Published in final edited form as:
*Curr Opin Lipidol*. 2010 June ; 21(3): 172–177. doi:10.1097/MOL.0b013e3283393867.

# Adipose Tissue Recruitment of Leukocytes

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## Abstract

**Purpose of Review—**In December of 2003, two seminal articles describing the presence of macrophages in obese adipose tissue (AT) were published. These AT macrophages (ATMs) are inflammatory and promote local and systemic insulin resistance. Due to the continuing rise in obesity around the world, understanding how these ATMs contribute to metabolic disorders is of much interest.

**Recent Findings—**Chemokines have been extensively studied for their role in ATM recruitment. Deficiency or antagonism of chemokine receptors that interact with multiple chemokine ligands reduces ATM accumulation. ATMs are now defined as either classically (M1) or alternatively (M2) activated. PPAR activation and adiponectin promote an M2 polarized state resulting in improved insulin sensitivity. Finally, recent studies have provided evidence that T lymphocytes, NKT cells, mast cells, and B cells also enter AT and may interact with macrophages and adipocytes.

**Summary—**Literature published during the past year has shown that macrophage recruitment to AT is only one of the important mediators of obesity-related insulin resistance. The phenotype of ATMs and recruitment of other immune cells to the AT play key roles in the overall contribution of AT to systemic metabolic outcomes of obesity.

### Keywords

macrophages; chemokines; T lymphocytes; polarization; PPAR

## INTRODUCTION

The incidence of insulin resistance (IR) is increased with obesity and is thought to arise from a state of chronic inflammation, characterized by elevated levels of circulating pro-inflammatory cytokines. It is now accepted that adipose tissue (AT) is the primary source of many inflammatory cytokines in obesity. The immune system has come to the forefront of obesity research. The novel discovery that pro-inflammatory macrophages are recruited to obese AT prompted an increased interest in the interplay between immune cells and metabolism [1, 2]. Since this discovery, many papers have been published describing the factors that lead to macrophage recruitment, the phenotype of AT macrophages (ATMs), and the presence of other types of immune cells in obese AT. Some of the most important discoveries in this field from the past year are highlighted in this review.

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## MACROPHAGE RECRUITMENT TO ADIPOSE TISSUE

Early reports focused on the probability that dead or dying adipocytes initiate macrophage recruitment to AT in obesity [3, 4]. Recent literature points to the idea that certain populations of circulating monocytes may be more susceptible to recruitment to AT. In addition, other molecules derived from AT, such as chemokines and inflammatory mediators, have also been evaluated for their role in recruiting and activating these monocytes/macrophages (summarized in Table 1).

### Monocyte Trafficking

Preferential trafficking of certain monocyte subpopulations to inflamed AT may contribute to obesity-induced inflammation. Lumeng and colleagues have identified macrophage galactose-type C-type lectin 1 (Mgl1) as being critical for the survival and migration of $7/4^{hi}$ monocytes, a population of cells that is recruited to sites of inflammation. Animals deficient in Mgl1 are protected from IR and the accumulation of ATMs, due to a reduction in circulating levels of these $7/4^{hi}$ inflammatory monocytes [23]. CCR2 has also been shown to play a key role in the migration of monocytes from the bone marrow into the circulation [24]. These studies point to the importance of differential recruitment of monocytes into the circulation and into sites of inflammation, supporting a model in which mobilization of specific monocyte subpopulations contributes to metabolic inflammation.

### Chemokines

Chemokines and their receptors are highly expressed in human visceral and subcutaneous AT in obesity [25, 26]. Most of these chemokines are thought to be derived from the stromal vascular fraction of AT [2] although their secretion from adipocytes has also been reported. To date, monocyte chemoattractant protein-1 (MCP-1) and its receptor, CCR2, is the most studied chemokine/receptor pair in ATM recruitment. However, controversy exists regarding the exact role of these molecules. Transgenic over-expression of MCP-1 from AT results in increased macrophage recruitment and worsened metabolic phenotype [5, 8]. In contrast, deficiency of MCP-1 or CCR2 results in reduced inflammatory ATM accumulation and protection from IR [5, 11, 12]. However, conflicting reports by Kirk *et al.* and Inoeye *et al.*, showed that MCP-1 deficiency does not decrease macrophage numbers in AT or improve insulin sensitivity [6, 7]. Despite this paradox, deficiency or pharmacological inhibition of CCR2 decreases ATMs in all reported studies [11, 13, 14]. Taken together, what is consistently demonstrated is that over-expression of MCP-1 in AT increases macrophage recruitment to AT, and that CCR2 deficiency decreases macrophage recruitment. However, whether deficiency of MCP-1 can reduce ATMs is not clear. A possible reason for the different findings regarding MCP-1 and CCR2 is that CCR2 is a functional receptor for several other chemokines including MCP-2, MCP-3, CCL7 and CCL8, which are all expressed in obese AT and could affect ATM recruitment [26].

In addition to MCP-1/CCR2, a few other chemokines have been studied. CXCL14 [9] and the receptor CXCR2 [15, 27] were noted to play a role in macrophage recruitment to AT. In humans, CCL5 (also known as RANTES) was demonstrated to positively correlate with inflammatory gene expression in visceral AT [10].

The contribution of different chemokines to the recruitment of ATMs is complex. Furthermore, even in studies showing that deficiency or antagonism of chemokines or chemokine receptors ameliorates the obesity-induced increase in ATMs, macrophage accumulation is never completely abolished, implicating chemokine-independent mechanisms for macrophage recruitment to AT during weight gain.

### Inflammatory Mediators

There are several reports of inflammatory mediators that, when inhibited or deleted, result in reduced ATM accumulation. In addition, many of these mediators induce chemokine expression, further promoting the recruitment of ATMs. Key inflammatory molecules that have been reported in the past year are briefly described below.

**Complement Factors—**The complement system is a vital part of the innate and adaptive immune response and is conserved across a wide range of species. The role of complement in the immune system has been understood since the early 1900's and several complement proteins including C3, Factor B, and adipsin have been found in adipose tissue. Recently, Mamane et al. showed that mice lacking the C3a receptor present a striking decrease in ATM infiltration and are resistant to diet-induced obesity, IR, and hepatic steatosis [16]. These studies provide a clear link between the complement system and ATM accumulation.

**Toll-Like Receptor 4—**Toll-like receptor 4 (TLR4) is a pattern recognition receptor that initiates inflammatory signaling events in response to lipopolysaccharide and saturated fatty acids. Several groups previously reported moderate effects of TLR4 mutations on AT inflammation [17–19]. Davis *et al.* showed that TLR4 mutant 10ScN mice have reduced ATM numbers and AT inflammation in response to a diet rich in saturated fatty acids [20]. Olefsky and colleagues demonstrated that high fat fed recipients of TLR4 deficient bone marrow had reduced ATMs and inflammatory cytokine expression in their AT [21]. Our laboratory has also shown that hematopoietic TLR4 deficiency results in reduced macrophage infiltration into AT in low fat diet fed mice [22]. Recent work by Han and colleagues has demonstrated that saturated fatty acids, acting through TLR4, upregulate the expression of chemokines such as MCP-1 [28] suggesting that saturated fatty acid-induced increases in chemokine levels may explain the decreased ATM recruitment seen in TLR4 deficient mice.

## MACROPHAGE PHENOTYPE IN ADIPOSE TISSUE

Macrophages and their monocyte precursors are highly heterogeneous cell populations. Subtypes of macrophages were originally defined *in vitro* as M1 "classically activated" and M2 "alternatively activated". Treatment of macrophages with LPS and IFNγ results in an M1, pro-inflammatory phenotype, while treatment with IL-4 or IL-13 results in an M2, anti-inflammatory phenotype [29]. M1 macrophages participate in the resolution of bacterial infections while M2 macrophages are involved in tissue homeostasis and repair.

In 2007, Lumeng *et al.* extended this M1/M2 macrophage paradigm to ATMs [30]. Their data demonstrated that obesity induces a phenotypic switch in ATMs from an anti-inflammatory M2 polarized state to a pro-inflammatory M1 state. The recruitment of this unique subset of M1 macrophages to the AT contributed to the chronic low-grade inflammation of obesity, which resulted in reduced adipocyte insulin sensitivity. M1 macrophages were recruited specifically to "crown-like structures" surrounding adipocytes, supporting the hypothesis that these inflammatory macrophages interact with adipocytes [12]. Thus, factors within the local milieu of AT can greatly influence the phenotype and activation status of these cells. The determinants of macrophage polarization are just beginning to be investigated and include PPARs and adiponectin.

### PPARs

PPARγ is an important molecular player in adipose tissue macrophage polarization. Stienstra *et al.* showed that PPARγ activation is associated with increased infiltration of ATMs. However, these macrophages were polarized to an anti-inflammatory M2 phenotype,

suggesting that PPARγ is critical for the alternative activation of macrophages [31]. Interestingly, it has also been shown that activation of immune cell PPARγ results in decreased macrophage infiltration due to inhibition of MCP-1 and CCR2 expression [32, 33].

Odegaard and colleagues found that PPARγ expression in macrophages is essential for the maturation of alternatively activated macrophages [34]. In fact, PPARγ response elements have been identified in the promoters of many of the genes expressed in M2 macrophages [34]. Macrophage PPARγ is critical for normal whole-body insulin sensitivity, and macrophage-specific deletion of this nuclear receptor resulted in glucose intolerance as well as skeletal muscle and hepatic IR [35]. PPARγ has also been identified as a mediator of the M2-induced switch to oxidative metabolism, as it promotes β-oxidation. This switch in metabolism prevents the accumulation of lipotoxic free fatty acids and reduces inflammation [34].

Another PPAR family member, PPARδ, has also been implicated in the regulation of macrophage polarization in AT [36]. Ablation of PPARδ blunted macrophage polarization to an M2 phenotype and resulted in adipocyte inflammation in co-culture experiments. Interestingly, *in vivo,* PPARδ is mainly involved in the polarization of Kupffer cells [37]. Therefore, while PPARγ is the main regulator of macrophage phenotype in AT, PPARδ seems to play a critical role in the liver.

### Adiponectin

Adiponectin is a fat-derived adipokine known to be down-regulated in obesity and diabetes. Previous studies have shown that adiponectin may have anti-inflammatory effects on macrophages [38–40]. However, the role of this adipokine in macrophage phenotype has only recently been investigated. Ohashi *et al.* showed that adiponectin promotes macrophage polarization to an anti-inflammatory phenotype and reduces reactive oxygen species levels [41]. Thus, decreased levels of adiponectin in obesity may allow for an M1 polarization and contribute to adipose tissue inflammation and systemic insulin resistance.

## RECRUITMENT OF OTHER IMMUNE CELLS TO ADIPOSE TISSUE

While macrophages were the first immune cell to be described in AT and are the most well-studied, recent reports also describe the infiltration of other leukocyte populations into AT.

### T Lymphocytes

Obesity results in a striking increase in $CD8^+$ T cells and a decrease in both $CD4^+$ helper and regulatory T cells ($T_{reg}$) in visceral AT [42–44]. Furthermore, T cells interact with macrophages and can influence their inflammatory status.

Nishimura *et al.* demonstrated that $CD8^+$ T cells present in AT contribute to macrophage infiltration [45]. First, they showed that infiltration of $CD8^+$ T cells precedes the appearance of macrophages. Second, CD8-deficient mice did not show increases in recruitment of M1 macrophages to AT upon high fat diet feeding. These animals were also more insulin sensitive than wild type mice. Third, adoptive transfer of $CD8^+$ cells led to a normalization of the infiltration of M1 macrophages. Finally, $CD8^+$ T cells isolated from obese AT induced peripheral blood monocyte differentiation into TNF-$\alpha^{high}$ macrophages [45]. Thus, this paper clearly establishes a role for $CD8^+$ T cells in the recruitment, differentiation, and activation of macrophages during obesity.

$CD4^+$ T helper and $T_{reg}$ cells also play a key role in determining the outcome of inflammatory responses. $T_H1$ cells are pro-inflammatory and enhance macrophage secretion

of inflammatory cytokines. $T_H2$ and $T_{reg}$ cells, in contrast, induce an anti-inflammatory M2 macrophage phenotype. Winer *et al.* have shown that HFD feeding leads to a $T_H1$ bias among the fat-associated $T_H$ cells. $T_H2$ and $T_{reg}$ populations are decreased, leading to an imbalance in the inflammatory environment of the AT [46]. This increase in the $T_H1/T_H2$ ratio leads to AT inflammation, recruitment of M1 macrophages, and IR.

$T_{reg}$ cells are involved in the appropriate control of immune responses. Decreased numbers of $T_{reg}$ cells have been reported in the AT of obese mice [45–47]. Feuerer *et al.* demonstrated that ablation of $T_{reg}$ cells, mimicking the decrease seen in obesity, leads to decreased insulin signaling in AT and liver, as well as increased inflammatory cytokine expression [47]. In contrast, increased activation of $T_{reg}$ cells resulted in decreased fasting glucose levels and increased IL-10 secretion. In addition, transcriptional profiling of $T_{reg}$ cells revealed a unique phenotype: AT-associated $T_{reg}$ cells over-expressed many genes involved in leukocyte migration and extravasation when compared to other $T_{reg}$ populations [47]. This profile suggests a critical role for AT-associated $T_{reg}$ cells in the control of adipose inflammation.

Interestingly, Rag1- and Rag2-null mice that lack B and T lymphocytes become more obese and insulin resistant than wild type mice [46, 48]. This IR is associated with increased macrophage and NK cell infiltration into the visceral AT, suggesting a protective role for lymphocytes in the generation of metabolic inflammation. Reconstitution of $Rag1^{-/-}$ mice with $CD4^+$, but not $CD8^+$, T cells normalized weight gain and decreased macrophage recruitment to AT [46]. These data indicate that $CD4^+$ $T_H2$ cells serve to reduce the inflammatory status of visceral AT.

Perhaps one of the most interesting aspects of all three T cell papers reviewed above is the finding that T cells in AT express a restricted T cell receptor repertoire, reminiscent of immune responses to viral pathogens. Adaptive immune cells, such as T cells, are only activated in response to T cell receptor interaction with a specific antigen. T cell receptor restriction in obese AT suggests that T cells may be recognizing self-antigen within this tissue. Thus, recent evidence convincingly demonstrates a vital role for adaptive immune cells in the pathogenesis of AT inflammation and IR.

## NKT Cells, Mast Cells and B Lymphocytes

NKT cells have also been observed in obese AT [49]. These innate-like T lymphocytes recognize lipid antigens. Depletion of NKT cells decreased IR and adipose inflammation upon high fat diet feeding, while activation of these cells exacerbated metabolic abnormalities. The involvement of NKT cells in obesity has led to speculation that lipid antigens may contribute to immune cell infiltration into AT.

Mast cells are traditionally thought of as mediators of allergic responses. Recently, mast cell involvement in many diseases, including obesity and diabetes, has been shown. Liu et al. demonstrated that mast cells accumulated in obese AT before the appearance of macrophages. Depletion of mast cells resulted in decreased weight gain and reduced AT macrophage content in obesity, suggesting that mast cells may be involved in ATM recruitment. Mast cell expression of IL-6 and IFN$\gamma$ increased protease expression in AT. These proteases play a key role in angiogenesis by degrading anti-angiogenic molecules [50]. Thus, mast cell-induced angiogenesis may allow for further recruitment of leukocytes to the AT.

While B cells appear to infiltrate AT very early after high fat feeding, their role in AT inflammation remains unclear [48]. Further studies are needed to determine whether B cells influence AT function or the recruitment of other leukocytes to the AT.

## CONCLUSIONS AND FUTURE DIRECTIONS

Significant progress has been made in identifying mechanisms by which macrophages are recruited to AT, the different phenotypes of ATMs, and the role of other immune cells in AT inflammation and IR. Future studies will continue to focus on the many different molecules involved in the initiation of macrophage recruitment to AT, including but not limited to the chemokines and inflammatory molecules described above. An area of future investigation is defining endogenous AT molecules that polarize ATMs toward M1 or M2 states, as well as the role that these different macrophages play in AT physiology. Finally, discerning the interplay of different cells of the innate and adaptive immune system, as well as identifying potential T cell antigens, is an exciting area of future research.

## Acknowledgments

**Funding Received**: AH Hasty is supported by NIH grant HL089466 and by a Career Development Award from the American Diabetes Association (1-07-CD-10). EK Anderson is supported by a Cellular, Biochemical, and Molecular Sciences Training Program Pre-doctoral Fellowship (NIH T32GM008554) and DA Gutierrez is supported by a supplement to HL089466-02S1.

Other than the funding information provided above, the authors have no financial interests or conflicts of interest to disclose.

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**Table 1**

Role of Different Molecules in Macrophage Recruitment to AT.

| Molecule | Model | Change in ATM | Insulin Sensitivity | Reference |
|---|---|---|---|---|
| **Chemokines** | | | | |
| **MCP-1** | Knockout | ↓ | Improved | [8] |
| **MCP-1** | Knockout | ↔ | No change | [11, 12] |
| **MCP-1** | AT overexpression | ↑ | Worsened | [7, 8] |
| **CXCL14** | Knockout | ↓ | Improved (females only) | [15] |
| **CCL5** | Elevated in visceral AT in humans | | Correlated with inflammatory cytokines in AT | [18] |
| **Chemokine Receptors** | | | | |
| **CCR2** | Knockout | ↓ | Improved | [9, 10] |
| **CCR2** | Pharmacologic antagonist | ↓ | Improved | [9, 13, 14] |
| **CCR2** | Bone marrow transplant of CCR2−/− into ob/ob mice | ↓ | Improved | [14] |
| **CXCR2** | Bone marrow transplant of CXCR2−/− into wild type mice | ↓ | Improved | [17] |
| **Inflammatory Mediators** | | | | |
| **Complement Factor 3a** | Receptor knockout | ↓ | Improved | [19] |
| **TLR4** | Deficiency | ↓ | Improved | [22] |
| **TLR4** | Mutation (C3H/HeJ) | ↔ but less inflammatory | Improved | [23, 24] |
| **TLR4** | Mutation (10ScN) on diet rich in saturated fatty acids | ↔ but less inflammatory | Improved | [25] |
| **TLR4** | Bone marrow transplantation of TLR4−/− in C57BL/6 with high fat diet feeding | ↓ | Improved | [26] |
| **TLR4** | Bone marrow transplantation of TLR4−/− in LDLR−/− with low fat diet feeding | ↓ | Unchanged | [27] |