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Adipose tissue inflammation is often a consequence of obesity and is characterized by infiltration and activation of immune cells that overproduce cytokines and chemokines. This apparent loss of immune regulation in obese adipose tissue contributes to the ongoing chronic inflammation that is thought to promote the degradation of metabolic parameters in obesity. Much recent work has sought to identify the immune cell subsets that are involved in adipose tissue inflammation, understand the mechanisms by which adipose tissue inflammation develops, and develop immunotherapeutic strategies to reverse this process. In this review, we describe the known mechanisms that underlie the loss of immune regulation in obesity-associated adipose tissue inflammation and set the stage for the development of novel therapeutic approaches. The Journal of Immunology, 2013, 191: 527–532.

Obesity is a risk factor for developing insulin resistance, defined as the inability of cells such as adipocytes, hepatocytes, and myocytes to respond normally to insulin and adequately activate pathways leading to glucose uptake. A commonly held view is that in a subset of obese, insulin-resistant individuals, β cell dysfunction ensues, leading to decreased insulin production, poor glucose regulation, and ultimately type 2 diabetes (T2D) (1, 2). It is also possible that β cell dysfunction arises prior to, or in parallel with, insulin resistance, because it can, in some cases, be detected well before the onset of T2D (3, 4). Investigation into the mechanisms which make obesity a risk factor for developing insulin resistance is an area of intense research, with increasing evidence for a major role of inflammation. Specifically, the development of excess adipose tissue (AT) is strongly associated with the development of chronic inflammation caused by infiltration of activated immune cells and overproduction of proinflammatory cytokines. Mechanistically, proinflammatory cytokines, such as TNF-α, can cause serine phosphorylation and inactivation of insulin receptor substrate-1, and hence block insulin receptor signaling in multiple cell types, including adipocytes and hepatocytes (5, 6).

Interesting, visceral adiposity is more tightly linked with metabolic abnormalities than s.c. adiposity (7, 8), possibly because visceral AT (VAT) is more vulnerable to loss of immune regulation and hence inflammation. For example, mast cell infiltration and a proportional decrease in T regulatory cells (Tregs) are more prominent in visceral than s.c. AT of obese individuals (9–11). Whether the initiating trigger is adiposity, inflammation, and/or other factors remains unknown. In this review, we discuss recent studies that are beginning to reveal a central role for loss of immune regulation as a major factor contributing to AT inflammation and obesity-associated pathologies.

AT inflammation is driven by innate and adaptive immune cells

Obesity-associated inflammation has long been attributed to the presence of elevated levels of proinflammatory cytokines. Only recently, however, have the cellular sources of these cytokines been investigated in detail, with current evidence pointing to roles for both innate and adaptive immune cells in obese AT. In terms of innate immune cells, one of the defining features of AT inflammation in obesity is a marked increase in the accumulation of macrophages that surround adipocytes in “crown-like structures” (12, 13). In contrast to the anti-inflammatory M2 macrophages typically found in lean AT, the macrophages in inflamed adipose tissue are predominantly inflammatory M1 macrophages that produce substantial amounts of proinflammatory cytokines such as TNF-α (14). In addition to macrophages, there is growing evidence for a role of other innate immune cells. For example, the AT in obese mice is also infiltrated by CD11c<sup>ch</sup> F4/80<sup>low</sup> dendritic cells, which have been shown to induce the differentiation of proinflammatory Th17 cells (15) and promote further macrophage infiltration (16). Similarly, mast cells, whose numbers are increased in obese AT, have also been shown to promote AT inflammation in obesity (17). Neutrophils also transiently infiltrate AT as early as 3 d after the initiation of a high-fat diet (HFD) in mice (18), and their production of elastase contributes to AT inflammation and may directly cause insulin resistance (19). Indeed, increased activity of neutrophil elastase has been detected in the serum of obese human...
Immune regulation is lost in obese AT

In parallel to the increase in proinflammatory cells, in obese AT, the steady-state high proportion of regulatory immune cells is also reduced (10, 11, 27). For example, in obese AT, macrophages undergo a phenotypic switch from the anti-inflammatory IL-10-producing M2 macrophages that normally occupy lean AT to proinflammatory M1 macrophages (14, 28, 29). Normally, the predominant M2 phenotype is maintained by IL-4, with eosinophils and Th2 cells thought to be major sources of this cytokine. Remarkably, 90% of IL-4-expressing cells in the AT are eosinophils, and evidence that AT M2 macrophages depend on IL-4- and IL-13-expressing eosinophils suggests these cells have an important role in sustaining alternative activation of macrophages in healthy AT (30). In support of a similar protective role for Th2 cells, transfer of wild-type but not STAT6−/− CD4+ T cells in obese AT express markers of effector memory cells and produce high amounts of IFN-γ (10, 24), suggesting that an overactive Th1 cell response could play a role in AT inflammation. Inferring CD8+ T cells also produce elevated levels of chemokines such as CCL5 and CXCL1 and thus contribute to the further recruitment of macrophages into AT (22, 24). Interestingly, because obese AT-resident T cells exhibit limited TCR diversity (24), specific Ags may drive these T cell responses. Although the nature of the relevant Ags remains unclear, there is some evidence that absorbed intestinal Ags could have a role (25). Studies using B cell–deficient mice or Ab-mediated B cell depletion have also shown that B cells contribute to obesity-associated inflammation in the VAT (21) and systemically (23). Interestingly, Winer et al. (21) found that B cells from obese HFD mice produce elevated levels of pathogenic IgG2c Abs, and that via an Fc-dependent mechanism, transfer of serum IgG from these mice rapidly induced insulin resistance in recipient mice. DeFuria et al. (23), however, did not observe an increase in anti-nuclear autoimmunity Abs in HFD mice, but rather that follicular B cells promoted cell-mediated inflammation. Collectively, these studies demonstrate that the progression of AT inflammation is strongly associated with overactive innate and adaptive immune responses. Which immune cells initiate the process, however, remains controversial. Although it is often argued that macrophages are the early perpetrators, some studies suggest that infiltration by adaptive immune cells precedes macrophage accumulation (21, 26).

Multiple factors contribute to the development of AT inflammation

What initiates the reprogramming of immune cells in obese AT toward proinflammatory subtypes? The answer is likely a combination of different endogenous and exogenous danger signals. In terms of endogenous signals, saturated fatty acids directly activate TLR4 and TLR2 in macrophages, and even in adipocytes themselves, resulting in proinflammatory cytokine production (35, 36). Saturated fatty acids, specifically pal-
mitate, can also activate the NLRP3 inflammasome, causing maturation and release of IL-1β by macrophages (37). In addition to dietary sources, fatty acids are also released from adipocytes during lipolysis, a process that occurs at an increased rate in obese AT (38). Because macrophages surround adipocytes (12, 13), they would be one of the first immune cell types to encounter fatty acids and other endogenous danger signals, such as ATP, that may be released by dying adipocytes. Notably, TNF-α secreted by stimulated macrophages can further stimulate lipolysis (39), resulting in a positive feedback loop that exacerbates AT inflammation. Interestingly, fatty acids inhibit differentiation of IFN-γ-producing Th1 cells (40), a finding that seems to contradict the observed accumulation of Th1 cells in obese AT, which has high free fatty acid levels. This apparent paradox might be explained by the dominant contribution of other factors, such as leptin (see below), that favor Th1 cell accumulation.

In addition to endogenous danger signals, pathogen-associated molecular patterns (PAMPs), such as LPS, are also found at chronically elevated levels in the plasma of obese mice (41). In humans, high-fat, high-carbohydrate meals induce an increase in plasma LPS in as little as 2 h (42). Because chronic low levels of LPS do not induce endotoxin tolerance in macrophages (43), a high-fat, high-carbohydrate diet could result in chronic innate immune-driven inflammation. Moreover, obesity reduces adiponectin levels (44), and because adiponectin can promote endotoxin tolerance (45), obesity may exacerbate the endotoxin-mediated effect by removing a potentially protective factor. Interestingly, a major source of PAMPs in obesity may be the intestinal microbiota: in mice, a HFD induces adherence and translocation of commensal bacteria from the intestine into the blood and AT, correlating with an increase in inflammatory cytokines (46). Moreover, a HFD causes a robust change in the composition of gut microbiota (47, 48), which could have a major influence on immune cell function (49). Thus, a HFD could disrupt the intestinal epithelial cell barrier and initiate inflammation by providing a source of microbial PAMPs and Ags that stimulate innate and adaptive immune cells in the VAT (25). A consideration is that inflammation itself may affect intestinal microbiota and barrier integrity. It is thus difficult to conclude with certainty that changes in intestinal microbiota precede and cause inflammation. Regardless, it is likely that changes in intestinal permeability contribute to a vicious cycle that exacerbates obesity-associated inflammation.

Corresponding with the aforementioned increase in endogenous and foreign danger signals, several chemokines are Proposed by guest on April 20, 2017 http://www.jimmunol.org/ Downloaded from

![FIGURE 1. The loss of immune regulation in obesity-associated AT inflammation. (A) Lean AT contains regulatory immune cells (blue) that suppress proinflammatory immune cells (red) and sustain alternative activation of macrophages via Th2-associated cytokines. Adipocytes in lean AT are of normal size and produce adiponectin, which has anti-inflammatory properties. (B) In contrast, obese AT is infiltrated with proinflammatory immune cells that produce high amounts of inflammatory cytokines and chemokines. M1 macrophages accumulate in crown-like structures around hypertrophic adipocytes that have increased rate of lipolysis, and secrete free fatty acids (FFA) that can serve as endogenous danger signals to stimulate production of inflammatory cytokines, such as TNF-α. Adipocytes in obese AT also have increased leptin production, which promotes Th1 cells and inhibits Treg expansion. The gut barrier is disrupted in obesity, causing gut Ags and PAMPs such as LPS to enter the AT and stimulate inflammation. Furthermore, immune cells in the blood migrate into the AT in response to heightened chemokine production.](image-url)
upregulated in obese AT compared with lean AT. The expression of CCL2, 5, 7, 8, 11, and 20, as well as CXCL14, is elevated in obese AT (50–52), creating a strong chemotactic gradient for innate and adaptive immune cells. Many of the studies on chemokines in AT have focused on CCL2 (MCP-1), and systemic deletion of CCL2 prevents macrophage accumulation in AT and ameliorates insulin resistance (53). These data suggest that chemokines produced by AT-resident immune cells or adipocytes themselves, which can also produce chemokines (54), significantly contribute to the development of AT inflammation.

An additional mechanism that could lead to obesity-related inflammation is a change in hormonal balance that affects regulatory immune cells. For example, leptin is an adipocyte-derived hormone that is produced at elevated levels in obesity (55) and acts directly on T cells to stimulate IFN-γ production, thereby promoting Th1 cell differentiation while suppressing Th2 cells (56) and the proliferation of Tregs (57). Leptin-induced IFN-γ production can stimulate adipocytes to increase MHC class II expression, causing a positive feedback pathway of T cell stimulation (26). Notably, leptin-deficient (ob/ob) and leptin receptor–deficient (db/db) mice are often used as a model of obesity, and although these mice do become obese, leptin-mediated exacerbation of obesity-associated inflammation is absent. Hence, the mechanisms driving AT inflammation in ob/ob and db/db mice may be distinct, especially in the T cell compartment, and likely cannot be directly extrapolated to wild-type mice. Counteracting the effects of leptin is adiponectin, another adipokine, which promotes M2 macrophage polarization (58) and inhibits T cell activation (59). Thus, a combination of increased leptin and reduced adiponectin production by adipocytes in obese AT worsens AT inflammation.

Restoring immune regulation in obesity improves metabolic parameters

Because AT inflammation has a key role in the development of obesity-associated pathologies, it seems logical that restoration of immune regulation in targeted tissues could be therapeutic in insulin resistance and T2D. Interestingly, some of the currently used therapeutic strategies for T2D have previously unknown effects on inflammation and may actually restore immune regulation. For example, metformin, the most commonly used drug for T2D, enhances the proportion and numbers of Tregs by activating AMP-activated protein kinase and promoting fatty acid oxidation, which is the primary biochemical pathway used by Tregs for cellular metabolism (40). Recently, it has also been shown that metformin therapy inhibits caspase-1 activation and IL-1β maturation in peripheral monocyte-derived macrophages in human obese T2D subjects (60). Peroxisome proliferator–activated receptor (PPAR)γ agonists, such as pioglitazone, are also commonly used in T2D and seem to have anti-inflammatory effects. Compared to peripheral Tregs, AT-resident Tregs express high levels of PPARγ, and pioglitazone enhances the interaction between PPARγ and Foxp3 (11). Remarkably, treating obese mice with pioglitazone prevents the obesity-driven reduction of the proportion of Tregs in AT (11), induces apoptosis of AT macrophages (61), and favors the restoration of M2 macrophages (28). However, whether the effects of these drugs on AT inflammation contributes to their mechanism of action in humans with T2D is unknown.

In addition to these pharmacological therapies, cell-based therapies that were originally designed to restore immune regulation in autoimmunity can also ameliorate obesity-associated pathologies in mouse models. For example, therapies that enrich Tregs, such as IL-2/anti–IL-2 complexes or anti-CD3 Abs, can alleviate both inflammation and insulin resistance in HFD models (10, 11, 62). Cell therapy with regulatory CD4+ latency-associated peptide+ T cells has a similar effect (62), as does increasing iNKT cell numbers by adoptive cell transfer, delivery of α-galactosylceramide to expand iNKT cells and stimulate production of IL-4 and IL-10 (27), or depletion of B cells using anti-CD20 Abs (21). In humans, it seems unlikely that anti-inflammatory therapy alone will be effective in T2D, and it will be important to test combination therapies that target both immune and metabolic parameters.

Conclusions

Obesity-associated AT inflammation appears to be caused by infiltration of inflammatory immune cells and a parallel loss, or functional reprogramming, of immunoregulatory cells. Together, these changes lead to a variety of positive feedback pathways that not only sustain chronic inflammation, but also contribute to the development of insulin resistance. There is clearly a role for both endogenous and exogenous danger signals in this process, and emerging research into the role of the microbiome will likely lead to considerable insight into how the first “danger” signals may arise (Fig. 1). Now that the essential roles of innate and adaptive immunity in metabolic dysregulation are recognized, a future area of focus will be to determine whether strategies that are designed to restore immune regulation can prevent and/or reverse this process. Many of the therapies that could be tested are already known to work in the setting of “traditional” immune-mediated diseases, and it will be of great interest to investigate whether these approaches will be similarly effective in metabolic diseases.

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References


