

# The role of adipokines in chronic inflammation

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**Abstract:** Adipose tissue has traditionally been defined as connective tissue that stores excess calories in the form of triacylglycerol. However, the physiologic functions attributed to adipose tissue are expanding, and it is now well established that adipose tissue is an endocrine gland. Among the endocrine factors elaborated by adipose tissue are the adipokines; hormones, similar in structure to cytokines, produced by adipose tissue in response to changes in adipocyte triacylglycerol storage and local and systemic inflammation. They inform the host regarding long-term energy storage and have a profound influence on reproductive function, blood pressure regulation, energy homeostasis, the immune response, and many other physiologic processes. The adipokines possess pro- and anti-inflammatory properties and play a critical role in integrating systemic metabolism with immune function. In calorie restriction and starvation, proinflammatory adipokines decline and anti-inflammatory adipokines increase, which informs the host of energy deficits and contributes to the suppression of immune function. In individuals with normal metabolic status, there is a balance of pro- and anti-inflammatory adipokines. This balance shifts to favor proinflammatory mediators as adipose tissue expands during the development of obesity. As a consequence, the proinflammatory status of adipose tissue contributes to a chronic low-grade state of inflammation and metabolic disorders associated with obesity. These disturbances are associated with an increased risk of metabolic disease, type 2 diabetes, cardiovascular disease, and many other pathological conditions. This review focuses on the impact of energy homeostasis on the adipokines in immune function.

**Keywords:** calorie restriction, obesity, adipose tissue, type 2 diabetes, macrophage, infection, chronic low-grade inflammation

## Introduction

It is now well recognized that adipose serves as a depot for excess energy storage and as an endocrine gland that produces several biological mediators known to regulate blood pressure, reproductive function, appetite, glucose homeostasis, angiogenesis, and immune function.<sup>1</sup> Adipose tissue produces both pro- and anti-inflammatory mediators that influence local and systemic inflammation. Among these mediators are the adipokines, proteins produced by cells within white adipose tissue that function as hormones.<sup>2</sup> As a family of mediators, the adipokines consist of true adipokines that are predominantly produced by pre- and mature adipocytes and classical cytokines that are produced by adipocytes as well as immune cells found in the stromal vascular fraction (SVF) of adipose tissue and many other cell types outside adipose tissue depots. The balance of pro- and anti-inflammatory adipokines is dictated by many different factors, including the nutritional/metabolic status of the host, the presence of

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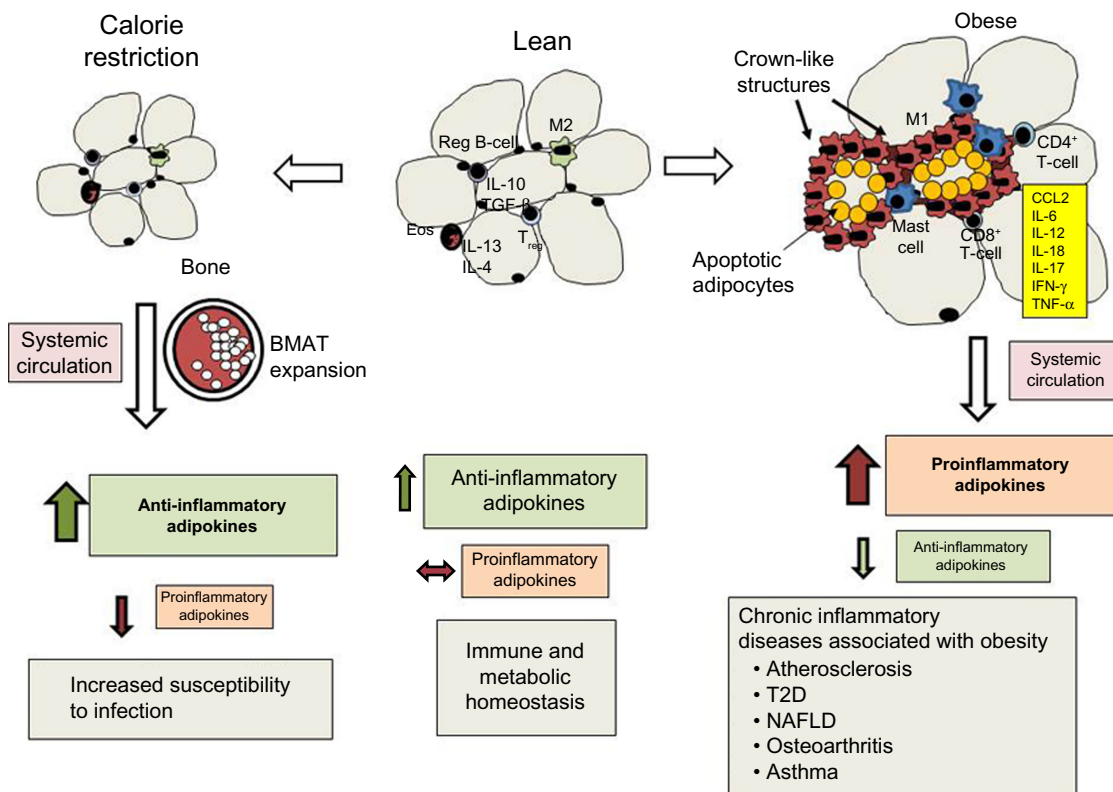
infection or systemic inflammation, oxidative stress, smoking status, age, and sex.<sup>3-9</sup> Most importantly, adipokines play a major role in the regulation of the inflammatory response in adipose tissue during the development of obesity and in response to infection or systemic inflammation. This review focuses on the ability of adipokines to regulate the inflammatory response in the setting of chronic calorie restriction and obesity.<sup>10-13</sup>

## Cellular composition of adipose tissue

Adipose tissue is composed of mature adipocytes, preadipocytes, mesenchymal cells, and cells within the SVF that include vascular endothelial and smooth muscle cells, fibroblasts, and several different leukocyte subsets (Figure 1). Interestingly, nearly all immune cells, such as resident macrophages, mast cells, monocytes, dendritic cells, natural killer cells, B-cells, T-cells, neutrophils, and eosinophils, have been found in adipose tissue.<sup>14-18</sup> These cells play a critical role in adipose tissue remodeling and repair in lean mice and humans. Although their function in calorie restriction is poorly understood, immune cell populations in general

decline during calorie restriction and increase in obesity. Resident and recruited macrophages are the most abundant type of immune cells in adipose tissue. These cells have been characterized as having M1 (classically activated) or M2 (alternatively activated) phenotypes. M1 macrophages appear to be primed for host defense against infection, while M2 macrophages are thought to play an important role in tissue remodeling and repair. Recent evidence suggests that this dichotomous classification may be an oversimplification, since macrophages may exhibit different phenotypes that span a spectrum of activation states.<sup>19,20</sup> They also play a critical role in orchestrating the inflammatory response in obesity and type 2 diabetes (T2D).<sup>21</sup>

Mast cells, which are known to mediate acute inflammation in type 1 hypersensitivity responses and host defense against parasitic organisms, are also found in adipose tissue.<sup>22</sup> Dendritic cells are professional antigen-presenting cells that recognize foreign antigens and present them to T-cells via major histocompatibility-complex molecules. Adipose tissue dendritic cells have been found in mice and humans and may play an important role in T-helper (T<sub>H</sub>)-17 cell responses.<sup>18,23</sup> The most abundant granulocyte found in blood, the neutrophil,



**Figure 1.** Effects of calorie restriction and obesity on adipose tissue leukocyte populations, adipokine secretion, and chronic inflammation.

**Notes:** Calorie restriction: VAT and SCAT adipocyte size declines but BMAT increases. Increased anti-inflammatory adipokines with greater risk of infectious disease. Lean state: IL-4, IL-13, IL-10 and TGF- $\beta$  maintain M2 macrophage phenotype with normal metabolic and immune homeostasis. Obese state: hypertrophy promotes rarefaction and apoptosis. M1 macrophages engulf necrotic adipocytes forming crown-like structures. Proinflammatory cytokines and adipokines promote inflammation and diseases associated with obesity.

**Abbreviations:** BMAT, bone marrow adipose tissue; T2D, type 2 diabetes; NAFLD, nonalcoholic fatty liver disease; SCAT, subcutaneous adipose tissue; VAT, visceral adipose tissue; Eos, eosinophils.

can also be found in adipose tissue. While these cells play a prominent role in host defense against bacterial infections, their function in adipose tissue is not clear. These cells transiently infiltrate murine adipose tissue with the initiation of high-fat-diet feeding and mediate insulin resistance in mice.<sup>24,25</sup> Natural killer (NK) cells, best known for their role in the early host response to viral infections and in killing tumor cells, have recently been shown to promote macrophage proliferation and polarization in adipose tissue and insulin resistance in mice fed a high-fat diet.<sup>26</sup>

B-cells are most commonly studied for their contribution to host defense against infection and autoimmune disease. In adipose tissue, several different B-cell subsets have been identified, and these cells contribute to local and systemic inflammation by secreting cytokines, producing antibodies, and presenting antigens to T-cells.<sup>27</sup> Finally, several different T-cell subsets, such as CD4<sup>+</sup> T<sub>H</sub> cells, which include T<sub>reg</sub>, T<sub>H</sub>1, and T<sub>H</sub>2, and CD8<sup>+</sup> T-cells, have been identified in adipose tissue, where they regulate local inflammation through the secretion of cytokines that influence the differentiation and polarization of macrophages.<sup>28,29</sup> The activation state, differentiation, and proliferation of immune cells in adipose tissue are profoundly influenced by anti- and proinflammatory cytokines, lipid mediators, and adipokines secreted within local fat pads and in circulation.<sup>30–34</sup>

## Anti-inflammatory adipokines

Adiponectin, C1q/TNF-related proteins (CTRPs), omentin, and secreted frizzled-related protein 5 (SFRP5) are anti-inflammatory adipokines produced by adipose tissue.<sup>35–38</sup> Adiponectin is the best-known and most abundant adipokine found in human serum, with concentrations typically in the µg/mL range.<sup>39</sup> Unlike other adipokines, which are found in greatest quantities in visceral and subcutaneous adipose tissue (SCAT), it is predominantly produced by bone marrow adipose tissue (BMAT).<sup>40</sup> Calorie restriction, aging, estrogen deficiency, T1D, and treatment with thiazolidinediones increase, while obesity, T2D, oxidative stress, and cigarette-smoke exposure decrease serum adiponectin levels.<sup>41–46</sup> Adiponectin is a complex molecule that forms low-, intermediate-, and high molecular weight complexes in circulation. Its effects are mediated through the AdipoR1 and AdipoR2 receptors, which activate AMPK in immune cells and tissues.<sup>47</sup> In particular, the high-molecular-weight complex has anti-inflammatory properties known to inhibit inflammation by blocking NF-κB activation and reducing such cytokines as TNFα, IL-6, and IL-18.<sup>2,48–50</sup>

Adiponectin-knockout mice exhibit enhanced inflammatory responses, suggesting a major role for adiponectin in suppressing systemic and tissue inflammation.<sup>31,51–53</sup> For

example, adiponectin attenuates vascular inflammation, which may play a protective role against aortic aneurism.<sup>51</sup> The protective effects of adiponectin in the vasculature may be mediated by locally produced perivascular adipose tissue.<sup>54</sup> Moreover, the lungs of adiponectin-knockout animals exhibit an emphysematous phenotype, with enlarged air spaces and activated alveolar macrophages capable of producing higher levels of TNFα and MMP12.<sup>31</sup> These animals also develop pulmonary arterial hypertension characterized by perivascular inflammation.<sup>53</sup> Adiponectin plays a protective role in acute lung injury and myocardial ischemia, where it reduces cellular infiltration.<sup>52,55–57</sup> In contrast to these studies showing a protective anti-inflammatory effect, adiponectin may play a proinflammatory role in arthritic joints by promoting COX2 expression and the synthesis of PGE<sub>2</sub>, which increases inflammation and pain.<sup>58</sup>

Much less is known regarding other adipokines with anti-inflammatory properties, such as CTRP, omentin, and SFRP5. The CTRPs are structurally similar to adiponectin, and at least 15 isoforms have been described.<sup>59</sup> CTRP3 has been shown to reduce cytokine production in human monocytes and adipocytes stimulated with lipopolysaccharide and free fatty acids by inhibiting TLR4 activation.<sup>59</sup> In addition, CTRP13 inhibits inflammation in lipid-loaded hepatocytes and improves insulin sensitivity.<sup>60</sup> Omentin is a novel adipokine that inhibits TNFα-induced endothelial cell COX2 expression and induces endothelial nitric oxide synthase.<sup>61</sup> SFRP5 has anti-inflammatory effects in adipose tissue and in macrophages that are mediated through the suppression of noncanonical Wnt5a/JNK signaling, which ultimately inhibits macrophage TNFα, IL-1β, and CCL2–MCP1 synthesis.<sup>62</sup> Clearly, there is a need to increase our understanding of the biology of these novel anti-inflammatory adipokines and their role in opposing the effects of proinflammatory mediators and adipokines.

## Proinflammatory adipokines

Leptin is the best known proinflammatory adipokine that increases in proportion to white adipose tissue mass, and was first described as a satiety hormone.<sup>11</sup> The long form of the leptin receptor, which is expressed by nearly all immune cells, initiates intracellular signaling to activate the tyrosine kinase JAK2, the latent transcription factor STAT3, MAPK, ERK1/2, and PI3K pathways that activate the innate immune response.<sup>63</sup> Leptin can directly enhance the production of several proinflammatory cytokines, such as IL-6, IL-12, IL-18, and TNFα, the chemokines IL-8 and CCL2/MCP-1, and the lipid mediators PGE<sub>2</sub>, cysteinyl leukotrienes (cysLTs), and leukotriene B<sub>4</sub> (LTB<sub>4</sub>) in peripheral blood monocytes

and resident tissue macrophages in mice and humans.<sup>8,64–67</sup> Leptin can also induce the production of reactive oxygen intermediates in macrophages, neutrophils, and endothelial cells and potentiate IFN $\gamma$ -induced expression of nitric oxide synthase.<sup>68–70</sup> Leptin enhances platelet aggregation and promotes leukocyte–endothelial cell interactions by increasing the expression of adhesion molecules on myeloid cells and vascular endothelial cells.<sup>68,71–73</sup> T<sub>H</sub>1 and T<sub>H</sub>17 responses are enhanced with leptin, which can also prevent T-cell apoptosis.<sup>74</sup>

Resistin and resistin-like molecules were first characterized in mice as mediators of insulin resistance, T2D, and metabolic syndrome.<sup>75</sup> While adipose tissue is the primary source of this adipokine in mice, monocytes and macrophages are the most important sources of resistin in humans.<sup>76</sup> In addition, there are substantial differences between mouse and human resistin amino acid sequence homology, indicating that the physiological actions of this adipokine may differ in mice and humans.<sup>77</sup> To address these controversial issues, Qatanani et al created a humanized mouse that expressed human resistin in macrophages but not adipose tissue that has provided a robust system to substantiate the importance of human resistin in T2D and obesity.<sup>76</sup> The proinflammatory effects of resistin are mediated through CAP1, recently identified as a receptor for resistin. It initiates cAMP-mediated PKA activation and NF- $\kappa$ B-related transcription of inflammatory cytokines in human monocytes.<sup>78</sup>

There are several other less studied proinflammatory adipokines that have been implicated in the promotion of inflammation associated with obesity, including chemerin, retinol binding protein 4 (RBP4), and lipocalin 2 (LCN2).<sup>2</sup> Chemerin is an adipocyte-derived chemoattractant for monocytes and dendritic cells that is produced by mature adipocytes. It is secreted as a prohormone that requires enzymatic cleavage by extracellular proteases.<sup>79</sup> RBP4 is a member of the lipocalin family of proteins that transports retinol from the liver to the peripheral tissues.<sup>80</sup> RBP4 is produced by the liver, adipose tissue, and macrophages. RBP4 may contribute to inflammation by activating adipose tissue antigen-presenting cells that promote T<sub>H</sub>1-cell polarization.<sup>81</sup> LCN2 is produced by adipocytes and is induced by inflammatory stimuli that activate NF- $\kappa$ B in adipose tissue.<sup>82</sup> LCN2, also referred to as neutrophil gelatinase-associated lipocalin, binds and transports hydrophobic molecules, such as retinoids, arachidonic acid, LTB<sub>4</sub>, platelet-activating factor, and steroids.<sup>82,83</sup> LCN2 also plays an important role in host defense against bacterial infections by sequestering iron.<sup>84</sup> Through the elaboration of anti- and proinflammatory adipokines that spill over into the systemic circulation, adipose tissue plays a critical role in

regulating the inflammatory response in the setting of calorie restriction and obesity.

## The impact of adipokines on immune function during calorie restriction

Prolonged calorie restriction reduces the amount of energy in the form of triacylglycerol (TAG) stored in adipose tissue. The size of individual adipocytes within visceral adipose tissue (VAT) declines. If caloric restriction is extended, SCAT declines as well, but this response requires more time.<sup>85</sup> In contrast, BMAT expands during calorie restriction, replacing active hematopoietic cells.<sup>40</sup> Calorie restriction also has a profound impact on the adipokines and mediators of inflammation produced within adipose tissue.

The production of anti-inflammatory adipokines, such as adiponectin, CTRP, omentin, and SFRP5, increases.<sup>40,86–88</sup> Unlike other adipokines, more adiponectin is produced by BMAT than by SCAT or VAT.<sup>40</sup> Adiponectin plays an important role in adipogenesis and insulin sensitivity via AMPK signaling, which promotes fatty acid oxidation and glucose uptake in skeletal muscle and liver.<sup>89,90</sup> The increase in omentin that accompanies calorie restriction may be protective against cardiovascular disease.<sup>37</sup> Omentin may reduce vascular inflammation associated with atherosclerosis, since it reduces macrophage adhesion to endothelial cells in vitro by inhibiting ICAM1 and VCAM1 expression.<sup>37</sup> SFRP5 may also play a protective role in cardiovascular disease.<sup>62</sup> The increased secretion of SFRP5 following calorie restriction in obese patients may contribute to improvements in atherosclerosis and protect against myocardial ischemia–reperfusion injury.<sup>62</sup> IL-10 has also been shown to increase during calorie restriction. It is produced by regulatory B-cells within adipose tissue, where it suppresses inflammatory cytokine production by resident CD8<sup>+</sup> T-cells.<sup>91</sup> T<sub>regs</sub> elaborate TGF $\beta$  and IL-10, which helps maintain an anti-inflammatory environment.<sup>28</sup> In contrast, the production of proinflammatory adipokines (leptin, resistin, RBP4), cytokines (IL-1 $\beta$ , IL-6, IL-17, TNF $\alpha$ ), chemokines (CCL2 and MIP2), and lipid mediators (cysLTs and LTB<sub>4</sub>) decline.<sup>3,10,33,76,92,93</sup> While calorie restriction has been shown to suppress inflammation, protect against cardiovascular disease, improve glucose homeostasis in T2D, and increase the life span of mice, it also has negative consequences on host defense against infection.<sup>3,94–96</sup>

Studies by Gardner et al evaluated the impact of a calorie-restricted diet on host defense against a mouse adaptive influenza virus, PR8, in young and aged mice.<sup>94,95</sup> In these studies, young and aged mice that consumed 40% fewer calories



than their ad libitum-fed counterparts exhibited greater weight loss, mortality, lung viral titers, and impaired NK-cell cytotoxic function following influenza virus infection.<sup>94,95</sup> Reduced IFN $\alpha$  and IFN $\beta$  production was also associated with increased viral burdens of young calorie-restricted mice.<sup>95</sup> In a similar study, refeeding calorie-restricted mice improved survival and nearly restored NK-cell numbers and cytotoxic function at all time points following influenza infection. While refeeding calorie-restricted mice reconstituted adipose tissue, it did not restore leptin to levels observed in ad libitum-fed animals, and this may have accounted for the differences in NK-cell numbers and function.<sup>96</sup>

Acute calorie restriction, a common occurrence in critically ill patients and starvation, rapidly mobilizes energy stores from adipose tissue, shrinking the size of VAT and SCAT adipose tissue. In general, both anti- and proinflammatory adipokines decline with prolonged fasting. For example, serum leptin levels decline rapidly and are disproportionately lower than would be expected for a given fat mass in humans and mice.<sup>4,97</sup> Unlike leptin, serum adiponectin levels remain stable after 3 days of fasting and decline slightly during a prolonged fast.<sup>98,99</sup> The decline of leptin in adaptation to starvation has been examined in murine models to determine the impact of leptin in thymic atrophy and pneumococcal pneumonia.<sup>3,10,92,100</sup> As leptin levels decline during fasting, glucocorticoid levels rise, and this contributes to peripheral blood T- and B-lymphocyte apoptosis and diminished thymic and bone marrow cellularity. These events are prevented if leptin levels are maintained during fasting.<sup>92,101</sup>

Fasting and chronic energy malnutrition are known to suppress the immune response to infection, and leptin levels may predict survival in severe acute childhood malnutrition.<sup>102</sup> In mice infected with *Streptococcus pneumoniae*, 48 hours of fasting reduced pulmonary bacterial clearance, and this was associated with reduced neutrophil counts in peripheral blood and bronchoalveolar lavage. Lung-homogenate cytokine (IL-6), chemokine (MIP2), and LTB<sub>4</sub> synthesis in alveolar macrophages were also reduced by fasting. Alveolar macrophages obtained from mice after fasting exhibited defective phagocytosis and killing of *S. pneumoniae*. Interestingly, all of these responses were restored when exogenous leptin was administered during fasting.<sup>3</sup> Using a similar model of leptin depletion by starvation and lipopolysaccharide-induced sepsis, Faggioni et al demonstrated that leptin improved survival, and this improvement was associated with lower levels of systemic TNF $\alpha$ .<sup>100</sup> These studies demonstrate the physiologic importance of the adipokines generated in calorie restriction and starvation, which play a crucial role in the host response

to infection and sepsis. Since infectious disease remains a leading cause of morbidity and mortality in undernourished patients and in severely malnourished children in low-income nations, more research is needed to understand the role of adipokines and immunosuppression associated with energy malnutrition.<sup>103</sup>

## Hyperplasia and hypertrophy of adipocytes in VAT and SCAT during obesity

In contrast to calorie restriction and starvation, obesity is characterized by energy excess and the expansion of white-adipose tissue that contributes to a chronic state of low-grade inflammation and increased risk of chronic disease (Figure 1). Adipose tissue expansion occurs as excess energy is stored in the form of TAG. Under conditions of normal metabolic homeostasis, the expansion of adipose tissue can buffer excess dietary lipids.<sup>85</sup> As excess energy accumulates, the adipose tissue must expand to store excess TAG through the process of adipocyte hyperplasia and hypertrophy.<sup>104,105</sup> Hyperplasia occurs through the differentiation of preadipocytes into mature adipocytes, and this process occurs in all adipose-tissue depots, but is more prominent in SCAT.<sup>106</sup> The enlargement of SCAT around the femoral gluteal area, also known as the gynoid pattern of obesity, is well suited for lipid buffering, and this helps maintain homeostasis during fluctuation of dietary lipids.<sup>106,107</sup> With regard to the role of adipokines in this process, adiponectin promotes adipogenesis and hyperplasia through the activation of PPAR $\gamma$ . SFRP5 expression increases during the expansion of adipose tissue, where it seems to play an important role in suppressing oxidative metabolism and adipocyte growth during obesity.<sup>108</sup> The expansion of SCAT via adipocyte hyperplasia is associated with a lower risk of metabolic disease, higher levels of adiponectin, and lower levels of proinflammatory adipokines.<sup>109–111</sup> In contrast, the expansion of adipose tissue through the process of hypertrophy is associated with adipose tissue inflammation.<sup>2</sup> While adipocyte hypertrophy occurs in all adipose tissue depots, its appearance in VAT is highly correlated with the accumulation of immune cells, proinflammatory adipokines, and metabolic dysfunction.<sup>2,112</sup>

## Changes in immune cell composition and phenotype in adipose tissue during obesity

As adipose tissue expands, the number of eosinophils and levels of IL-13 and IL-4 decline in mice and humans.<sup>113</sup>

The population of T-cells changes as well, with a decline  $T_{reg}$  cells and increases in  $CD4^+$  and  $CD8^+$  T-cells.<sup>28,29,114</sup> In addition to a decline in anti-inflammatory cytokine and adipokine levels, the number of  $CD4^+$  T-cells that secrete the  $T_H1$  cytokine  $IFN\gamma$  and  $CD8^+$  T-cells increases, promoting the differentiation of resident macrophages into the classically activated or M1-macrophage phenotype.<sup>21,29</sup> A substantial increase in adipose tissue macrophages occurs as a consequence of the recruitment of peripheral blood monocytes that respond to chemokines (CCL2, CXCL5).<sup>14</sup> Neutrophils are also recruited to adipose tissue following dietary high-fat feeding in mice, and the chemokines for their recruitment have not been identified.<sup>115</sup> Finally, mast cells also increase in the SVF of VAT in obese mice and human subjects, and these cells contribute to the proinflammatory state by releasing  $TNF\alpha$ , IL-6, and lipid mediators, such as cysLTs.<sup>16,116</sup>

Upon further expansion, the proinflammatory cytokines IL-6,  $TNF\alpha$ , and IL-18 and adipokines leptin and resistin promote a proinflammatory environment and contribute to metabolic dysfunction.<sup>11,117–121</sup> The expansion of individual adipocytes is limited by the extracellular matrix and hypoxia resulting from rarefaction.<sup>122</sup> As a consequence, these cells undergo apoptosis and eventually necrosis.<sup>104</sup> Crown-like structures are frequently found in adipose tissue sections from obese mice and humans, and these are necrotic adipocytes surrounded by M1 macrophages.<sup>13,104</sup> There are distinct differences in the type and number of inflammatory cells within adipose tissue depots in VAT and SCAT of lean and obese human subjects, and these differences are correlated with metabolic disease risk.<sup>123</sup> Compared with VAT, there are fewer macrophages, mast cells, and other immune cells in SCAT, suggesting less adipose tissue inflammation in SCAT compared with VAT.<sup>16</sup> Crown-like structures in obese mice are also more prevalent in VAT versus SCAT.<sup>16</sup> In total, the location and quality of excess adipose tissue may profoundly influence the inflammatory state of obese individuals.

## Adipose tissue inflammation

Inflammation most often occurs in response to infection, irritation, allergic and autoimmune responses, or tissue trauma and is classically characterized by the cardinal signs of inflammation, which include heat, redness, swelling, pain, and loss of function.<sup>124</sup> These responses develop as a consequence of the production of proinflammatory mediators, such as lipid mediators (prostaglandins and leukotrienes), cytokines, chemokines, and cellular debris resulting from the release of intracellular constituents or “danger” signals.<sup>124</sup> These mediators can induce vasodilation, increase

microvascular permeability, activate local immune cells, increase the production of leukocytes from the bone marrow, recruit peripheral blood leukocytes to the site of inflammation, and trigger nociceptors to induce the sensation of pain. Unlike the classic inflammatory response that is activated by pattern-recognition receptors during an infection, the inflammatory response in obesity is initiated by intrinsic signals, such as nutrient sensing, the unfolded protein response, and endoplasmic reticulum stress, and is often referred to as meta-inflammation.<sup>125</sup> These intrinsic signals promote an inflammatory response through the activation of the NF- $\kappa$ B-signaling pathway, the production of proinflammatory cytokines, generation of reactive oxygen species, and proinflammatory adipokine synthesis by adipocytes and immune cells within adipose tissue.<sup>125</sup> Conversely, anti-inflammatory adipokine synthesis, eg, adiponectin, declines as a consequence of the unfolded protein response and endoplasmic reticulum stress.<sup>126</sup> Under these circumstances, resident and recruited leukocytes within adipose tissue elaborate proinflammatory mediators that not only contribute to local inflammation but spill over into the systemic circulation, causing a chronic state of low-grade inflammation.

## Contribution of adipokines to inflammation associated with obesity

Proinflammatory adipokines, which increase in obese individuals, contribute to systemic inflammation and diseases associated with obesity. For example, leptin levels are correlated with the severity of illness in several diseases, such as osteoarthritis, multiple sclerosis, nonalcoholic fatty liver disease, hepatic fibrosis, renal disease, atherosclerosis, and thrombosis.<sup>34,127–135</sup> Resistin levels are elevated in obese humans and are associated with a greater risk of cardiovascular disease.<sup>106</sup> Resistin may promote chronic inflammation and insulin resistance by enhancing monocyte recruitment through the induction of CCL2 in inflamed VAT in humans and atherosclerosis by promoting monocyte foam cell formation and endothelial cell interactions with the vascular endothelium.<sup>136,137</sup> Likewise, chemerin inhibits the maturation of preadipocytes and alters the metabolic functions of mature adipocyte cell lines in vitro.<sup>138</sup> While chemerin levels in human subjects are correlated with obesity and metabolic syndrome, a causal role for chemerin in adipose tissue inflammation and obesity-associated disease has not been reported.<sup>139</sup> In addition, RBP4 is produced by the liver, adipose tissue, and macrophages, and its expression increases with increasing body mass index, waist circumference,

and visceral adiposity in human subjects.<sup>140,141</sup> It inhibits intracellular signaling events induced by insulin, such as phosphorylation of IRS1, and contributes to insulin resistance in T2D.<sup>142,143</sup> RBP4 may contribute to inflammation by activating adipose tissue antigen-presenting cells that promote T<sub>H</sub>1-cell polarization.<sup>81</sup> Finally, LCN2 may play a critical role in cardiovascular disease associated with obesity, since it is markedly elevated in atherosclerotic plaques.<sup>144</sup> However, a causal role for LCN2 in vascular tissue remodeling in atherosclerotic lesions associated with obesity has not been established, and additional research is needed to understand the role of LCN2 in diseases associated with obesity.

## Conclusion

Adipose tissue produces several endocrine factors, cytokines, and chemokines that regulate physiologic processes and immune function. Among these mediators are the adipokines, hormones produced by adipocytes, and cells within the SVF of adipose tissue. There are pro- and anti-adipokines that provide a means of communication between energy stored in adipose tissue and several organ systems to integrate metabolism with several physiologic functions. As adipose tissue shrinks during calorie restriction, anti-inflammatory adipokines rise and proinflammatory adipokines decline, resulting in increased insulin sensitivity and suppressed immune function. As adipose tissue expands during obesity, there is an increase in proinflammatory and a reduction in anti-inflammatory adipokines, which contributes to local and systemic inflammation and disturbances in glucose homeostasis. Future therapeutic interventions may target adipokines and their intracellular signaling cascades to enhance immune function in calorie restriction or ameliorate chronic inflammation and T2D in obese patients.

## Disclosure

The author reports no conflicts of interest in this work.

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