



Published in final edited form as:

Sci Transl Med. 2023 November 22; 15(723): eadf9382. doi:10.1126/scitranslmed.adf9382.

Metaflammation in obesity and its therapeutic targeting

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Abstract

Obesity-associated inflammation is a systemic process that affects all metabolic organs. Prominent among these is adipose tissue, where cells of the innate and adaptive immune system are markedly changed in obesity, implicating these cells in a range of processes linking immune memory to metabolic regulation. Furthermore, weight loss and weight cycling have unexpected effects on adipose tissue immune populations. Here, we review the current literature on the roles of various immune cells in lean and obese adipose tissue. Within this context, we discuss pharmacological and nonpharmacological approaches to obesity treatment and their impact on systemic inflammation.

INTRODUCTION

Obesity [defined by body mass index (BMI) > 30 kg/m²] is highly prevalent worldwide, with more than 42% of the US population considered obese (1), and obesity rates have more than doubled in over 70 countries since 1980 (2). Obesity is a major risk factor for a constellation of noncommunicable diseases including cardiovascular disease, type 2 diabetes mellitus, and cancer (3). Although obesity is known to be associated with a heightened inflammatory milieu in all metabolic organs, a unifying mechanistic link between immune responses to obesity and cardiometabolic complications has been challenging to delineate, limiting the potential for therapeutic advancements. However, evidence continues to suggest that nutrient excess elicits a chronic low-grade inflammatory response that may underlie cardiometabolic complications, which has expanded into the study of “metaflammation”

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Competing interests: G.S. reports advisory fees from Rhythm Pharmaceuticals, Novo Nordisk, and Eli Lilly outside the submitted work. The other authors declare that they have no competing interests.

(4). Here, we present an overview of the links between obesity and inflammation, discuss the immunologic memory triggered by obesity, and review the metabolic response to nutrient oversupply in immune cells (immune cell bioenergetics). Last, we identify clinical approaches targeting obesity and their impact on inflammation.

OVERVIEW OF OBESITY-ASSOCIATED INFLAMMATION

Obesity is accompanied by chronic low-grade inflammation in metabolically impactful tissues such as adipose tissue (AT), liver, skeletal muscle, pancreatic islets, and the brain (Fig. 1). Inflammatory cytokine signaling can interfere with insulin signaling pathways leading to impaired glucose uptake and uncontrolled lipolysis, ultimately resulting in ectopic lipid storage and propagating insulin resistance in a vicious cycle. Although this Review will focus on AT, immune contributions to other organs are summarized in these excellent articles (4–8). AT immune cells serve a wide range of homeostatic functions that are modified upon obesity. In addition to the loss of their regulatory functions, heightened inflammatory phenotypes of immune cells in AT are typically met with systemic complications such as insulin resistance, hyperglycemia, and dyslipidemia—contributing to greater cardiometabolic disease risk. In addition, excessive pro-inflammatory cytokine release into the circulation is often present in obesity and metabolic syndrome, suggesting the induction of inflammatory processes as a clinical biomarker for metabolic disease risk (9). Thus, localized and systemic inflammatory processes provide potential targets for immune-mediated therapies to treat metabolic disease.

In mice, most studies have analyzed epididymal white AT from male animals. However, other visceral adipose depots (perirenal, mesenteric, and omental AT), as well as inguinal subcutaneous white AT and brown AT depots, may also be relevant to systemic dysfunction associated with AT inflammation. Furthermore, tissue-specific adipose depots such as perivascular and epicardial AT, as well as fat around skin and lymph nodes, are important for tissue homeostasis and may be altered in obesity, although their discussion is beyond the scope of this article. In humans, most studies have analyzed subcutaneous and omental white AT depots. Although the inflammatory response in AT is more extreme in mice, ample human data suggest that similar changes in the immune landscape occur in humans. For example, the number of macrophages in visceral AT is elevated in obese compared with lean individuals, associated with insulin resistance (10), and predictive of hemoglobin A1c (HbA1c) concentrations (11).

ADIPOSE TISSUE MACROPHAGES

Macrophage polarization

In a simplified and dichotomous paradigm, macrophages have been described as either classically activated M1-like or alternatively activated M2-like. These extreme states are based on *in vitro* polarization with cytokines in an effort to generate macrophage populations specialized to respond to environmental cues from stimuli within the tissues. M1-like macrophages defend against intracellular pathogens and are characterized by the production of pro-inflammatory cytokines [for example, interleukin-6 (IL-6), IL-1 β , and tumor necrosis factor- α (TNF- α)] and expression of inducible nitric oxide synthase

(iNOS). M2-like macrophages are induced by IL-4 and IL-13 and present a tissue-repair phenotype characterized by the release of anti-inflammatory cytokines [for example, IL-10, IL-12, and transforming growth factor- β (TGF- β)]. In contrast to in vitro stimulation of macrophage phenotypes, macrophages in vivo exist along a spectrum of polarization states, and individual cells can simultaneously express genes/proteins of both M1/M2 phenotypes (12, 13).

Macrophage polarization in AT has been an area of interest in the immunometabolism field. In AT of mice and humans, M1- and M2-like macrophages express immune cell surface markers F4/80, CD11b, and CD64 but also contain unique identifiers specific to their population. M1-like macrophages express CD11c in mice and humans (10, 14, 15) and major histocompatibility complex class II (MHCII) in mice (16), whereas M2-like signatures include CD206, CD163, and TIM4 in mice (17) and CD206 in humans (10, 11). Studies identifying macrophage subpopulations in obesity have also revealed dissimilarities between mice and humans (18). For example, subcutaneous AT CD206⁺ CD11c⁺ cells are positively associated with insulin resistance in humans, but this double-positive population may be less prevalent in mice (10, 19). As in other tissues, the simple M1/M2 dichotomy is not sufficient to explain the full range of macrophage phenotypes in AT. Fortunately, technological and analytical advances in single-cell RNA sequencing, mass cytometry, and spatial transcriptomics are emerging in the immunometabolism field (11, 19–22), allowing for the profiling of functionally diverse immune cell populations.

Additional insights into AT macrophage (ATM) polarization can be made when considering the local AT milieu, which is rich in lipids, glucose, and insulin. Thus, a metabolically activated (MMe) macrophage phenotype in obesity provides a more accurate description of the ATM polarization state than the “M1” nomenclature (12, 13). In vivo cell surface abundance of CD36, PLIN2, and ABCA1 in ATMs from humans with obesity is a signature of the lipid-handling functions of MMe cells (13). In vitro MMe macrophages can be generated by metabolic stimuli (palmitic acid, glucose, and insulin). A detailed description of the function of these lipid-handling macrophages in AT is provided below.

Specialized resident macrophage function in AT homeostasis

Macrophages are the most abundant immune cell population in AT in both genetic and diet-induced obesity (23, 24). In the lean state, macrophages represent about 10% of all AT immune cells and can expand to represent more than 40% of all immune cells in obesity (15, 23). Macrophages present a high degree of plasticity and readily adapt to environmental cues to preserve tissue homeostasis. The diversity of tissue-resident macrophage populations within tissues is indicative of their homeostatic functions ranging from tissue repair, clearance of cellular debris, and metabolic regulation. Specifically in AT, their functions include buffering lipids and other critical molecules, antigen presentation, and coordinating both intercellular and interorgan cross-talk.

Lipid uptake and partitioning—MMe polarization is characterized by the expression of lipid-handling genes and proteins (13). Similar lipid-handling ATM populations have also been identified by expression of CD9 (called CD9⁺ATMs) (25) and Trem2 [called

lipid-associated macrophages (LAMs)] (26). The association of lipid-laden ATMs with CD9 and Trem2 markers has also been identified in humans (11). MMe, CD9⁺, and LAMs in AT are proposed to aid in the uptake and storage of lipids in an effort to limit ectopic lipid accumulation. In addition to their transcriptional profile linked to lipid handling, they are also localized to crown-like structures to aid with lipid scavenging around dead adipocytes. Other studies of lipid-handling ATMs report transcriptional characteristics of lysosomal biogenesis and lysosomal-dependent lipid metabolism, suggesting that an autophagy-dependent mechanism is up-regulated to aid in dead adipocyte degradation and fatty acid recycling (27). ATM localization to crown-like structures around dead adipocytes, coupled with a transcriptional pattern for lipid uptake and catabolism, offers a unique role for lipid uptake and storage in ATMs. In addition, adipocytes have been shown to release lipid-filled exosomes that are sensed by immune cells and directly contribute to bone marrow-derived monocyte differentiation into an MMe-like phenotype (28). Although not intuitive that macrophages would be required to buffer lipids in AT when adipocytes themselves can store large amounts of triglyceride, the reports described here support this function for ATMs.

Iron handling—Iron is required for normal homeostatic functions but is detrimental when in excess. We have described a subset of iron-rich macrophages—coined MFe^{hi}—that protect adipocytes from iron overload through an intrinsic capacity for iron uptake and storage (29, 30). Obesity results in fewer MFe^{hi} cells and lower iron content within the MFe^{hi} cells with concurrent adipocyte overload, suggesting that iron handling by MFe^{hi} cells is important for adipocyte iron homeostasis (29). Furthermore, iron transfer between macrophages and adipocytes in coculture was accelerated when the macrophages were MMe-polarized, with a net increased iron accumulation in the adipocytes (31). Adipocyte iron concentrations are relevant to systemic metabolic health because adipocyte-specific overload via ferroportin deficiency results in glucose intolerance (32), whereas reducing adipocyte iron concentrations via transferrin receptor deficiency results in protection from obesity-related metabolic dysfunction (33). In addition, increased iron localization within the mitochondrial matrix of ATMs promotes an inflammatory phenotype in ATMs and directly elevates mitochondrial iron content in adipocytes. In contrast, low macrophage iron content is associated with an M2-like phenotype and improved glucose tolerance (34). Thus, published data strongly support the role of ATMs in AT iron homeostasis, which may be particularly important for limiting the oxidative stress and insulin resistance common in obesity.

Catecholamine uptake and catabolism—Sympathetic innervation by norepinephrine signaling robustly promotes lipolysis. Nerve-associated macrophages in AT have been termed sympathetic neuron-associated macrophages (SAMs) (35). SAMs have been reported to increase with obesity (35) and to decrease with aging (36). SAMs are localized to nerve bundles, and their role is to coordinate sympathetic tone by regulating norepinephrine uptake and catabolism. In the context of obesity, increased activation and recruitment of SAMs to AT aim to protect from norepinephrine spillover. Ablation of the ability of SAMs to endocytose and degrade norepinephrine results in the browning of white fat and weight loss (35). Furthermore, this cell population appears to be conserved in humans (35), making it

a potential target for weight loss. The decline of SAMs with aging also provides a partial explanation for why aging humans have a defect in white AT lipolysis (36). Given the link between catecholamine and lipid metabolism, SAMs appear to be an important immune cell population poised to limit lipolysis from AT by catecholamines and likely preserve further glucose intolerance in obesity and aging.

Antigen presentation—Another intriguing function of ATMs is antigen presentation, which should not come as a surprise given the existence of memory CD4⁺ and CD8⁺ T cells in AT (described further below). Murine ATMs express MHCII and human ATMs express *HLA-D*, indicative of antigen presentation capability (11). Interestingly, the antigen presentation markers *CD1A-E* are elevated in lipid-rich CD11c⁺ ATMs. In mouse models, a dynamic interaction between ATMs and CD4⁺ T cells was demonstrated, and deficiency of MHCII resulted in fewer CD4⁺ T cells in the AT (37). Furthermore, the transfer of activated antigen-presenting cells into lean mice results in AT inflammation and impaired insulin action systemically (38). Antigen presentation may also be relevant to CD8⁺ T cell activation, because in obesity, CD8⁺ T cells increase in number and in clonality (39).

Intercellular mitochondria transport—Recent studies have suggested that macrophages are able to coordinate both intercellular and interorgan mitochondrial transfer through the uptake of extracellular vesicles or free mitochondria (40, 41). In the context of obesity, mitochondrial transfer between adipocytes and ATMs can be attenuated by saturated fatty acids, resulting in mitochondrial release into the circulation either as free mitochondria or within extracellular vesicles for peripheral tissue uptake (40). Furthermore, genetic disruption of mitochondrial uptake by macrophages results in systemic metabolic dysregulation (41). When considering the iron-handling phenotype of ATMs, it is possible that some of the iron transfer between adipocytes and ATMs could be attributed to this mitochondrial transfer. Whether all ATMs can participate in mitochondrial transfer or whether a unique subset is responsible for this function is unknown.

Together, these data demonstrate the pleiotropic homeostatic functions of resident ATMs. Therefore, therapeutic strategies targeting ATMs need to be considered carefully because some populations serve a conserved and beneficial impact relative to their anatomic location and role in metabolism.

Macrophage recruitment and differentiation

Tissue macrophages originate from either resident yolk-sac progenitors that proliferate within the tissue environment or the recruitment of bone marrow–derived monocytes into regions of tissue inflammation. Specifically, bone marrow–derived monocytes expressing Ly6C migrate from their peripheral origins to inflammatory sites signaled by chemokine ligands/receptors such as CCL2/CCR2 (42). For example, CCR2⁺ Ly6C⁺ monocytes are thought to differentiate into M1-like macrophages after recruitment to AT, and deletion of CCR2 on macrophages results in decreased monocyte influx into AT (15, 42).

After monocyte recruitment to the site of tissue inflammation, environmental cues from the tissue niche become drivers for macrophage differentiation and polarization. Unlike adaptive immune cells that have high antigen specificity, innate immune cells do not

express specific antigen recognition receptors (43). Therefore, macrophage polarization is activated by cell surface receptor response to ligands in the tissue microenvironment. Specifically, pattern recognition receptors (PRRs) are key components of the host immune system, initiating pathogen recognition and transcriptional activation to respond to specific pathogens of interest. Within the PRR family, Toll-like receptor (TLR) signaling has been demonstrated in early activation of the innate immune response, in which TLRs are proposed to “sense” nutrient excess by stimulation of their ligands [from saturated fatty acids and lipopolysaccharide (LPS)] to initiate signaling pathways aimed to meet the cellular and bioenergetic needs of the cell (44). The canonical model for TLR activation has been important for understanding signals responsible for inducing a pro-inflammatory environment in obesity and AT insulin resistance (45). For example, TLR activation by ligands activates nuclear factor κ B (NF- κ B) signaling to produce inflammatory cytokines as well as the Nod like receptor (NLR) family of innate immune sensors, specifically the NLRP3 inflammasome, which in turn regulates the activation of caspase-1 to cleave cytokines such as pro-IL-1 β to their active form (46, 47). Therefore, IL-1 β represents another inflammatory mediator that may impair insulin signaling and induce lipolysis. In summary, monocyte activation through the innate immune response aims to alleviate tissue stress caused by obesity but may follow with metabolic consequences.

Macrophage bioenergetics in obesity

Macrophage bioenergetics and polarization—Over the past 15 years, immunologists have developed a greater appreciation for the role of intrinsic immunometabolism, or bioenergetic pathways, in immune cell function (48). Preferential use of glycolysis or oxidative phosphorylation (OX PHOS) for adenosine 5⁰-triphosphate (ATP) production allows metabolites to be generated for cellular functions such as proliferation, redox balance, inflammatory signaling, hypoxia-inducible factor-1 α (HIF1 α) activation, and epigenetic modifications. Interestingly, the relationship between fuel utilization and cell polarization is reciprocal because activating certain metabolic pathways can influence cell differentiation and polarization, and cell polarization can affect the use of bioenergetic pathways (Fig. 2). For example, fatty acid oxidation of oleic acid can induce M2 polarization (49), and using IL-4 for M2 polarization drives OX PHOS (50).

In the AT, intrinsic immunometabolism has been primarily studied in macrophages (51). In a resting state, lean ATMs have relatively low metabolic activity (52, 53). After adipose expansion, ATMs increase OX PHOS, typically associated with M2 polarization, and glycolysis, typically associated with M1 polarization. This unique bioenergetic state supports the data suggesting that ATMs are not M1 or M2 but have a unique “metabolically activated” polarization (13).

Whereas cytokine production in lean ATMs is supported by fatty acid, glucose, and glutamine utilization, cytokine production in obese ATMs is supported by glycolysis (52). Glycolytic macrophages often express high levels of the glucose transporter Glut1, and thus, Glut1 myeloid deficiency was hypothesized to improve fatty acid uptake and oxidation in ATMs (54). However, there were no differences in body weight, adiposity, or fasting blood glucose in myeloid Glut1-deficient mice compared with controls after high-fat diet (HFD)

feeding. There were, however, unstable atherosclerotic lesions and defective phagocytosis in *Ldlr*^{-/-} mice lacking myeloid Glut1, suggesting several metabolic functions of Glut1 in macrophages to maintain tissue homeostasis.

Together, the current body of literature suggests that signals in the AT environment (lipids, glucose, and hormones) contribute not only to MMe polarization but also to the unique bioenergetics of ATMs in obesity. However, there is still much to understand about how we can target ATM metabolism in obesity. Microarray analysis of ATMs has highlighted changes in gene expression across many metabolic pathways, including one-carbon metabolism, amino acid metabolism, amino/nucleotide sugar metabolism, fructose/mannose metabolism, glycerolipid metabolism, and sphingolipid metabolism (52). Moreover, obese AT is an environment with elevated concentrations of lactate and iron, which likely drive their own metabolic programs in adipose immune cells (55). Thus, more research is warranted to understand the contribution of each metabolic pathway to macrophage function and to determine whether one or more of the metabolic pathways can be targeted to improve ATM function in obesity.

Other innate immune cells in AT

Other populations of innate immune cells also reside in AT. These include eosinophils, mast cells, neutrophils, dendritic cells (DCs), and innate lymphoid cells (ILCs). Whether eosinophils and mast cells contribute to AT homeostasis or dysfunction remains controversial (56–58) (Fig. 3). Thus, we focus our attention here on DCs and ILCs.

Dendritic cells—DCs in AT have been consistently grouped within macrophage clusters because of overlapping CD11c⁺ expression despite their functional diversity (59). Specifically, DCs have been identified in humans as CD11c⁺ CD1c⁺ (60) and in mice as CD11c⁺ CD64⁻ (59) or CD11c^{high} F4/80^{low} (60). Furthermore, DC subpopulations can be classified into conventional DC (cDC) subsets, comprising cDC1s and cDC2s. Previous reports have demonstrated that DC recruitment into AT is mediated by CCR2 and CCR7 and is increased in HFD-fed mice (59) and positively associated with BMI in humans (60). Specific functions for DCs are still incompletely understood, but they are proposed to serve as antigen-presenting cells to signal CD4⁺ T cell activation. In addition, DCs induce T helper 17 (T_H17) differentiation in mice and associate with T_H17 T cells in humans (60).

Innate lymphoid cells—ILCs are proposed to be regulators and responders to the inflammatory response to obesity. ILCs can be clustered by group 1 (ILC1), group 2 (ILC2), and group 3 (ILC3) based on cell surface markers and cytokine release (61). Consistent with innate cells, ILCs respond to cytokines produced by local macrophages and DCs and are absent of antigen receptors (62, 63). ILC1 activation is induced by IL-12 cytokines, by which IL-12R/STAT4 signaling mediates ILC1 activation and stimulates interferon- γ (IFN- γ) release (62, 63). In mice, ILC1s are largely tissue-resident whereas natural killer (NK) cells are recruited from bone marrow precursors and are present in circulation (64). Activation of ILC1 and NK cells by local cytokines serves as a feed-forward response to increase a pro-inflammatory environment necessary to induce immune responses to obesity. ILC2s are an innate immune cell population associated with type 2 immunity and

maintained by IL-33 (65). ILC2s are attenuated in HFD-fed mice and humans with obesity (65). Interestingly, ILC-2s promote adipocyte precursor differentiation toward a beige phenotype in mice, suggesting a potential role for type 2 ILCs to regulate tissue homeostasis by environmental cues triggered by IL-33 (65, 66).

Summary and future directions of innate AT immunity

Together, extensive literature now shows that macrophages and other innate immune cells play a key role in the pathogenesis of obesity and inflammation. Environmental cues that trigger the recruitment and differentiation of innate immune cells are exacerbated by obesity, and the polarization of macrophages into distinct phenotypes serves to modify AT function. Understanding how obesity alters the molecular and functional characteristics of macrophage subpopulations will continue to be critical for developing therapeutic strategies targeting inflammation.

ADAPTIVE IMMUNE CELL POPULATIONS IN OBESITY

T lymphocytes

T cells comprise the largest proportion of adaptive immune cells in AT, with CD4⁺ and CD8⁺ T cells predominating. They each play a unique role in AT homeostasis in the lean condition and in AT inflammation with obesity.

CD4⁺ T cells—CD4⁺ T cells can be divided into two broad categories: pro-inflammatory (T_H1 and T_H17) and anti-inflammatory [T_H2 and T_{reg} (regulatory T cells)]. In lean AT, the CD4⁺ to CD8⁺ ratio is 3:1; however, obesity increases the CD8⁺ T cell population (67). This in turn increases the ratio of inflammatory T_H1 to anti-inflammatory T_H2 CD4⁺ T cells. In addition, the T_{reg} population, important for maintaining homeostasis within the AT, is reduced by up to 70% in HFD-fed mice (68). Forced reduction in the T_{reg} population markedly increases the macrophage and effector T cell population within AT (68). This shift toward a more pro-inflammatory population is most prevalent in visceral AT and contributes to obesity-associated AT inflammation. In models of diet-induced obesity, T_{regs} are reduced and concentrated in the crown-like structures surrounding adipocytes, indicating their role in the maintenance of systemic metabolism (78). T_{regs} are abundant in lean AT and express genes involved in lipid metabolism (CD36, DGAT1, and LDLR) driven by peroxisome proliferator-activated receptor γ (PPAR γ) (79). Deletion of PPAR γ specifically in T_{regs} increases the infiltration of pro-inflammatory macrophages and monocytes after HFD feeding and abolishes the insulin-sensitizing effect of pioglitazone, a US Food and Drug Administration (FDA)-approved medication for type 2 diabetes.

CD8⁺ T cells—Diet-induced obesity evokes an early increase in CD8⁺ effector T cells and subsequent macrophage infiltration into visceral AT depots in mice (67) and subcutaneous AT in humans (69). CD8⁺ T cells interact with local macrophages to elicit macrophage differentiation, activation, and migration, inciting inflammation that contributes to insulin resistance. CD8⁺ T cell infiltration precedes the reduction in the T_{reg} population. CD8 depletion studies resulted in an inhibition of inflammatory macrophage infiltration and the downstream inflammatory cascade typically observed in obese AT (69). An expanding area

of research is related to the observation that T cell exhaustion, most commonly associated with the tumor microenvironment and viral infections, also increases within obese AT in mice and humans (20, 70, 71). Specifically, these exhausted CD8⁺ T cells are effector memory T cells, which express PD1 and TIGIT at the surface protein level and *Pdcd1*, *Tox*, *Entpd1*, *Tigit*, and *Lag3* at the gene level. The relevance of T cell exhaustion to AT inflammation and function in obesity is not fully known.

Gamma-delta ($\gamma\delta$) T cells— $\gamma\delta$ T cells are a class of tissue-resident lymphocytes present in both mice and humans with primary roles in defending against pathogens in epithelial tissues such as the skin, gut, and lungs (72). $\gamma\delta$ T cells are also present in AT, comprising ~4 to 11% of CD3⁺ T cells in mice (73). $\gamma\delta$ T cells are unique in that they respond to antigen presentation similar to conventional T cells but also respond to cytokines, bridging a gap between innate and adaptive immunity. In mice, $\gamma\delta$ T cells in AT have been shown to increase in obesity and are noted to secrete cytokines IL-17 (73, 74) and TNF- α (75). IL-17 released by $\gamma\delta$ T cells may limit adipogenesis (73), increase M1-like (CD11c⁺ CD206⁻) macrophages (75), and limit glucose tolerance (73, 75). In humans, circulating $\gamma\delta$ T cells are decreased with obesity (76), yet omental AT $\gamma\delta$ T cells are increased (77). Future studies profiling $\gamma\delta$ T cells in obesity should identify innate signals responsible for $\gamma\delta$ T cell activation and downstream T cell activation by $\gamma\delta$ T cells.

T cell clonality in obesity

One hallmark of adaptive immunity is the clonal expansion of specific T and B cell populations after exposure to specific antigens. Remarkably, restricted T cell receptor (TCR) sequences have been identified on CD4⁺ and CD8⁺ T cells isolated from AT in mice (37, 69). What is even more interesting is that with obesity, T_{reg} clonal expansion decreases (68), whereas CD8⁺ clonal expansion increases. T_{regs} isolated from lean visceral AT have a restricted TCR sequence, suggesting that they are responding to a select population of local antigens. Regarding CD8⁺ T cells in obese AT, little is known about potential antigens. In our study, the amino acid sequences corresponding to the complementarity determining region 3 of clonal TCRs were characterized as positively charged and nonpolar (80). Isolevuglandins are negatively charged and detected in high amounts within ATMs, suggesting that they may be one component of the AT microenvironment capable of stimulating CD8⁺ T cell proliferation (80). However, the identification of specific antigens driving CD8⁺ T cell clonal expansion is still needed. Furthermore, the mechanisms regulating CD8⁺ T cell expansion in human obesity remain unclear.

B lymphocytes

In contrast to regulatory B-1 cells, B-2 cells in AT create an inflamed environment, secreting more pro-inflammatory cytokines, such as IL-6 and IFN- γ , at the expense of anti-inflammatory cytokines, specifically IL-10 (81). Excess adiposity results in the accumulation of B-2 cells in visceral AT, worsening inflammation of the tissue. In pan B cell-null mice, adipocyte hypertrophy was mitigated, macrophage infiltration was substantially decreased, and glucose tolerance was improved (81). The hypertrophic obesity and worsened glucose tolerance seen in B cell null animals are influenced by the ability of the B cells to regulate T cells in the AT. In T cell activation studies, cells from B

cell-deficient mice had reduced pro-inflammatory cytokine production. The role of B cell and T cell interactions in AT inflammation was further confirmed when RAG1^{-/-} mice were reconstituted with B cells from 16 weeks in HFD-fed mice. Despite the reconstitution, fasting glucose, insulin, and glucose tolerance were not worsened, suggesting that B cells require the presence of T cells for their impact on metabolic function (82).

Summary and future directions of adaptive AT immunity

The contribution of adaptive immune cells to AT homeostasis and dysfunction remains an intriguing area of research. Outstanding questions include the following: Why do T cells change in degree of clonality with obesity (with decreased T_{regs} and increased CD4⁺ and CD8⁺ cells)? Are there specific antigens that can be targeted to reduce AT inflammation? And how are T cell exhaustion and B cell antibody production related to AT function? Furthermore, whereas the bioenergetics of T cells in the context of cancer is well documented, whether the AT milieu changes intrinsic T cell metabolism is not known. For example, although T_{regs} are well primed to metabolize lipids for their regulatory functions in homeostasis, there is still much to learn about the metabolism of other adipose immune cell types (T cells and B cells, and their subpopulations) in lean and obese AT.

IMMUNE RESPONSE TO WEIGHT LOSS AND REGAIN

Weight cycling is loosely defined as the repeated gain and loss of body mass. Most of the literature on weight cycling was published several decades ago and sought to determine whether fluctuations in body weight have a negative impact on food efficiency and energy requirements. More recent studies have revealed an association between weight cycling and increased risk of insulin resistance and cardiovascular disease (83, 84). One of the first studies addressing this issue reported a 10% increase in the 25-year risk of coronary death in men who weight-cycled compared with those who maintained a stable weight (83). In addition, multiple recent publications suggest that weight regain after substantial weight loss has negative consequences on metabolic health in humans (84, 85). Emerging studies provide evidence that AT immune memory may be involved in the metabolic consequences of weight cycling.

Adaptive immune memory to metabolic signals

To interrogate the cell types and molecular contributors to weight cycling, researchers have turned to mouse models that can recapitulate many of the adverse metabolic sequelae of weight cycling. In mice, prior obesity results in weight regain at a faster rate, greater fat accumulation, and an adaptive immune response characterized by type I immune cells (86–88). CD4⁺ T cells have been thoroughly studied in mouse models of weight cycling (82). Rag1^{-/-} (lacking T and B cells), TCRβ^{-/-} (lacking CD4 and CD8 T cells), and H2A^{-/-} (lacking CD4 T cells) mice were protected from accelerated weight regain (87). Interestingly, when reconstituted with CD4⁺ T cells from wild-type mice with a history of obesity, both Rag1^{-/-} and TCRβ^{-/-} mice gained weight more quickly than those that received CD4⁺ T cells from lean controls (87). Work from our laboratory showed an increase in CD8⁺ effector memory T cells in AT of weight-cycled mice (20, 88). Unanswered questions remain regarding how extreme the weight loss and regain must

be, whether the number of weight cycles matters, whether T cell clonality is different in weight cycling versus maintained obesity, and the degree to which the immune landscape in human AT is affected by weight cycling. These findings suggest that adaptive immune cell populations within AT are highly plastic and that further work should be conducted to better characterize these populations in AT and within metabolically active tissues at each stage of weight cycling.

The reason for the immune changes induced by weight cycling can be garnered by assessing the AT immune landscape after weight loss. Surprisingly, AT of animals that have lost weight does not fully revert to a lean anti-inflammatory phenotype (Fig. 3) (20, 89, 90). In addition, recent work indicates that the highest proportion of T and B cells occurs during the weight-loss phase of weight cycling (20). These data suggest that although weight loss improves systemic metabolic processes, the AT immune system may “remember” previous obesity and become overly activated upon weight regain.

Innate immune memory to metabolic signals

Although immunological memory is historically considered characteristic of only adaptive immune cells, recent work suggests that innate immune cells can also develop nonspecific memory (91). Activation of PRRs by β -glucan, the *Mycobacterium tuberculosis* vaccine (BCG), and even oxidized low-density lipoprotein (LDL) can drive metabolic activation and persistent epigenetic remodeling to prime cells for a more robust response after second stimuli. Specifically, innate stimuli can drive glycolytic ATP production so that metabolic intermediates like acetyl-CoA can help acetylate histones (92). These histone modifications can hold open regions of chromatin at glycolytic and inflammatory genes for faster transcription upon subsequent activation.

Although this response may be evolutionarily protective in responses to infection, it appears detrimental in chronic disease. We have recently shown that bone marrow-derived macrophages can develop enhanced secondary activation after priming with AT-conditioned media or palmitate, which is dependent on TLR4 and suppressed with metformin or pan methyltransferase inhibition. In addition, ATMs from previously obese mice secrete more inflammatory cytokines after ex vivo activation with LPS and are more inflammatory after weight regain (93). Similarly, others have shown that a ketogenic diet and palmitate injections worsen systemic LPS-induced inflammation via ceramide production (94) and stearic acid (via TLR4) and that previous obesity induces chromatin remodeling in ATMs, which predisposes mice to worsened macular degeneration (95). Other innate immune stimuli have shown a role in mevalonate and changes in genes related to fatty acid metabolism and OX PHOS (92). Thus, ATMs appear uniquely situated to develop innate immune memory in response to activation and uptake of lipids, and future research should aim to understand how ATM memory affects both metabolic and immunological diseases.

Together, these data suggest that multiple arms of the immune system remember previous obesity, and clinical approaches to weight loss should strive for long-term efficacy. Moreover, further understanding of the signals that drive and maintain immunological memory to obesity may provide additional therapeutic targets to mitigate diseases associated with weight regain.

CLINICAL APPROACHES TARGETING OBESITY AND METAINFLAMMATION IN HUMANS

Trials with anti-inflammatory therapies

Although chronic inflammation has been strongly linked to metabolic diseases such as atherosclerotic cardiovascular disease and type 2 diabetes, compared with lipid- and glucose-lowering drugs, anti-inflammatory therapies are nascent with regard to clinical application. One of the first studies focused on salsalate and glycemic control in patients with type 2 diabetes (96). At three different doses, salsalate treatment resulted in significant decreases in HbA1c concentrations and other markers of glycemic control. More recently, the CANTOS (Canakinumab Anti-Inflammatory Thrombosis Outcomes Study) trial, with ~10,000 patients, provided proof of concept that targeting an inflammatory cytokine (in this case, IL-1 β) could reduce the incidence of a composite primary end-point of myocardial infarction, stroke, and cardiovascular death (97). Interestingly, cancer mortality was also decreased in the canakinumab-treated groups. However, the incidence of serious infection was seen in one out of every 750 patients. This does not diminish enthusiasm for the idea of using anti-inflammatory agents to treat cardiometabolic disease; however, other approaches, such as improving pro-resolving processes to limit the acute inflammatory response, are now considered to be a better approach (98).

Lifestyle interventions for obesity

Weight loss, either via lifestyle modification, medication, or surgery, is the primary recommended intervention for obesity and its associated cardiometabolic complications. Moderate amounts of weight loss (~5% body weight) result in improved metabolic outcomes in humans (99). Clinical trials have found that moderate weight loss does not affect AT inflammation in adults with obesity despite improved insulin sensitivity. Rather, more progressive weight loss (~11 to 16%) sufficiently reduced both systemic and AT inflammation (99). Therefore, we speculate that the immune response to weight loss in humans is a biphasic response, where macrophage subpopulations are increased in AT to undergo tissue remodeling and buffer lipid accumulation derived by lipolysis (100) but may be reduced with sustained weight loss. However, given the strong data showing sustained inflammatory immune cells in AT of mice that have lost weight, more extensive studies are needed in humans. Here, we highlight pharmacological and surgical approaches for weight loss and discuss their impact on AT and systemic inflammation.

Dietary modifications—The effects of negative energy balance on pro-inflammatory markers have been studied clinically in individuals with obesity. In the clinical weight management setting, patients are advised to focus on unprocessed foods with an emphasis on whole grains, lean protein, fresh fruits and vegetables, and limited refined sugars and flour. One study suggested that a reduction in high-sensitivity C reactive protein (CRP) and IL-6 occurs when energy homeostasis is achieved after a decline in fat mass (101). However, antioxidant-rich foods containing carotenoids, mixed tocopherols, vitamin C, or selenium have not consistently been shown to reduce inflammatory markers (102). Oftentimes, patients choose a dairy-free diet as a method to induce weight loss despite a lack of

evidence to suggest increases in weight, fat, visceral AT, and subcutaneous ATM number, subcutaneous AT inflammatory gene expression, and circulating cytokines from dairy foods (103). The Mediterranean diet on the other hand, characterized by a high consumption of legumes, nuts, seeds, and olive oil, and a moderate consumption of protein, has been shown to reduce inflammation (104).

Physical activity—The American Heart Association recommends at least 150 min/week of exercise to promote and maintain health. In the clinical weight management setting, patients are counseled on physical activity, both structured and unstructured, consistent with standard of care guidelines. In one study, routine exercise over 6 and 12 months resulted in decreased levels of leptin, adiponectin, resistin, homocysteine, and IL-6, particularly in patients who were overweight (BMI, ≥ 25 and <30 kg/m²) (105). Intensive exercise focused on structure and consistency may be necessary to produce a hypo-inflammatory state, especially in persons with obesity (106).

Pharmacological intervention

Pharmacologic interventions directly aimed at reducing inflammatory cytokines have demonstrated success as measured by reductions in CRP and IL-6 in the circulation and a resultant decrease in cardiovascular events (97), yet none is standard of care in obesity at this time. Pharmacological interventions aimed to mitigate the metabolic effects of obesity, specifically type 2 diabetes, have focused on pathways involved in insulin action. Serendipitously, these have sometimes resulted in the added benefit of weight loss. These pathways include incretins and sodium-glucose co-transporter 2 (SGLT2) inhibitors, which we will highlight below.

Glucagon-like peptide 1 receptor agonists—The incretin effect describes the phenomenon that oral glucose increases pancreatic insulin secretion to a greater degree than intravenous glucose. This is due to the secretion of incretin hormones glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide 1 (GLP-1) from the gut. GIP and GLP-1 act directly on β cells to promote insulin secretion. GLP-1 is lower in individuals with obesity and increases after bariatric surgery (107). GLP-1 receptor agonists (GLP-1RAs) decrease blood glucose, cause weight loss, and decrease composite death from cardiovascular causes, nonfatal stroke, and myocardial infarction in patients with diabetes (108, 109).

In animal models, GLP-1RAs have been shown to decrease inflammation. In obese animals, treatment with GLP-1RAs decreases AT inflammatory cytokines and causes a switch from a pro-inflammatory to an anti-inflammatory macrophage phenotype (110, 111). GLP-1RA treatment of nonobese diabetic mice with new-onset diabetes increases T_{regs} (112). Furthermore, GLP-1RA treatment reduces atherosclerosis in *ApoE* and *LDLr* knockout animals by inhibiting inflammatory pathways in the vasculature (113). Despite the therapeutic potential for GLP-1RAs to modify inflammation in animals and limit cardiovascular outcomes in humans, their effects on AT immune profile in humans are still unconfirmed.

Human studies have provided contradictory results. In two studies of adults with obesity and type 2 diabetes, GLP-1RAs increased circulating adiponectin concentration and decreased circulating concentrations of pro-inflammatory cytokines TNF- α , IL-1 β , and IL-6; soluble CD163; and M1-like ATMs (114, 115). However, a different group found that GLP-1RAs increased circulating MCP-1, expression of TNF- α , MCP-1, and markers of extracellular matrix deposition in AT (116). Despite the promising effects of GLP-1RAs to improve cardiometabolic outcomes and glucose tolerance, variations in the length of these clinical trials range from 8 weeks to 1 year and are typically in patients with type 2 diabetes (Table 1). Therefore, the effect of GLP-1RAs on obesity independent of metabolic disease onset is unknown. In addition, more studies rigorously profiling the impact of GLP-1RAs on AT immune cell phenotype are warranted. Last, controlled trials comparing the effect of GLP-1RAs independent of weight loss or in combination with lifestyle interventions could identify additional therapeutic potential.

Sodium-glucose cotransporter 2 inhibitors—Sodium-glucose cotransporter 2 (SGLT2) is responsible for the reabsorption of 90 to 97% of the filtered glucose in the kidneys. SGLT2 inhibitors cause glucosuria, reduce HbA1c, and induce weight loss of 2 to 3 kg (117). Large cardiovascular outcome trials have also demonstrated that SGLT2 inhibitors significantly decrease major adverse cardiovascular events in patients with type 2 diabetes and with established cardiovascular disease and are effective at primary and secondary prevention of heart failure and chronic kidney disease (118).

Similar to GLP-1RAs, SGLT2 inhibitors also decrease inflammation in animals and may decrease inflammation in humans, as reviewed recently (119). SGLT2 inhibitors decrease the production of pro-inflammatory cytokines (IL-6 and TNF- α) in vitro in mouse and human cell lines and in vivo after LPS stimulation (120). In diabetic, atherosclerosis-prone *ApoE* knockout mice, SGLT2 inhibitors decrease aortic pro-inflammatory gene expression independently of weight loss (121) and decrease NLRP3 inflammasome activation (122, 123). Last, SGLT2 inhibitors skew ATMs from pro-inflammatory to anti-inflammatory phenotypes in a mouse model of diet-induced obesity (124). In humans, SGLT2 inhibitors decrease NLRP3 inflammasome activation in blood-derived macrophages after 30 days of in vivo treatment (125) and in human aortic smooth muscle cells after in vitro IL-17A stimulation (126). In addition, SGLT2 inhibitors increase circulating adiponectin in multiple studies (119, 127, 128). Add-on SGLT2 inhibitors in people with type 2 diabetes decrease CRP, which correlates with improvements in insulin resistance (129). Controlled clinical studies identifying the effect of SGLT2 inhibitors on tissue-specific immune cell populations (such as those in AT) are still lacking, as well as the effect of therapies in combination with or independent of weight loss. Despite the promising impact of SGLT2 inhibitors in a diabetic population, the effect in nonclinical populations with obesity is as of yet unknown.

Bariatric surgery

Adipocyte-derived inflammatory factors are elevated in individuals with obesity and contribute to the metabolic and vascular derangements common in obesity. Given the well-established link between adiposity and a pro-inflammatory state, it is plausible that marked weight loss seen after bariatric surgery would yield a reduction in inflammation.

Surprisingly, studies show variable changes in inflammatory markers postoperatively [reviewed in (130)].

Diabetes remission occurs in more than 75% of patients 2 years after Roux-en-Y gastric bypass (RYGB), and oftentimes, the improvement in glycemic control is seen immediately postoperatively, before significant weight loss occurs (131). There is debate about the exact mechanism underlying this phenomenon. We know that glycemic improvement is partially attributed to increased incretin secretion, but one other theory is that inflammatory cytokines are markedly reduced after surgery. This could also account for the reduction in cardiovascular complications of obesity after bariatric surgery as well (132).

Although inflammation may be difficult to quantify, there are key inflammatory markers that have been studied in the post-RYGB population, with the most cited being IL-6, TNF- α , CRP, and serum amyloid A (SAA). IL-6 is a cytokine that is implicated in obesity-related metabolic decline. Most RYGB studies agree that this cytokine can increase in the acute postoperative period but show a long-term downtrend over 1 year postoperatively (130). One study showed a different triphasic pattern of interleukin response: a sharp decrease at 3 months, then a steady rise to presurgical values at 6 months, and at 12 months a downtrend that depended on BMI and metabolic status change (133). Smaller studies looking at changes in TNF- α post-RYGB do not show consistent trends, where TNF- α has been shown to increase 3 months after surgery and return to presurgical baseline (134). However, a recent meta-analysis of 116 studies evaluating TNF- α response 12 months after surgery showed a significant decrease compared with baseline (135). CRP is an acute-phase liver protein strongly associated with inflammatory states and cardiovascular disease. Studies show a consistent reduction in CRP after various types of bariatric surgical procedures, including RYGB, vertical sleeve gastrectomy, and laparoscopic adjustable gastric banding. CRP was reduced by 82% at 1 year postoperative in a study of 66 participants with obesity who underwent RYGB, and the reduction was higher in those without insulin resistance (136). Furthermore, a longitudinal analysis using high-sensitivity CRP testing showed a progressive decline in this marker at 3, 6, and 12 months after RYGB, and this correlated with BMI, insulin, and HOMA-IR (134). SAA is another acute-phase reactant produced in the liver in response to inflammation and has shown positive correlations with atherosclerosis. The aforementioned studies show a consistent reduction in SAA as well across various bariatric surgical procedures, although a decrease in SAA is not as pronounced as a reduction in CRP (136).

In summary, the evidence confirms a reduction in the acute-phase reactants CRP and SAA after bariatric surgery, but changes in inflammatory cytokines are inconsistent. This may be partially due to drastic changes in calorie intake postoperatively and perhaps macronutrient composition as well. Additional studies are needed to assess the long-term impact of bariatric surgery on inflammatory markers.

Emerging therapies

Whereas older-generation anti-obesity pharmacotherapies can achieve approximately 3 to 7% weight loss from baseline, more recent therapeutics have shown more than 15% weight loss. These include incretin therapies such as semaglutide and tirzepatide, both of

which have proven safety and tolerability. Semaglutide (2.4 mg) is now FDA-approved for chronic weight management, and tirzepatide is expected to be FDA-approved for obesity in light of the recent SURMOUNT-1 study showing 22.5% weight loss (137). Although 3 to 5% weight loss signifies clinically meaningful weight loss, >10 to 15% weight loss can revert or improve more serious inflammatory diseases such as nonalcoholic fatty liver and cardiovascular disease. In addition, the cardiovascular risk profile of semaglutide in patients with type 2 diabetes has been shown to be noninferior to placebo (138, 139). Clinically, for patients with metabolic derangements and worsening inflammatory processes, these newer therapies are highly preferred over the older-generation compounds. Presently, studies are ongoing, with SELECT (Semaglutide Effects on Cardiovascular Outcomes in People with Overweight or Obesity) being the first cardiovascular clinical trial to measure the superiority of major adverse cardiovascular events reduction for an anti-obesity medication, semaglutide. As more novel obesity agents gain FDA approval, insights into their mechanisms of action and effect on inflammation can enhance our clinical application of these drugs to target not only severe obesity but also weight-related complications.

CONCLUSION

Understanding the direct and indirect effects of obesity-induced metaflammation will be important to further understand how obesity accelerates cardiometabolic disease. Despite tremendous efforts to identify cellular mediators contributing to metabolic dysfunction in obesity, pharmacological approaches targeting a single mechanism remain difficult because of the diversity of innate and adaptive immune cells altered in obesity. Technological advancements and availability of multiomics platforms will continue to improve our understanding of immune populations that are either associated with or directly causative of metabolic dysfunction and to propose new therapeutic targets. Researchers should continue to address whether obesity-induced modifications in immune cell populations are causal to poor metabolic health outcomes. Similarly, an important question for pharmacological research in obesity is to identify whether therapies directly targeting weight loss additionally mitigate inflammation driven by obesity or whether the weight-loss effects of obesity drive the attenuated inflammatory phenotype independent of pharmacological intervention.

Acknowledgments

Funding:

Authors on this work are funded by the Department of Veterans Affairs Research Career Scientist IK6 BX005649 (to A.H.H.), the National Institutes of Diabetes and Digestive and Kidney Diseases R01DK121520 (to A.H.H.), the NIH Molecular Endocrinology Training Program T32DK007563 (to J.N.G. and M.W.S.), the American Heart Association Postdoctoral Fellowship 20POST35120547 (to H.L.C.), and the National Center for Advancing Translational Sciences KL2TR002245 (to M.M.).

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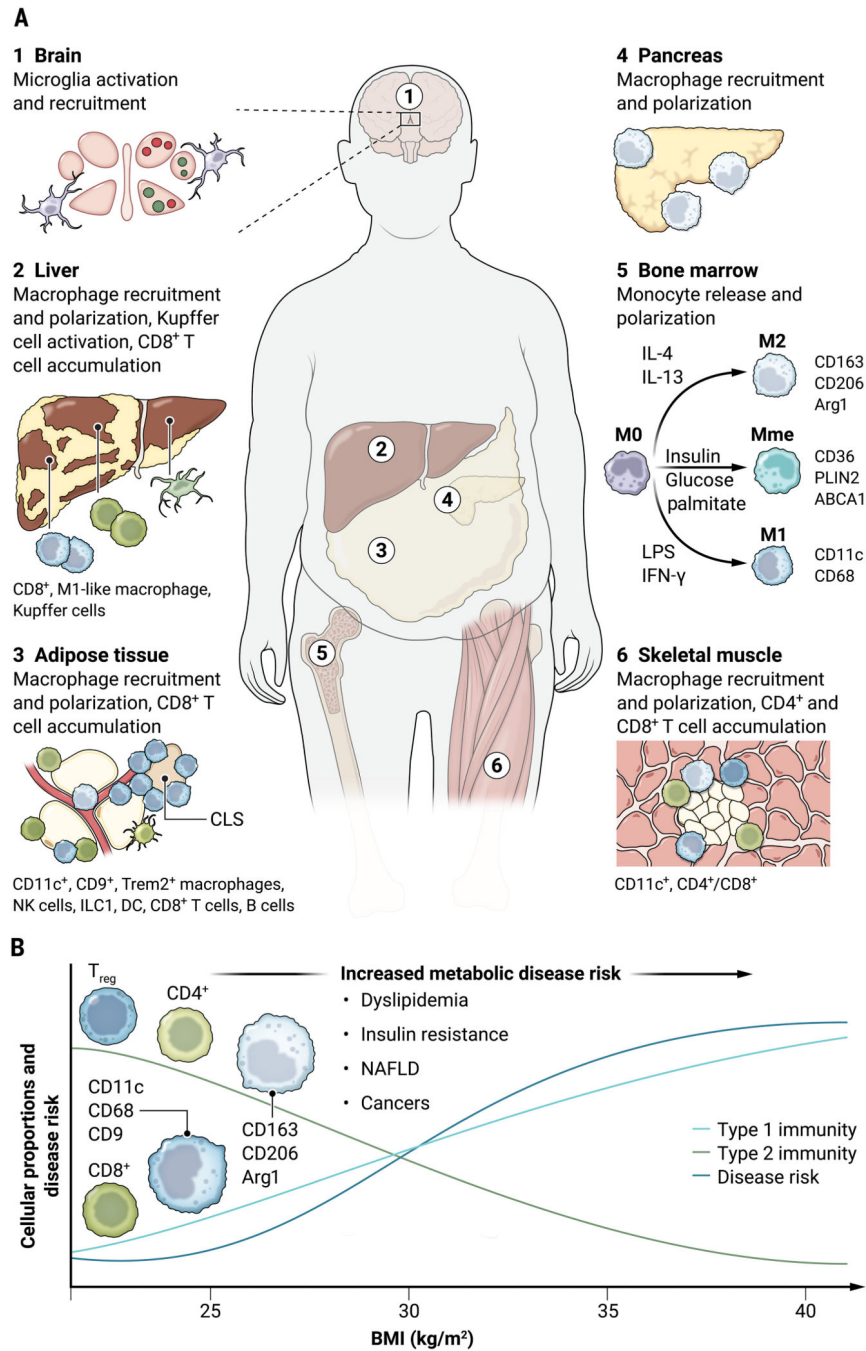


Fig. 1. Organ-specific inflammatory responses in obesity.

(A) Inflammation is a coordinated immune response aimed to alleviate stresses induced by obesity and occurs in tissues such as liver, pancreas, adipose tissue, skeletal muscle, and the brain. Ectopic lipid accumulation in these tissues can initiate monocyte recruitment, macrophage polarization toward pro-inflammatory states, CD8⁺ T cell accumulation, and excess accumulation of pro-inflammatory mediators. (B) Immune response to positive energy balance within the stromal compartments of these tissues increases type 1 immunity (light blue line) including M1-like innate immune cells and CD8⁺ T cells. Conversely,

obesity attenuates type 2 immunity (green line) phenotype, resulting in reduced M2-like innate immune cells as well as T_{reg} and $CD4^+$ adaptive immune cells. This reciprocal relationship between type 1 and type 2 immunity in obesity is proposed to underlie tissue homeostasis and insulin resistance (dark blue line). CLS, crown-like structure; NAFLD, nonalcoholic fatty liver disease.

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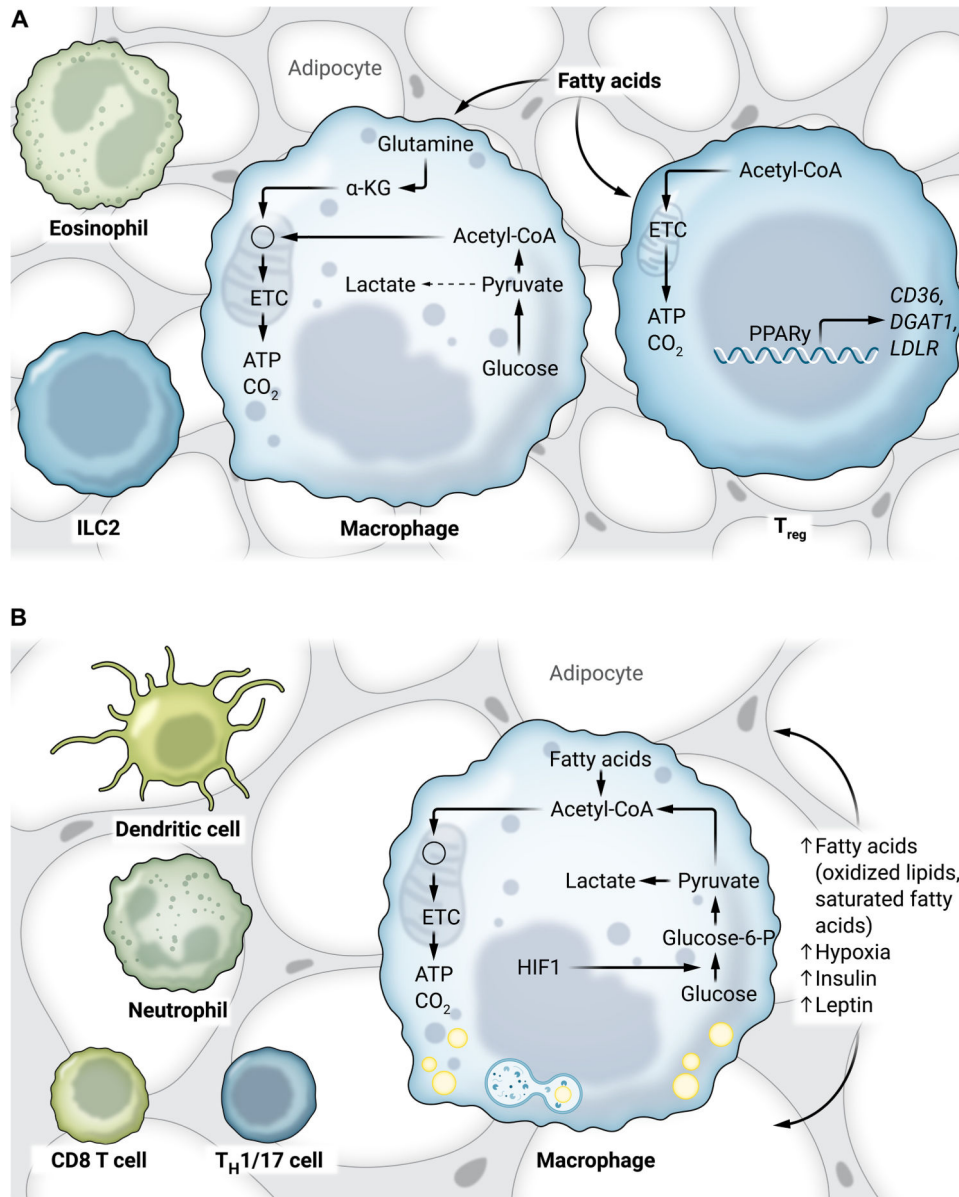


Fig. 2. AT macrophages have distinct metabolic phenotypes.

(A) In lean AT, macrophages have a low metabolic demand. T_{regs} use oxidative phosphorylation, and PPAR γ drives gene expression of lipid handling-related genes. The metabolism of other adipose immune cells is unknown. (B) In obese adipose tissue, macrophages have heightened glycolysis and oxidative phosphorylation, likely driven by increases in more inflammatory lipids, hypoxia, insulin, and leptin signaling. Other cell types including $\text{T}_{\text{H}}1/17$, T lymphocytes, neutrophils, and dendritic cells are also speculated to modify their metabolic phenotype in obesity.

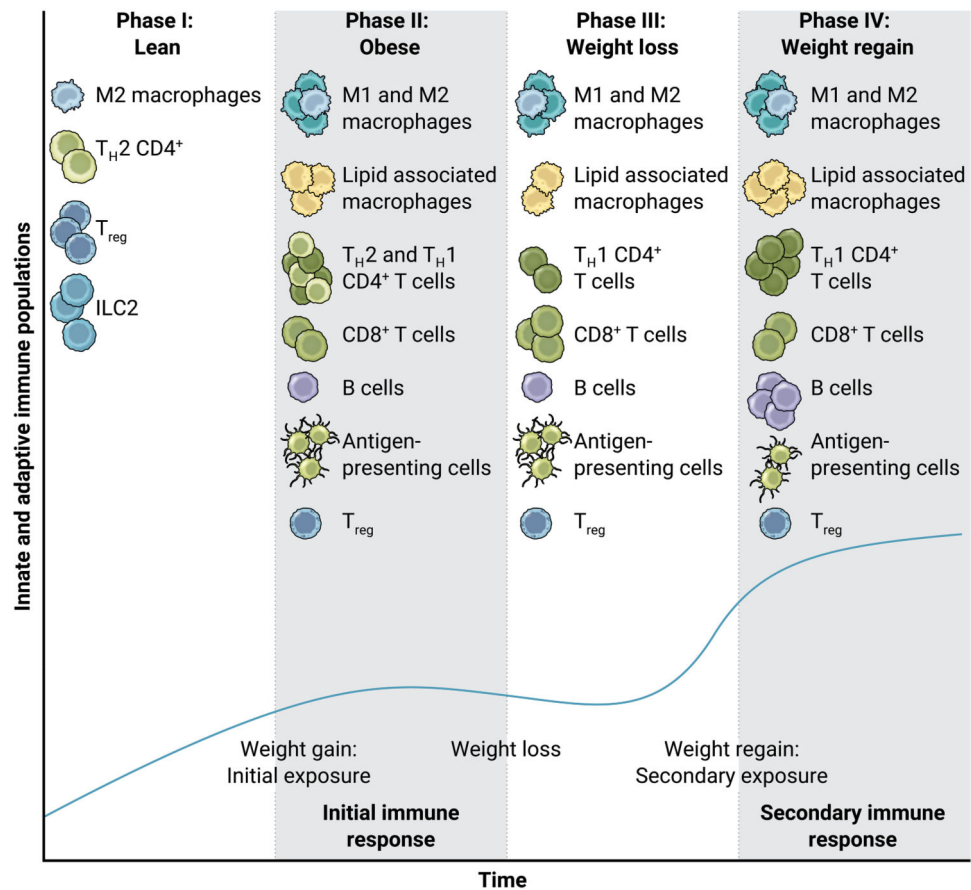


Fig. 3. Innate and adaptive immune cell response to weight cycling.

Lean AT is often composed of type 2 immune cells (for example, M2-like macrophages, T_H2 $CD4^+$ T cells, and T_{reg} s). In obesity, both innate and adaptive immune cell recruitment result in greater type 1 immune cell populations, resulting in the influx of M1-like macrophages, T_H1 $CD4^+$ T cells, and $CD8^+$ T cells. Conversely, the T_{reg} population is diminished in obesity. In the event of weight loss, inflammatory macrophages and memory T cells remain intact, whereas T_{reg} populations do not increase back to their lean proportion. Therefore, in the event of weight regain (as in weight cycling), effector T cell populations interact with antigen-presenting cells that had accumulated from the previous obesity cycle, resulting in even greater adaptive immune cell populations (including $CD8^+$ T cells, $CD4^+$ T cells, and B cells). The dark blue curve on the graph indicates the innate and adaptive immune cell populations shown per bout of weight gain, loss, and regain.

Table 1.
Anti-inflammatory effects of GLP-IRAs and SGLT2is in human clinical studies.

Direction of statistically significant effects shown for the drug of interest (GLP-IRA or SGLT2i). CRP, c-reactive protein; HbA1c, hemoglobin A1c; IL, interleukin; MCP-1, monocyte chemoattractant protein-1; ND, not done; RCT, randomized controlled trial; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; TNF, tumor necrosis factor.

	Population characteristics	Study design	#	CRP	Cytokines	Adipokines	Notes
GLP-1 receptor agonists							
Bunck <i>et al.</i> (140)	T2DM on metformin	RCT GLP-IRA exenatide versus insulin for 1 year	36 exenatide 33 insulin	↓	↔ IL-6 and MCP-1	↑ Adiponectin ↓ Leptin	Change in weight correlated with CRP and leptin
Derosa <i>et al.</i> (141)	Uncontrolled T2DM on metformin	RCT GLP-IRA exenatide versus sulfonylurea for up to 12 months	63 exenatide 65 sulfonylurea	↓	ND	ND	Similar degree of HbA1c lowering between treatments
Chaudhuri <i>et al.</i> (115)	Obesity and T2DM	RCT of GLP-IRA exenatide versus placebo for up to 12 weeks	12 exenatide 12 placebo	ND	↓ <i>TNFA</i> , <i>IL1B</i> , <i>TLR2</i> , and <i>TLR4</i> expression in PBMCs ↓ Circulating MCP-1 and IL-6	ND	Decrease in SAA
Hogan <i>et al.</i> (114)	T2DM	Observational study of add-on GLP-IRA therapy for 8 weeks	10	ND	↓ sCD163, TNF-α, IL-1β, and IL-6	↑ Adiponectin	Inflammatory changes independent of weight loss or change in glycemia
Mazidi <i>et al.</i> (142)	Variable	Meta-analysis of RCTs for effects of GLP-IRA on CRP	7 trials	↓	ND	ND	
Pastel <i>et al.</i> (116)	T2DM	RCT GLP-IRA liraglutide versus diet for 4 months	22 liraglutide 8 diet	ND	↑ <i>TNFA</i> , <i>MCP-1</i> , and <i>TGFB</i> expression in adipose ↑ MCP-1	ND	
Anholm <i>et al.</i> (143)	Newly diagnosed T2DM with coronary artery disease on stable statin therapy	RCT crossover of GLP-IRA liraglutide + metformin versus placebo + metformin for 12 weeks	39	↓	↔ TNF-α	ND	
Savchenko <i>et al.</i> (144)	T2DM on metformin and glimepiride	Observational study of add-on GLP-IRA liraglutide for 6 weeks	15	ND	↓ <i>TNFA</i> , <i>TLR2</i> , and <i>TLR4</i> expression in PBMCs ↔ <i>IL-2</i> and <i>NOD-1</i> ↑ <i>SIRT1</i> expression	ND	

	Population characteristics	Study design	n	CRP	Cytokines	Adipokines	Notes
SGLT2 inhibitors							
Matsumura <i>et al.</i> (128)	T2DM on insulin	Observational study of add-on SGLT2i canagliflozin for 3 days	15	ND	↔TNF-α	↑Adiponectin	↓Markers of oxidative stress
Garvey <i>et al.</i> (127)	T2DM inadequately controlled on metformin	RCT of SGLT2i canagliflozin versus sulfonylurea for 52 weeks	100 canagliflozin 100 sulfonylurea	↔	↓IL-6 ↑TNF-α	↓Leptin ↑Adiponectin	
Hattori (129)	T2DM	RCT SGLT2i empagliflozin versus placebo for 1 year	51 empagliflozin 51 placebo	↓	ND	ND	ND
Sato <i>et al.</i> (145)	T2DM with coronary artery disease	RCT SGLT2i dapagliflozin versus conventional treatment for 6 months	20 dapagliflozin 20 conventional treatment	ND	↓TNF-α	ND	ND
Heerspink <i>et al.</i> (146)	T2DM and albuminuria	RCT of SGLT2i canagliflozin versus sulfonylurea for up to 2 years	207 canagliflozin 89 sulfonylurea	ND	↓TNFR1 and IL-6 ↔CCL2, CCL5	ND	↓MMP-7 and fibronectin 1
Iannantuoni <i>et al.</i> (147)	T2DM	Observational study of SGLT2i empagliflozin for 24 weeks	15	↓	↑IL-10	ND	Reduction in leukocyte superoxide production
Latva-Rasku <i>et al.</i> (148)	T2DM	RCT SGLT2i dapagliflozin versus placebo for 8 weeks	15 dapagliflozin 16 placebo	ND	↓IL-6 ↔TNF-α and MCP-1	ND	Decreased visceral adipose tissue
Sezai <i>et al.</i> (149)	T2DM and heart failure	SGLT2i canagliflozin for 12 months	35	↓	ND	ND	ND
Bray <i>et al.</i> (119)	T2DM ± secondary characteristics	Systematic review of effects of SGLT2 inhibition on biomarkers of inflammation	23 studies	↓	↓IL-6 and TNF-α	↑Adiponectin	↓markers of oxidative stress
Kim <i>et al.</i> (125)	T2DM and high cardiovascular risk	RCT of SGLT2i empagliflozin versus sulfonylurea effects on blood-derived macrophages <i>ex vivo</i>	29 empagliflozin 32 sulfonylurea	ND	↓IL-1β and TNF-α from macrophages <i>ex vivo</i>	ND	ND
Nishimiya <i>et al.</i> (150)	T2DM and nonalcoholic fatty liver disease	SGLT2i canagliflozin for 6 months	9	↓	↔TNF-α	↔Adiponectin and leptin	
Sposito <i>et al.</i> (151)	T2DM and increased carotid intima-media thickness	RCT of SGLT2i dapagliflozin versus sulfonylurea for 12 weeks	48 dapagliflozin 49 sulfonylurea	↔	↔IL-2, IL-6, and TNF-α	ND	ND