Published in final edited form as:

Obes Rev. 2015 February ; 16(2): 127–136. doi:10.1111/obr.12242.

Macrophage recruitment in obese adipose tissue

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Abstract

Obesity is characterized as a chronic state of low-grade inflammation with progressive immune cell infiltration into adipose tissues. Adipose tissue macrophages play critical roles in the establishment of the chronic inflammatory state and metabolic dysfunctions. The novel discovery that pro-inflammatory macrophages are recruited to obese adipose tissue prompted an increased interest in the interplay between immune cells and metabolism. Since this discovery, many works have been published investigating the factors that lead to macrophage recruitment, the phenotypic change of adipose tissue macrophages, and metabolic dysfunctions. Adipokines and chemokines are key mediators that play crucial roles in crosstalk between adipocytes and macrophages and in regulating the adipose tissue inflammation. In the present review, we discuss the obesity-mediated adipose tissue remodeling, and particularly, the role of adipokines/chemokines in macrophage recruitment to obese adipose tissue. This review provides new insights into the physiological role of these factors and identifies a potential therapeutic target for obesity and associated disorders.

Keywords

Macrophage; Adipokine; Chemokine; Obesity

I. Introduction

Obesity is characterized as a chronic state of low-grade inflammation with progressive immune cell infiltration into adipose tissue (AT). The incidences of metabolic disorders including insulin resistance (IR), type 2 diabetes mellitus (T2DM) and cardiovascular disease are increased with obesity and are thought to arise from the chronic inflammation¹. It is now accepted that AT is the primary source of many pro-inflammatory cytokines. The novel discovery that pro-inflammatory macrophages are recruited to obese AT prompted an increased interest in the interplay between immune cells and metabolism^{2,3}.

The findings from animal studies and *in vitro* experiments have suggested that adipose tissue macrophages (ATMs) play critical roles in the establishment of the chronic inflammatory

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Conflict of Interest Statement: None of the authors have financial disclosure or conflict of interest

state and metabolic dysfunctions such as T2DM and IR^{4,5}. Either genetic or diet-induced adipocyte expansion promotes the accumulation of macrophages in AT in the mice and the majority of obese patients^{2,3,6}. Upon activation, immature bone-marrow derived peripheral monocytes migrate into the site of inflammation and differentiate into tissue macrophages⁷. Macrophage numbers and/or pro-inflammatory gene expression in AT are positively associated with adipocyte size in obese mice and are negatively associated with weight loss in obese humans^{2,8}. Conversely, obese mice with genetically ablated macrophage inflammatory signaling such as nuclear factor- κ B (NF- κ B) signaling are protected against inflammation and present improved insulin sensitivity⁹.

Although recruitment of macrophages into AT involves interactions of innate and adaptive immunity in multiple organs, at its core lays a unique crosstalk between adipocytes and macrophages. In the present review, we discuss the obesity-mediated adipose tissue remodeling, and particularly, the role of adipokines/chemokines in macrophage recruitment to obese adipose tissue. This review provides new insights into the physiological role of these factors and identifies a potential therapeutic target for obesity and associated disorders.

II. Adipose tissue and adipose tissue macrophages

In addition to the storage of energy in the form of lipids, AT has been recognized as the largest endocrine organ secreting several hormones such as leptin¹⁰ and adiponectin¹¹, growth factors (vascular endothelial growth factor)¹², pro- and anti-inflammatory mediators (α 4 integrin, interleukin (IL)-6, IL-1 β and tumor necrosis factor (TNF)- α)^{3,13}, and complement proteins^{14,15}. These factors that are released by AT are collectively referred to as adipokines¹⁶. AT is mainly composed of adipocytes which regulate fat mass and nutrient homeostasis and release adipokines into the tissue. AT also includes a heterogeneous constellation of endothelial cells, adipocyte precursors, nerve terminals, fibroblasts, blood vessels, and leukocytes collectively termed as the “stromal vascular compartment”. Each of these cells and structural components contribute to the synthesis and turnover of extracellular matrix components that collectively create unique microenvironments within AT depending on the adipose depots, sex, age, diet, and species¹⁷.

Macrophages and their monocyte precursors are highly heterogeneous cell populations. Upon the cytokine polarization, macrophages are divided into classically activated macrophages (M1) and alternatively activated macrophages (M2), which present different activators, markers, and function. M1 can be induced by interferon- γ alone or in concert with microbial stimuli or cytokines, while M2 can be induced by IL-4, IL-10, IL13, and IL-33¹⁸; in general, M1 are characterized by an IL-12^{high}, IL-23^{high}, and IL-10^{low} phenotype, in contrast, the various forms of M2 generally express an IL-10^{high}, IL-12^{low}, and IL-23^{low} phenotype¹⁸; M1 participate as inducer and effector cells in polarized Th1 responses, and mediate resistance against intracellular parasites and tumors, while M2 function generally express high levels of scavenger-, mannose-, and galactose-type receptors, and contribute to tissue remodeling¹⁹, promotion of angiogenesis and tumor progression²⁰. In 2007, Lumeng *et al.* extended this M1/M2 macrophage paradigm into ATMs²¹. Their data indicated that ATM phenotype changed from an anti-inflammatory M2

polarized state to a pro-inflammatory M1 state when obesity occurred, which contributed to the chronic low-grade inflammation of obesity.

III. Obesity-mediated adipose tissue remodeling

With excessive weight gain, extreme increases in adipocyte size are accompanied by an elevated frequency of adipocyte death and macrophage recruitment^{22, 23}. The elevated adipocyte death rate could partly be explained by hypoperfusion causing an inadequate supply of oxygen in the face of expanding AT²⁴. Obesity-associated AT remodeling has been first described by Cinti in 2005 as the existence of significant numbers of so-called “crown-like structures (CLS)”, consisting of macrophages surrounding dead adipocytes in both obese mice and humans²². The high prevalence of CLS is highly correlated to AT inflammation and metabolic disorder and considered to be pathological lesions in AT of obese subjects²⁵.

During AT remodeling, adipocyte death may be sufficient to initiate macrophage infiltration and induce AT inflammation¹⁷. This hypothesis has been further substantiated by the study demonstrating that the preponderance of ATMs in lean and obese mice and humans is selectively localized to individual dead adipocytes and that the frequency of adipocyte death is increased over 30-fold in an obese mouse model as well as in obese humans²². A nearly complete remodeling of the epididymal fat depot has been observed in a murine diet-induced obesity model, characterized as frequency of adipocyte death, an increase of depot weight and ATM accumulation²⁶. Despite the close association of adipocyte death with the macrophage infiltration, whether the macrophages respond to or directly contribute to adipocyte death remains unclear. Researchers hypothesized that the small molecules released by dead adipocytes may activate toll-like receptors (TLRs) on the macrophages and neighboring adipocytes, inducing a release of pro-inflammatory factors¹⁷.

IV. Crosstalk between adipocytes and macrophages establish and maintain the chronic state of inflammation

The interaction between adipocytes and macrophages aggravates the chronic inflammation in obese AT²⁷. Pro-inflammatory adipokines such as monocyte chemoattractant protein-1 (MCP-1) and TNF- α ²⁸, and saturated FAs released by adipocytes interact with TLR4 complex, inducing NF- κ B activation in resident macrophages^{29, 30}. Conversely, activated macrophages also release pro-inflammatory chemokines including MCP-1, recruiting the monocytes from circulation into the site of AT inflammation³¹. Once infiltrated into the AT, monocytes become matured and interact with adipocytes in a paracrine manner through TNF- α production, increasing the production of pro-inflammatory adipokines and reducing the production of anti-inflammatory adiponectin²⁹. This crosstalk between adipocytes and macrophages establishes and maintains the chronic inflammation state in obese AT through persistently recruiting new macrophages/monocytes from circulation (Figure 1).

Adipokines and chemokines are key mediator linking the adipocytes and ATMs and regulating AT inflammation. As described above, AT has been recognized as the largest endocrine organ secreting a variety of adipokines. Following the onset of obesity, the

secretory status of adipocytes can be modified by the changes in the cellular composition of the tissue, including alterations in the number, phenotype and localization of immune, vascular and structural cells. Recent evidence suggests that obesity-induced changes in adipokine secretion can influence the AT function through recruiting the immune cells and promoting inflammatory responses¹. Obesity not only recruits more macrophages, but also upregulates the expression of chemokines and their receptors in AT from obese mice and humans^{3, 32}. ATMs appear to secrete the majority of inflammatory chemokines and their accumulation contributes to the development of systemic IR.

The current review discusses the key adipokines and chemokines that have roles in ATM accumulation. The presented adipokines include TNF- α , leptin, adiponectin, secreted frizzled-related protein 5 (SFRP5), growth factor, fatty acids and other AT-derived factors. Several chemokines, such as MCP-1 and CXCL5, are in fact known as adipokines. In this review, these two molecules are discussed with other chemokines because of their similar structure.

Adipokines

1. TNF- α —TNF- α is a pro-inflammatory cytokine that has been noted as one of active participants in the development of obesity-related diseases³³. TNF- α may contribute to adipokine dysregulation in adipocytes and an increased level of TNF- α was found in ATs of obese murine models³⁴. In humans, TNF- α expression correlated with body mass index, percentage of body fat, and hyperinsulinemia, whereas weight loss decreased TNF- α level³⁵. TNF- α levels were also found to positively associated with other markers of IR³⁶, while short-term treatment with TNF- α inhibitor in obese patients reduced systemic inflammatory markers without improving insulin sensitivity³⁷.

TNF- α converting enzyme (TACE) is the major factor that induces soluble TNF- α and has been implicated as a central regulator in obesity and AT inflammation³⁸. Previous studies have shown that TACE activity is significantly higher in diet-induced obese mice compared with control group³⁹; and that TACE knock-out mice are protected against obesity-induced IR and diabetes⁴⁰. In addition, a recent study showed that serum macrophage-related chemokine levels and the number of CLS were significantly elevated in ATs of TACE-transgenic mice fed with HFD⁴¹. These findings collectively suggested that TACE could be a possible therapeutic target of obesity-related diseases.

2. Leptin—Leptin is one of the most important AT-derived hormones, involving in both innate and adaptive immunity⁴². Obesity is associated with an increased level of leptin prevailing in the expanding AT⁴³, suggesting the potential role of leptin in obesity-mediated inflammation. Leptin-deficient (ob/ob) and leptin receptor-deficient (db/db) mice have been well generated and shown less macrophage infiltration and inflammatory gene expression in AT, in spite of increased weight gain and adiposity³. Furthermore, Dib *et al.* report that C57BLJ mice reconstituted with db/db bone marrow, when placed on a high-fat diet, have significant lower body weight and adiposity, attenuated macrophage infiltration, and subsequently diminished AT inflammation⁴⁴. Leptin may affect macrophage infiltration to AT through the upregulation of adhesion molecules in the endothelial cells of the stromal

vascular compartment⁴⁵. However, despite the convincing nature of these findings from the different groups, there are equally convincing data showing that leptin does not influence weight gain and macrophage infiltration in AT^{46, 47}. The contrasting results generated from these studies may be caused by different background strain, potential effects of gut microbiota, different baseline of body weight, and different percent fat in the diet⁴⁸. Taken together, these key elements must be considered to further evaluate the role of leptin in the macrophage recruitment in the future studies.

3. Adiponectin—Adiponectin is another novel AT-derived hormone that modulates a number of metabolic processes, such as glucose regulation and fatty acid oxidation⁴⁹. Adiponectin is almost exclusively synthesized by adipocytes and is present at high levels (3-30 µg/ml) in the blood relative to other adipokines⁵⁰. Previous studies have shown that adiponectin may suppress lipid accumulation and have anti-inflammatory effects on macrophages^{51, 52}; and that adiponectin promotes macrophage polarization to an anti-inflammatory phenotype⁵³. Ohashi K *et al.* report that ATMs isolated from adiponectin knock-out mice displayed increased M1 markers and decreased M2 markers; while *in vitro*, the treatment of macrophages with recombinant adiponectin led to an increase in the levels of M2 markers⁵³. Thus, adiponectin-mediated modulation of macrophage function and phenotype may contribute to its role in reducing inflammation within AT.

4. SFRP5—A recent study reported the identification of SFRP5 as a new adipokine with anti-inflammatory properties that modulates inflammation and metabolic function⁵⁴. SFRP5 was downregulated in the ATs of various obese rodents as well as in the visceral AT of obese patients with AT inflammation and IR¹. SFRP5-deficient mice had impaired insulin sensitivity and increased fatty liver disease that were associated with increased accumulation of macrophages and enhanced production of pro-inflammatory cytokines in ATs⁵⁴. In addition, systemic administration of SFRP5 to obese mice led to improved IR⁵⁴. SFRP5 deficiency exacerbates obesity-induced AT inflammation and metabolic dysfunction through activation of c-Jun N-terminal kinases 1 in adipose tissue¹.

5. Serum amyloid A and hyaluronan—Other adipocyte-derived factors such as serum amyloid A (SAA) and hyaluronan also facilitate monocyte adhesion and chemotaxis. SAA is produced by the liver, adipocytes, and macrophages in response to inflammatory stimuli^{55, 56}. In obesity, inducible forms of SAA are highly expressed in AT in mice and humans⁵⁷. SAA can activate endothelial cells and recruit monocytes by increasing the expression of adhesion molecules including intracellular adhesion molecule-1 (ICAM-1) and vascular adhesion molecule-1 (VCAM-1) in a NF-κB dependent manner⁵⁸. Hyaluronan, a nonsulfated glycosaminoglycan lacking a core protein, binds monocytes via cluster of differentiation 44 receptor (CD44). CD44 deficient mice exhibit a remarkable reduction in the number of macrophages, suggesting the crucial role of hyaluronan in macrophage recruitment⁵⁹. Adipocyte hypertrophy causes an increase of production of SAA and hyaluronan, which exist as part of a complex matrix that increases the adhesion and retention of monocytes⁶⁰. This complex also has monocyte chemotactic activity which is dependent on the presence of SAA3 and hyaluronan but independent of MCP-1⁶⁰.

6. Vascular endothelial growth factor—Vascular endothelial growth factor is a key factor involved in AT angiogenesis. Transgenic mice overexpressing vascular endothelial growth factor in white AT present elevated macrophage infiltration with a higher number of M2 anti-inflammatory and fewer M1 pro-inflammatory macrophages than wild-type littermates after feeding with high fat diet (HFD) ⁶¹. These transgenic mice can avoid IR through maintaining an anti-inflammatory milieu, providing a potential therapeutic strategy for the prevention of obesity and IR.

7. Fatty acids—AT regularly releases FAs through the process known as lipolysis, in which involves the breakdown of lipids and hydrolysis of triglycerides into glycerol and free FAs. Obesity causes an increase in basal lipolysis and in local extracellular free FA concentrations, which involves a complex interacting between adipokines (IL-6 and TNF- α) and other small AT-derived molecules. Basal lipolysis is chronically elevated in obese AT compared with lean persons ⁶². Kosteli et al. report that the peak in ATM numbers coincide with the peak in the circulating concentration of free FAs and AT lipolysis, while dietary and genetic manipulations that reduce lipolysis decrease ATM recruitment ⁶². These data lead them to conclude that lipolysis may promote macrophage accumulation via increased level of free FAs. Lipoxigenases (LOs) catalyze the dioxygenation of polyunsaturated FAs in lipids, playing a critical role in FA-mediated inflammation and IR. In 12/15LO knockout mice, macrophage recruitment and IR induced by high fat diet are significantly blocked, suggesting the role of 12/15LO in the macrophage recruitment and the development of IR ¹⁵.

Macrophages express a variety of free FA receptors including TLRs, CD36, and GPCRs ⁶³⁻⁶⁵. Upon binding to the receptors, saturated FAs regulate chemotactic factor expression by a mechanism involving the generation of reactive oxygen species, NF- κ B, and peroxisome proliferator-activated receptor γ ⁶⁶. TLR4 binds to free FAs such as palmitate and stearate indirectly via an endogenous ligand like Fetuin-A ⁶⁷, causing the activation of NF- κ B and subsequent formation of pro-inflammatory cytokines and prostaglandins via increased expression of cyclooxygenase-2 ^{30, 68}. Inhibition of TLR4 signaling has been shown as an attractive therapeutic strategy for treatment of obesity-induced IR. In macrophages, casitas B-cell lymphoma-b suppresses saturated FA-induced TLR4 signaling by ubiquitination and degradation of TLR4. Casitas B-cell lymphoma-b deficiency mice show enhanced HFD-induced IR through saturated FA-mediated macrophage activation ⁶⁹. CD36, the class B scavenger receptor, facilitates uptake of long chain FAs and contributes to inflammatory responses by promoting macrophage infiltration into AT and expression of pro-inflammatory cytokines ⁷⁰. CD36 knockout mice show improved insulin sensitivity and reduced inflammation within AT ⁷¹. GPCR120 selectively binds omega-3 FAs such as α -linolenate and docosahexaenote ⁷² and leads to blockage of NF- κ B resulting in reduced inflammatory responses ⁶⁵. Macrophages also express GPCR105 linking between innate immunity and metabolism. Myeloid cell-specific GPCR105 ablation prevents inflammation and improves insulin sensitivity by inhibiting macrophage recruitment in diet-induced obese mice ⁷³.

In vitro, saturated FAs such as palmitate induce extracellular release of histone H3 in part through reactive oxygen species and c-Jun N-terminal kinases signaling. Extracellular H3

activates endothelial cells to express adhesion molecules such as ICAM-1 and VCAM-1 that recognize and interact with integrins, thereby facilitating the firm adhesion of leukocytes to endothelial cells and contributing to leukocyte trafficking ⁶⁹.

Chemokines

1. Chemokine/chemokine receptor—The chemokine superfamily is a group of small (8-10 kDa), positively charged, secreted proteins with a 20%-50% sequence homology, acting as chemotactic molecules for various cell types. There are over 50 human chemokines divided into four families based upon the separation of the first 2 cysteine residues. The two largest families are the CXC family, in which these two cysteines are separated by any single amino acid, and the CC families, in which these two cysteine residues are adjacent. The remaining two small chemokine families are the XC family having only one of the first two cysteines, and the CX3C family, in which the first two cysteines are separated by three amino acids ⁷⁴.

The majority of chemokine receptors are seven-transmembrane G protein-coupled receptors (GPCRs) with 77% amino acid identity that associate with heterotrimeric G-proteins. GPCRs are divided into four families that are named after the ligand families, and function in monomers, homodimers, and heterodimers ⁷⁴. The chemokine-chemokine receptor system functions not only in many physiological processes such as development, wound repair, and immunity, but also in pathological processes including chronic inflammation, IR, autoimmune diseases, cancer, and viral infections ⁷⁵. Over-expression of chemokines and/or their receptors induced by chronic inflammatory stimulation such as obesity can result in inappropriate leukocyte accumulation into AT and IR.

2. CC chemokines and their receptors—CC chemokines belong to the β -chemokine family in which the first two N-terminal cysteine residues are adjacent. MCPs (MCP-1/CCL2) ²⁸, macrophage inflammatory proteins (MIP α /CCL3 and MIP β /CCL4), and regulated upon activation, normal T cell expressed and secreted (RANTES/CCL5) are all CC chemokines ⁷⁵. These chemokines attract most monocytes via binding to their receptors.

To date, MCP-1-CCR2 system is the most well studied chemokine-chemokine receptor system in ATM recruitment. Over-expression of MCP-1 in AT causes macrophage recruitment and IR in aP2-MCP-1 mice ³¹, while the decrease of MCP-1 attenuates inflammation by suppressing macrophage recruitment to AT ⁷⁶. Human study indicates that although obesity is associated with the increased expression of several chemokine genes in AT, only MCP-1 is secreted into the extracellular space, where it influences the function of adipocytes and acts as recruitment factor of macrophages ⁷⁷. MCP-1 directs recruitment of pro-inflammatory macrophages to sites of inflammation ⁷⁸. In addition to blood monocyte recruitment, local proliferation of macrophages (only in visceral adipose tissue rather than others including liver and spleen) driven by MCP-1 contributes to obesity-associated adipose tissue inflammation ⁷⁹. CCR2 influences the development of obesity, AT inflammation, and IR, and plays a role in the maintenance of ATMs and IR once obesity is established ⁸⁰. Both in vivo and in vitro evidence supports that CCR2 in BM cells plays a

role in the recruitment of macrophages into obese AT ⁸¹. CCR2 antagonist (CCX417) can reduce inflammation in AT in models of T2DM ⁸².

However, controversy exists regarding the exact role of this system. In contrast to these findings, Inouye et al. report that MCP-1 may not be crucial for AT macrophage recruitment ⁸³. In that study, they used male 6-week-old MCP-1 deficient mice to evaluate the macrophage infiltration after 28 weeks of HFD feeding. Surprisingly, MCP-1 deficient mice on HFD showed alterations of metabolic function, but no reductions in ATMs compared with wild-type mice, indicating that MCP-1 has effects on metabolism that are independent of its macrophage-recruiting capabilities ⁸³. Their results were confirmed by another group in the following year ⁸⁴. Taken together, all reported studies show that over-expression of MCP-1 in AT elevates macrophage recruitment ^{31, 85}, and that CCR2 deficiency or inhibition reduces macrophage recruitment ^{80-82, 86, 87}. However, whether deficiency of MCP-1 can reduce macrophage recruitment and improve insulin sensitivity remains conflicting ^{76, 83, 84}. The complexity and redundancy of chemokine signaling may account for these conflicting results. In fact, CCR2 is a functional receptor shared by several other chemokines including MCP-2, MCP-3, CCL7 and CCL8, which are all expressed in obese AT and may affect macrophage recruitment ^{32, 88}.

In addition of MCP-1-CCR2 system, the compelling evidence indicates that RANTES-CCR5 system also plays a crucial role in obesity-induced AT inflammation and IR by regulating both macrophage recruitment and phenotype. RANTES participates in the recruitment of blood monocytes through triggering adhesion and transmigration of blood monocytes to/through endothelial cells of human white AT ⁸⁹. CCR5 deficient mice are protected from IR induced by HFD feeding and are related to both reduction of total ATM content and an anti-inflammatory phenotype, indicating that CCR5 plays a critical role in ATM recruitment and polarization and IR ⁹⁰. CCR5 also binds to MIP-1 α , which has been shown the capability of inducing monocyte/macrophage infiltration. Inhibition of MIP-1 α can reduce macrophage infiltration and activation mediated by downregulation of CCR5 ⁹¹.

3. CXC chemokines and their receptors—CXCL5-CXCR2 system represents a link between obesity, inflammation, and IR ^{92, 93}. CXCL5 is highly expressed in AT compared to liver and muscle and the plasma level is elevated in obese subjects ⁹². CXCR2 deficient mice are protected against obesity-induced IR ⁹³. CXCL14, a chemokine for macrophages and dendritic cells, is involved in recruitment of macrophages into white AT and contributes to IR ^{94, 95}. The receptor of CXCL14 has not yet been identified. HFD-fed CXCL14-deficient mice have impaired ATMs mobilization and improved insulin sensitivity. Interestingly, both of the studies reveal that the phenotype of improved insulin sensitivity and reduced macrophage infiltration is more prominent in female CXCL14 deficient mice than male mice, indicating that gender is a key factor that affects the inflammation mediated by CXCL14. Over-expression of CXCL14 in skeletal muscle can restore obesity-induced IR in CXCL14 deficient female mice ⁹⁴.

4. CX3C chemokines and their receptors—Fractalkine-CX3CR1 system contributes to macrophage recruitment and inflammation in atherosclerosis ⁹⁶, but their role in obesity-induced ATM accumulation remains controversial. In contrast to other reports that failed to

detect difference in HFD-induced body weight and adiposity in CX3CR1-deficient mice and controls ^{97, 98}, a recent study showed that CX3CR1-deficient mice fed 10 weeks HFD presented lower monocyte number and expressed significantly less MCP-1, IL-1 α and TNF- α in the white AT than wild-type animals, highlighting the importance of this system in macrophage recruitment in AT ⁹⁹.

V. Conclusion

Significant progress has been conducted to identify the molecules that regulate ATM recruitment and their roles of in obesity-related diseases. Adipokines have both pro-inflammatory and anti-inflammatory effects and the balance between these effects in normal state of nutrition determines the local and systemic inflammatory status. Imbalanced adipokine production during overnutrition contributes to AT inflammation and obesity-related diseases. Chemokines have roles in recruitment of monocytes from circulation and *in situ* proliferation of ATMs. Pharmacological blockade of the binding between chemokines and their receptors has been used to prevent or treat obesity-related diseases in both animal study and clinical trials. There are many questions, however, that have yet to be addressed particularly due to the complexity and redundancy of adipokine/chemokine signaling. Thus, further investigation of the functions and mechanisms of key adipokines/chemokines will lead to a better understanding of the pathogenesis of obesity and related disorders. Moreover, therapeutic strategies that counteract the dysregulation of adipokine production could be a potential and promising means for treating obesity-related diseases.

Acknowledgements

This work was supported by NIH grants 60035870

Abbreviations

AT	adipose tissue
IR	insulin resistance
T2DM	type 2 diabetes mellitus
ATM	adipose tissue macrophage
IL	interleukin
TNF	tumor necrosis factor
TACE	TNF- α converting enzyme
FAs	fatty acids
CLS	crown-like structures
TLR	toll-like receptors
MCP	monocyte chemotactic protein
NF-κB	nuclear factor- κ B

SFRP5	secreted frizzled-related protein 5
GPCR	G protein-coupled receptor
SAA	serum amyloid A
ICAM	intracellular adhesion molecule
VCAM	vascular adhesion molecule
CD	cluster of differentiation
HFD	high fat diet
LO	lipoygenase

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Figure 1. The role of crosstalk between adipocytes and macrophages in macrophage recruitment (1) obese adipocytes expand their sizes and break the balance between the levels of pro-inflammatory and anti-inflammatory adipokines; (2) obesity causes an increase in local concentration of extracellular fatty acids through upregulation of basal lipolysis, which involves multiple adipokines as well as other adipose tissue-derived proteins; free fatty acids can bind macrophages either directly via CD36 or indirectly via the ligand of Fetuin-A; (3) adipocytes communicate with macrophages via pro-inflammatory adipokines in a paracrine pathway; these adipokines bind macrophages via TLR4 or CCR2; (4) upon binding to fatty acids and adipokines, the resident macrophages can be activated and then transduce the signal into nucleus where NF-κB is activated, thereby contributing to the release of pro-inflammatory chemokines such as MCP-1; (5) adipocytes also secrete amyloid A that activates the adhesion molecules, promoting the monocyte trafficking; (6) monocytes move toward the higher concentration of MCP-1 via binding to CCR2, which is the process known as chemotaxis; (7) matured monocytes contribute to macrophage accumulation within AT; (8) MCP-1-driven *in situ* proliferation of macrophages also contributes to macrophage accumulation; macrophages encircle the dead adipocytes caused by obesity, forming crown-like structure. TLR: toll-like receptor; CD36: cluster of differentiation 36; MCP-1: monocyte chemoattractant protein-1; CCR2: C-C chemokine receptor type 2; NF-κB: nuclear factor-κB.