Adipocyte 2:2, 99–103; April/May/June 2013; © 2013 Landes Bioscience

CCR5

A novel player in the adipose tissue inflammation and insulin resistance?

Tsuguhito Ota

Department of Cell Metabolism and Nutrition; Brain/Liver Interface Medicine Research Center; Kanazawa University; Kanazawa, Ishikawa Japan

Keywords: adipose tissue macrophage, inflammation, chemokine, chemokine receptor, CCR5, obesity, insulin resistance, MCP-1, CCR2, TNF-α

Abbreviations: ATM, adipose tissue macrophage; CCR5, C-C motif chemokine receptor 5; MCP-1, monocyte chemoattractant protein-1; CCR2, C-C motif chemokine receptor 2; TNF-α, tumor necrosis factor-α

Submitted: 07/03/12

Revised: 09/28/12

Accepted: 10/01/12

http://dx.doi.org/10.4161/adip.22420

Correspondence to: Tsuguhito Ota;
Email: tota@staff.kanazawa-u.ac.jp

Commentary to: Kitade H, Sawamoto K, Nagashimada M, Inoue H, Yamamoto Y, Sai Y, et al. CCR5 plays a critical role in obesity-induced adipose tissue inflammation and insulin resistance by regulating both macrophage recruitment and M1/M2 status. Diabetes 2012; 61:1680-90; PMID:22474027; http://dx.doi.org/10.2337/db11-1506

Adipose tissue macrophage (ATM) accumulation through C-C motif chemokine receptor 2 (CCR2) and its ligand monocyte chemoattractant protein-1 (MCP-1) is considered pivotal in the development of insulin resistance. However, our new study has demonstrated that CCR5, a different CC chemokine receptor, plays an important role in the ATM recruitment and activation and subsequent development of insulin resistance (see the recent article in *Diabetes*). Although recent human studies have shown upregulation of the expression of not only MCP-1-CCR2 but also other CC chemokines and their receptors in the visceral fat of obese individuals, it is not known if CCR5 is involved in ATM recruitment and insulin resistance. This article has shown several new important observations. First, expression of CCR5 and its ligands is significantly increased and is equal to that of CCR2 and its ligands in the white adipose tissue (WAT) of obese mice, particularly in the macrophage fraction. Second, fluorescence-activated cell sorter analysis clearly demonstrates a robust increase in accumulation of CCR5$^+$ ATMs in response to a high fat (HF) diet. Third, and most important, two distinct models, both *Ccr5*$^{-/-}$ mice and chimeric mice lacking CCR5 only in myeloid cells, are protected from insulin resistance and diabetes through reduction in ATM accumulation. Finally, it is interesting that an alternatively activated, M2-dominant shift in ATM is induced in obese *Ccr5*$^{-/-}$ mice. Taken together, these data indicate that CCR5 is a novel link between obesity, adipose tissue inflammation, and insulin resistance.

Recruitment and Activation of Adipose Tissue Macrophages in Obesity

Obesity involves a state of chronic low-grade systemic inflammation.[1,2] This inflammation causes insulin resistance and metabolic disorders including type 2 diabetes and metabolic syndrome. Obesity-associated systemic inflammation is characterized by increased concentrations of circulating proinflammatory cytokines and the activation of inflammatory pathways that interfere with insulin signaling, including MAP kinases, mTOR/S6 kinases and IKKβ/NFκB. Although the factors that initiate this inflammatory response remain to be fully identified, increasing evidence supports the conclusion that obesity-induced inflammation is mediated primarily by immune cells such as the macrophages and T lymphocytes in metabolic tissues. In particular, a significant advance in our understanding of obesity-associated inflammation and insulin resistance has been the recognition of the critical role of adipose tissue macrophages (ATMs). ATMs are a prominent source of proinflammatory cytokines, including TNF-α and IL-6, which can block insulin action in metabolic tissues, such as adipose tissue, skeletal muscle and liver autocrine/paracrine signaling, and cause systemic insulin resistance via endocrine signaling, serving as a potential link between inflammation and insulin resistance.[3] In both humans and rodents, ATMs accumulate in adipose tissue with increasing body weight and their content correlates positively with insulin resistance.[4-6] Recently, it has been observed that the macrophage phenotype might also be closely linked with the development of insulin resistance in addition to its connection with a quantitative change in macrophage infiltration and accumulation in obese adipose tissue.[7,8] Importantly, tissue macrophages are phenotypically heterogeneous and have been characterized according to their activation/polarization state as M1 ("classically activated" proinflammatory macrophages) or M2 ("alternatively activated" noninflammatory macrophages).[7-9] M2 ATMs predominate in lean mice, whereas obesity induces the accumulation of M1 ATMs with high TNF-α, IL-6 and iNOS expressions, leading to a proinflammatory environment in white adipose tissue (WAT). Thus, both the recruitment and proinflammatory activation of ATMs are required for the development of insulin resistance in obese mice.

Complexity and Redundancy of Chemokine System in Inflammation and Disease

Chemokines are a family of small cytokines that induce leukocyte chemotaxis. Chemokines were first discovered as cytokines that are chemotactic for neutrophils and monocytes and that are involved in the development of allergic and autoimmune diseases. Many studies have been conducted to identify the roles of chemokines in acute, neutrophil-predominant inflammation and chronic, monocyte- and lymphocyte-predominant inflammation.[10,11] To date, more than 50 chemokines exhibiting various physiological and pathological properties have been discovered. Based on the motif patterns involving two N-terminal cysteine residues, chemokines are classified into the following four subfamilies: CXC, CC, C and CX3C (where X is any amino acid residue).[9,12] The CXC chemokines are chemotactic primarily for neutrophils and are known for their involvement in acute inflammation whereas most CC chemokines act on monocytes, T lymphocytes, eosinophiles and basophils, which mediate chronic inflammation and allergy.[9,13]

Chemokines appear to exhibit a high degree of functional redundancy. All chemokines signal via seven-transmembrane G-protein-coupled receptors and chemokine receptors have overlapping ligand specificities. Currently, 19 chemokine receptors have been identified, including 11 CC chemokine receptors (CCR1–11), six CXC chemokine receptors (CXCR1–6), and one each of C (XCR1) and CX3C chemokine receptor (CX3CR1). Although some chemokines have a one-to-one specificity (specific receptor), cases of multiple chemokine ligands binding to the same receptor (shared receptor) have also been reported.[9,13] For example, four chemokine ligands, including CCL2, also known as MCP-1 (MCP-1/CCL2), MCP-2/CCL8, MCP-3/CCL7 and MCP-4/CCL13, bind to the C-C motif chemokine receptor (CCR)2. Even when multiple ligands interact with a single receptor, different effects are produced by different ligands because their binding affinities and the resulting effect differ. Furthermore, because chemokines are differently expressed, distributed and regulated in cells and tissue, they may play different roles in physiological conditions or diseases.

MCP-1- CCR2 Axis Plays a Central Role in Obesity-Induced Insulin Resistance

The interaction of MCP-1, a prototype of the CC chemokine,[14,15] with its receptor CCR2 is considered pivotal in obesity-induced insulin resistance. Previous work by several groups has demonstrated that mice with targeted deletions in the genes for *Mcp-1/Ccl2* and its receptor *Ccr2* have decreased ATM content, decreased inflammation in fat and protection against high-fat (HF) diet-induced insulin resistance.[16,17] Conversely, mice overexpressing MCP-1 in adipose tissues have increased numbers of ATMs along with insulin resistance.[16,18] Therefore, the MCP-1-CCR2 axis is of central importance for promoting ATM recruitment and insulin resistance in mice. More recent studies, however, have produced conflicting results and indicated greater complexity than suggested by earlier reports. Loss of MCP-1 neither attenuates obesity-associated macrophage recruitment to WAT nor improves metabolic function, suggesting that MCP-1 is not critical for obesity-induced ATM recruitment and systemic insulin resistance.[19,20] Furthermore, although *Ccr2*$^{-/-}$ mice fed a HF diet have fewer macrophages in WAT compared with WT mice,[17] CCR2 deficiency does not normalize ATM content and insulin resistance to the levels in lean animals, indicating that ATM recruitment and subsequent insulin resistance are also regulated by MCP-1-CCR2 independent signals. The complexity and redundancy of chemokine signaling may account for these conflicting results. In fact, other chemokine systems have also been implicated in ATM infiltration in obese mice.[21-23] However, additional unidentified chemokine/chemokine receptor pathways that may play significant roles in ATM recruitment and insulin sensitivity remain to be fully identified.

CCR5 Links Obesity to Insulin Resistance by Regulating Both Macrophage Recruitment and Polarization

In a recent issue of *Diabetes*, Kitade et al.[24] identified and characterized a critical role for CCR5, a different CC chemokine receptor, in the regulation of the adipose tissue inflammatory response to obesity and the development of insulin resistance; this article also offered several important observations (**Fig. 1**). First, expression of CCR5 and its ligands is significantly increased and is equal to that of CCR2 and its ligands in the WAT of obese mice, particularly in the macrophage fraction. Second, fluorescence-activated cell sorter (FACS) analysis clearly demonstrates a robust increase in CCR5^{+} ATMs in response to a HF diet even after normalizing for stromal vascular cell number and fat weight. Third, and most important, *Ccr5*$^{-/-}$ mice are protected from insulin resistance, hepatic steatosis and diabetes induced by HF feeding. It is noteworthy that two distinct models, both *Ccr5*$^{-/-}$ mice and chimeric mice lacking CCR5 only in myeloid cells, are protected from HF diet-induced hyperinsulinemia and glucose intolerance through, at least in part, a reduction in ATM accumulation. Finally, it is interesting that an M2-dominant shift in ATM is induced in obese *Ccr5*$^{-/-}$ mice.

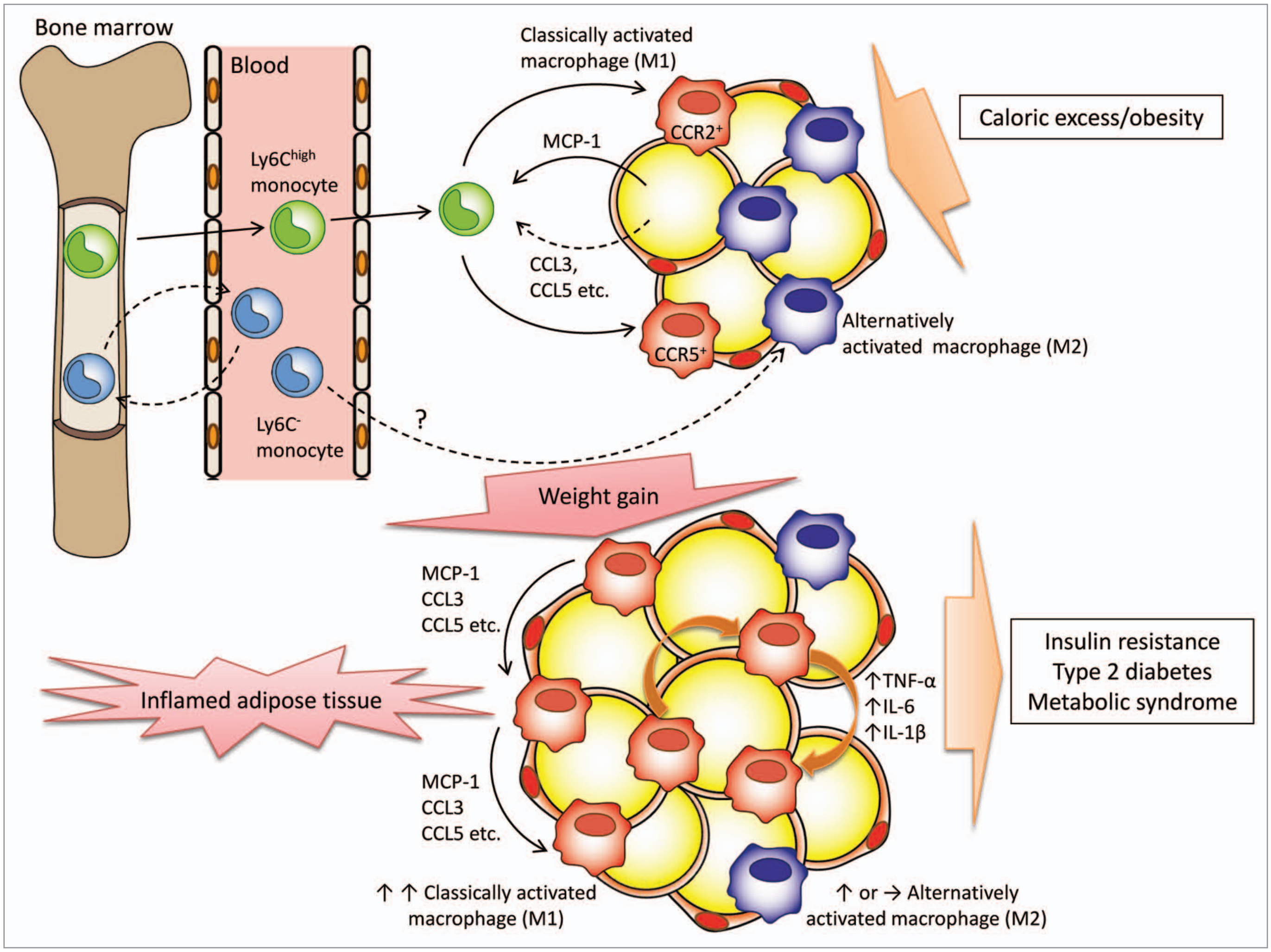

Figure 1. Hypothetical role of CCR5 and MCP-1-CCR2 in the development and maintenance of obesity-induced adipose tissue inflammation. Obese adipose tissue is characterized by both the recruitment and proinflammatory activation of ATMs. Adipocytes or preadipocytes begin to secrete MCP-1 as well as other chemokines, such as CCL3 and CCL5 (ligands for CCR5) in obesity. Thereafter, $CCR2^+$ and/or $CCR5^+$ macrophages accumulate and presumably maintain the inflammation as M1 or classically activated macrophages in obese adipose tissue. $Ly6C^{high}$ monocytes exit the bone marrow in a CCR2-dependent manner and are recruited to inflamed tissues. CCR5 may also regulate recruitment of $Ly6C^{high}$ and $Ly6C^-$ monocytes and their fate as M1/M2 ATMs. Once these ATMs are present and active, they, along with adipocytes and other cell types, could perpetuate a vicious cycle of ATM recruitment, production of inflammatory cytokines such as TNF-α, IL-6 and IL-1β, and impairment of adipocyte function. Therefore, CCR5, independently from and/or cooperatively with CCR2, plays a pivotal role in the induction and maintenance of obesity-induced inflammation and insulin resistance.

Therefore, we conclude that deficiency of CCR5 causes an M2-dominant phenotypic shift in ATMs, which contributes to the attenuation of obesity-induced insulin resistance.

The study conducted by Kitade et al.[24] provides new information about the role of CCR5, a new chemokine system, in obesity-induced insulin resistance in an animal model. It is important that the effects of CCR5 do not appear to result from global alterations in adipocyte biology. Thus, decreased ATM recruitment does not appear to be secondary to changes in adiposity because the adipocyte size of obese *Ccr5*$^{-/-}$ mice and age-matched controls is similar. Moreover, expression of adipocyte-derived factors such as leptin and adiponectin in WAT and plasma levels are similar between genotypes. Additionally, a bone marrow transplantation study revealed that lack of CCR5 expression in macrophages alone was sufficient to protect mice from the HF diet-induced insulin resistance; this was associated with a marked reduction in ATM infiltration. These data support the conclusion that $CCR5^+$ ATMs are important in the development and maintenance of obesity-induced adipose tissue inflammation and insulin resistance in mice. Recent human studies have also shown upregulation of the expression of not only MCP-1-CCR2 but also other CC chemokines (CCL5, CCL7, CCL8 and CCL11) and their receptors (CCR1, CCR3 and CCR5) in the visceral fat of morbidly obese individuals in whom macrophage infiltration has been confirmed.[25] Taken together, CCR5-mediated signals in the adipose tissue may be involved, in some way, in the induction and maintenance of obesity-induced inflammation and in the development of insulin resistance in both rodents and humans.

CCR2 and CCR5: Common or Distinct Roles in Insulin Resistance?

Do the two CC chemokine receptors, CCR2 and CCR5, play common or unique roles in obesity-induced adipose tissue inflammation and insulin resistance? Importantly, no significant compensatory increase in the expression for CCR2, or vice versa, has been found.[24] Therefore, CCR5, independently from and/or cooperatively with CCR2, plays a role in the maintenance of ATM dysfunction and insulin resistance once obesity and its metabolic consequences have been established (**Fig. 1**). Moreover, similar to the case in *Ccr5*$^{-/-}$ mice, HF diet-induced increased fat mass and adipocyte size are minimally affected by *Ccr2* deficiency, and obese *Ccr2*$^{-/-}$ mice matched for adiposity with controls showed reduced ATM recruitment and improved systemic insulin sensitivity.[17] Therefore, the effects of either CCR5 or CCR2 do not appear to result from global alterations in adipocyte biology. However, HF feeding promotes accumulation of CD11c^{+} MGL1^{-} (M1) macrophages in WAT of WT mice, whereas increase in M1 ATMs are markedly suppressed in *Ccr5*$^{-/-}$ mice.[24] In contrast, CD11c^{-} MGL1^{+} (M2) expression within ATMs is increased in *Ccr5*$^{-/-}$ mice on a HF diet, suggesting that deficiency of CCR5 causes an M2-dominant phenotypic shift in ATMs, which contributes to the attenuation of obesity-induced insulin resistance. It is noteworthy that we used highly specific gating strategies to determine pure populations of ATMs and M1 and M2 ATMs.[24] FACS analysis clearly demonstrates a decrease in M1 ATMs that is reciprocal to an increase in M2 ATMs in HF diet-fed *Ccr5*$^{-/-}$ mice. Interestingly, such a phenotypic switch is not observed in *Ccr2*$^{-/-}$ mice[8] although the gating strategies used to define ATMs by FACS in that study were slightly different from those used in this study.

CCR5 is preferentially expressed on Th1 cells.[26] Recent studies have demonstrated that obesity is associated with increased accumulation of not only macrophages but also T cells in adipose tissue. Wu et al. showed that RANTES/CCL5 mRNA levels are highly correlated with the T cell marker CD3 in human visceral adipose tissue.[27] However, the numbers of CD3^{+} T cells, CD4^{+} T cells and CD8^{+} T cells did not differ in WAT of HF diet-fed WT and *Ccr5*$^{-/-}$ mice,[24] suggesting that CCR5 deficiency affects ATM recruitment more prominently. One important question concerns whether the loss of CCR5 affects the M1/M2 status in the bone marrow or peripheral blood. In mice, two major distinct subsets of blood monocytes have been reported: Ly6C^{high} and Ly6C^{-} monocytes. The former, called proinflammatory/classical monocytes, preferentially accumulate in atherosclerotic plaques and exhibit a strong inflammatory response to lipopolysaccharide.[28] In contrast, the latter, known as resident/remodeling/patrolling monocytes, participate in the resolution of inflammation.[29] Both Ly6C^{high} and Ly6C^{-} monocytes are recruited to sites of inflammation or injury (**Fig. 1**).[30] Although the relationship between the monocyte subtypes and their fate as M1/M2 macrophages remains unknown, the Ly6C^{-} monocyte population is predominant over the Ly6C^{high} monocyte population in HF-fed *Ccr5*$^{-/-}$ mice (data not shown).[24] These findings suggest that loss of CCR5 causes alteration of Ly6C^{high} and Ly6C^{-} monocyte subsets at the level of either bone marrow or peripheral blood, and that this contributes to the M2-dominant shift of ATM in obese *Ccr5*$^{-/-}$ mice.

The study conducted by Kitade et al.[24] provides new information regarding the role of CCR5 as a novel link among obesity, adipose tissue inflammation, and insulin resistance in an animal model. However, many questions have yet to be answered, including how CCR5 and its ligands are induced in response to either a HF diet or obesity, how CCR5 regulates M2 macrophages, which metabolic tissue/organ is responsible for enhanced insulin sensitivity in *Ccr5*$^{-/-}$ mice and of the 50 chemokines in metabolic diseases, what distinct roles are played by CCR5?

In conclusion, Kitade et al.[24] present compelling evidence that CCR5 plays a crucial role in obesity-induced adipose tissue inflammation and insulin resistance by regulating both macrophage recruitment and M1/M2 status. In light of these new data, CCR5 may be a promising therapeutic target for insulin resistance, metabolic syndrome, and type 2 diabetes. However, further work is required to gain a systematic understanding of how CCR5 and MCP-1-CCR2 as well as other chemokine systems, connect obesity, inflammation, and insulin resistance.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Acknowledgments

This work was supported by the following grants to T.O.: Program for Improvement of Research Environment for Young Researchers from the Special Coordination Funds for Promoting Science and Technology, Grant-in-Aid for Young Scientists (B) (22790854) from the Ministry of Education, Culture, Sports, Science and Technology of Japan, Uehara Memorial Foundation, Kanae Foundation for the Promotion of Medical Science, Japan Heart Foundation/Novartis Grant for Research Award on Molecular and Cellular Cardiology and Banyu Life Science Foundation International. The author thanks Dr M. Nagashimada for drawing the figure.

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