin 17 (IL-17) in CD4+ T cells [142]. These effects highlight adiponectin's role in counterbalancing inflammation and improving metabolic outcomes (Figure 5).

Adipocytes recruit immune cells into WAT by producing a spectrum of pro-inflammatory cytokines and chemokines such as interleukin (IL)-6, IL8, CXCL2, and chemokine (C-C motif) ligand 2 (CCL2)/monocyte chemoattractant protein 1 (MCP1), whose gene expression and protein secretion are markedly increased in obesity [3]. In both humans and mice, adipocyte-derived MCP1 is markedly increased and represents a key mediator of macrophage infiltration into AT during obesity [143–145]. MCP1 appears to be particularly important, as it has been proposed to initiate adipose inflammation by recruiting inflammatory cells from the bloodstream into WAT [144,146]. Studies in mice demonstrate that MCP1 production and signaling are determinants for the onset and progression of WAT inflammation [20]. Although a number of different cell types in WAT may produce MCP1, adipocytes are of particular interest, as adipocyte-derived MCP1 can sustain local inflammation independently of macrophages or leukocytes in human WAT [147].

5. Role of Adipocyte-Derived Extracellular Vesicles in White Adipose Tissue Inflammation

Adipocytes also secrete EVs, which serve as a novel and highly dynamic mode of intercellular communication with other cells and tissues [148–151]. These EVs contain a variety of bioactive substances, including adipokines, lipids, microRNAs (miRNAs), and even mitochondria [152–154]. These components play crucial roles in influencing inflammation and metabolism both locally and throughout the body. One of the most abundant adipokines found in WAT-derived EVs is adiponectin, which retains its insulin-sensitizing and anti-inflammatory properties when delivered through EVs [152].

EVs are divided into two major subtypes: exosomes, which are 40–150 nm in size and formed through endosomal trafficking and exocytosis, and microvesicles, which are 100–1000 nm and generated by direct budding from the cell membrane [155]. EV release is enhanced in obesity but suppressed by caloric restriction or lipodystrophy [150]. A HFD, particularly enriched with palmitate, strongly stimulates EV release [150]. EVs are taken up by target cells via endocytosis, pinocytosis, or phagocytosis, guided by surface adhesion molecules that confer cell-type specificity [156]. Adipocytes represent a major source of circulating miRNAs, with over 60% of EV-derived miRNAs in mice originating from adipocytes [157]. This allows adipocytes to control protein production in other cells through post-transcriptional regulation.

In mice, miRNAs within adipocyte-derived EVs regulate the inflammasome activation, IL-1β production, and macrophage polarization, and influence insulin secretion from pancreatic β cells, thereby linking adipocyte-derived EV signaling to systemic metabolic and inflammatory homeostasis [158,159]. In humans, this regulatory axis appears to shift toward pathology in the setting of obesity. EVs released from adipose tissue, particularly from visceral depots, of individuals with obesity amplify inflammatory responses by stimulating macrophages to produce pro-inflammatory cytokines [160]. These findings underscore the dual nature of adipocyte-derived EVs, which can act as finely tuned regulators of metabolic homeostasis under physiological conditions but become powerful drivers of chronic inflammation and metabolic disease when adipose tissue function is disrupted.

A particularly striking discovery is that adipose-derived EVs can carry mitochondria. This finding extends the concept of mitochondria from static intracellular energy producers to transferable organelles capable of intercellular exchange—a phenomenon termed intercellular mitochondrial transfer [161]. Mitochondrial extrusion via EVs, demonstrable in organelle-tracking mouse models, depends strongly on mitophagy and other quality-control pathways. It is typically activated under conditions of autophagy deficiency, serving as an alternative mechanism to remove dysfunctional organelles. Enlarged adipocytes with

mitochondrial dysfunction and impaired autophagic flux [162] are major contributors to mitochondria-containing EVs, which are enriched in phosphatidylglycerol, a mitochondrial phospholipid precursor for cardiolipin synthesis [163]. Importantly, mitochondria-bearing EVs are actively internalized by resident macrophages, promoting their anti-inflammatory polarization [164]. This regulatory axis, however, becomes disrupted under nutrient excess: dietary lipid overload increases the efflux of adipose-derived EVs into the circulation [165], leading to phosphatidylglycerol dysregulation and contributing to the systemic inflammatory milieu characteristic of obesity [166].

6. Adipocyte Antigen Presentation and Adaptive Immunity

Both adipocytes and macrophages play crucial roles in shaping adaptive immune responses within WAT. Selective knockout of the MHCII pathway, responsible for antigen presentation, has revealed that adipocytes and macrophages contribute comparably to this immune function [167,168]. Interestingly, in both humans and mice, the expression of the MHCII pathway in adipocytes rises sharply within as little as two weeks of a HFD in lean subjects [169]. This early activation occurs in both subcutaneous and visceral fat depots, indicating that adipocytes act as early initiators of immune activation and inflammatory signaling in response to dietary stress [169]. The importance of adipocyte antigen presentation has been further underscored by genetic studies in murine models. Adipocyte-specific deletion of H2Ab1, a key component of the MHCII antigen presentation, significantly attenuates inflammation in WAT and improves insulin sensitivity under obese conditions [170]. Remarkably, this phenotype was independent of the T regulatory cells (Treg) abundance within WAT, suggesting that adipocyte-derived MHCII signaling specifically contributes to pro-inflammatory changes associated with obesity [170]. In contrast to macrophages, adipocytes appear to be the primary responders initiating this process, whereas macrophage participations emerge at later stages of pathological progression.

7. Adipocyte Apoptosis as a Catalyst of Inflammation in White Adipose Tissue

Adipocyte death is a critical early event that triggers macrophage infiltration into WAT, thereby contributing to the onset and progression of insulin resistance in obesity, as observed in both humans and mice [171]. Dying adipocytes release a spectrum of pro-inflammatory signals that recruit immune cells to the tissue, driving local inflammation [172]. In the obese state, this inflammatory milieu sustains and amplifies adipocyte demise by engaging multiple programmed cell death pathways, including pyroptosis, apoptosis, and necroptosis, collectively referred to as PANoptosis, or inflammatory cell death [173–177]. This phenomenon is particularly prominent in obesity, where macrophages surround apoptotic adipocytes, forming characteristic CLS [178]. Among the key mediators in this process is the NOD-like receptor (NLR), a family of pattern recognition receptors (PRRs) expressed in macrophages, which sense damage-associated molecular patterns (DAMPs) released from stressed or dying adipocytes [179,180]. In macrophages, NLR activation leads to the formation of the inflammasome, a multiprotein complex that activates caspase-1, leading to the cleavage of pro-IL-1β and pro-IL-18 [181]. Diet-induced obesity enhances the production of caspase-1 and IL-1β in WAT, thereby exacerbating local inflammation [182].

One of the key molecular regulators of adipocyte apoptosis is caspase-8, which has both apoptotic and non-apoptotic functions. Caspase-8 is a key initiator of the death receptor (DR)-mediated extrinsic apoptosis pathway [183]. In this signaling cascade, Fas, a prototypical DR, binds to its ligand FasL, leading to the recruitment of Fas-associated death domain (FADD) and caspase-8, forming the death-inducing signaling complex (DISC).

Caspase-8 is subsequently activated through auto-cleavage and, in turn, activates caspase-3, which executes programmed cell death [184]. Experimental evidences indicate that caspase-8 expression is increased in the WAT of both humans and mice in obesity, where it correlates with insulin resistance [185]. The FAT-ATTAC (Fat Apoptosis Through Targeted Activation of Caspase-8) mouse model has been instrumental in elucidating the role of caspase-8-mediated apoptosis in WAT. In this model, forced expression and dimerization-induced activation of caspase-8 trigger adipocyte death, leading to local inflammation and impaired glucose tolerance [186]. As a result of caspase-8 activation, there is an increase in macrophage infiltration into the WAT [187]. In contrast, adipocyte-specific knockdown of caspase-8 confers protection against glucose intolerance and weight gain in mice fed HFD. These mice display reduced WAT inflammation and diminished activation of both canonical and non-canonical NF-κB signaling pathways [185]. This indicates that caspase-8 plays a critical role in regulating both apoptosis and inflammation within WAT. Further research underscores the role of FADD, the adaptor protein involved in death receptor signaling, in modulating WAT inflammation and metabolism. Adipocyte-specific deletion of FADD reduces inflammation and enhances fatty acid oxidation via PPAR-α activation, thereby conferring resistance to HFD-induced obesity [188]. Moreover, FADD haploinsufficient mice ($Fadd^{+/-}$) exhibit reduced WAT mass and downregulated expression of adipogenic and lipogenic genes [189]. Cellular studies corroborate these findings; in vitro inhibition of FADD impairs adipocyte differentiation and suppresses the expression of adipogenic and lipogenic genes in cultured adipocytes. Conversely, overexpression of FADD accelerates adipocyte apoptosis [189]. These findings suggest that FADD not only promotes apoptosis but also regulates lipid metabolism and adipocyte differentiation. In conclusion, adipocyte death, driven by molecular regulators such as caspase-8 and FADD, fuels local inflammation and impacts systemic metabolism.

8. Preadipocytes: Immune-like Cells

In murine WAT, two main functionally distinct groups of adipose progenitor cells (APCs) residing within major WAT depots (inguinal and perigonadal) have been identified. The first group, commonly referred to as "preadipocytes," exhibits a robust potential for adipogenesis both in vitro and in vivo, and is characterized by enriched expression of *Pparg* and other markers associated with terminal adipocyte differentiation [33,190–192]. The second group, known as "fibro-inflammatory" progenitors (FIPs), shows less commitment to adipocyte differentiation [36,37,193]. Instead, these cells are distinguished by a fibro-inflammatory phenotype, actively secreting extracellular matrix components and pro-inflammatory cytokines [36]. These APCs are predominantly found in interstitial niches, often in proximity to blood vessels and lymphatics [190,193]. This strategic spatial arrangement enables them to sense metabolic cues and interact with vasculature-associated immune cells.

The signaling mechanisms from adipose stromal cells, including APCs, are critical in maintaining niches that support type 2 immune cells. Type 2 immunity mediates defense against helminths, contributes to allergic inflammation, and supports tissue homeostasis and repair. It involves innate cells such as group 2 innate lymphoid cells (ILC2s) and eosinophils, as well as adaptive type 2 helper T (Th2) cells, all characterized by the production of interleukins IL-4, IL-5, and IL-13 [194]. For instance, eosinophil recruitment into WAT is modulated by the chemokine CCL11, which is secreted by APCs in response to IL-4 and IL-13 [195] or by mature adipocytes following sympathetic activation [196]. IL-33 has emerged as a pivotal mediator in these niches, particularly in regulating anti-inflammatory Tregs and ILC2s [197]. Within WAT, PDGFRα+Pdpn+ APCs have been identified as the primary source of IL-33 [198,199]. These APCs not only facilitate the accumulation of

anti-inflammatory lymphocytes but also actively sustain a TH2 immune milieu, crucial for WAT homeostasis [198]. The switch in IL-33 source in aged WAT is associated with a senescence-like phenotype of ILC2, indicating that the cellular context of IL-33 production might impact ILC2 functionality and contribute to age-related metabolic dysfunction [200]. Thus, APCs serve as key orchestrators of type 2 immunity, playing an indispensable role in preserving WAT integrity and immune balance.

On the other hand, type 2 immune reaction is vital for WAT remodeling and plasticity of preadipocytes [194]. For example, IL-4Rα signaling in PDGFRα+ cells promotes the expansion of adipocyte precursors [201]. Additionally, adipose eosinophils, macrophages, and Th2 cells produce TGFβ cytokines [202–204], which drive proliferation over differentiation in APCs. However, once APCs commit to the adipocyte lineage (ICAM1+ preadipocytes), they become resistant to TGFβ's proliferative effects [205]. In addition, TGFβ3 has been identified as a specific regulator that enhances adipocyte precursor proliferation, thereby contributing to the homeostatic control of adipocyte number in vivo [206].

Thus, type 2 cytokines dynamically regulate the balance between APC proliferation and differentiation, enabling the tissue to adapt rapidly to changing conditions. This includes shifting toward hyperplasia rather than hypertrophy in response to excess calories. This adaptive mechanism highlights the critical role of type 2 inflammation in preserving the structural and functional flexibility of WAT.

9. Conclusions and Perspectives

White adipose tissue is now recognized as a dynamic immunometabolic organ in which adipocytes and their progenitors actively shape both local and systemic immune responses. Far from passive lipid stores, adipocytes act as endocrine and paracrine hubs, releasing adipokines, cytokines, lipids, and extracellular vesicles that regulate inflammation, insulin sensitivity, and tissue homeostasis. In obesity, chronic metabolic stress, hypoxia, and adipocyte death reprogram these cells toward a pro-inflammatory state, promoting immune cell recruitment and amplifying local and systemic metabolic dysfunction.

Despite these advances, key questions remain unresolved. What signals initiate adipose inflammation? Which cell types respond first, and how is this response coordinated over time? How do adipocytes, APCs, immune cells, and stromal elements communicate to support adipose expansion, and when does this initially adaptive response become maladaptive and pathological? Addressing these questions requires reframing adipocytes as active drivers, rather than passive targets, of immune–metabolic crosstalk. While this adipocyte-centric perspective simplifies an inherently complex system, it offers a powerful framework for understanding WAT dysfunction in obesity. Ultimately, resolving these interactions will require integrative, high-resolution approaches capable of capturing the spatial and temporal diversity of adipose-resident cells. Such insights are essential to understand how tissue homeostasis and plasticity are maintained and how chronic metabolic stress and aging disrupt this balance, driving fibrosis, immune dysregulation, and loss of metabolic resilience. Elucidating when and how this transition occurs will be critical for developing strategies to restore adipose tissue health in metabolic disease.

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References

1. Sakers, A.; De Siqueira, M.K.; Seale, P.; Villanueva, C.J. Adipose-tissue plasticity in health and disease. *Cell* **2022**, *185*, 419–446. [CrossRef] [PubMed]
2. Jacks, R.D.; Lumeng, C.N. Macrophage and T cell networks in adipose tissue. *Nat. Rev. Endocrinol.* **2024**, *20*, 50–61. [CrossRef] [PubMed]
3. Reilly, S.M.; Saltiel, A.R. Adapting to obesity with adipose tissue inflammation. *Nat. Rev. Endocrinol.* **2017**, *13*, 633–643. [CrossRef] [PubMed]
4. Lecoutre, S.; Rebière, C.; Maqdasy, S.; Lambert, M.; Dussaud, S.; Abatan, J.B.; Dugail, I.; Gautier, E.L.; Clément, K.; Marcelin, G. Enhancing adipose tissue plasticity: Progenitor cell roles in metabolic health. *Nat. Rev. Endocrinol.* **2025**, *21*, 272–288. [CrossRef]
5. Kane, H.; Lynch, L. Innate Immune Control of Adipose Tissue Homeostasis. *Trends Immunol.* **2019**, *40*, 857–872. [CrossRef]
6. Russo, L.; Lumeng, C.N. Properties and functions of adipose tissue macrophages in obesity. *Immunology* **2018**, *155*, 407–417. [CrossRef]
7. Mathis, D. Immunological goings-on in visceral adipose tissue. *Cell Metab.* **2013**, *17*, 851–859. [CrossRef]
8. Hagberg, C.E.; Spalding, K.L. White adipocyte dysfunction and obesity-associated pathologies in humans. *Nat. Rev. Mol. Cell Biol.* **2023**, *25*, 270–289. [CrossRef]
9. Bradley, D.; Deng, T.; Shantaram, D.; Hsueh, W.A. Orchestration of the Adipose Tissue Immune Landscape by Adipocytes. *Annu. Rev. Physiol.* **2024**, *86*, 199–223. [CrossRef]
10. Morigny, P.; Boucher, J.; Arner, P.; Langin, D. Lipid and glucose metabolism in white adipocytes: Pathways, dysfunction and therapeutics. *Nat. Rev. Endocrinol.* **2021**, *17*, 276–295. [CrossRef]
11. Deng, T.; Lyon, C.J.; Minze, L.J.; Lin, J.; Zou, J.; Liu, J.Z.; Ren, Y.; Yin, Z.; Hamilton, D.J.; Reardon, P.R.; et al. Class II major histocompatibility complex plays an essential role in obesity-induced adipose inflammation. *Cell Metab.* **2013**, *17*, 411–422. [CrossRef] [PubMed]
12. Samuel, V.T.; Shulman, G.I. The pathogenesis of insulin resistance: Integrating signaling pathways and substrate flux. *J. Clin. Investig.* **2016**, *126*, 12–22. [CrossRef] [PubMed]
13. Lumeng, C.N.; Saltiel, A.R. Inflammatory links between obesity and metabolic disease. *J. Clin. Investig.* **2011**, *121*, 2111–2117. [CrossRef] [PubMed]
14. Hotamisligil, G.S. Inflammation, metaflammation and immunometabolic disorders. *Nature* **2017**, *542*, 177–185. [CrossRef]
15. Kammoun, H.L.; Kraakman, M.J.; Febbraio, M.A. Adipose tissue inflammation in glucose metabolism. *Rev. Endocr. Metab. Disord.* **2014**, *15*, 31–44. [CrossRef]
16. Osborn, O.; Olefsky, J.M. The cellular and signaling networks linking the immune system and metabolism in disease. *Nat. Med.* **2012**, *18*, 363–374. [CrossRef]
17. Glass, C.K.; Olefsky, J.M. Inflammation and lipid signaling in the etiology of insulin resistance. *Cell Metab.* **2012**, *15*, 635–645. [CrossRef]
18. Rosen, E.D.; Kajimura, S. Is it time to rethink the relationship between adipose inflammation and insulin resistance? *J. Clin. Investig.* **2024**, *134*, e184663. [CrossRef]

19. Yan, K. Recent advances in the effect of adipose tissue inflammation on insulin resistance. *Cell. Signal.* **2024**, *120*, 111229. [CrossRef]
20. Kanda, H.; Tateya, S.; Tamori, Y.; Kotani, K.; Hiasa, K.; Kitazawa, R.; Kitazawa, S.; Miyachi, H.; Maeda, S.; Egashira, K.; et al. MCP-1 contributes to macrophage infiltration into adipose tissue, insulin resistance, and hepatic steatosis in obesity. *J. Clin. Investig.* **2006**, *116*, 1494–1505. [CrossRef]
21. Kraakman, M.J.; Kammoun, H.L.; Allen, T.L.; Deswaerte, V.; Henstridge, D.C.; Estevez, E.; Matthews, V.B.; Neill, B.; White, D.A.; Murphy, A.J.; et al. Blocking IL-6 trans-Signaling Prevents High-Fat Diet-Induced Adipose Tissue Macrophage Recruitment but Does Not Improve Insulin Resistance. *Cell Metab.* **2015**, *21*, 403–416. [CrossRef] [PubMed]
22. Patsouris, D.; Li, P.P.; Thapar, D.; Chapman, J.; Olefsky, J.M.; Neels, J.G. Ablation of CD11c-Positive Cells Normalizes Insulin Sensitivity in Obese Insulin Resistant Animals. *Cell Metab.* **2008**, *8*, 301–309. [CrossRef] [PubMed]
23. Lecoutre, S.; Lambert, M.; Drygalski, K.; Dugail, I.; Maqdasy, S.; Hautefeuille, M.; Clément, K. Importance of the Microenvironment and Mechanosensing in Adipose Tissue Biology. *Cells* **2022**, *11*, 2310. [CrossRef] [PubMed]
24. Zatterale, F.; Longo, M.; Naderi, J.; Raciti, G.A.; Desiderio, A.; Miele, C.; Beguinot, F. Chronic Adipose Tissue Inflammation Linking Obesity to Insulin Resistance and Type 2 Diabetes. *Front. Physiol.* **2020**, *10*, 1607. [CrossRef]
25. Shimobayashi, M.; Albert, V.; Woelnerhanssen, B.; Frei, I.C.; Weissenberger, D.; Meyer-Gerspach, A.C.; Clement, N.; Moes, S.; Colombi, M.; Meier, J.A.; et al. Insulin resistance causes inflammation in adipose tissue. *J. Clin. Investig.* **2018**, *128*, 1538–1550. [CrossRef]
26. Tam, C.S.; Viardot, A.; Clément, K.; Tordjman, J.; Tonks, K.; Greenfield, J.R.; Campbell, L.V.; Samocha-Bonet, D.; Heilbronn, L.K. Short-term overfeeding may induce peripheral insulin resistance without altering subcutaneous adipose tissue macrophages in humans. *Diabetes* **2010**, *59*, 2164–2170. [CrossRef]
27. Tian, X.Y.; Ganeshan, K.; Hong, C.; Nguyen, K.D.; Qiu, Y.; Kim, J.; Tangirala, R.K.; Tonotonoz, P.; Chawla, A. Thermoneutral Housing Accelerates Metabolic Inflammation to Potentiate Atherosclerosis but Not Insulin Resistance. *Cell Metab.* **2016**, *23*, 165–178. [CrossRef]
28. Zamarron, B.F.; Mergian, T.A.; Cho, K.W.; Martinez-Santibanez, G.; Luan, D.; Singer, K.; DelProposto, J.L.; Geletka, L.M.; Muir, L.A.; Lumeng, C.N. Macrophage proliferation sustains adipose tissue inflammation in formerly obese mice. *Diabetes* **2017**, *66*, 392–406. [CrossRef]
29. Cottam, M.A.; Caslin, H.L.; Winn, N.C.; Hasty, A.H. Multiomics reveals persistence of obesity-associated immune cell phenotypes in adipose tissue during weight loss and weight regain in mice. *Nat. Commun.* **2022**, *13*, 2950. [CrossRef]
30. Lee, Y.S.; Li, P.; Huh, J.Y.; Hwang, I.J.; Lu, M.; Kim, J.I.; Ham, M.; Talukdar, S.; Chen, A.; Lu, W.J.; et al. Inflammation is necessary for long-term but not short-term high-fat diet-induced insulin resistance. *Diabetes* **2011**, *60*, 2474–2483. [CrossRef]
31. Wernstedt Asterholm, I.; Tao, C.; Morley, T.S.; Wang, Q.A.; Delgado-Lopez, F.; Wang, Z.V.; Scherer, P.E. Adipocyte inflammation is essential for healthy adipose tissue expansion and remodeling. *Cell Metab.* **2014**, *20*, 103–118. [CrossRef]
32. Zhu, Q.; An, Y.A.; Kim, M.; Zhang, Z.; Zhao, S.; Zhu, Y.; Asterholm, I.W.; Kusminski, C.M.; Scherer, P.E. Suppressing adipocyte inflammation promotes insulin resistance in mice. *Mol. Metab.* **2020**, *39*, 101010. [CrossRef]
33. Ghaben, A.L.; Scherer, P.E. Adipogenesis and metabolic health. *Nat. Rev. Mol. Cell Biol.* **2019**, *20*, 242–258. [CrossRef]
34. Marcelin, G.; Gautier, E.L.; Clement, K. Adipose Tissue Fibrosis in Obesity: Etiology and Challenges. *Annu. Rev. Physiol.* **2022**, *84*, 135–155. [CrossRef] [PubMed]
35. Marcelin, G.; Silveira, A.L.M.; Martins, L.B.; Ferreira, A.V.M.; Clément, K. Deciphering the cellular interplays underlying obesity-induced adipose tissue fibrosis. *J. Clin. Investig.* **2019**, *129*, 4032–4040. [CrossRef] [PubMed]
36. Marcelin, G.; Ferreira, A.; Liu, Y.; Atlan, M.; Aron-Wisnewsky, J.; Pelloux, V.; Botbol, Y.; Ambrosini, M.; Fradet, M.; Rouault, C.; et al. A PDGFRα-Mediated Switch toward CD9high Adipocyte Progenitors Controls Obesity-Induced Adipose Tissue Fibrosis. *Cell Metab.* **2017**, *25*, 673–685. [CrossRef] [PubMed]
37. Hepler, C.; Shan, B.; Zhang, Q.; Henry, G.H.; Shao, M.; Vishvanath, L.; Ghaben, A.L.; Mobley, A.B.; Strand, D.; Hon, G.C.; et al. Identification of functionally distinct fibro-inflammatory and adipogenic stromal subpopulations in visceral adipose tissue of adult mice. *Elife* **2018**, *7*, e39636. [CrossRef]
38. Roh, H.C.; Kumari, M.; Taleb, S.; Tenen, D.; Jacobs, C.; Lyubetskaya, A.; Tsai, L.T.Y.; Rosen, E.D. Adipocytes fail to maintain cellular identity during obesity due to reduced PPARγ activity and elevated TGFβ-SMAD signaling. *Mol. Metab.* **2020**, *42*, 101086. [CrossRef]
39. Rodbell, M. Metabolism of isolated fat cells. I. effects of hormones on glucose metabolism and lipolysis. *J. Biol. Chem.* **1964**, *239*, 375–380. [CrossRef]
40. Cheng, L.; Zhang, S.; MacLennan, G.T.; Williamson, S.R.; Davidson, D.D.; Wang, M.; Jones, T.D.; Lopez-Beltran, A.; Montironi, R. Laser-assisted microdissection in translational research: Theory, technical considerations, and future applications. *Appl. Immunohistochem. Mol. Morphol. AIMM* **2013**, *21*, 31–47. [CrossRef]
41. Richardson, G.M.; Lannigan, J.; Macara, I.G. Does FACS perturb gene expression? *Cytometry A* **2015**, *87*, 166–175. [CrossRef] [PubMed]

42. Roh, H.C.; Tsai, L.T.-Y.; Lyubetskaya, A.; Tenen, D.; Kumari, M.; Rosen, E.D. Simultaneous Transcriptional and Epigenomic Profiling from Specific Cell Types within Heterogeneous Tissues In Vivo. *Cell Rep.* **2017**, *18*, 1048–1061. [CrossRef] [PubMed]
43. Bäckdahl, J.; Franzén, L.; Massier, L.; Li, Q.; Jalkanen, J.; Gao, H.; Andersson, A.; Bhalla, N.; Thorell, A.; Rydén, M.; et al. Spatial mapping reveals human adipocyte subpopulations with distinct sensitivities to insulin. *Cell Metab.* **2021**, *33*, 1869–1882.e6. [CrossRef] [PubMed]
44. Jones, J.E.C.; Rabhi, N.; Orofino, J.; Gamini, R.; Perissi, V.; Vernochet, C.; Farmer, S.R. The Adipocyte Acquires a Fibroblast-Like Transcriptional Signature in Response to a High Fat Diet. *Sci. Rep.* **2020**, *10*, 2380. [CrossRef]
45. Massier, L.; Jalkanen, J.; Elmastas, M.; Zhong, J.; Wang, T.; Nono Nankam, P.A.; Frendo-Cumbo, S.; Bäckdahl, J.; Subramanian, N.; Sekine, T.; et al. An integrated single cell and spatial transcriptomic map of human white adipose tissue. *Nat. Commun.* **2023**, *14*, 1438. [CrossRef]
46. Emont, M.P.; Jacobs, C.; Essene, A.L.; Pant, D.; Tenen, D.; Colleluori, G.; Di Vincenzo, A.; Jørgensen, A.M.; Dashti, H.; Stefek, A.; et al. A single-cell atlas of human and mouse white adipose tissue. *Nature* **2022**, *603*, 926–933. [CrossRef]
47. Sárvári, A.K.; Van Hauwaert, E.L.; Markussen, L.K.; Gammelmark, E.; Marcher, A.B.; Ebbesen, M.F.; Nielsen, R.; Brewer, J.R.; Madsen, J.G.S.; Mandrup, S. Plasticity of Epididymal Adipose Tissue in Response to Diet-Induced Obesity at Single-Nucleus Resolution. *Cell Metab.* **2021**, *33*, 437–453.e5. [CrossRef]
48. Czech, M.P. Cellular basis of insulin insensitivity in large rat adipocytes. *J. Clin. Investig.* **1976**, *57*, 1523–1532. [CrossRef]
49. Olefsky, J.M. Effects of fasting on insulin binding, glucose transport, and glucose oxidation in isolated rat adipocytes: Relationships between insulin receptors and insulin action. *J. Clin. Investig.* **1976**, *58*, 1450–1460. [CrossRef]
50. Olefsky, J.M. Insensitivity of large rat adipocytes to the antilipolytic effects of insulin. *J. Lipid Res.* **1977**, *18*, 459–464. [CrossRef]
51. Pellegrinelli, V.; Carobbio, S.; Vidal-Puig, A. Adipose tissue plasticity: How fat depots respond differently to pathophysiological cues. *Diabetologia* **2016**, *59*, 1075–1088. [CrossRef] [PubMed]
52. Virtue, S.; Vidal-Puig, A. Adipose tissue expandability, lipotoxicity and the Metabolic Syndrome—An allostatic perspective. *Biochim. Biophys. Acta-Mol. Cell Biol. Lipids* **2010**, *1801*, 338–349. [CrossRef] [PubMed]
53. Frayn, K. Adipose tissue as a buffer for daily lipid flux. *Diabetologia* **2002**, *45*, 1201–1210. [CrossRef] [PubMed]
54. Sinton, M.C.; Kajimura, S. From fat storage to immune hubs: The emerging role of adipocytes in coordinating the immune response to infection. *FEBS J.* **2025**, *292*, 1868–1883. [CrossRef]
55. Kilicarslan, M.; de Weijer, B.A.; Simonyté Sjödin, K.; Aryal, P.; ter Horst, K.W.; Cakir, H.; Romijn, J.A.; Ackermans, M.T.; Janssen, I.M.; Berends, F.J.; et al. RBP4 increases lipolysis in human adipocytes and is associated with increased lipolysis and hepatic insulin resistance in obese women. *FASEB J.* **2020**, *34*, 6099–6110. [CrossRef]
56. Yang, R.Z.; Lee, M.J.; Hu, H.; Pollin, T.I.; Ryan, A.S.; Nicklas, B.J.; Snitker, S.; Horenstein, R.B.; Hull, K.; Goldberg, N.H.; et al. Acute-phase serum amyloid A: An inflammatory adipokine and potential link between obesity and its metabolic complications. *PLoS Med.* **2006**, *3*, 0884–0894. [CrossRef]
57. Moraes-Vieira, P.M.; Yore, M.M.; Sontheimer-Phelps, A.; Castoldi, A.; Norseen, J.; Aryal, P.; Sjödin, K.S.; Kahn, B.B. Retinol binding protein 4 primes the NLRP3 inflammasome by signaling through Toll-like receptors 2 and 4. *Proc. Natl. Acad. Sci. USA* **2020**, *117*, 31309–31318. [CrossRef]
58. Calkin, A.C.; Tontonoz, P. Transcriptional integration of metabolism by the nuclear sterol-activated receptors LXR and FXR. *Nat. Rev. Mol. Cell Biol.* **2012**, *13*, 213–224. [CrossRef]
59. Mikkelsen, T.S.; Xu, Z.; Zhang, X.; Wang, L.; Gimble, J.M.; Lander, E.S.; Rosen, E.D. Comparative epigenomic analysis of murine and human adipogenesis. *Cell* **2010**, *143*, 156–169. [CrossRef]
60. Tontonoz, P.; Hu, E.; Spiegelman, B.M. Stimulation of adipogenesis in fibroblasts by PPAR gamma 2, a lipid-activated transcription factor. *Cell* **1994**, *79*, 1147–1156. [CrossRef]
61. Tontonoz, P.; Spiegelman, B.M. Fat and Beyond: The Diverse Biology of PPARγ. *Annu. Rev. Biochem.* **2008**, *77*, 289–312. [CrossRef] [PubMed]
62. De Siqueira, M.K.; Li, G.; Zhao, Y.; Wang, S.; Ahn, I.S.; Tamboline, M.; Hildreth, A.D.; Larios, J.; Schcolnik-Cabrera, A.; Nouhi, Z.; et al. PPARγ-dependent remodeling of translational machinery in adipose progenitors is impaired in obesity. *Cell Rep.* **2024**, *43*, 114945. [CrossRef] [PubMed]
63. Lefterova, M.I.; Haakonsson, A.K.; Lazar, M.A.; Mandrup, S. PPAR gamma and the global map of adipogenesis and beyond. *Trends Endocrinol. Metab.* **2014**, *25*, 293–302. [CrossRef] [PubMed]
64. Corrales, P.; Vidal-Puig, A.; Medina-Gómez, G. PPARs and Metabolic Disorders Associated with Challenged Adipose Tissue Plasticity. *Int. J. Mol. Sci.* **2018**, *19*, 2124. [CrossRef]
65. Vidal-Puig, A.; Jimenez-Liñan, M.; Lowell, B.B.; Hamann, A.; Hu, E.; Spiegelman, B.; Flier, J.S.; Moller, D.E. Regulation of PPAR gamma gene expression by nutrition and obesity in rodents. *J. Clin. Investig.* **1996**, *97*, 2553–2561. [CrossRef]
66. Medina-Gomez, G.; Virtue, S.; Lelliott, C.; Boiani, R.; Campbell, M.; Christodoulides, C.; Perrin, C.; Jimenez-Linan, M.; Blount, M.; Dixon, J.; et al. The link between nutritional status and insulin sensitivity is dependent on the adipocyte-specific peroxisome proliferator-activated receptor-gamma2 isoform. *Diabetes* **2005**, *54*, 1706–1716. [CrossRef]

67. Lecoutre, S.; Pourpe, C.; Butruille, L.; Marousez, L.; Laborie, C.; Guinez, C.; Lesage, J.; Vieau, D.; Eeckhoute, J.; Gabory, A.; et al. Reduced PPARγ2 expression in adipose tissue of male rat offspring from obese dams is associated with epigenetic modifications. *FASEB J.* **2018**, *32*, 2768–2778. [CrossRef]
68. Delerive, P.; Fruchart, J.C.; Staels, B. Peroxisome proliferator-activated receptors in inflammation control. *J. Endocrinol.* **2001**, *169*, 453–459. [CrossRef]
69. Hou, Y.; Moreau, F.; Chadee, K. PPARγ is an E3 ligase that induces the degradation of NFκB/p65. *Nat. Commun.* **2012**, *3*, 1300. [CrossRef]
70. Pascual, G.; Fong, A.L.; Ogawa, S.; Gamliel, A.; Li, A.C.; Perissi, V.; Rose, D.W.; Willson, T.M.; Rosenfeld, M.G.; Glass, C.K. A SUMOylation-dependent pathway mediates transrepression of inflammatory response genes by PPAR-gamma. *Nature* **2005**, *437*, 759–763. [CrossRef]
71. Pedersen, D.J.; Guilherme, A.; Danai, L.V.; Heyda, L.; Matevossian, A.; Cohen, J.; Nicoloro, S.M.; Straubhaar, J.; Noh, H.L.; Jung, D.; et al. A Major Role of Insulin in Promoting Obesity-Associated Adipose Tissue Inflammation. *Mol. Metab.* **2015**, *4*, 507–518. [CrossRef] [PubMed]
72. Sakamoto, K.; Butera, M.A.; Zhou, C.; Maurizi, G.; Chen, B.; Ling, L.; Shawkat, A.; Patlolla, L.; Thakker, K.; Calle, V.; et al. Overnutrition causes insulin resistance and metabolic disorder through increased sympathetic nervous system activity. *Cell Metab.* **2025**, *37*, 121–137.e6. [CrossRef] [PubMed]
73. Zhao, S.; Li, N.; Zhu, Y.; Straub, L.; Zhang, Z.; Wang, M.Y.; Zhu, Q.; Kusminski, C.M.; Elmquist, J.K.; Scherer, P.E. Partial leptin deficiency confers resistance to diet-induced obesity in mice. *Mol. Metab.* **2020**, *37*, 100995. [CrossRef]
74. Czech, M.P. Insulin action and resistance in obesity and type 2 diabetes. *Nat. Med.* **2017**, *23*, 804–814. [CrossRef]
75. Pasarica, M.; Sereda, O.R.; Redman, L.M.; Albarado, D.C.; Hymel, D.T.; Roan, L.E.; Rood, J.C.; Burk, D.H.; Smith, S.R. Reduced Adipose Tissue Oxygenation in Human Obesity: Evidence for Rarefaction, Macrophage Chemotaxis, and Inflammation Without an Angiogenic Response. *Diabetes* **2009**, *58*, 718–725. [CrossRef]
76. Rausch, M.E.; Weisberg, S.; Vardhana, P.; Tortoriello, D.V. Obesity in C57BL/6J mice is characterized by adipose tissue hypoxia and cytotoxic T-cell infiltration. *Int. J. Obes.* **2008**, *32*, 451–463. [CrossRef]
77. Lee, Y.S.; Kim, J.; Osborne, O.; Oh, D.Y.; Sasik, R.; Schenk, S.; Chen, A.; Chung, H.; Murphy, A.; Watkins, S.M.; et al. Increased Adipocyte O_2 Consumption Triggers HIF-1α, Causing Inflammation and Insulin Resistance in Obesity. *Cell* **2014**, *157*, 1339–1352. [CrossRef]
78. Lee, K.Y.; Gesta, S.; Boucher, J.; Wang, X.L.; Kahn, C.R. The differential role of Hif1β/Arnt and the hypoxic response in adipose function, fibrosis, and inflammation. *Cell Metab.* **2011**, *14*, 491–503. [CrossRef]
79. Seo, J.B.; Riopel, M.; Cabrales, P.; Huh, J.Y.; Bandyopadhyay, G.K.; Andreyev, A.Y.; Murphy, A.N.; Beeman, S.C.; Smith, G.I.; Klein, S.; et al. Knockdown of Ant2 Reduces Adipocyte Hypoxia And Improves Insulin Resistance in Obesity. *Nat. Metab.* **2019**, *1*, 86–97. [CrossRef]
80. Reid, M.A.; Dai, Z.; Locasale, J.W. The impact of cellular metabolism on chromatin dynamics and epigenetics. *Nat. Cell Biol.* **2017**, *19*, 1298–1306. [CrossRef]
81. Petrus, P.; Lecoutre, S.; Dollet, L.; Wiel, C.; Sulen, A.; Gao, H.; Tavira, B.; Laurencikiene, J.; Rooyackers, O.; Checa, A.; et al. Glutamine Links Obesity to Inflammation in Human White Adipose Tissue. *Cell Metab.* **2020**, *31*, 375–390.e11. [CrossRef] [PubMed]
82. Lecoutre, S.; Maqdasy, S.; Petrus, P.; Ludzki, A.; Couchet, M.; Mejhert, N.; Rydén, M. Glutamine metabolism in adipocytes: A bona fide epigenetic modulator of inflammation. *Adipocyte* **2020**, *9*, 620–625. [CrossRef] [PubMed]
83. Lecoutre, S.; Maqdasy, S.; Rizo-Roca, D.; Renzi, G.; Vlassakev, I.; Alaeddine, L.M.; Higos, R.; Jalkanen, J.; Zhong, J.; Zareifi, D.S.; et al. Reduced adipocyte glutaminase activity promotes energy expenditure and metabolic health. *Nat. Metab.* **2024**, *6*, 1329–1346. [CrossRef] [PubMed]
84. Kim, H.H.; Shim, Y.R.; Kim, H.N.; Yang, K.; Ryu, T.; Kim, K.; Choi, S.E.; Kim, M.J.; Woo, C.; Chung, K.P.S.; et al. xCT-mediated glutamate excretion in white adipocytes stimulates interferon-γ production by natural killer cells in obesity. *Cell Rep.* **2023**, *42*, 112636. [CrossRef]
85. Digirolamo, M.; Newby, F.D.; Lovejoy, J. Lactate production in adipose tissue: A regulated function with extra-adipose implications. *FASEB J.* **1992**, *6*, 2405–2412. [CrossRef]
86. Krycer, J.R.; Quek, L.E.; Francis, D.; Fazakerley, D.J.; Elkington, S.D.; Diaz-Vegas, A.; Cooke, K.C.; Weiss, F.C.; Duan, X.; Kurdyukov, S.; et al. Lactate production is a prioritized feature of adipocyte metabolism. *J. Biol. Chem.* **2020**, *295*, 83–98. [CrossRef]
87. Feng, T.; Zhao, X.; Gu, P.; Yang, W.; Wang, C.; Guo, Q.; Long, Q.; Liu, Q.; Cheng, Y.; Li, J.; et al. Adipocyte-derived lactate is a signalling metabolite that potentiates adipose macrophage inflammation via targeting PHD2. *Nat. Commun.* **2022**, *13*, 5208. [CrossRef]
88. Maqdasy, S.; Lecoutre, S.; Renzi, G.; Frendo-Cumbo, S.; Rizo-Roca, D.; Moritz, T.; Juvany, M.; Hodek, O.; Gao, H.; Couchet, M.; et al. Impaired phosphocreatine metabolism in white adipocytes promotes inflammation. *Nat. Metab.* **2022**, *4*, 190–202. [CrossRef]

89. Renzi, G.; Vlassakev, I.; Hansen, M.; Higos, R.; Lecoutre, S.; Elmastas, M.; Hodek, O.; Moritz, T.; Alaeddine, L.M.; Frendo-Cumbo, S.; et al. Epigenetic suppression of creatine kinase B in adipocytes links endoplasmic reticulum stress to obesity-associated inflammation. *Mol. Metab.* **2025**, *92*, 102082. [CrossRef]
90. Renzi, G.; Higos, R.; Vlassakev, I.; Bello, A.A.; Omar-Hmeadi, M.; Hansen, M.; Merabtene, F.; Rouault, C.; Hodek, O.; Massier, L.; et al. Creatine kinase B regulates glycolysis and de novo lipogenesis pathways to control lipid accumulation during adipogenesis. *Cell Rep.* **2025**, *44*, 116489. [CrossRef]
91. Sun, K.; Tordjman, J.; Clément, K.; Scherer, P.E. Fibrosis and adipose tissue dysfunction. *Cell Metab.* **2013**, *18*, 470–477. [CrossRef] [PubMed]
92. Divoux, A.; Tordjman, J.; Lacasa, D.; Veyrie, N.; Hugol, D.; Aissat, A.; Basdevant, A.; Guerre-Millo, M.; Poitou, C.; Zucker, J.D.; et al. Fibrosis in human adipose tissue: Composition, distribution, and link with lipid metabolism and fat mass loss. *Diabetes* **2010**, *59*, 2817–2825. [CrossRef]
93. Halberg, N.; Khan, T.; Trujillo, M.E.; Wernstedt-Asterholm, I.; Attie, A.D.; Sherwani, S.; Wang, Z.V.; Landskroner-Eiger, S.; Dineen, S.; Magalang, U.J.; et al. Hypoxia-Inducible Factor 1 Induces Fibrosis and Insulin Resistance in White Adipose Tissue. *Mol. Cell. Biol.* **2009**, *29*, 4467–4483. [CrossRef] [PubMed]
94. Khan, T.; Muise, E.S.; Iyengar, P.; Wang, Z.V.; Chandalia, M.; Abate, N.; Zhang, B.B.; Bonaldo, P.; Chua, S.; Scherer, P.E. Metabolic Dysregulation and Adipose Tissue Fibrosis: Role of Collagen VI. *Mol. Cell. Biol.* **2009**, *29*, 1575–1591. [CrossRef] [PubMed]
95. Spencer, M.; Yao-Borengasser, A.; Unal, R.; Rasouli, N.; Gurley, C.M.; Zhu, B.; Peterson, C.A.; Kern, P.A. Adipose tissue macrophages in insulin-resistant subjects are associated with collagen VI and fibrosis and demonstrate alternative activation. *Am. J. Physiol. Endocrinol. Metab.* **2010**, *299*, E1016–E1027. [CrossRef]
96. Pellegrinelli, V.; Heuvingh, J.; Du Roure, O.; Rouault, C.; Devulder, A.; Klein, C.; Lacasa, M.; Clément, E.; Lacasa, D.; Clément, K. Human adipocyte function is impacted by mechanical cues. *J. Pathol.* **2014**, *233*, 183–195. [CrossRef]
97. Hunt, C.R.; Ro, J.H.S.; Dobson, D.E.; Min, H.Y.; Spiegelman, B.M. Adipocyte P2 gene: Developmental expression and homology of 5′-flanking sequences among fat cell-specific genes. *Proc. Natl. Acad. Sci. USA* **1986**, *83*, 3786–3790. [CrossRef]
98. Cook, K.S.; Groves, D.L.; Min, H.Y.; Spiegelman, B.M. A developmentally regulated mRNA from 3T3 adipocytes encodes a novel serine protease homologue. *Proc. Natl. Acad. Sci. USA* **1985**, *82*, 6480–6484. [CrossRef]
99. Rosen, B.S.; Cook, K.S.; Yaglom, J.; Groves, D.L.; Volanakis, J.E.; Damm, D.; White, T.; Spiegelman, B.M. Adipsin and complement factor D activity: An immune-related defect in obesity. *Science* **1989**, *244*, 1483–1487. [CrossRef]
100. Choy, L.N.; Rosen, B.S.; Spiegelman, B.M. Adipsin and an endogenous pathway of complement from adipose cells. *J. Biol. Chem.* **1992**, *267*, 12736–12741. [CrossRef]
101. Lo, J.C.; Ljubicic, S.; Leibiger, B.; Kern, M.; Leibiger, I.B.; Moede, T.; Kelly, M.E.; Chatterjee Bhowmick, D.; Murano, I.; Cohen, P.; et al. Adipsin is an adipokine that improves β cell function in diabetes. *Cell* **2014**, *158*, 41–53. [CrossRef] [PubMed]
102. Gómez-Banoy, N.; Guseh, J.S.; Li, G.; Rubio-Navarro, A.; Chen, T.; Poirier, B.A.; Putzel, G.; Rosselot, C.; Pabón, M.A.; Camporez, J.P.; et al. Adipsin preserves beta cells in diabetic mice and associates with protection from type 2 diabetes in humans. *Nat. Med.* **2019**, *25*, 1739–1747. [CrossRef] [PubMed]
103. Hotamisligil, G.; Shargill, N.; Spiegelman, B. Adipose Expression of Tumor Necrosis Factor α: Direct Role in Obesity-Linked Insulin Resistance. *Science* **1993**, *259*, 87–91. [CrossRef]
104. Weisberg, S.P.; Mccann, D.; Desai, M.; Rosenbaum, M.; Leibel, R.L.; Ferrante, A.W. Obesity is associated with macrophage accumulation. *J. Clin. Investig.* **2003**, *112*, 1796–1808. [CrossRef] [PubMed]
105. Xu, H.; Barnes, G.T.; Yang, Q.; Tan, G.; Yang, D.; Chou, C.J.; Sole, J.; Nichols, A.; Ross, J.S.; Tartaglia, L.A.; et al. Chronic inflammation in fat plays a crucial role in the development of obesity-related insulin resistance. *J. Clin. Investig.* **2003**, *112*, 1821–1830. [CrossRef]
106. Xu, H.; Teoman Uysal, K.; David Becherer, J.; Arner, P.; Hotamisligil, G.S. Altered tumor necrosis factor-α (TNF-α) processing in adipocytes and increased expression of transmembrane TNF-α in obesity. *Diabetes* **2002**, *51*, 1876–1883. [CrossRef]
107. Stephens, J.M.; Pekala, P.H. Transcriptional repression of the GLUT4 and C/EBP genes in 3T3-L1 adipocytes by tumor necrosis factor-α. *J. Biol. Chem.* **1991**, *266*, 21839–21845. [CrossRef]
108. Gao, Z.; Hwang, D.; Bataille, F.; Lefevre, M.; York, D.; Quon, M.J.; Ye, J. Serine phosphorylation of insulin receptor substrate 1 by inhibitor κB kinase complex. *J. Biol. Chem.* **2002**, *277*, 48115–48121. [CrossRef]
109. Ozes, O.N.; Akca, H.; Mayo, L.D.; Gustin, J.A.; Maehama, T.; Dixon, J.E.; Donner, D.B. A phosphatidylinositol 3-kinase/Akt/mTOR pathway mediates and PTEN antagonizes tumor necrosis factor inhibition of insulin signaling through insulin receptor substrate-1. *Proc. Natl. Acad. Sci. USA* **2001**, *98*, 4640–4645. [CrossRef]
110. Hotamisligil, G.S. Endoplasmic Reticulum Stress and the Inflammatory Basis of Metabolic Disease. *Cell* **2010**, *140*, 900–917. [CrossRef]
111. Rodríguez, A.; Gómez-Ambrosi, J.; Catalán, V.; Rotellar, F.; Valentí, V.; Silva, C.; Mugueta, C.; Pulido, M.R.; Vázquez, R.; Salvador, J.; et al. The ghrelin O-acyltransferase-ghrelin system reduces TNF-α-induced apoptosis and autophagy in human visceral adipocytes. *Diabetologia* **2012**, *55*, 3038–3050. [CrossRef]

112. Uysal, K.T.; Wiesbrock, S.M.; Marino, M.W.; Hotamisligil, G.S. Protection from obesity-induced insulin resistance in mice lacking TNF-alpha function. *Nature* **1997**, *389*, 610–614. [CrossRef]
113. Hotamisligil, G.S.; Arner, P.; Caro, J.F.; Atkinson, R.L.; Spiegelman, B.M. Increased adipose tissue expression of tumor necrosis factor-α in human obesity and insulin resistance. *J. Clin. Investig.* **1995**, *95*, 2409–2415. [CrossRef] [PubMed]
114. Paquot, N.; Castillo, M.J.; Lefèbvre, P.J.; Scheen, A.J. No Increased Insulin Sensitivity After a Single Intravenous Administration of a Recombinant Human Tumor Necrosis Factor Receptor: Fc Fusion Protein in Obese Insulin-Resistant Patients. *J. Clin. Endocrinol. Metab.* **2000**, *85*, 1316–1319. [PubMed]
115. Ofei, F.; Hurel, S.; Newkirk, J.; Sopwith, M.; Taylor, R. Effects of an Engineered Human anti-TNF-alpha Antibody (CDP571) on Insulin Sensitivity and Glycemic Control in Patients With NIDDM. *Diabetes* **1996**, *45*, 881–885. [CrossRef] [PubMed]
116. Di Rocco, P.; Manco, M.; Rosa, G.; Greco, A.V.; Mingrone, G. Lowered tumor necrosis factor receptors, but not increased insulin sensitivity, with infliximab. *Obes. Res.* **2004**, *12*, 734–739. [CrossRef]
117. Clément, K.; Ferré, P. Genetics and the pathophysiology of obesity. *Pediatr. Res.* **2003**, *53*, 721–725. [CrossRef]
118. Zhang, Y.; Proenca, R.; Maffei, M.; Barone, M.; Leopold, L.; Friedman, J.M. Positional cloning of the mouse obese gene and its human homologue. *Nature* **1994**, *372*, 425–432. [CrossRef]
119. Friedman, J. 20 YEARS OF LEPTIN: Leptin at 20: An overview. *J. Endocrinol.* **2014**, *223*, T1–T8. [CrossRef]
120. Friedman, J. The long road to leptin. *J. Clin. Investig.* **2016**, *126*, 4727–4734. [CrossRef]
121. Halaas, J.L.; Gajiwala, K.S.; Maffei, M.; Cohen, S.L.; Chait, B.T.; Rabinowitz, D.; Lallone, R.L.; Burley, S.K.; Friedman, J.M. Weight-reducing effects of the plasma protein encoded by the obese gene. *Science* **1995**, *269*, 543–546. [CrossRef]
122. Pelleymounter, M.A.; Cullen, M.J.; Baker, M.B.; Hecht, R.; Winters, D.; Boone, T.; Collins, F. Effects of the obese gene product on body weight regulation in ob/ob mice. *Science* **1995**, *269*, 540–543. [CrossRef] [PubMed]
123. Campfield, L.A.; Smith, F.J.; Guisez, Y.; Devos, R.; Burn, P. Recombinant mouse OB protein: Evidence for a peripheral signal linking adiposity and central neural networks. *Science* **1995**, *269*, 546–549. [CrossRef]
124. Stephens, T.W.; Basinski, M.; Bristow, P.K.; Bue-Valleskey, J.M.; Burgett, S.G.; Craft, L.; Hale, J.; Hoffmann, J.; Hsiung, H.M.; Kriauciunas, A.; et al. The role of neuropeptide Y in the antiobesity action of the obese gene product. *Nature* **1995**, *377*, 530–532. [CrossRef] [PubMed]
125. Weigle, D.S.; Bukowski, T.R.; Foster, D.C.; Holderman, S.; Kramer, J.M.; Lasser, G.; Lofton-Day, C.E.; Prunkard, D.E.; Raymond, C.; Kuijper, J.L. Recombinant ob protein reduces feeding and body weight in the ob/ob mouse. *J. Clin. Investig.* **1995**, *96*, 2065–2070. [CrossRef] [PubMed]
126. Schwartz, M.W.; Peskind, E.; Raskind, M.; Boyko, E.J.; Porte, D. Cerebrospinal fluid leptin levels: Relationship to plasma levels and to adiposity in humans. *Nat. Med.* **1996**, *2*, 589–593. [CrossRef]
127. Considine, R.V.; Sinha, M.K.; Heiman, M.L.; Kriauciunas, A.; Stephens, T.W.; Nyce, M.R.; Ohannesian, J.P.; Marco, C.C.; McKee, L.J.; Bauer, T.L.; et al. Serum Immunoreactive-Leptin Concentrations in Normal-Weight and Obese Humans. *N. Engl. J. Med.* **1996**, *334*, 292–295. [CrossRef]
128. Zhao, S.; Zhu, Y.; Schultz, R.D.; Li, N.; He, Z.; Zhang, Z.; Caron, A.; Zhu, Q.; Sun, K.; Xiong, W.; et al. Partial Leptin Reduction as an Insulin Sensitization and Weight Loss Strategy. *Cell Metab.* **2019**, *30*, 706–719.e6. [CrossRef]
129. Abella, V.; Scotece, M.; Conde, J.; Pino, J.; Gonzalez-Gay, M.A.; Gómez-Reino, J.J.; Mera, A.; Lago, F.; Gómez, R.; Gualillo, O. Leptin in the interplay of inflammation, metabolism and immune system disorders. *Nat. Rev. Rheumatol.* **2017**, *13*, 100–109. [CrossRef]
130. Faggioni, R.; Moser, A.; Feingold, K.R.; Grunfeld, C. Reduced leptin levels in starvation increase susceptibility to endtoxic shock. *Am. J. Pathol.* **2000**, *156*, 1781–1787. [CrossRef]
131. Gainsford, T.; Willson, T.A.; Metcalf, D.; Handman, E.; Mcfarlane, C.; Ng, A.; Nicola, N.A.; Alexander, W.S.; Hilton, D.J. Leptin can induce proliferation, differentiation, and functional activation of hemopoietic cells. *Proc. Natl. Acad. Sci. USA* **1996**, *93*, 14564–14568. [CrossRef] [PubMed]
132. Mancuso, P.; Gottschalk, A.; Phare, S.M.; Peters-Golden, M.; Lukacs, N.W.; Huffnagle, G.B. Leptin-Deficient Mice Exhibit Impaired Host Defense in Gram-Negative Pneumonia. *J. Immunol.* **2002**, *168*, 4018–4024. [CrossRef] [PubMed]
133. Lord, G.M.; Matarese, G.; Howard, J.K.; Baker, R.J.; Bloom, S.R.; Lechler, R.I. Leptin modulates the T-cell immune response and reverses starvation- induced immunosuppression. *Nature* **1998**, *394*, 897–901. [CrossRef]
134. Saucillo, D.C.; Gerriets, V.A.; Sheng, J.; Rathmell, J.C.; MacIver, N.J. Leptin Metabolically Licenses T Cells for Activation To Link Nutrition and Immunity. *J. Immunol.* **2014**, *192*, 136–144. [CrossRef] [PubMed]
135. Lindsay, R.S.; Funahashi, T.; Hanson, R.L.; Matsuzawa, Y.; Tanaka, S.; Tataranni, P.A.; Knowler, W.C.; Krakoff, J. Adiponectin and development of type 2 diabetes in the Pima Indian population. *Lancet* **2002**, *360*, 57–58. [CrossRef]
136. Yamauchi, T.; Kamon, J.; Waki, H.; Terauchi, Y.; Kubota, N.; Hara, K.; Mori, Y.; Ide, T.; Murakami, K.; Tsuboyama-Kasaoka, N.; et al. The fat-derived hormone adiponectin reverses insulin resistance associated with both lipoatrophy and obesity. *Nat. Med.* **2001**, *7*, 941–946. [CrossRef]

137. Stefan, N.; Vozarova, B.; Funahashi, T.; Matsuzawa, Y.; Weyer, C.; Lindsay, R.S.; Youngren, J.F.; Havel, P.J.; Pratley, R.E.; Bogardus, C.; et al. Plasma adiponectin concentration is associated with skeletal muscle insulin receptor tyrosine phosphorylation, and low plasma concentration precedes a decrease in whole-body insulin sensitivity in humans. *Diabetes* **2002**, *51*, 1884–1888. [CrossRef]
138. Scherer, P.E.; Williams, S.; Fogliano, M.; Baldini, G.; Lodish, H.F. A novel serum protein similar to C1q, produced exclusively in adipocytes. *J. Biol. Chem.* **1995**, *270*, 26746–26749. [CrossRef]
139. Wang, Z.V.; Scherer, P.E. Adiponectin, the past two decades. *J. Mol. Cell Biol.* **2016**, *8*, 93–100. [CrossRef]
140. Kim, J.-Y.; van de Wall, E.; Laplante, M.; Azzara, A.; Trujillo, M.E.; Hofmann, S.M.; Schraw, T.; Durand, J.L.; Li, H.; Li, G.; et al. Obesity-associated improvements in metabolic profile through expansion of adipose tissue. *J. Clin. Investig.* **2007**, *117*, 2621–2637. [CrossRef]
141. Ohashi, K.; Parker, J.L.; Ouchi, N.; Higuchi, A.; Vita, J.A.; Gokce, N.; Pedersen, A.A.; Kalthoff, C.; Tullin, S.; Sams, A.; et al. Adiponectin promotes macrophage polarization toward an anti-inflammatory phenotype. *J. Biol. Chem.* **2010**, *285*, 6153–6160. [CrossRef] [PubMed]
142. Surendar, J.; Frohberger, S.J.; Karunakaran, I.; Schmitt, V.; Stamminger, W.; Neumann, A.L.; Wilhelm, C.; Hoerauf, A.; Hübner, M.P. Adiponectin limits ifn-γ and il-17 producing cd4 t cells in obesity by restraining cell intrinsic glycolysis. *Front. Immunol.* **2019**, *10*, 2555. [CrossRef] [PubMed]
143. Sartipy, P.; Loskutoff, D.J. Monocyte chemoattractant protein 1 in obesity and insulin resistance. *Proc. Natl. Acad. Sci. USA* **2003**, *100*, 7265–7270. [CrossRef] [PubMed]
144. Weisberg, S.P.; Hunter, D.; Huber, R.; Lemieux, J.; Slaymaker, S.; Vaddi, K.; Charo, I.; Leibel, R.L.; Ferrante, A.W. CCR2 modulates inflammatory and metabolic effects of high-fat feeding. *J. Clin. Investig.* **2006**, *116*, 115–124. [CrossRef]
145. Bruun, J.M.; Lihn, A.S.; Pedersen, S.B.; Richelsen, B. Monocyte chemoattractant protein-1 release is higher in visceral than subcutaneous human adipose tissue (AT): Implication of macrophages resident in the AT. *J. Clin. Endocrinol. Metab.* **2005**, *90*, 2282–2289. [CrossRef]
146. Kamei, N.; Tobe, K.; Suzuki, R.; Ohsugi, M.; Watanabe, T.; Kubota, N.; Ohtsuka-Kowatari, N.; Kumagai, K.; Sakamoto, K.; Kobayashi, M.; et al. Overexpression of monocyte chemoattractant protein-1 in adipose tissues causes macrophage recruitment and insulin resistance. *J. Biol. Chem.* **2006**, *281*, 26602–26614. [CrossRef]
147. Meijer, K.; de Vries, M.; Al-Lahham, S.; Bruinenberg, M.; Weening, D.; Dijkstra, M.; Kloosterhuis, N.; van der Leij, R.J.; van der Want, H.; Kroesen, B.J.; et al. Human primary adipocytes exhibit immune cell function: Adipocytes prime inflammation independent of macrophages. *PLoS ONE* **2011**, *6*, e17154. [CrossRef]
148. Crewe, C.; Joffin, N.; Rutkowski, J.M.; Kim, M.; Zhang, F.; Towler, D.A.; Gordillo, R.; Scherer, P.E. An Endothelial-to-Adipocyte Extracellular Vesicle Axis Governed by Metabolic State. *Cell* **2018**, 695–708.e13. [CrossRef]
149. Kranendonk, M.E.G.; Visseren, F.L.J.; Van Balkom, B.W.M.; Nolte-'T Hoen, E.N.M.; Van Herwaarden, J.A.; De Jager, W.; Schipper, H.S.; Brenkman, A.B.; Verhaar, M.C.; Wauben, M.H.M.; et al. Human adipocyte extracellular vesicles in reciprocal signaling between adipocytes and macrophages. *Obesity* **2014**, *22*, 1296–1308. [CrossRef]
150. Flaherty, S.E.; Grijalva, A.; Xu, X.; Ables, E.; Nomani, A.; Ferrante, A.W. A lipase-independent pathway of lipid release and immune modulation by adipocytes. *Science* **2019**, *363*, 989–993. [CrossRef]
151. Ogawa, R.; Tanaka, C.; Sato, M.; Nagasaki, H.; Sugimura, K.; Okumura, K.; Nakagawa, Y.; Aoki, N. Adipocyte-derived microvesicles contain RNA that is transported into macrophages and might be secreted into blood circulation. *Biochem. Biophys. Res. Commun.* **2010**, *398*, 723–729. [CrossRef] [PubMed]
152. Blandin, A.; Amosse, J.; Froger, J.; Hilairet, G.; Durcin, M.; Fizanne, L.; Ghesquière, V.; Prieur, X.; Chaigneau, J.; Vergori, L.; et al. Extracellular vesicles are carriers of adiponectin with insulin-sensitizing and anti-inflammatory properties. *Cell Rep.* **2023**, *42*, 112866. [CrossRef] [PubMed]
153. Borcherding, N.; Brestoff, J.R. The power and potential of mitochondria transfer. *Nature.* **2023**, *623*, 283–291. [CrossRef] [PubMed]
154. Crewe, C.; Scherer, P.E. Intercellular and interorgan crosstalk through adipocyte extracellular vesicles. *Rev. Endocr. Metab. Disord.* **2022**, *23*, 61–69. [CrossRef]
155. Jeppesen, D.K.; Zhang, Q.; Franklin, J.L.; Coffey, R.J. Extracellular vesicles and nanoparticles: Emerging complexities. *Trends Cell Biol.* **2023**, *33*, 667–681. [CrossRef]
156. Mulcahy, L.A.; Pink, R.C.; Carter, D.R.F. Routes and mechanisms of extracellular vesicle uptake. *J. Extracell. Vesicles* **2014**, *3*, 24641. [CrossRef]
157. Thomou, T.; Mori, M.A.; Dreyfuss, J.M.; Konishi, M.; Sakaguchi, M.; Wolfrum, C.; Rao, T.N.; Winnay, J.N.; Garcia-Martin, R.; Grinspoon, S.K.; et al. Adipose-derived circulating miRNAs regulate gene expression in other tissues. *Nature* **2017**, *542*, 252. [CrossRef]
158. Pan, Y.; Hui, X.; Chong Hoo, R.L.; Ye, D.; Cheung Chan, C.Y.; Feng, T.; Wang, Y.; Ling Lam, K.S.; Xu, A. Adipocyte-secreted exosomal microRNA-34a inhibits M2 macrophage polarization to promote obesity-induced adipose inflammation. *J. Clin. Investig.* **2019**, *129*, 834–849. [CrossRef]

159. Zhang, Y.; Mei, H.; Chang, X.; Chen, F.; Zhu, Y.; Han, X. Adipocyte-derived microvesicles from obese mice induce M1 macrophage phenotype through secreted miR-155. *J. Mol. Cell Biol.* **2016**, *8*, 505–517. [CrossRef]
160. Lago-Baameiro, N.; Camino, T.; Vazquez-Durán, A.; Sueiro, A.; Couto, I.; Santos, F.; Baltar, J.; Falcón-Pérez, J.M.; Pardo, M. Intra and inter-organ communication through extracellular vesicles in obesity: Functional role of obesesomes and steatosomes. *J. Transl. Med.* **2025**, *23*, 207. [CrossRef]
161. Chandel, N.S.; Falk, M.J.; Santos, J.H.; Brestoff, J.R.; Lechuga-Vieco, A.V.; Sancak, Y.S.; Chen, Q.; Elorza, A.A.; Quintana-Cabrera, R. Mitochondria transfer. *Nat. Metab.* **2025**, *7*, 1716–1719. [CrossRef]
162. Soussi, H.; Reggio, S.; Alili, R.; Prado, C.; Mutel, S.; Pini, M.; Rouault, C.; Clément, K.; Dugail, I. DAPK2 Downregulation Associates With Attenuated Adipocyte Autophagic Clearance in Human Obesity. *Diabetes* **2015**, *64*, 3452–3463. [CrossRef] [PubMed]
163. Blandin, A.; Dugail, I.; Hilairet, G.; Ponnaiah, M.; Ghesquière, V.; Froger, J.; Ducheix, S.; Fizanne, L.; Boursier, J.; Cariou, B.; et al. Lipidomic analysis of adipose-derived extracellular vesicles reveals specific EV lipid sorting informative of the obesity metabolic state. *Cell Rep.* **2023**, *42*, 112169. [CrossRef] [PubMed]
164. Brestoff, J.R.; Wilen, C.B.; Moley, J.R.; Li, Y.; Zou, W.; Malvin, N.P.; Rowen, M.N.; Saunders, B.T.; Ma, H.; Mack, M.R.; et al. Intercellular Mitochondria Transfer to Macrophages Regulates White Adipose Tissue Homeostasis and Is Impaired in Obesity. *Cell Metab.* **2021**, *33*, 270–282.e8. [CrossRef]
165. Borcherding, N.; Jia, W.; Giwa, R.; Field, R.L.; Moley, J.R.; Kopecky, B.J.; Chan, M.M.; Yang, B.Q.; Sabio, J.M.; Walker, E.C.; et al. Dietary lipids inhibit mitochondria transfer to macrophages to divert adipocyte-derived mitochondria into the blood. *Cell Metab.* **2022**, *34*, 1499–1513.e8. [CrossRef] [PubMed]
166. Kayser, B.D.; Lhomme, M.; Prifti, E.; Da Cunha, C.; Marquet, F.; Chain, F.; Naas, I.; Pelloux, V.; Dao, M.C.; Kontush, A.; et al. Phosphatidylglycerols are induced by gut dysbiosis and inflammation, and favorably modulate adipose tissue remodeling in obesity. *FASEB J.* **2019**, *33*, 4741–4754. [CrossRef]
167. Blaszczak, A.M.; Bernier, M.; Wright, V.P.; Gebhardt, G.; Anandani, K.; Liu, J.; Jalilvand, A.; Bergin, S.; Wysocki, V.; Somogyi, A.; et al. Obesogenic Memory Maintains Adipose Tissue Inflammation and Insulin Resistance. *Immunometabolism* **2020**, *2*, e200023. [CrossRef]
168. Cho, K.W.; Morris, D.L.; delProposto, J.L.; Geletka, L.; Zamarron, B.; Martinez-Santibanez, G.; Meyer, K.A.; Singer, K.; O'Rourke, R.W.; Lumeng, C.N. An MHC II-dependent activation loop between adipose tissue macrophages and CD4+ T cells controls obesity-induced inflammation. *Cell Rep.* **2014**, *9*, 605–617. [CrossRef]
169. Bradley, D.; Smith, A.J.; Blaszczak, A.; Shantaram, D.; Bergin, S.M.; Jalilvand, A.; Wright, V.; Wyne, K.L.; Dewal, R.S.; Baer, L.A.; et al. Interferon gamma mediates the reduction of adipose tissue regulatory T cells in human obesity. *Nat. Commun.* **2022**, *13*, 5606. [CrossRef]
170. Blaszczak, A.M.; Wright, V.P.; Anandani, K.; Liu, J.; Jalilvand, A.; Bergin, S.; Nicoloro, S.M.; Czech, M.P.; Lafuse, W.; Deng, T.; et al. Loss of Antigen Presentation in Adipose Tissue Macrophages or in Adipocytes, but Not Both, Improves Glucose Metabolism. *J. Immunol.* **2019**, *202*, 2451–2459. [CrossRef]
171. Alkhouri, N.; Gornicka, A.; Berk, M.P.; Thapaliya, S.; Dixon, L.J.; Kashyap, S.; Schauer, P.R.; Feldstein, A.E. Adipocyte apoptosis, a link between obesity, insulin resistance, and hepatic steatosis. *J. Biol. Chem.* **2010**, *285*, 3428–3438. [CrossRef] [PubMed]
172. Hildebrandt, X.; Ibrahim, M.; Peltzer, N. Cell death and inflammation during obesity: "Know my methods, WAT(son)". *Cell Death Differ.* **2023**, *30*, 279–292. [CrossRef] [PubMed]
173. Leven, A.S.; Gieseler, R.K.; Schlattjan, M.; Schreiter, T.; Niedergethmann, M.; Baars, T.; Baba, H.A.; Özçürümez, M.K.; Sowa, J.P.; Canbay, A. Association of cell death mechanisms and fibrosis in visceral white adipose tissue with pathological alterations in the liver of morbidly obese patients with NAFLD. *Adipocyte* **2021**, *10*, 558–573. [CrossRef] [PubMed]
174. Giordano, A.; Murano, I.; Mondini, E.; Perugini, J.; Smorlesi, A.; Severi, I.; Barazzoni, R.; Scherer, P.E.; Cinti, S. Obese adipocytes show ultrastructural features of stressed cells and die of pyroptosis. *J. Lipid Res.* **2013**, *54*, 2423–2436. [CrossRef]
175. Gao, J.; Xiong, A.; Liu, J.; Li, X.; Wang, J.; Zhang, L.; Liu, Y.; Xiong, Y.; Li, G.; He, X. PANoptosis: Bridging apoptosis, pyroptosis, and necroptosis in cancer progression and treatment. *Cancer Gene Ther.* **2024**, *31*, 970–983. [CrossRef]
176. Deepa, S.S.; Unnikrishnan, A.; Matyi, S.; Hadad, N.; Richardson, A. Necroptosis increases with age and is reduced by dietary restriction. *Aging Cell* **2018**, *17*, e12770. [CrossRef]
177. Frühbeck, G.; Catalán, V.; Valentí, V.; Moncada, R.; Gómez-Ambrosi, J.; Becerril, S.; Silva, C.; Portincasa, P.; Escalada, J.; Rodríguez, A. FNDC4 and FNDC5 reduce SARS-CoV-2 entry points and spike glycoprotein S1-induced pyroptosis, apoptosis, and necroptosis in human adipocytes. *Cell. Mol. Immunol.* **2021**, *18*, 2457–2459. [CrossRef]
178. Murano, I.; Barbatelli, G.; Parisani, V.; Latini, C.; Muzzonigro, G.; Castellucci, M.; Cinti, S. Dead adipocytes, detected as crown-like structures, are prevalent in visceral fat depots of genetically obese mice. *J. Lipid Res.* **2008**, *49*, 1562–1568. [CrossRef]
179. Jin, C.; Flavell, R.A. Innate sensors of pathogen and stress: Linking inflammation to obesity. *J. Allergy Clin. Immunol.* **2013**, *132*, 287–294. [CrossRef]

180. Shi, Y.; Evans, J.E.; Rock, K.L. Molecular identification of a danger signal that alerts the immune system to dying cells. *Nature* **2003**, *425*, 516–521. [CrossRef]
181. Paik, S.; Kim, J.K.; Silwal, P.; Sasakawa, C.; Jo, E.K. An update on the regulatory mechanisms of NLRP3 inflammasome activation. *Cell. Mol. Immunol.* **2021**, *18*, 1141–1160. [CrossRef] [PubMed]
182. Vandanmagsar, B.; Youm, Y.H.; Ravussin, A.; Galgani, J.E.; Stadler, K.; Mynatt, R.L.; Ravussin, E.; Stephens, J.M.; Dixit, V.D. The NLRP3 inflammasome instigates obesity-induced inflammation and insulin resistance. *Nat. Med.* **2011**, *17*, 179–188. [CrossRef] [PubMed]
183. Muzio, M.; Chinnaiyan, A.M.; Kischkel, F.C.; O'Rourke, K.; Shevchenko, A.; Ni, J.; Scaffidi, C.; Bretz, J.D.; Zhang, M.; Gentz, R.; et al. FLICE, a novel FADD-homologous ICE/CED-3-like protease, is recruited to the CD95 (Fas/APO-1) death-inducing signaling complex. *Cell* **1996**, *85*, 817–827. [CrossRef] [PubMed]
184. Muzio, M.; Stockwell, B.R.; Stennicke, H.R.; Salvesen, G.S.; Dixit, V.M. An induced proximity model for caspase-8 activation. *J. Biol. Chem.* **1998**, *273*, 2926–2930. [CrossRef]
185. Luk, C.T.; Chan, C.K.; Chiu, F.; Shi, S.Y.; Misra, P.S.; Li, Y.Z.; Pollock-Tahiri, E.; Schroer, S.A.; Desai, H.R.; Sivasubramaniyam, T.; et al. Dual Role of Caspase 8 in Adipocyte Apoptosis and Metabolic Inflammation. *Diabetes* **2023**, *72*, 1751–1765. [CrossRef]
186. Pajvani, U.B.; Trujillo, M.E.; Combs, T.P.; Iyengar, P.; Jelicks, L.; Roth, K.A.; Kitsis, R.N.; Scherer, P.E. Fat apoptosis through targeted activation of caspase 8: A new mouse model of inducible and reversible lipoatrophy. *Nat. Med.* **2005**, *11*, 797–803. [CrossRef]
187. Fischer-Posovszky, P.; Wang, Q.A.; Asterholm, I.W.; Rutkowski, J.M.; Scherer, P.E. Targeted deletion of adipocytes by apoptosis leads to adipose tissue recruitment of alternatively activated M2 macrophages. *Endocrinology* **2011**, *152*, 3074–3081. [CrossRef]
188. Zhuang, H.; Wang, X.; Zha, D.; Gan, Z.; Cai, F.; Du, P.; Yang, Y.; Yang, B.; Zhang, X.; Yao, C.; et al. FADD is a key regulator of lipid metabolism. *EMBO Mol. Med.* **2016**, *8*, 895–918. [CrossRef]
189. Tang, J.; Ma, Y.; Li, M.; Liu, X.; Wang, Y.; Zhang, J.; Shu, H.; Liu, Z.; Zhang, C.; Fu, L.; et al. FADD regulates adipose inflammation, adipogenesis, and adipocyte survival. *Cell Death Discov.* **2024**, *10*, 323. [CrossRef]
190. Tang, W.; Zeve, D.; Suh, J.M.; Bosnakovski, D.; Kyba, M.; Hammer, R.E.; Tallquist, M.D.; Graff, J.M. White Fat Progenitor Cells Reside in the Adipose Vasculature. *Science* **2008**, *322*, 583–586. [CrossRef]
191. Zeve, D.; Tang, W.; Graff, J. Fighting fat with fat: The expanding field of adipose stem cells. *Cell Stem Cell* **2009**, *5*, 472–481. [CrossRef] [PubMed]
192. Berry, R.; Jeffery, E.; Rodeheffer, M.S. Perspective Weighing in on Adipocyte Precursors. *Cell Metab.* **2013**, *19*, 8–20. [CrossRef] [PubMed]
193. Cannavino, J.; Gupta, R.K. Mesenchymal stromal cells as conductors of adipose tissue remodeling. *Genes. Dev.* **2023**, *37*, 781. [CrossRef] [PubMed]
194. Kabat, A.M.; Pearce, E.L.; Pearce, E.J. Metabolism in type 2 immune responses. *Immunity* **2023**, *56*, 781–800. [CrossRef]
195. Rana, B.M.J.; Jou, E.; Barlow, J.L.; Rodriguez-Rodriguez, N.; Walker, J.A.; Knox, C.; Jolin, H.E.; Hardman, C.S.; Sivasubramaniam, M.; Szeto, A.; et al. A stromal cell niche sustains ILC2-mediated type-2 conditioning in adipose tissue. *J. Exp. Med.* **2019**, *216*, 1999–2009. [CrossRef]
196. Huang, Z.; Zhong, L.; Lee, J.T.H.; Zhang, J.; Wu, D.; Geng, L.; Wang, Y.; Wong, C.M.; Xu, A. The FGF21-CCL11 Axis Mediates Beiging of White Adipose Tissues by Coupling Sympathetic Nervous System to Type 2 Immunity. *Cell Metab.* **2017**, *26*, 493–508.e4. [CrossRef]
197. DiSpirito, J.R.; Mathis, D. Immunological contributions to adipose tissue homeostasis. *Semin. Immunol.* **2015**, *27*, 315–321. [CrossRef]
198. Spallanzani, R.G.; Zemmour, D.; Xiao, T.; Jayewickreme, T.; Li, C.; Bryce, P.J.; Benoist, C.; Mathis, D. Distinct immunocyte-promoting and adipocyte-generating stromal components coordinate adipose tissue immune and metabolic tenors. *Sci. Immunol.* **2019**, *4*, eaaw3658. [CrossRef]
199. Mahlakõiv, T.; Flamar, A.L.; Johnston, L.K.; Moriyama, S.; Putzel, G.G.; Bryce, P.J.; Artis, D. Stromal cells maintain immune cell homeostasis in adipose tissue via production of interleukin-33. *Sci. Immunol.* **2019**, *4*, eaax0416. [CrossRef]
200. Goldberg, E.L.; Shchukina, I.; Youm, Y.H.; Ryu, S.; Tsusaka, T.; Young, K.C.; Camell, C.D.; Dlugos, T.; Artyomov, M.N.; Dixit, V.D. IL-33 causes thermogenic failure in aging by expanding dysfunctional adipose ILC2. *Cell Metab.* **2021**, *33*, 2277–2287.e5. [CrossRef]
201. Lee, M.W.; Odegaard, J.I.; Mukundan, L.; Qiu, Y.; Molofsky, A.B.; Nussbaum, J.C.; Yun, K.; Locksley, R.M.; Chawla, A. Activated type 2 innate lymphoid cells regulate beige fat biogenesis. *Cell* **2015**, *160*, 74–87. [CrossRef]
202. Kabat, A.M.; Hackl, A.; Sanin, D.E.; Zeis, P.; Grzes, K.M.; Baixauli, F.; Kyle, R.; Caputa, G.; Edwards-Hicks, J.; Villa, M.; et al. Resident TH2 cells orchestrate adipose tissue remodeling at a site adjacent to infection. *Sci. Immunol.* **2022**, *7*, eadd3263. [CrossRef]
203. Nawaz, A.; Aminuddin, A.; Kado, T.; Takikawa, A.; Yamamoto, S.; Tsuneyama, K.; Igarashi, Y.; Ikutani, M.; Nishida, Y.; Nagai, Y.; et al. CD206+ M2-like macrophages regulate systemic glucose metabolism by inhibiting proliferation of adipocyte progenitors. *Nat. Commun.* **2017**, *8*, 286. [CrossRef]

204. Yu, X.; Hu, Y.; Lim, H.Y.; Li, Z.; Jaitin, D.A.; Yang, K.; Kong, W.T.; Xu, J.; Bejarano, D.A.; Bied, M.; et al. Septal LYVE1+ macrophages control adipocyte stem cell adipogenic potential. *Science* **2025**, *389*, eadg1128. [CrossRef]
205. Merrick, D.; Sakers, A.; Irgebay, Z.; Okada, C.; Calvert, C.; Morley, M.P.; Percec, I.; Seale, P. Identification of a mesenchymal progenitor cell hierarchy in adipose tissue. *Science* **2019**, *364*, 6438. [CrossRef]
206. Petrus, P.; Mejhert, N.; Corrales, P.; Lecoutre, S.; Li, Q.; Maldonado, E.; Kulyté, A.; Lopez, Y.; Campbell, M.; Acosta, J.R.; et al. Transforming Growth Factor-β3 Regulates Adipocyte Number in Subcutaneous White Adipose Tissue. *Cell Rep.* **2018**, *25*, 551–560.e5. [CrossRef]