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## Metabolic Inflammation and Insulin Resistance in Obesity

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### Abstract

Obesity is becoming an epidemic in the United States and worldwide and increases risk for many diseases, particularly insulin resistance, type 2 diabetes, and cardiovascular disease. The mechanisms linking obesity with these diseases remain incompletely understood. Over the past 2–3 decades, it has been recognized that in obesity, inflammation, with increased accumulation and inflammatory polarization of immune cells, takes place in various tissues, including adipose tissue, skeletal muscle, liver, gut, pancreatic islet, and brain, and may contribute to obesity-linked metabolic dysfunctions, leading to insulin resistance and type 2 diabetes. Therapies targeting inflammation have shed light on certain obesity-linked diseases, including type 2 diabetes and atherosclerotic cardiovascular disease, but remain to be tested further and confirmed in clinical trials. This review focuses on inflammation in adipose tissue and its potential role in insulin resistance associated with obesity.

### Keywords

obesity; adipose tissue; inflammation; insulin resistance; Metabolism

### Introduction

Obesity is becoming a global epidemic and has nearly tripled worldwide since the 1970s. In 2016, more than 1.9 billion adults—39% of the world adult population—were overweight and more than 650 million were obese.<sup>1</sup> Of note, 340 million children and adolescents aged 5–19 years and 41 million children under age 5 were overweight or obese worldwide.<sup>1</sup> In the United States, more than 93 million adults—~40% of the adult population—and nearly 20% of children and adolescents aged 6–19 years were obese in 2015–2016.<sup>2</sup>

Obesity increases risks for many diseases, particularly insulin resistance and type 2 diabetes (T2DM). However, the underlying mechanisms remain incompletely understood. Over the last 2 decades, it has been recognized that obesity is associated with chronic low-grade

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inflammation in a variety of tissues, including adipose tissue (AT), skeletal muscle, liver, pancreas islet, intestine, and even brain.<sup>3-9</sup> Both innate and adaptive immune cells can participate in obesity-linked inflammation, which, importantly, may serve as a causal link between obesity and insulin resistance and T2DM.<sup>3-9</sup> In this review, we will summarize some advances in obesity-linked metabolic inflammation, AT inflammation in particular, and its potential role in development of insulin resistance, the basis for T2DM.

## Type 1 and type 2 inflammation

Inflammation can be broadly classified as type 1 and type 2 inflammation, as initially described for adaptive immune response of CD4<sup>+</sup> T lymphocytes, i.e., T helper 1 (Th1) and 2 (Th2) cells, respectively,<sup>10</sup> depending on the stimuli/environments. Type 1 and type 2 inflammation involves different types of inflammatory cells, which express or produce distinct panels of inflammatory molecules via specific transcription factors and exert different functions (Table 1) (see reviews<sup>10-12</sup>). The term “proinflammation” or “inflammation” (including in this review) generally refers to type 1 inflammation. In contrast, in certain cases, type 2 inflammation is described or generalized as “anti-inflammation.”

## Inflammation in obesity

The first evidence for obesity-linked inflammation was from a report of elevated TNF $\alpha$  in AT in obesity.<sup>13</sup> Since then, numerous studies have consistently shown increased inflammation in AT in obese animals and humans. Although inflammation takes place in a variety of tissues when obesity occurs, most of our knowledge on obesity-linked inflammation still derives from studies of AT.

### Inflammation in visceral (VAT) and subcutaneous (SAT) AT:

The initial study attributed AT inflammation to adipocytes, the main resident cells in AT.<sup>13</sup> Indeed, adipocytes can become inflamed and secrete a variety of inflammatory molecules.<sup>13-16</sup> However, since the identification of macrophages in AT,<sup>17,18</sup> macrophages and various other immune cells (Supplemental Table I) have been demonstrated to be the main inflammatory cells that release the majority of inflammatory molecules in AT of obese animals and humans.<sup>3-9</sup>

**Macrophages:** The increase in macrophages is one of the hallmarks of obesity-linked inflammation in AT.<sup>3,17-22</sup> Macrophages reside in AT, including VAT and SAT, in lean conditions and, with development of obesity, increase progressively and constitute the largest immune cell population in AT with established obesity.<sup>3,17,18,20,22</sup> The initial study showed that the percentage of macrophages was positively correlated with adipocyte size and body mass in all AT depots examined, including VAT (perigonadal, perirenal, and mesenteric AT) and SAT in mice and SAT in humans.<sup>17</sup> However, most studies of AT inflammation in mice have focused on perigonadal VAT.<sup>18,19,21</sup> Histologically, in obesity, macrophages surround dead or dying adipocytes forming crown-like structures (CLS).<sup>17,21</sup> Besides the change in numbers, AT macrophages can switch phenotypes from M0- or M2-like in lean conditions to M1-like in obesity, with increased expression of type 1 cytokines

such as TNF $\alpha$ , IL-1 $\beta$ , and IL-6.<sup>21,23</sup> In obesity, AT macrophages express high levels of CD11c,<sup>19–21</sup> a  $\beta$ 2 integrin that is commonly used to define dendritic cells in mice. Indeed, CD11c<sup>+</sup> cells in obese AT express high levels of MHCII and include macrophages and dendritic cells, both of which contribute to AT inflammation.<sup>19,24,25</sup> Compared to CD11c<sup>-</sup> macrophages, CD11c<sup>+</sup> cells in obese AT express higher levels of inflammatory markers,<sup>21</sup> contribute to obesity-linked AT inflammation,<sup>26</sup> and therefore have been commonly considered “M1” macrophages in AT in obese mice. However, the phenotypic switch of AT macrophages may be more complex than the classical M1–M2 paradigm. Kratz et al showed that in obesity, macrophages in AT, including VAT in obese mice and VAT and SAT in obese humans, polarize into a “metabolically activated” phenotype, which is associated with elevated levels of type 1 inflammatory markers and also markers involved in lipid metabolism, such as CD36, ABCA1, and Plin2, that have been considered M2 markers.<sup>27</sup> CD11c<sup>+</sup> macrophages in AT of obese humans mostly coexpress CD206, a pattern recognition receptor also commonly considered an M2 marker,<sup>28</sup> supporting a mixed phenotype rather than distinct M1 or M2 phenotype of AT macrophages.<sup>28</sup> Indeed, CD11c<sup>+</sup>CD206<sup>+</sup> macrophages from AT of obese humans express high levels of type 1 cytokines such as TNF $\alpha$ , IL-1 $\beta$ , and IL-6 and also IL-10, a type 2 cytokine.<sup>28</sup> Of note, although most animal studies focus on VAT inflammation or indicate greater macrophage accumulation in VAT than SAT,<sup>18,19,21,27</sup> SAT appears to contain more CD11c<sup>+</sup>CD206<sup>+</sup> macrophages than VAT in obese women.<sup>28</sup>

Recent studies employing single-cell RNA-seq identified a CD9- and CD63-expressing macrophage population that expands in VAT of mice and humans with obesity.<sup>29,30</sup> Compared to another macrophage population, which expresses Ly-6C and is also increased in AT of obese mice, CD9<sup>+</sup> macrophages, which are Ly-6c<sup>-</sup>, are the predominant macrophages forming CLS, express high levels of type 1 cytokines such as MCP-1, IL-1, and TNF $\alpha$ , and can initiate inflammatory responses in lean AT, supporting an important role of CD9<sup>+</sup> macrophages in AT inflammation.<sup>29</sup> CD9<sup>+</sup> macrophages also express Trem2, have a transcriptional signature of lipid metabolism and lysosomal pathways, are filled with intracellular lipids, and are therefore termed Trem2<sup>+</sup> lipid-associated macrophages,<sup>29,30</sup> perhaps similar to a metabolically activated phenotype.<sup>27</sup> The relation of CD9<sup>+</sup>Trem2<sup>+</sup> macrophages with CD11c<sup>+</sup> macrophages remains to be determined. However, an earlier study indicated that obesity initiates lysosome biogenesis associated with lipid accumulation in AT macrophages, CD11c<sup>+</sup> macrophages in particular,<sup>31</sup> suggesting that the newly identified CD9<sup>+</sup> macrophages may share large similarities with the early described CD11c<sup>+</sup> macrophages in obese AT.

**T lymphocytes:** T cells are also increased in AT, with higher frequency in VAT than in SAT, of obese mice and humans<sup>14,32,33</sup> and highly correlated with systemic inflammation in humans.<sup>32</sup> Increases in AT T cells may precede and contribute to the increases in AT macrophages in mice fed high-fat diet (HFD).<sup>34–39</sup>  $\alpha\beta$ T cells as compared to  $\gamma\delta$ T cells appear to have greater increases in obese AT.<sup>40</sup> Within  $\alpha\beta$ T cells, CD8<sup>+</sup> T cells show greater increases than CD4<sup>+</sup> T cells in AT of obese mice.<sup>36,38</sup>

**CD8<sup>+</sup> T cells:** In mice fed HFD, CD8<sup>+</sup> T cells increase early in VAT, but not SAT, and, along with macrophages, participate in CLS formation.<sup>36</sup> In obesity, VAT CD8<sup>+</sup> T cells polarize into effector memory or effector phenotypes expressing high levels of IFN $\gamma$  and activation markers such as CD69.<sup>36,38,41</sup> In mice, depletion of CD8<sup>+</sup> T cells attenuates and adoptive transfer of CD8<sup>+</sup> T cells exacerbates obesity-associated macrophage accumulation and inflammation in VAT,<sup>36</sup> supporting an important role of CD8<sup>+</sup> T cells in AT macrophage accumulation and inflammation in obesity.

**CD4<sup>+</sup> T cells:** Within AT CD4<sup>+</sup> T cells, the frequency of IFN $\gamma$ -expressing Th1 cells is increased with obesity and is higher in VAT than SAT in both mice and humans.<sup>32,40,42</sup> However, Th1 frequency in both AT depots correlates positively with inflammation in mice and humans.<sup>32,35,40,43–46</sup> Ablation of the Th1 cytokine IFN $\gamma$  attenuates AT inflammation, suggesting a crucial role of Th1 in AT inflammation.<sup>37,40</sup> In contrast, regulatory T cells (Treg), usually a small portion of CD4<sup>+</sup> T cells in lymphoid organs, are enriched in AT, particularly VAT, in lean conditions but dramatically decreased in VAT with obesity. Induction of AT Treg protects against obesity-associated AT inflammation.<sup>47,48</sup> The proportion of Th2 cells in both VAT and SAT negatively correlates with systemic inflammation and insulin resistance in humans, indicating a protective role of Th2 cells in inflammation and metabolic dysfunction.<sup>32</sup> Indeed, a study showed that with adoptive transfer into obese Rag1-null T cell-deficient mice, CD4<sup>+</sup> T cells polarized into Th2, which was associated with reversal of enhanced weight gain and insulin resistance in recipient mice.<sup>42</sup> However, another study indicated that transfer of naive CD4<sup>+</sup> T cells in Rag1-null mice resulted in a Th1 response in AT.<sup>25</sup> In addition, IL-17-producing Th17 cells and IL-22-expressing Th22 are increased in SAT in humans with obesity.<sup>25,32</sup> Nevertheless, Th17 frequency is higher in VAT than SAT of obese humans.<sup>32</sup>

**$\gamma\delta$ T cells:**  $\gamma\delta$ T cells account for approximately 30% of total CD3<sup>+</sup> T cells in VAT in lean conditions and may increase in AT with obesity.<sup>40,49,50</sup> HFD-induced obesity in mice increased TNF $\alpha$ -expressing  $\gamma\delta$ T cells in VAT.<sup>50</sup> Deficiency of  $\gamma\delta$ T cells or only V $\gamma$ 4 and V $\gamma$ 6 subsets reduced AT inflammation, with decreased accumulation of macrophages, CD11c<sup>+</sup> M1-like macrophages in particular, in VAT of mice, supporting an essential role of  $\gamma\delta$ T cells in obesity-linked inflammation.<sup>50</sup>  $\gamma\delta$ T cells may also be a major source of IL-17A in AT, and IL-17A-expressing  $\gamma\delta$ T cells are increased in both VAT and SAT of mice with obesity induced by HFD or associated with aging.<sup>39,49,51</sup>

**NKT cells:** NKT cells are a heterogeneous subset of T cells that express markers for  $\alpha\beta$ T cells,  $\alpha\beta$ TCR, and NK cells and can produce both Th1 and Th2 cytokines. Depending on the TCR repertoire, NKT cells can be classified into type I NKT cells, which express the invariant TCR $\alpha$  (V $\alpha$ 14-J $\alpha$ 18 in mice, V $\alpha$ 24-J $\alpha$ 18 in humans) and are therefore also called invariant NKT (iNKT), and type II NKT, which do not express this invariant TCR $\alpha$  chain.<sup>39</sup> Studies of the change and role of NKT in AT inflammation have generated inconsistent data. Some studies indicated that HFD in mice increased or activated VAT NKT, including iNKT, and that deficiency of NKT or iNKT reduced and activation of iNKT cells enhanced macrophage infiltration and inflammation in VAT in mice, indicating a promoting role of NKT, including iNKT, cells in obesity-linked AT inflammation.<sup>52–54</sup> In contrast, other

studies showed that iNKT cells are enriched in lean VAT, decreased with obesity, and may play a protective role in obesity-linked AT inflammation, by producing type 2 cytokines such as IL-10 and IL-4.<sup>55-57</sup>

**B lymphocytes:** B cells, particularly B2, are also elevated in VAT of mice on HFD and present in CLS in SAT of obese humans.<sup>33,58-60</sup> Compared to those from lean mice, B cells from obese mice exhibit a type 1 inflammatory phenotype with increased production of type 1 cytokines such as IL-6 and pathogenic IgG antibodies.<sup>58,61</sup> Deficiency or depletion of B cells decreases and adoptive transfer of B2 cells increases AT inflammation in obese mice.<sup>58,59,61,62</sup> B cells, particularly B2 cells, may contribute to AT inflammation by producing type 1 cytokines and pathogenic IgG antibodies, activation of macrophages and T cells, and modulation of Treg.<sup>58,61</sup> In contrast, B1 cells and regulatory B cells reside in VAT and SAT of mice and humans in normal conditions, are reduced with obesity, and may play a protective role in obesity-linked inflammation, possibly by producing IgM antibodies and IL-10 and suppressing CD8<sup>+</sup> T cell activation.<sup>62-64</sup> In lean mice, SAT appears to contain more B cells, with higher expression of IL-10, than VAT.<sup>64</sup>

**Neutrophils:** Neutrophils are the most abundant leukocytes in peripheral blood in humans. HFD feeding in mice resulted in an early and sustained infiltration of neutrophils in AT, mainly VAT.<sup>65-68</sup> Neutrophils may contribute to AT inflammation by secreting elastase, myeloperoxidase, and IL-1 $\beta$  and interacting with adipocytes recruiting monocytes/macrophages. Ablation of neutrophil elastase or myeloperoxidase reduces AT inflammation with decreased macrophage content and expression of inflammatory molecules.<sup>66,67,69</sup> Neutrophils are also activated in peripheral blood and present in both SAT and VAT of humans with morbid obesity.<sup>33</sup> Weight loss by bariatric surgery in humans reduced neutrophil content in both fat pads.<sup>33</sup>

**Eosinophils:** Eosinophils, usually a small portion of leukocytes in peripheral blood, are enriched in both VAT and SAT in normal conditions but drastically reduced with obesity.<sup>70-72</sup> In lean mice, VAT appears to contain more eosinophils than SAT.<sup>70,73</sup> Caloric restriction, microbiota depletion, helminth infection, or CCR2 deficiency in obese mice elevates AT eosinophils, which positively correlate with M2-like macrophages and type 2 cytokines.<sup>70,73-75</sup> Further studies show that AT eosinophils may play a role in inducing M2-like macrophages and suppressing type 1 inflammation via IL-4- and IL-13-mediated mechanisms.<sup>70,76-78</sup> However, another study showed that elevating AT eosinophils in obese mice by administering recombinant IL-5 did not alter AT M2-like macrophages and other inflammatory markers, suggesting that eosinophils may not have a direct role in promoting macrophage M2-like phenotype and regulating inflammation in obese AT.<sup>71</sup>

**Mast cells:** Mast cells are a type of immune cells that participate in allergic responses and inflammation by releasing a variety of inflammatory molecules, including cytokines/chemokines, histamine, serotonin, and proteases. Studies show that mast cells are also elevated and activated in VAT and SAT of mice and humans with obesity<sup>79-81</sup> and may contribute to AT inflammation by producing various inflammatory mediators such as IL-6

and IFN $\gamma$ .<sup>79,80</sup> Genetic ablation or pharmacological stabilization of mast cells in mice decreases AT inflammation.<sup>79,80</sup>

**Innate lymphoid cells (ILCs):** ILCs are a heterogeneous group of immune cells of the lymphoid lineage but lack the antigen-specific B or T cell receptors. Based on the cytokine and transcriptional signatures, ILCs can be classified into 3 subsets: group 1 ILCs (ILC1 and NK cells), group 2 ILCs (ILC2), and group 3 ILCs (ILC3), which simulate Th1, Th2, and Th17 and express Th1 cytokines, type 2 cytokines, and IL-17A, respectively. Obesity increases VAT, but not SAT, NK cell numbers and NK cell expression of type 1 cytokines, including IFN $\gamma$  and TNF $\alpha$ . Genetic ablation or antibody depletion of NK cells reduces and expansion or adoptive transfer of NK cells exaggerates macrophage accumulation and inflammation in VAT with obesity.<sup>82–84</sup> Obesity may also enhance ILC1 in SAT and VAT, which produces IFN $\gamma$  and can therefore accelerate M1-like polarization of macrophages and contribute to AT inflammation.<sup>85–87</sup> In contrast, ILC2 reside in VAT and SAT of both mice and humans in lean conditions, decrease with obesity, and may play an important role in normal AT homeostasis, including maintenance of eosinophils and M2-like macrophages.<sup>76,88,89</sup>

### **Inflammation in intermuscular/perimuscular AT:**

In addition to expansion of VAT and SAT, obesity is also associated with expansion of AT in skeletal muscle between muscle fibers, so-called intermuscular/intermyocellular AT (IMAT), and AT surrounding skeletal muscle, so-called perimuscular AT (PMAT).<sup>6,17,20,22,26,45</sup> IMAT and PMAT are extramyocellular fat but different from SAT, and expand with obesity and also aging.<sup>6,51,90–92</sup> IMAT/PMAT are highly correlated with insulin resistance and may directly regulate muscle insulin sensitivity.<sup>90–93</sup> A large number of studies indicated that inflammation also occurs in IMAT/PMAT in humans and mice with obesity. Similar to inflammation in VAT or SAT, IMAT/PMAT inflammation is mainly evidenced by increased immune cells, particularly macrophages and T cells,<sup>6,7,17,20,22,26,45,94–96</sup> which can also form CLSs surrounding dead or dying adipocytes.<sup>45</sup> Immune cells in IMAT/PMAT also show type 1 inflammatory phenotypes in obesity, with macrophages mostly expressing CD11c and exhibiting M1-like phenotypes, and T cells (CD4<sup>+</sup>) exhibiting Th1 phenotype with reduction in Treg.<sup>6,20,45,95</sup> Consistently, type 1 cytokines such as TNF $\alpha$  and IFN $\gamma$  are increased and type 2 cytokines such as IL-10 are decreased in skeletal muscle in obesity.<sup>6,20,45,94–96</sup>

### **Mechanisms for obesity-linked inflammation**

The mechanisms underlying obesity-linked inflammation remain poorly understood and may vary depending on tissue types and location. Immune cell recruitment, interactions, and activation releasing inflammatory molecules may constitute the major component of AT inflammation; however, the causal factors for these processes are largely unknown. Below, we discuss potential mechanisms for obesity-linked inflammation in AT (Figure 1).



**Immune cell recruitment:**

During obesity development, inflammation and recruitment of immune cells, mainly type 1 inflammatory cells, start early in AT.<sup>65,66,68,96–98</sup> In particular, neutrophils start to increase in VAT of mice after 3 days on HFD.<sup>65,66</sup> Increases in T cells appear to precede and contribute to the increases in macrophages in VAT of mice with diet-induced obesity.<sup>34–36</sup> However, increases in macrophages occur earlier than increases in T cells in IMAT/PMAT during obesity development in mice.<sup>45</sup> Macrophages that expand in obese AT appear to be mainly derived from recruited monocytes, including Ly-6C<sup>high</sup>, which are CD11c<sup>-</sup>, and Ly-6C<sup>low</sup>, which are CD11c<sup>+</sup>,<sup>99,100</sup> monocytes.<sup>19,21,23,29,30,101–103</sup>

For immune cell recruitment, interactions of chemokines with chemokine receptors on immune cells play crucial roles. Indeed, a large number of chemokines such as MCP-1, RANTES, fractalkine, KC, and MIP-2 $\alpha$  are increased early and persistently in AT with obesity.<sup>14,65,68,96–98,104</sup> Both immune cells and adipocytes/preadipocytes can produce chemokines,<sup>13–16,45,69,96</sup> which may play key roles in immune cell recruitment and inflammation in AT in obesity. MCP-1/CCR2 and RANTES/CCR5 pathways contribute to obesity-linked AT inflammation by recruiting immune cells such as macrophages and T cells<sup>14,45,104–107</sup> whereas MIP-2 $\alpha$  may be essential for neutrophil recruitment in AT in obesity.<sup>68</sup> In addition, the arachidonic acid-derived leukotriene LTB<sub>4</sub> is upregulated in VAT of obese mice and mediates macrophage recruitment in VAT in obesity.<sup>108</sup> Interactions of adhesion molecules on immune cells and their receptors on endothelial cells also play pivotal roles in immune cell migration. Lymphocyte function-associated antigen-1 (LFA-1), a  $\beta$ 2 integrin, plays an essential role in T cell infiltration and accumulation in VAT and IMAT/PMAT of obese mice, likely by interacting with ICAM-1 on endothelial cells or antigen-presenting cells.<sup>38,45</sup> ICAM-1 may also play an important role in neutrophil recruitment in AT in obesity.<sup>68</sup>  $\alpha$ 4 integrin and PSGL-1, a primary ligand on immune cells for P-selectin and E-selectin, may contribute to HFD-induced AT inflammation by mediating monocyte recruitment.<sup>109,110</sup> In addition to recruitment, increased proliferation and impaired egress of macrophages and T cells may also contribute to accumulation of these immune cells in VAT in obesity.<sup>38,44,103,111,112</sup>

**Immune cell interaction and activation:**

Once recruited into AT, immune cells and also adipocytes can interact with each other through secreted molecules or direct cell–cell contact, leading to immune cell (and adipocyte) activation, polarization, and inflammation (Figure 1).

Cytokines/chemokines are important mediators for immune cell activation. A variety of type 1 cytokines such as TNF $\alpha$ , IFN $\gamma$ , and IL-12 are increased in AT in obesity and are involved in obesity-linked AT immune cell activation and type 1 inflammation.<sup>13,37,45,94,113,114</sup> TNF $\alpha$ , the signature cytokine of M1 macrophages, and its downstream intracellular IKK/NF- $\kappa$ B and JNK pathways, and IFN $\gamma$ , the signature cytokine of Th1 that is also produced by ILC1 and mast cells, with its intracellular JAK/STAT1 pathway, are crucial for obesity-induced AT macrophage M1-like polarization and inflammation.<sup>37,45,79,83,115–117</sup> IL-12, mainly produced by M1 macrophages/dendritic cells, and its downstream signaling molecule STAT4, play crucial roles in Th1 polarization and CD8<sup>+</sup> T cell activation and also

contribute to ILC1 accumulation in AT with obesity.<sup>38,85,114</sup> In addition, elastase, myeloperoxidase, and cathelicidin produced by neutrophils may contribute to AT macrophage accumulation and activation in obesity.<sup>66,67,118</sup>

In contrast to AT type 1 inflammation in obesity, type 2 inflammation dominates in AT in lean healthy conditions, in which type 2 cytokines play essential roles in AT immune homeostasis. For example, IL-33, which is mainly produced by AT stromal cells, is important for maintenance of Treg and ILC2 in AT. Treg are protective against type 1 inflammation and autoimmunity, and ILC2 may play a role in accumulation and maintenance of eosinophils, Th2 cells, and M2 macrophages by producing type 2 cytokines such as IL-5, IL-4, and IL-13.<sup>47,70,76,89,119</sup> In contrast, IFN $\gamma$  may suppress AT ILC2 activation and Treg accumulation in obesity.<sup>89</sup>

Immune cells can also interact with each other and with adipocytes through direct contact. In mice with obesity, AT macrophages/dendritic cells and also adipocytes can activate T cells and induce T cell proliferation and Th1 polarization through the MHCII-TCR pathway.<sup>24,35,43,44</sup> Further, costimulators/co-inhibitors expressed on antigen-presenting cells and T cells are important for antigen-presenting cell–T cell interaction. CD40 and B7 molecules (CD80 and CD86) are induced in AT of obese mice.<sup>120–122</sup> CD40 ligand may play a promoting role in T cell and M1-like macrophage accumulation and inflammation in AT of obese mice.<sup>123</sup> However, CD40 may function as an inhibitor for AT inflammation in obesity.<sup>120,121</sup> Similarly, CD80/CD86 may have a protective role in AT inflammation in mice with obesity.<sup>122</sup> In contrast, OX40, a costimulatory molecule that is increased on AT CD4<sup>+</sup> T cells in obesity, and CD11c expressed mainly on macrophages/dendritic cells may promote T cell activation and Th1 polarization in obese mice.<sup>19,124</sup> In addition, ILC2 can interact with AT macrophages upon HFD feeding through the PD-1–PD-L1 pathway, leading to impaired ILC2 function,<sup>125</sup> and with Treg via ICOSL-ICOS or with AT stromal cells via LFA-1–ICAM-1 in normal conditions sustaining ILC2 and Treg cells and type 2 inflammatory environment in AT.<sup>89,119</sup>

### Triggers and sustainers:

Despite the above discussion on AT immune cell accumulation and activation in obesity, the signals that trigger and maintain these inflammatory changes are not well known and may include multiple factors, which are discussed below.

**Dietary component and fatty acids (FAs):** In mice with diet-induced obesity, inflammation in AT starts early after initiating HFD and persists as long as HFD is maintained.<sup>65,66,96–98</sup> On the other hand, AT inflammation is reduced quickly after switching from HFD to normal chow.<sup>126,127</sup> These data suggest that diet may play an important role in regulation of AT inflammation. Indeed, the main HFD-derived dietary component, long-chain saturated FAs such as palmitic acid, induces inflammation including expression of chemokines and type 1 cytokines in a variety of cell types, including adipocytes and macrophages, possibly by interaction with pattern recognition receptors such as TLR4 and TLR2 and activation of NF- $\kappa$ B and JNK pathways and the NLRP3 inflammasome, which all indeed play essential roles in obesity-linked AT inflammation.



6,15,20,128–131 Adipocyte-derived chemokines may play an important role in initiation of immune cell accumulation and inflammation in AT upon HFD feeding.<sup>14–16</sup> With the progression of obesity, dietary FAs and other signals such as damage-associated molecular patterns, which are produced by stressed or damaged cells and bind to pattern recognition receptors, may play pivotal roles in maintenance of AT inflammation by inducing macrophage M1 polarization.<sup>6,20,21,128–131</sup>

**Hypoxia:** During obesity development, rapid expansion of AT (adipocyte hypertrophy), with insufficient AT vascularization and also increased adipocyte oxygen consumption, results in AT hypoxia,<sup>132–134</sup> which can activate hypoxia-inducible factors (HIFs), a family of transcription factors.<sup>135</sup> Indeed, obesity in mice induces early and consistent upregulation of HIF1 $\alpha$  in AT, associated with AT inflammation.<sup>132,133</sup> Deletion of HIF1 $\alpha$  in adipocytes reduces and overexpression of HIF1 $\alpha$  in AT exacerbates HFD-induced AT inflammation in mice.<sup>132,134,136</sup> By activating HIF-1 $\alpha$ , hypoxia can induce adipocyte expression of chemokines such as MCP-1 and LTB<sub>4</sub>,<sup>132</sup> which may contribute to AT inflammation by initiating immune cell accumulation and inflammation in AT. In addition, AT hypoxia may also contribute to AT inflammation by enhancing macrophage M1-like polarization, in which HIF1 $\alpha$  and other signaling molecules such as JNK play essential roles.<sup>137–139</sup> These studies indicate that similar to FAs, hypoxia may play a crucial role in initiation and maintenance of AT inflammation by inducing adipocyte expression of chemokines recruiting immune cells and by inducing macrophage M1-like polarization, mainly via HIF1 $\alpha$ - and JNK-mediated mechanisms.

**Intestinal microbiota and LPS:** Large numbers of studies show that obesity or HFD feeding is associated with alterations in intestinal microbiota, with increases in LPS-containing microbiota, and increased intestinal permeability,<sup>140,141</sup> which can raise plasma levels of LPS leading to so-called metabolic endotoxemia.<sup>142,143</sup> Experimental endotoxemia induced by low-dose injection of LPS induces AT inflammation in healthy humans and animals, supporting a direct role of metabolic endotoxemia in AT inflammation.<sup>142,144,145</sup> LPS in metabolic endotoxemia may contribute to AT inflammation by eliciting type 1 inflammation including inducing expression of type 1 cytokines and chemokines in adipocytes and macrophages via interactions with TLR4 and CD14.<sup>142,146</sup> In support of this hypothesis, germ-free mice or mice with antibiotic treatment to reduce metabolic endotoxemia or deletion of CD14, TLR4, or the related signaling molecule have ameliorated AT inflammation induced by HFD or obesity.<sup>128,146</sup> Therefore, metabolic endotoxemia, resulting from alterations in intestinal microbiota and increased intestinal permeability, may also play a role in triggering and maintaining obesity-linked AT inflammation by impacting adipocytes, macrophages, and other immune cells.<sup>140,141</sup>

## Inflammation and metabolism

### Inflammation and insulin resistance:

As described above, in healthy conditions, normal AT homeostasis is associated with type 2 inflammatory environment (Figures 1 and 2). In contrast, obesity with insulin resistance is associated with type 1 inflammation in AT. While insulin resistance may precede and

contribute to AT (type 1) inflammation,<sup>147</sup> most studies still support that inflammation plays a causal role in the development of insulin resistance. Alternatively, inflammation may play differential roles at different conditions or stages of obesity. Once initiated, inflammation and insulin resistance may exacerbate each other. AT inflammation may contribute to local (AT) and systemic insulin resistance through autocrine effects of inflammatory cells/ molecules on insulin signaling and metabolism in adipocytes and endocrine effects of inflammatory molecules secreted by AT (known as adipokines) on insulin sensitivity in other tissues, particularly skeletal muscle and liver. In addition, adverse effects of inflammation on preadipocyte/adipocyte metabolism can accelerate fat spillover from AT to skeletal muscle and liver, resulting in ectopic fat deposition and insulin resistance in these tissues, which play vital roles in systemic insulin resistance and T2DM.<sup>5,6,22,148,149</sup>

**Contributions of AT inflammation to insulin resistance:** Since the report of increased inflammation in AT in obesity, the association and potential contribution of AT inflammation to obesity-linked insulin resistance and T2DM have been revealed by numerous studies (Figure 2).

Earlier studies showed associations of increased AT TNF $\alpha$  and macrophages with insulin resistance in obese mice and humans.<sup>13,17,18</sup> The increase in AT macrophages appears to precede insulin resistance in mice with HFD-induced obesity.<sup>18</sup> Increasing AT macrophage content in mice by overexpressing MCP-1 was associated with exacerbated insulin resistance.<sup>106</sup> Increasing AT inflammation by experimental endotoxemia also induces insulin resistance in healthy humans and mice.<sup>142,144,145</sup> On the other hand, reductions in AT macrophages or TNF $\alpha$  by depletion of macrophages or TNF $\alpha$  or ablation of MCP-1 or its receptor in mice was associated with improved insulin resistance.<sup>26,106,107,113</sup> All these data support a casual role of AT macrophages and TNF $\alpha$  in development of insulin resistance.

Increased AT T cells, particularly CD8<sup>+</sup> effector/effector memory T cells and CD4<sup>+</sup> Th1 cells, are associated with insulin resistance in both mice and humans.<sup>14,32,35,40,43–46</sup> Genetic deficiency of CD8<sup>+</sup> T cells or Th1 cells in  $\alpha\beta$ T cell–null mice or ablation of IFN $\gamma$  or T-bet, the master transcription factor for Th1 polarization, improves insulin resistance in obese mice, whereas adoptive transfer of Th1 or CD8<sup>+</sup> T cells exacerbates insulin resistance in mice fed HFD,<sup>36,37,40,45,150</sup> supporting contributions of Th1 cells and CD8<sup>+</sup> T cells to development of obesity-linked insulin resistance. In contrast, adoptive transfer or expansion of Th2 cells or Treg prevents obese mice from developing insulin resistance,<sup>42,47,48</sup> suggesting a protective role of type 2 immune cells in obesity-linked insulin resistance.

In addition, B2 cells, neutrophils, NK cells, and ILC1 have been shown to contribute to development of insulin resistance in obesity.<sup>58,59,61,66,67,82–87</sup> In contrast, B1 cells, Breg cells, and ILC2 may protect against obesity-linked insulin resistance.<sup>62–64,76,88,89</sup> A role of mast cells was demonstrated in development of obesity-linked insulin resistance in some,<sup>79</sup> but not other,<sup>80,151</sup> studies. Whereas some studies revealed a promoting role of NKT, including iNKT and type II NKT, in development of insulin resistance in obesity,<sup>52–54</sup> other studies showed a protective role of iNKT cells against this effect.<sup>55–57</sup> Eosinophils were initially demonstrated to protect against obesity-induced insulin resistance.<sup>70</sup> However,

elevation of AT eosinophils in obese mice by administering recombinant IL-5 did not improve insulin resistance.<sup>71</sup>

**Molecular mechanisms:** The molecular mechanisms by which AT inflammation contributes to insulin resistance are not well understood and may be multifactorial. Most immune cells may contribute to obesity-linked insulin resistance through macrophages and T cells,<sup>53,58,61,82,84,87</sup> which release type 1 cytokines such as TNF $\alpha$ , IL-1 $\beta$ , and IFN $\gamma$  that can adversely regulate metabolism and cause insulin resistance in a variety of cell types, including adipocytes and skeletal muscle myocytes, by paracrine or endocrine effects. These cytokines act through interactions with their receptors on the cells, activating a series of intracellular signaling pathways (see below), which impair insulin signaling and induce insulin resistance in the cells (see the detailed review<sup>6</sup>).

**IKK/NF- $\kappa$ B pathway:** The IKK/NF- $\kappa$ B pathway is mainly activated by cytokines such as TNF $\alpha$  and IL-1 $\beta$  and also by saturated FAs and damage-associated molecular patterns such as high-mobility group box 1 released from stressed or damaged cells. This pathway exhibits enhanced activation in various tissues including AT in obesity and may contribute to insulin resistance via IKK-mediated serine phosphorylation of insulin receptor substrate-1 (IRS-1) or insulin receptor (IR), with inhibition of insulin-induced tyrosine phosphorylation and downstream signaling.

**JNKs and MAPKs:** JNKs and other MAPKs such as p38 MAPK can be activated by TNF $\alpha$ , IL-1 $\beta$ , ER stress, and saturated FAs and may induce insulin resistance by mediating serine and threonine phosphorylation of IRSs, leading to impairment in the interaction of IRSs with IR and downstream insulin signaling.

**PKCs:** Both conventional PKCs and novel PKCs rely on diacylglycerol for full activation. Studies show that obesity or HFD feeding can activate PKCs, which may contribute to insulin resistance by inducing serine or threonine phosphorylation of IR or IRS-1, resulting in impairment of downstream insulin signaling.

**JAK/STAT/SOCS pathways:** The main signaling for IFN $\gamma$ , the Th1 signature cytokine, is the JAK1/JAK2/STAT1 pathway, whereas IL-6 mainly activates the STAT3 pathway. Both STAT1 and STAT3 pathways can become activated in obesity and may contribute to insulin resistance through their downstream molecules, suppressor of cytokines signaling (SOCS) proteins, particularly SOCS1 and SOCS3, which can repress IR tyrosine kinase activity, interrupt the interaction of IR with IRSs, and promote IRS degradation, thereby impairing insulin signaling.

**“Noninflammatory role” of AT macrophages in insulin resistance:** In addition to their inflammatory role, AT macrophages may impact insulin sensitivity and glucose homeostasis via other pathways that are not directly related to inflammation. Obesity induces lysosome biogenesis associated with lipid catabolism and accumulation in AT macrophages, particularly CD11c<sup>+</sup> macrophages<sup>31</sup> or the recently identified Trem2<sup>+</sup> macrophages.<sup>29,30</sup> Deficiency of Trem2 in mice on HFD leads to reversal of the phenotype and reduction of lipid accumulation in AT Trem2<sup>+</sup> macrophages, which are associated with

exacerbated adipocyte hypertrophy, accelerated adiposity, and exaggerated glucose intolerance,<sup>30</sup> indicating that lipid metabolism and accumulation in AT macrophages may play a role in control of HFD-induced adiposity and metabolic disease. Consistently, lipid storage in AT macrophages can regulate systemic glucose homeostasis and insulin sensitivity.<sup>152,153</sup>

### Immunoregulation of AT browning (Figure 2):

Recent studies show that immune cells can regulate brown AT activity or white AT browning, thereby influencing adiposity and metabolism.<sup>154</sup> An initial study showed that cold exposure increased M2-like macrophages in AT, which released catecholamines that activated brown AT and white AT browning.<sup>155</sup> Eosinophils and type 2 cytokines, including IL-4 and IL-13, can promote white SAT browning and protect against obesity by inducing macrophage M2 polarization.<sup>78</sup> Type 2 immune cells and cytokines may also mediate AT browning elicited by caloric restriction, microbiota depletion, or meteorin-like, a circulating factor that is induced in muscle by exercise and in AT with cold exposure.<sup>74,75,77</sup> However, the studies on the role of eosinophils and M2 macrophages in promoting AT browning have been challenged by other studies that showed no or minimal role of M2 macrophages or eosinophils in AT browning.<sup>71,154,156</sup> ILC2 can promote AT browning and protect against obesity by producing methionine-enkephalin peptides that can directly induce UCP1 expression in white AT<sup>88</sup> or through type 2 signaling.<sup>157</sup> iNKT cells may promote white AT browning by inducing FGF21 production.<sup>154</sup> In addition, PLZF<sup>+</sup>  $\gamma\delta$ T cells, a subset of  $\gamma\delta$ T cells, increase thermogenic activity in brown and white AT under cold exposure.<sup>49</sup>

In contrast to type 2 inflammation, type 1 inflammation has mostly been shown to suppress AT browning induced by cold or  $\beta$ 3 agonist. M1-like macrophages and the cytokines TNF $\alpha$  and IL-1 $\beta$  inhibit UCP1 expression in AT/adipocytes in vitro and in vivo.<sup>158–160</sup> Direct macrophage–adipocyte contact mediated by interaction of  $\alpha$ 4 integrin on macrophages and VCAM-1 on adipocytes also plays a role in M1-like macrophage-mediated suppression of AT browning.<sup>160</sup> In addition, IFN $\gamma$  inhibits adipocyte UCP1 expression and browning in tissue culture<sup>161,162</sup> and may mediate the inhibitory effects of CD8<sup>+</sup> T cells on AT browning in mice.<sup>163</sup> Importantly, reduction in type 1 inflammation or anti-inflammatory (type 1 inflammation) drugs enhance (“derepress”) AT browning or brown AT activity.<sup>116,164</sup> Of note, IL-10, usually functioning as an anti-inflammatory cytokine, inhibits AT browning by repressing thermogenic gene expression in adipocytes.<sup>165</sup> In addition, Pirzgalska et al described a type of macrophage in AT that is tightly associated with sympathetic neurons, so-called sympathetic neuron-associated macrophages, which are increased in obesity and inhibit thermogenesis by clearing noradrenaline.<sup>166</sup> Mast cells may inhibit AT browning by releasing serotonin in obesity,<sup>167</sup> but they promote AT browning by secreting histamine in cold.<sup>168</sup>

### Inflammation and AT remodeling (Figure 2):

AT remodeling is a complex process by which AT is adapted to various stimuli including HFD feeding and obesity. During obesity development, adipocytes quickly become enlarged and hypertrophic. At same time, extracellular matrix remodeling and angiogenesis are initiated to accommodate AT expansion. Appropriate remodeling is essential for healthy AT

expansion over excessive nutrients. Dysfunctional remodeling may contribute to development of obesity-linked metabolic disorders.

Inflammation plays important but complex roles in AT remodeling. Studies from Scherer's group indicated that inflammation in adipocytes is essential for healthy AT expansion, extracellular matrix remodeling, and angiogenesis and that suppression of adipocyte inflammation results in AT dysfunction and systemic metabolic disease.<sup>169</sup> Macrophages may contribute to AT remodeling in several different ways. At the tips of growing AT, macrophages may promote AT angiogenesis and extracellular matrix remodeling by producing VEGF, MMP1, and MMP12.<sup>170,171</sup> Several cytokines such as TNF $\alpha$  and IL-8 secreted by macrophages have proangiogenic roles, thereby possibly contributing to healthy AT expansion and remodeling.<sup>171</sup> M2-like macrophages may support adipogenesis during AT remodeling.<sup>170</sup> In obesity, macrophages, by secreting cytokines such as TNF $\alpha$  and TGF $\beta$  or expressing macrophage-inducible C-type lectin, may suppress adipogenesis but promote AT fibrosis, which is generally considered to contribute to AT dysfunction in obesity.<sup>170-172</sup> In mice with diet-induced obesity, macrophage inflammation is associated with widespread fibrosis and adipocyte death in VAT.<sup>173</sup> Certain chemokines such as CXCL10 and CXCL11, which are upregulated in obese AT and possibly produced by T cells and macrophages, suppress angiogenesis,<sup>174</sup> thereby possibly contributing to AT hypoxia in obesity. AT ILC1 may contribute to AT fibrosis by activating TGF $\beta$  signaling.<sup>86</sup> Mast cells may play a role in fibrosis by releasing MCP-6 that induces collagen V expression in AT.<sup>175</sup> T cells, particularly activated T cells, and the Th1 cytokine IFN $\gamma$  adversely regulate adipogenesis.<sup>14,40</sup> T cells may also regulate fibrosis in other tissues, but it remains to be determined whether T cells have the same effects in AT.

## Targeting inflammation to treat obesity-linked metabolic disease

Because of the role of inflammation in obesity, targeting inflammation represents a new therapy for obesity-linked diseases, including insulin resistance and T2DM. Indeed, numerous animal studies have shown benefit of reduction or suppression of inflammation for obesity-linked insulin resistance and metabolic disease. Moreover, multiple antidiabetic drugs possess anti-inflammatory properties. Importantly, (pre)clinical trials testing the efficacy of anti-inflammatory drugs in treating insulin resistance and T2DM have generated some promising results. However, in general, the clinical approach of specifically targeting inflammation to treat metabolic disease remains challenging (see reviews<sup>176,177</sup>).

The classical broad spectrum anti-inflammatory drugs, salicylates, reduce inflammation and lower blood glucose levels in humans with obesity and/or insulin resistance and T2DM.<sup>176-180</sup> Another generic anti-inflammatory drug, methotrexate, lowers HbA1c levels in patients with rheumatoid arthritis.<sup>181</sup> However, the recent Cardiovascular Inflammation Reduction Trial (CIRT) revealed that low-dose methotrexate did not reduce IL-1 $\beta$ , IL-6, or CRP levels, failed to show benefits on cardiovascular effects, and had more adverse events in individuals with a history of myocardial infarction or multivessel coronary disease and with either T2DM or metabolic syndrome,<sup>182</sup> making this drug unlikely to be used to treat cardiovascular disease and perhaps also T2DM. Colchicine, another anti-inflammatory drug,

was recently shown to lower risk of cardiovascular disease in secondary prevention.<sup>183</sup> Whether colchicine is effective in treating T2DM remains to be determined.

Several other anti-inflammatory drugs targeting specific pathways have also been tested for treatment or prevention of T2DM. Given the role of the NLRP3 inflammasome in obesity-linked AT inflammation,<sup>130,131</sup> targeting the NLRP3 inflammasome or its downstream molecules including IL-1 $\beta$  and IL-18 may represent a potential therapeutic approach for obesity-related inflammation and metabolic dysfunctions. Indeed, IL-1 $\beta$  antagonists, including canakinumab, an anti-IL-1 $\beta$  antibody, and anakinra, an IL-1R antagonist, have been shown to reduce inflammation and lower blood levels of glucose or HbA1c in several trials.<sup>176,177,184–187</sup> However, IL-1 $\beta$  inhibition by canakinumab in the CANTOS trial did not show long-term benefits in reducing HbA1c and reductions in incident T2DM.<sup>186</sup> The potential of other therapies targeting the NLRP3 inflammasome pathway in treating T2DM remains to be assessed. Treatment with inhibitors for TNF $\alpha$  did not generate consistent results for glucose- or HbA1c-lowering effects.<sup>176,177</sup> In addition, targeting immune cell infiltration represents another type of anti-inflammatory therapy. Indeed, antagonists for chemokine receptors such as CCR2 or CCR2 and CCR5 have been shown to reduce AT inflammation and improve insulin sensitivity in animal models of obesity<sup>188</sup> and modestly improved glycemia in humans with T2DM in a small cohort.<sup>189</sup> Clinical trials are also testing effects of anti-inflammatory drugs on diabetic complications. CCR2/CCR5 dual antagonists showed efficacy in treating diabetic nephropathy and nonalcoholic steatohepatitis with fibrosis in humans.<sup>190,191</sup> A Jak1/Jak2 inhibitor, which inhibited inflammation and improved insulin resistance in obese mice,<sup>45</sup> decreased inflammation, reduced albuminuria, and also lowered HbA1c in humans with T2DM and diabetic kidney disease.<sup>192</sup>

Additionally, caloric restriction or intermittent fasting has been shown to benefit health, including reducing obesity and improving metabolism.<sup>126,193–195</sup> Caloric restriction or intermittent fasting also reduces AT inflammation,<sup>126,127,196</sup> which may, at least partially, contribute to the beneficial effect of the dietary intervention on obesity-related metabolism.

## Conclusion and Perspectives

A large body of evidence has shown increased inflammation in varieties of tissues in obesity, which is mainly characterized by increased accumulation and type 1 inflammatory polarization of various immune cells, including innate and adaptive immune cells. Diets, tissue microenvironment, and other factors such as gut microbiota may all contribute to initiation and maintenance of tissue inflammation. Inflammation, particularly long-term chronic inflammation, may play important roles in development and progression of obesity-linked insulin resistance and T2DM through multiple pathways regulating metabolism. Reduction or inhibition of inflammation is mostly associated with improvements in insulin resistance and metabolic functions in animal models of obesity and therefore holds promise as a new therapy for obesity-linked metabolic disease. To date, clinical studies testing the efficacy of therapies targeting inflammation for human metabolic disease have generated some promising results, but, in general, remain challenging and unsatisfactory. Inflammation is a very complex process involving a wide variety of inflammatory cells and pathways. Our



current knowledge about the particular pathways for obesity-linked inflammation, especially related to human obesity, is still limited and hinders the development of novel, specific “obesity-targeted” anti-inflammatory approaches. Future studies will need to focus on identification of new pathways and related candidate targets specific for obesity-linked inflammation, which may lead to development of new therapies for obesity-related metabolic disease. Furthermore, obesity and most related diseases involving inflammation are a long-term, chronic process. The potential benefits versus side effects, impairment of host immunity in particular, of long-term systemic use of inflammation-targeting therapies will need to be carefully evaluated. Future studies will also need to explore the potential of targeting inflammation in specific organs/tissues to treat obesity-linked metabolic disease. Further advances in our knowledge of the role and mechanism of inflammation in metabolic disease and development of new technologies will create new opportunities to develop novel therapies for metabolic disease associated with obesity.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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## Non-standard Abbreviations and Acronyms

<b>AT</b>	adipose tissue
<b>CIRT</b>	Cardiovascular Inflammation Reduction Trial
<b>CLS</b>	crown-like structures
<b>FAs</b>	fatty acids
<b>HFD</b>	high-fat diet
<b>HIF</b>	hypoxia-inducible factor
<b>ILC</b>	innate lymphoid cells
<b>IMAT</b>	intermuscular/intermyocellular adipose tissue
<b>iNKT</b>	invariant NKT cells
<b>IR</b>	insulin receptor

<b>IRS</b>	insulin receptor substrate
<b>LFA-1</b>	lymphocyte function-associated antigen-1
<b>PMAT</b>	perimuscular adipose tissue
<b>SAT</b>	subcutaneous adipose tissue
<b>T2DM</b>	type 2 diabetes
<b>Th</b>	T helper
<b>Treg</b>	regulatory T cells
<b>VAT</b>	visceral adipose tissue

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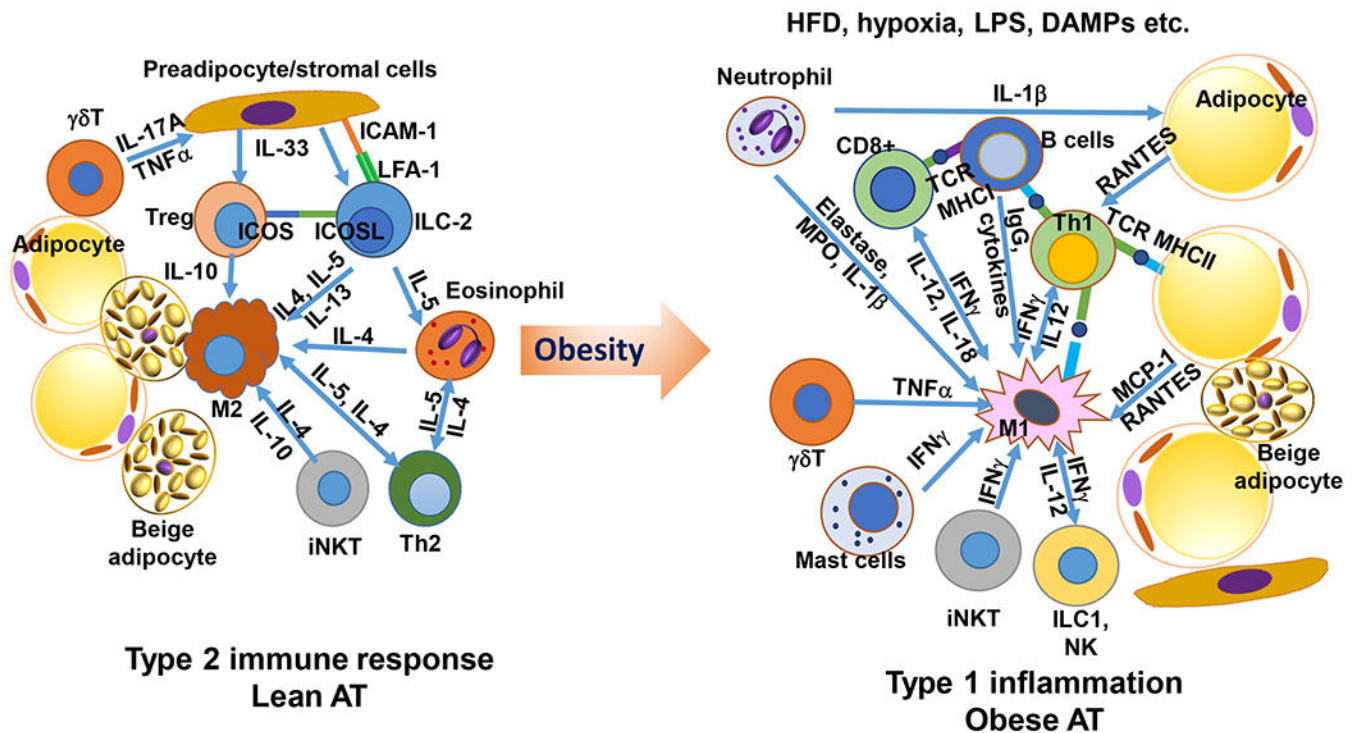


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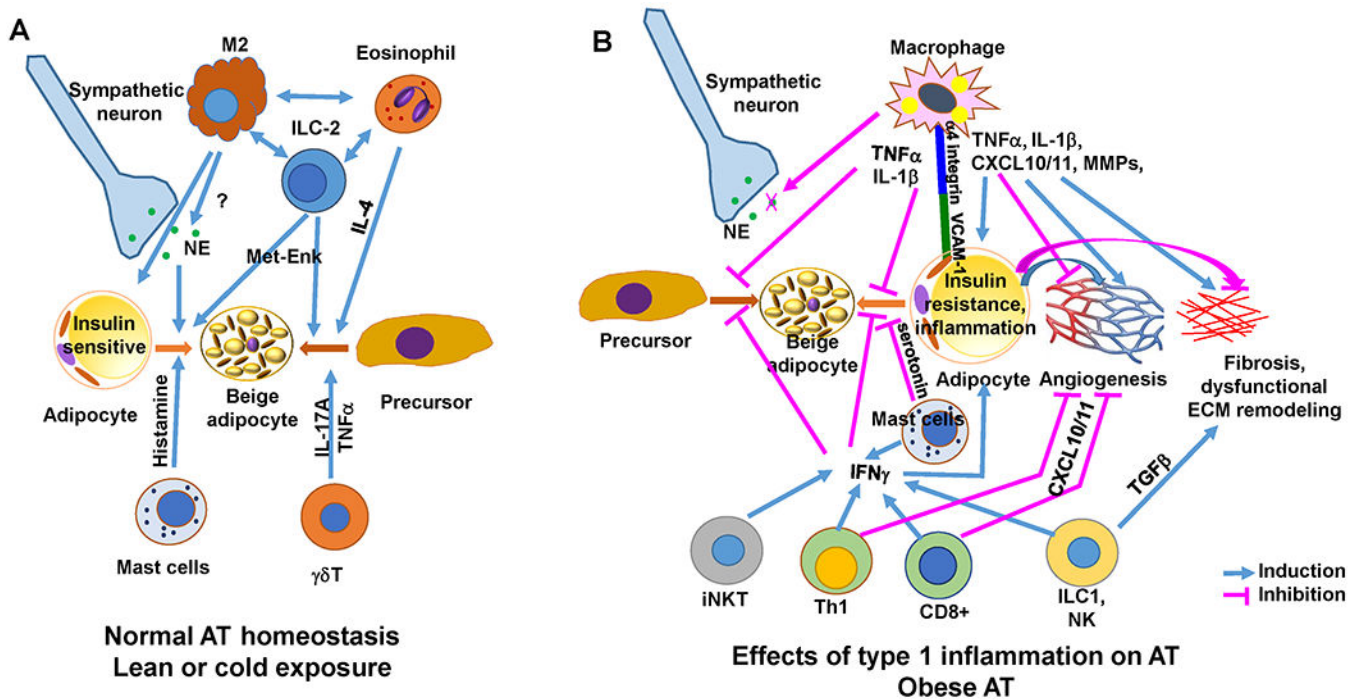
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**Figure 1. Regulation of inflammation in adipose tissue (AT).**

In lean conditions, AT is enriched with type 2 immune cells, including alternatively activated M2-like macrophages (M2), innate lymphoid type 2 cells (ILC2), regulatory T cells (Treg), T helper type 2 cells (Th2), eosinophils, and others, which interact with each other by producing type 2 cytokines such as interleukin-4 (IL-4), IL-5, and IL-13 and also by direct contact via interactions of cell surface molecules, to maintain a type 2 immune environment. With the development of obesity, particularly induced by high-fat diet (HFD), dietary saturated fatty acids, along with AT hypoxia, danger-associated molecular patterns (DAMPs), and “metabolic endotoxemia” with increased plasma levels of lipopolysaccharide (LPS) that develop in obesity, may promote type 1 inflammation in AT, with increased inflammation in adipocytes and elevated number and type 1 inflammatory polarization or “metabolically activated” activation of a variety of immune cells, including macrophages, T cells, B cells, neutrophils, and others, which produce a large number of type 1 inflammatory molecules and also interact directly with each other to induce a type 1 inflammatory environment in AT. ICAM-1 indicates intercellular adhesion molecule–1; ICOS, inducible costimulator; ICOSL, inducible costimulator ligand; IFN $\gamma$ , interferon- $\gamma$ ; ILC, innate lymphoid cells; iNKT, invariant natural killer T cells; LFA-1, leukocyte function-associated antigen–1; MCP-1, monocyte chemoattractant protein–1; MHC, major histocompatibility complex; MPO, myeloperoxidase; NK, natural killer cells; RANTES, regulated on activation, normal T cell expressed and secreted; TCR, T-cell receptor; and TNF $\alpha$ , tumor necrosis factor- $\alpha$ . (Illustration Credit: Ben Smith).



**Figure 2. Impact of inflammation on AT metabolism and remodeling.**

**A.** In lean conditions, with a type 2 immune environment, various immune cells through different mechanisms contribute to maintenance of normal AT functions including adipocyte insulin sensitivity and beige adipogenesis. **B.** In obesity, type 1 inflammatory or metabolically activated immune cells may contribute to AT dysfunctions by adversely regulating adipocyte metabolism and AT remodeling, including induction of insulin resistance in adipocytes, suppression of beige adipogenesis, and induction of dysfunctional AT remodeling. Studies also show that in obesity, adipocyte inflammation may be essential for healthy AT expansion and remodeling and that lipid storage within AT macrophages may protect against obesity-linked adipocyte dysfunctions. ECM indicates extracellular matrix; MET-ENK, methionine-enkephalin; MMPs, matrix metalloproteinases; NE, norepinephrine; TGF $\beta$ , transforming growth factor- $\beta$ ; and VCAM-1, vascular cell adhesion molecule-1. (Illustration Credit: Ben Smith).

**Table 1.**

Comparison of type 1 and type 2 inflammation

	<b>Type 1</b>	<b>Type 2</b>
Stimuli	LPS, IFN $\gamma$ , TNF $\alpha$ , IL-12	IL-10, IL-4/IL-13, allergens
Major cells	Th1, CD8+ T <sub>EM</sub> /T <sub>E</sub> , M1 macrophages, neutrophils	Th2 cells, M2 macrophages, eosinophils, ILC2
Secreted cytokines	IFN $\gamma$ , TNF $\alpha$ , IL-1 $\beta$ , IL-6, IL-12	IL-4, IL-5, IL-10, IL-13, TGF $\beta$
Transcription factors	T-bet (Th1), STAT1, NF- $\kappa$ B, IRF5	STAT3, STAT6, IRF4, GATA3, PPAR $\gamma$
Major functions	Defense against intracellular pathogens	Immunoregulation, tissue remodeling, allergy, defense against extracellular parasites

GATA3 indicates GATA binding protein 3; IFN $\gamma$ , interferon- $\gamma$ ; IL, interleukin; ILC, innate lymphoid cells; IRF, interferon regulatory factor; LPS, lipopolysaccharide; NF- $\kappa$ B, nuclear factor- $\kappa$ B; PPAR $\gamma$ , peroxisome proliferator-activated receptor- $\gamma$ ; STAT, signal transducer and activator of transcription; T<sub>E</sub>, effector T cells; T<sub>EM</sub>, effector memory T cells; Th, T helper; and TNF $\alpha$ , tumor necrosis factor- $\alpha$ .

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