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Chapter 6

Adipokines Involved in Macrophage Recruitment

Dayea Kim, Jong Hyuk Yoon, Jaeyoon Kim and Sung Ho Ryu

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1. Introduction

Recent studies have reported adipose tissue as a crucial site for the generation of inflammatory responses and mediators in metabolic syndrome. In addition to the intrinsic properties of adipocytes in energy storage and metabolic homeostasis, adipose tissue serves as a key area for the interaction of adipocytes with other factors of the immune system.

An important feature of inflammation is recruitment of immune cells such as neutrophils, eosinophils, and macrophages. Macrophage infiltration of adipose tissue in obese conditions has been studied in both mice and humans. It has been suggested that expanding adipocytes or neighboring pre-adipocytes could start to produce chemotactic signals inducing to macrophage recruitment, and this event is linked to systemic inflammation and insulin resistance.

In this chapter, we describe several chemotactic factors that have been implicated in the recruitment of inflammatory monocytes and macrophages into adipose tissue.

2. Body

2.1. Adipose tissue inflammation

2.1.1. Adipose tissue as a site of inflammation: expansion of adipose tissue induces an inflammatory response that contributes to metabolic disorders

2.1.1.1. Composition and function of adipose tissue

Adipose tissue is connective tissue composed primarily of adipocytes. The highest percentage of cells within adipose tissue is adipocytes; other cell types present in adipose tissue are

collectively termed the stromal vascular fraction (SVF), which includes pre-adipocytes, adipose tissue macrophages, fibroblasts, and endothelial cells. Adipose tissue primarily plays a role in the storage of energy in the form of lipids when nutrients are in excess or in the regulation of homeostasis of non-shivering thermogenesis. Adipose tissue regulates whole body energy homeostasis by responding rapidly and dynamically to changes in nutrient deprivation and excess through regulation of adipocyte size and number [1, 2]. In this reaction, free fatty acids (FFAs) are released from lipoproteins by lipoprotein lipase (LPL) and enter the adipocyte, where they are reassembled into triglycerides by esterification onto glycerol. Adipose tissue also provides feedback for hunger and diet to the brain under normal conditions through secretion of hormones [3].

2.1.1.2. Adipose tissue mediates obesity-induced inflammation

Obesity negatively affects the functioning of peripheral tissues, including adipose tissue, skeletal muscle, the pancreas, liver, heart, joints, and central nervous system (CNS) [4]. The fundamental characteristic of obesity is chronic imbalance between caloric intake and energy expenditure, resulting in the storage of excess nutrients in white adipose tissue (WAT) [5]. WAT was traditionally considered a long-term energy storage organ, but it is now known that it has a key role in the systemic regulation of metabolism. The metabolic function is largely mediated by the ability of WAT to secrete numerous proteins [6, 7]. The cytokines secreted by adipose tissue are called adipokines. In the obese state, the secretory status of adipose tissue is modified by changes in the cellular composition, including diverse alterations in the number, phenotype, and localization of immune, vascular, and structural cells [6]. Adipose tissue in obese human patients and in animal models of obesity are infiltrated by a large number of macrophages, and this recruitment is linked to systemic inflammation and insulin resistance [8, 9]. The secretion of most adipokines is upregulated in the obese state, and these proteins primarily include proinflammatory cytokines such as monocyte chemotactic protein-1 (MCP-1), TNF-α, and interleukin (IL)-6, which function to promote the development of a chronic and systemic inflammatory state and contribute to metabolic dysfunction [6, 10, 11]. Therefore, adipose tissue-mediated inflammation is a considered to be a pathophysiological condition (Figure 1).

Increased levels of the cytokine TNF-α in adipose tissue of obese mice were the first discovered link between inflammation and obesity [12]. This discovery was soon followed by many studies describing changes in the levels of inflammatory molecules between obese and lean states in animals as well as humans. It is now known that, in addition to TNF-α, an array of inflammatory cytokines including IL-6, IL-1β, MCP-1, and others are increased in obese tissues [13, 14].

2.1.2. Obesity-mediated macrophage recruitment into adipose tissue and metabolic disease

It is generally accepted that obesity causes adipocytes to secrete chemokines such as MCP-1 and leukotriene B4 (LTB4), which provide a chemotactic gradient that recruits monocytes into adipose tissue, where they become adipose tissue macrophages (ATMs) (Figure 2). Once proinflammatory ATMs migrate into adipose tissue, they also secrete their own cytokines,

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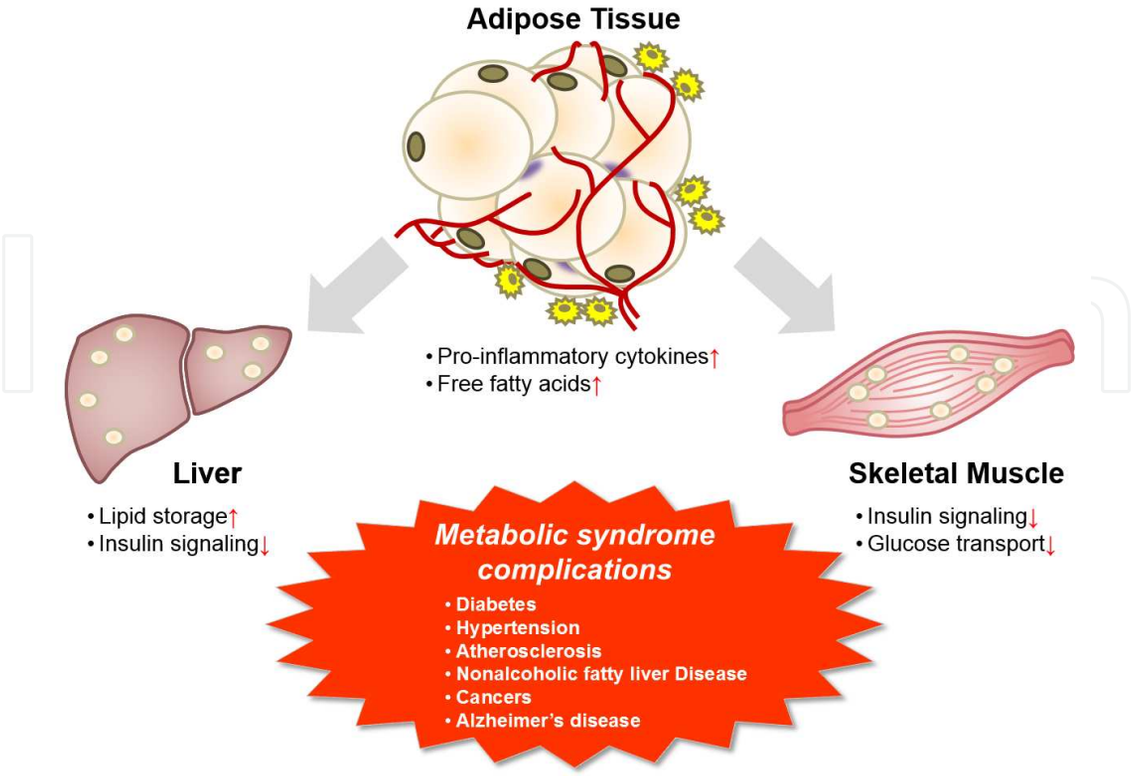

Figure 1. Adipose tissue affects peripheral metabolic tissues and induces diverse metabolic syndrome complications

recruit additional macrophages, and ultimately set up an amplified inflammatory process [15]. Specifically, ATMs together with hypertrophic adipocytes, pre-adipocytes, and other immune cells produce an array of chemokines, proinflammatory cytokines, and metabolites that induce endothelial activation during obesity. This reaction causes endothelial cells to produce various cellular adhesion molecules such as ICAMs, selectins, vascular cell adhesion molecules, and PECAM-1. Through a rolling and adhesion step, monocytes slow down and finally bind to endothelial adhesion proteins via selectin ligands and integrins. After a series of events including actin-dependent spreading, polarization, the monocytes undergo integrin-dependent lateral migration on the luminal surface of the endothelium. Then, the monocytes migrate across the endothelium, either through para-or transcellular routes [16]. After entering adipose tissue, macrophages undergo differentiation towards M1-or M2-like macrophages (See Section 2.2) [17]. Differentiation processes can occur according to their initial circulating phenotype and/or in response to local micro-environmental stimuli. However, repolarization of M1 macrophages into M2 macrophages and conversely, proliferation of macrophages within the adipose tissue still remain unclear [17].

The recruitment of macrophages into adipose tissue is the initial and important event in obesity-induced inflammation and metabolic disease [15]. Activation of tissue macrophages, as the outcome, triggers the secretion of proinflammatory cytokines, which can induce insulin resistance in various pathways. Genetic studies using knockout (KO) and transgenic techniques to disable macrophage-mediated inflammatory pathways also support this pathway [15].

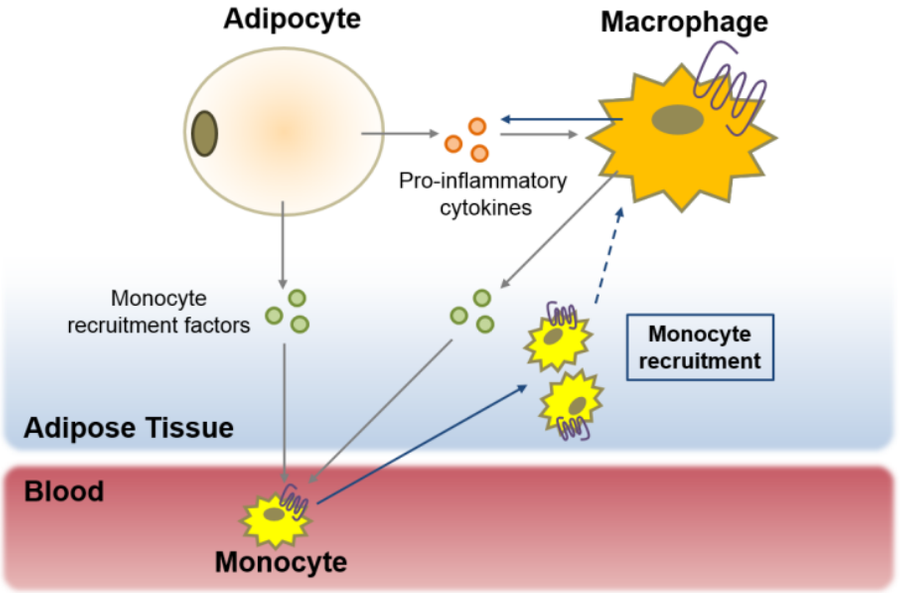

Figure 2. Adipokines induce obesity-mediated immune cell recruitment into adipose tissue

2.2. Adipose tissue macrophages: types and functions in metabolic disease

2.2.1. Origin and function of ATM

Pre-adipocytes have been shown to convert to macrophages [18], but most ATMs migrate from blood monocytes during obesity. Bone-marrow transplantation experiments using transgenic mice with antigenically distinct forms of the CD45 protein, a leukocyte marker, showed that 85% of ATMs after 6 weeks of a high fat diet (HFD) were from donor cells, which indicates that blood circulating monocytes migrated into adipose tissue while receiving the HFD [9]. Therefore, there are likely some signals that attract blood monocytes to adipose tissue (see Section 2.3). Since ATMs are the primary source for proinflammatory cytokines in adipose tissue, it was hypothesized that ATMs might be the critical player for systemic insulin resistance. Several studies have supported this hypothesis in *in vivo* models. For example, myeloid-specific IKKβ KO mice showed improved insulin sensitivity with the HFD [19], and mice with JNK1 and 2 deficiencies in macrophages were obese but were still insulin sensitive with fewer macrophages and lower proinflammatory cytokine expression in adipose tissues [20]. These studies suggested that changes in macrophage activation might affect whole body insulin sensitivity.

2.2.2. General aspects of macrophage activation

Macrophages are a heterogeneous cell population exhibiting a wide spectrum of phenotypes due to cellular differentiation, wide spread tissue distribution, and responsiveness to many

endogenous and exogenous stimuli. Macrophage activation has been defined across 2 separate polarization states, M1 and M2 [21]. M1 macrophages are referred to as classical activated macrophages where activation is dependent on products of specifically activated T helper 1 (T_H1)-type lymphocytes and natural killer cells. Similar to interferon-gamma (IFN-γ) [22] and IL-12, IL-18 is presented by antigen presenting cells (APCs). M1 macrophages secrete high levels of proinflammatory cytokines (TNF-α, IL-6, IL-12) and generate reactive oxygen species (ROS) through the actions of inducible nitric oxide synthase (NOS2). M2 macrophages are activated by IL-4 and IL-13, cytokines produced generally in a T_H-2-type response, which is referred to as alternative activation. This type of activation is believed to be involved in allergic, cellular, and humoral responses to parasitic and extracellular pathogens. M2 macrophages secrete low levels of proinflammatory cytokines and high level of anti-inflammatory cytokines [21]. Three different subsets of M2 macrophages have been identified, including M2a, M2b, and M2c. IL-4 and IL-13 lead to M2a macrophages, immune complexes in combination with IL-1b or lipopolysaccharide (LPS) drive the M2b subtype, whereas IL-10, TGF-β, or glucocorticoids induce M2c macrophages [23]. In alternative activation, IL-4 and IL-13 upregulate expression of the mannose receptor and MHC class II molecules, which stimulate endocytosis and antigen, while intracellular enzymes such as arginase are implicated in cell recruitment and granuloma formation.

2.2.3. Activation of adipose tissue macrophages (ATMs)

Originally, ATMs were suggested to have roles in the production of proinflammatory cytokines [8, 9]; therefore, it seems plausible that most ATMs are M1 macrophages in obesity. In initial pioneering studies regarding ATMs, ATM content was determined by F4/80 or CD11b antibodies, which are common macrophage markers that cannot differentiate between M1 and M2 macrophages. Subsequent studies have shown that ATMs are operationally defined across M1 to M2 polarization states. Using flow cytometry, it was shown that ATM from lean mice showed the M2 macrophage phenotype, but ATMs that accumulated following a HFD exhibited the proinflammatory M1 phenotype. Based on these data, it was suggested that ATMs underwent a phenotypic switch from the M2 polarization state to a more M1 polarization state [24]. In line with ATM polarization, ATMs with M1-like activation were characterized by $F4/80^+/CD11b^+/CD11c^+$surface markers, whereas $F4/80^+/CD11b^+/CD11c^-$cells were present following M2-like activation [24, 25]. Since F4/80 and CD11c were primarily considered as surface markers for macrophages and dendritic cells, respectively, these ATMs with triple positive surface markers are unusual in that they have both macrophage and dendritic cell features [25]. These data are supported by the fact that $CD11c^+$cells have a deleterious effect on insulin resistance; it was shown that selective depletion of $CD11c^+$cells reversed insulin resistance with a HFD [26]. A recent article showed the temporal dynamics of macrophage activation where it was shown that M2 ATM polarization was enhanced in the early phase of obesity (both in the *ob*/*ob* model and the diet-induced obesity (DIO) model), and M1 polarization was subsequently gradually enhanced [27]. These data indicate that there are temporal and spatio differences between M1 and M2 macrophages during obesity. While M2 macrophages (resident macrophages) were localized to interstitial spaces between adipocytes in lean mice, M1 ATMs surrounded dead adipocytes with DIO, thus forming crown-like structures

(CLSs) [28]. However, the activation status of ATMs does not seem to be static. Whereas HFD-induced insulin resistance followed by a normal chow diet could reverse body insulin sensitivity, mice still contained a similar level of $CD11c^+$ATMs in adipose tissue, but these macrophages no longer exhibited inflammatory pathway markers [29]. Furthermore, a class of macrophages that express a marker for both M1 and M2 (i.e., $CD11c^+$, $CD209a^+$) was identified in obese adipose tissues. These macrophages were likely transformed from M2 to M1 macrophages through lipid accumulation [27]. Therefore, there might be some mechanism to regulate activation of ATMs in adipose tissue along with obesity development.

2.2.4. Regulation of ATM polarization

Classical activation of macrophages (M1) is induced by Toll-like receptor (TLR) ligands and IFN-γ, while alternative activation of macrophages (M2) is induced by IL-4/IL-13 (M2a), immune complexes (M2b), or anti-inflammatory cytokines IL-10 or TGF-β (M2c) to mediate Th1/Th2 immune responses [30]. In the classical activation of macrophages, adipose tissue secretes FFAs, which can activate TLR4 [31] by lipolysis and IFN-γ. On the other hand, it was shown that adipocytes secrete Th2 cytokines such as IL-4 and IL-13, which is important for alternative macrophage activation [32]. Adiponectin is also reported to induce M2 polarization, which was shown using adiponectin KO mice and adenoviral delivery of adiponectin [33].

In terms of intracellular signaling in adipose tissue macrophages, transcription factors and related machinery that regulate ATM polarization have been studied. Peroxisome proliferator–activated receptor gamma (PPARγ) is one of most striking regulators because it is known as a master regulator of adipogenesis. However, PPARγ was expressed at relatively high levels in monocytes and macrophages [34], and it was reported that PPARγ activation reduced proinflammatory cytokines in monocytes/macrophages [35, 36]. When PPARγ was knocked out in macrophages, bone marrow-derived macrophages showed impaired alternative macrophage activation, and these mice were obese, with an insulin resistant and glucose intolerant phenotype following HFD feeding [37]. PPARδ, another PPAR family member, is also important for ATM polarization. Myeloid-specific KO of PPARδ resulted in enhanced adipose tissue inflammation and insulin resistance, which is consistent with the M1 polarization phenotype [32]. PGC-1β, a co-activator of the PPAR family, is also clearly involved in alternative macrophage activation by cooperating with STAT6, which is a critical signal mediated by Th2 cytokines [38]. In addition, Krüppel-like factor 4 (KLF4), which belongs to the zinc finger class of DNA-binding transcriptional regulators, was suggested to be a master regulator of macrophage polarization during obesity. KLF4 expression was markedly reduced in obese adipose tissue, and KLF4 deficiency exhibited an enhanced inflammatory response. In particular, myeloid specific KO of KLF4 led to obesity, insulin resistance, and impaired glucose tolerance [39]. Interferon regulatory factor 4 (IRF4) is also known to be involved in ATM polarization. Macrophage-specific IRF4 KO mice exhibited significant insulin resistance and adipose tissue inflammation with a HFD [40].

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2.3. Adipose tissue-derived chemotactic factors and macrophage recruitment in metabolic diseases

Human studies and mouse models have both been used to identify the chemokines and associated receptors that are elevated in obese adipose tissue [41] and those that contribute to monocyte recruitment [17].

2.3.1. MCP-1 and CCR2

MCP-1 (CCL2) is produced mostly by macrophages and endothelial cells and is a potent chemotactic factor for monocytes [42-44]. The level of MCP-1 in both WAT and plasma was increased in obese mice [45], suggesting that MCP-1 might be an adipokine whose expression is increased in obesity [46].

Binding of MCP-1 to its receptor CCR2 is considered crucial in obesity-induced insulin resistance. Several groups have demonstrated that mice with targeted deletions in the genes for *Mcp-1* and its receptor *Ccr2* have decreased ATM content, decreased inflammation in WAT, and protection against obesity-induced insulin resistance [46, 47]. On the contrary to this, mice overexpressing MCP-1 in adipose tissue had increased ATM and insulin resistance [46, 48]. Therefore, the MCP-1-CCR2 axis is important to promote ATM recruitment and insulin resistance in mice. Recent studies; however, have shown conflicting results and indicate a greater complexity than suggested by previous reports. In studies done by several groups, results showed that loss of MCP-1 did not attenuate obesity-associated macrophage recruitment to WAT or improve metabolic function, suggesting that MCP-1 is not pivotal for obesity-induced macrophage recruitment and systemic insulin resistance [49, 50]. Furthermore, although $Ccr2^{-/-}$mice fed a HFD had fewer macrophages in WAT compared with wild type (WT) mice [47], CCR2 deficiency did not normalize ATM content and insulin resistance to the levels in lean mice, indicating that ATM recruitment and insulin resistance are also regulated by MCP-1-CCR2 independent signals. The intricacy and redundancy of chemokine signaling may account for these conflicting results.

2.3.2. CCL3, CCL5, CCR1, and CCR5

Macrophage inflammatory protein-1 (MIP-1/CCL3) is a CC chemokine with upregulated expression in obese WAT of humans and mice. CCL3 transcript and protein are remarkably elevated in WAT of *ob*/*ob*, *db*/*db*, and DIO mice [8, 51]. In obese humans, the expression of CCL3 and its receptors CCR1 and CCR5 were increased in omental and subcutaneous WAT compared with normal weight individuals [41]. Moreover, expression of CCL3 and CCR1 in WAT was positively correlated with fasting blood insulin levels in humans [41, 52, 53]. Although many reports have shown a functional role of CCL3 in obesity, the consequences of this have not been established [54].

Keophiphath et al. identified CCL5 as the most upregulated gene in human pre-adipocytes provided with macrophage-secreted factors [55]. Although its role and its target receptors in human WAT are unknown, this chemokine is involved in blood monocyte recruitment to inflammatory sites by binding to the G-protein-coupled receptors CCR1, CCR3, and CCR5.

CCL5 production in fibroblasts, platelets, and monocytes/macrophages is a known feature of inflammatory disorders [56]. In atherosclerosis, CCL5, via CCR1 and CCR5, contributes to transmigration of monocytes and T cells in atherogenic lesions [57].

Kitade et al. revealed that CCR5 plays a crucial role in the regulation of adipose tissue inflammation in obesity and the development of insulin resistance [58]. Expression of CCR5 and its ligands is highly increased in WAT of both *ob*/*ob* and DIO mice. FACS analysis clearly demonstrated that $CCR5^{+}$macrophages accumulate in WAT of obese mice. The loss of CCR5 improved obesity-induced insulin resistance in mice. Both $Ccr5^{-/-}$mice fed a HFD and mice deficient in *Ccr5* bone marrow-derived cells showed ameliorated insulin sensitivity and protection from obesity-induced insulin resistance via reduction of ATM accumulation.

2.3.3. LTB4 and BLT-1

LTB4 is a kind of proinflammatory lipid mediator generated from arachidonic acid [59, 60]. LTB4 is rapidly produced by activated leukocytes, it promotes leukocyte chemotaxis, and regulates proinflammatory cytokines [59, 61]. The biological actions of LTB4 are mediated by an interaction with a G protein-coupled receptor termed BLT-1 [61]. Although the LTB4/BLT-1 axis plays a critical role in host defense during acute infection, chronic activation of this pathway provides continuous inflammation, which is feature of inflammatory pathologies such as atherosclerosis and arthritis [62-67]. Moreover, LTB4 levels increased in adipose tissue of both mice and rats consuming a HFD [67-69]. Spite et al. reported that deficiency of BLT-1 protects against the progression of insulin resistance in DIO by regulating ATM accumulation and inflammation in peripheral tissues [70].

2.3.4. Fractalkine (CX3CL1) and CX3CR1

CX3CL1, a chemokine that binds to a single known receptor (CX3CR1), is involved in the recruitment and adhesion of both monocytes and T cells in atherosclerosis and rheumatologic disorders [71]. CX3CR1 is a G-protein-coupled receptor expressed in many leukocyte subtypes [72, 73] and promotes leukocyte activation and survival [74]. To develop macrophage-rich atherosclerotic lesions, CX3CR1 is required for monocyte recruitment. [75, 76]. Digby et al. suggested that adipocytes also expressed CX3CL1 and that CX3CR1 signaling in macrophages was inhibited by PPARγ agonists [77]. Moreover, modulation of the CX3CL1/CX3CR1 system can regulate chronic inflammatory diseases, including atherosclerosis, independent of CCL2/CCR2 [78], which indicates that this also occur in adipose tissue inflammation and its related complications. Recently, Shah et al. found that CX3CL1 is one of markedly upregulated genes in human adipose tissue through *in vivo* inflammation by using a microarray of adipose tissue mRNA during experimental endotoxemia [79, 80].

2.3.5. CXCL14

CXCL14 (originally designated as BRAK, BMAC, or Mip-2g) is expressed in WAT, brown adipose tissue (BAT), and skeletal muscle, which indicates that it may have a role in adipogenesis, myogenesis, and metabolic complications. CXCL14, as a chemoattractant, is

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required for activated tissue macrophages and dendritic cells [81-87]. Nara et al. generated *Cxcl14* deficient mice and described that CXCL14 is involved in the obesity-induced infiltration of macrophages into WAT, serum adipokine levels, hepatic steatosis, and attenuation of insulin signaling in skeletal muscle; thereby, contributing to systemic insulin resistance in DIO mice [88].

2.3.6. Osteopontin

Osteopontin (OPN) is a secreted matrix glycoprotein and proinflammatory cytokine that has previously been reported as a major element of cell-mediated immunity [89]. Many studies have provided evidence that OPN is secreted by macrophages at sites of inflammation where it mediates monocyte adhesion [90], migration [91], differentiation [92], and phagocytosis [93]. OPN play a role in the development of atherosclerosis. OPN induces chemotaxis of monocytes and elevates cellular migration through a direct interaction with its receptors [94, 95]. Nomiyama et al. demonstrated that OPN secretion is upregulated during obesity and greatly expressed in ATMs of DIO mice, characterizing OPN as an adipokine. OPN deficiency attenuated ATM accumulation, adipose tissue inflammation and improved whole body insulin resistance [96].

2.3.7. Apoptosis inhibitor of macrophage (AIM/CD5L)

AIM [97] is incorporated into adipocytes via CD36-associated endocytosis, and it mediated lipolysis by suppressing the activity of fatty acid synthase (FAS) [98]. AIM is a member of the scavenger receptor cysteine-rich superfamily and was initially characterized as an apoptosis inhibitor that supports the survival of macrophages against apoptosis-inducing stimuli [97]. AIM is a direct target for regulation by nuclear receptor liver X receptor/retinoid X receptor (LXR/RXR) heterodimers [99, 100], and it is exclusively produced by tissue macrophages. As a secreted molecule, AIM is found in both human and mouse blood [97, 100-103] and increases in blood with the progression of obesity in DIO mice [98]. AIM-associated lipolysis is responsible for the obesity-induced recruitment of ATMs. Kurokawa et al. demonstrated the role of AIM in the initiation of adipose tissue inflammation that links obesity and insulin resistance [104]. Firstly, AIM-induced lipolysis is required for macrophage recruitment into obese adipose tissues. Increased blood AIM levels induce dynamic lipolysis in obese adipose tissues, augmenting local extracellular fatty acid concentrations to a level sufficient for the stimulation of TLR4, which promotes chemokine production by adipocytes and macrophage infiltration. Secondly, an increase in blood AIM is required as well as adipocyte hypertrophy for the initiation of macrophage recruitment. In *AIM* deficient mice, although the level of AIM-independent lipolysis escalated in line with adipocyte hypertrophy [98], it may not reach a level sufficient for macrophage infiltration. Thirdly, crosstalk between adipocytes and macrophages within adipose tissue establishes a vicious circle that accelerates inflammation; saturated fatty acids brought about by lipolysis activated TLR4 to induce TNFα, which in turn activated the TNFα receptor to produce inflammatory cytokines [105]. This response induces a further progression of inflammation, lipolysis, and macrophage recruitment.

2.3.8. Macrophage migration inhibitory factor (MIF)

MIF is a multifunctional proinflammatory cytokine which is responsible for inflammatory processes. The primary source and target of MIF have been identified as macrophages [106]. MIF is rapidly released in response to inflammatory stimuli such as lipopolysaccharide, TNF-α, and IFN-γ. MIF can have both paracrine and autocrine effects [106-108]. MIF elevates adipose tissue inflammation through amplification of migration, recruitment, and activation of leukocytes at the site of inflammation through upregulation of adhesion molecules such as ICAM-1 and MCP-1 [109-111]. MIF can utilize its chemotactic properties via CXCR2 and CXCR4 in macrophages and T cells, respectively [111]. The interaction of MIF with CXCR4 on the surface of fibroblasts and T cells induced CXCL8 secretion [112]. Interestingly, the alternative MIF receptor CD74, which is traditionally involved in the activation of the mitogen-activated protein kinases pathway, has recently been demonstrated to also mediate macrophage chemotactic responses [113, 114]. Although these roles in macrophage recruitment have been demonstrated, a recent study showed MIF-/-mice did not exhibit significant changes in ATM content compared to WT mice when fed a HFD [115].

3. Conclusion

Adipose tissue inflammation and macrophage infiltration are well-established features of obesity. ATMs are separated into at least two groups: M1 and M2. In obesity, more than 90% of recruited monocytes become M1 macrophages that can secrete proinflammatory cytokines resulting in adipose tissue inflammation and insulin resistance. Many studies have identified adipokines that can recruit monocytes into adipose tissue in obesity. Consequently, adipose tissue-derived chemokines may be promising therapeutic targets for insulin resistance and metabolic diseases. Although modulation of a single chemokine can affect the chemotaxis of monocytes when they are studied individually, it is likely that chemokines have overlapping functions in the more complex *in vivo* environment. Moreover, the complicated process of monocyte recruitment and subsequent differentiation into M1 or M2 macrophages in obese adipose tissue appears to be substantially different in mouse and human obesity, which emphasizes the need for investigations in humans. Therefore, whether macrophage depletion stands for an appropriate tool to ameliorate adipose tissue homeostasis and restore insulin resistance in obesity remains an open question.

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Author details

Dayea Kim[1], Jong Hyuk Yoon[1], Jaeyoon Kim[2] and Sung Ho Ryu[1*]

*Address all correspondence to: sungho@postech.ac.kr

1 Department of Life Sciences, Pohang University of Science and Technology (POSTECH), Pohang, Gyeongbuk, Republic of Korea

2 The Rolf Luft Research Center for Diabetes and Endocrinology, Karolinska Institutet, Stockholm, Sweden

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