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Adipocyte and Chemokines: A Link between Preadipocyte/Adipocyte and Macrophage in Adipocyte-Related Pathologies

- Review -

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Abstract

This review will present a brief overview on the adipocytokines and chemokines in terms of their classifications and functions, and further discuss the most recent results of chemokine research into their regulation of adipocyte functions and/or adipocyte-related pathologies. The potential link between preadipocytes/adipocytes and macrophages will also be highlighted.

Key words: adipocytokines, chemokine, adipocyte, preadipocyte, macrophage, obesity, inflammation, diabetes, atherosclerosis, adipocyte-related pathologies

ADIPOCYTE AND ADIPOCYTOKINES

Obesity, which increases the risk for many pathological processes including diabetes, cardiovascular diseases, and certain cancers, is characterized by an increase in adipocyte size (hypertrophy) and in the cell numbers (hyperplasia). Until recently, adipocytes have been considered to function only for the storage of excess energy in fat. However, adipocytes are now believed to be endocrine secretory cells, producing biologically active substances such as hormones, growth factors, cytokines, and other factors, which are collectively called adipocytokines (1,2). These molecules are involved in regulating adipocyte function and metabolism via a network of endocrine, paracrine, and autocrine signals, and thus modulate adipocyte biology.

Adipocytokines include tumor necrosis factor α (TNF α), interleukin-6 (IL-6), macrophage colony-stimulating factor (MCSF), plasminogen activator inhibitor-1 (PAI-1), angiotensinogen, tissue factor, transforming growth factor-β (TGF-β), leptin, adiponectin, resistin, and specific chemokines (Fig. 1). Adipocytokines are generally elevated with increasing adiposity, and closely associated with the adipocyte-related pathologies (e.g. diabetes and atherosclerosis) (2,3). TNF α is involved in insulin resistance in obesity. TNF α decreases the expression of the insulin-sensitive glucose transporter 4 (GLU4) and insulin receptor substrate-1 (IRS-1), and increases serine phosphorylation of IRS-1 and specific phosphorylation of the insulin receptor, thus in turn, impairing insulin signaling (4). IL-6 inhibits insulin signal transduction in the hepatocyte by the modulation of the suppressor of cytokine signaling-3 pathway (5). PAI-1 is an anti-fibrinolytic protein, and the levels of PAI-1 in plasma are correlated with visceral obesity. Overproduced PAI-1 by excessive adipocytes is associated with vascular thrombosis (1). Adiponectin is an adipocyte-specific protein, which has a structural similarity to complement factor Clq. Adiponectin regulates glucose and lipid hometostasis, and enhances insulin sensitivity (6). Circulating levels of adiponectin in plasma decrease in obesity and insulin resistance. Unlike other adipocytokines, adiponectin has

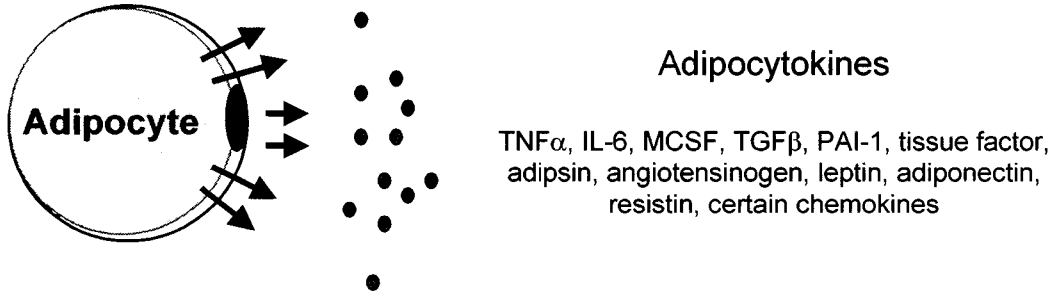

Fig. 1. Adipocyte secrets a variety of biologically active molecules called adipocytokines.

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anti-atherosclerotic, anti-diabetic, and anti-inflammatory properties (6,7). Recent studies have shown that preadipocyte/adipocyte expresses chemotactic cytokines called chemokines and their receptors (8). This indicates that the preadipocyte/adipocyte is both the source and the target of proinflammatory chemokine signals, and may be involved in the autocrine and/or paracrine signaling pathway, which influences adipocyte functions.

CHEMOKINES AND THEIR FUNCTIONS

Chemokines are a superfamily of structurally related small (8~14 kDa) chemotactic cytokines, most of which are inflammatory mediators. Chemokines play a pivotal role in leukocyte trafficking to sites of inflammation and their activation (9,10). Depending on the number and position of conserved cysteines, four classes of chemokines (CC, CXC, C, and CX3C) have been identified and characterized (Fig. 2). CC chemokine (β-chemokine), monocyte chemoattractant protein-1 (MCP-1), has two cysteines in a row. CXC chemokine (α -chemokine), interleukin-8 (IL-8), has the first two cysteines separated by a single amino acid residue. C chemokine (lymphotactin) has a single cysteine residue. Finally, CX3C chemokine (fractalkine) has the first two cysteines separated by three amino acid residues (9,10). About 50 human chemokines have been identified (Table 1). Chemokines interact with seven transmembrane domain G protein-coupled receptors, expressed on the surface of their target cells (11). About 20 chemokine receptors have been identified; CC (CCR1 through 11), 6 CXC (CXCR1 through 6), 1 CX3C (CXCR1), 1 XC (XCR1) receptors (Table 1).

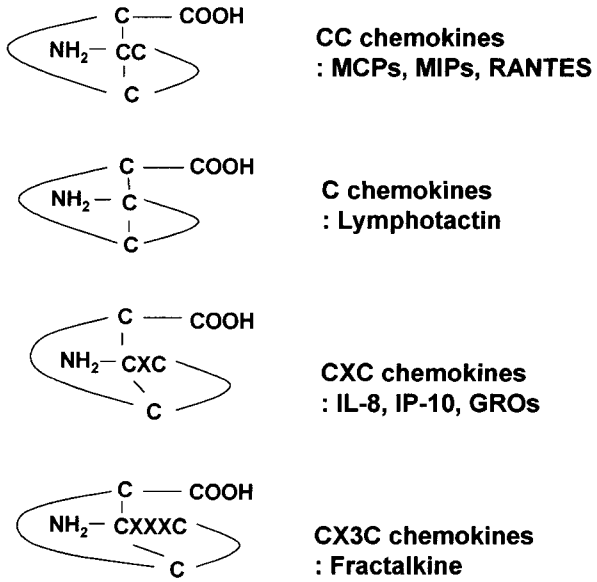

Fig. 2. Schematic view of chemokine families. MCPs, monocyte chemoattractant proteins; MIPs, macrophage inflammatory proteins; Lkn-1, leukotactin-1; RANTES, regulated on activation normal T-cell expressed and secreted; IL-8, interleukin-8; GRO, growth-related oncogene; IP-10, γ -interferon-inducible protein.

In general, chemokines function to induce chemotaxis,

Table 1. CC, CXC, C, and CX3C chemokines and receptors

Chemokine	Receptor	Cell source
CC chemokine		
I-309[1)]/CCL1[2)]	CCR8	T cell, Mast cell
MCP-1/CCL2	CCR2	Monocyte, VEndo, FB, SM, Adipo
MIP-1 α /CCL3	CCR1, CCR5	Mono, Macro, T, B, Neut, Mast, Adipo
RANTES/CCL5	CCR1, CCR3, CCR5	T, Mono, Macro, FB, VEndo, Plate, Eosi
MRP2/CCL9,10	CCR1	Murine Macro, Murine Adipo
Eotaxin/CCL11	CCR3	T, Eosi, Macro
Lkn-1/CCL15	CCR1, CCR3	Mono, Macro
CXC chemokine		
GROs/CXCL1	CXCR2, CXCR1	Mono
IL-8/CXCL8	CXCR1, CXCR2	Mono, Macro, FB, VEndo, Mast, Epi, Adipo
MIG/CXCL9	CXCR3	IFN γ -activated monocyte
IP-10/CXCL10	CXCR3	Monom FB, VEndo
C chemokine		
Lymphotactin/XCL1	XCR1	Activated T cell, Thymus
CX3C family		
Fractalkine/CX3CL1	CX3CR1	VEndo

[1)]Common name, [2)]Systematic nomenclature; MCP-1, monocyte chemoattractant protein-1; MIP-1 α, macrophage inflammatory protein-1 α; RANTES, regulated on activation normal T-cell expressed and secreted; MRP-2, macrophage inflammatory protein-related protein-2; Lkn-1, leukotactin-1; GRO, growth-related oncogene; MIG, monokine induced by γ -interferon; IP-10, γ -interferon-inducible protein; Macro, macrophage; Mono, monocyte; VEndo, vascular endothelial cell; Epi, epithelial cell; Eosi, eosinophil; Neut, neutrophil; FB, fibroblast; SM, smooth muscle cell; Mast, mast cell. More information on chemokine ligands and their receptors can be found in http://cytokine.medic.kumamoto-u.ac.jp/CFC/CK/Chemokine.html.

which is a non-random and directional movement of cells from a lower to a higher concentration of the chemoattractants (9,10). Chemokines are produced by both immune cells (e.g. leukocytes) and non-immune cells (e.g. endothelial cells) constitutively or upon activation. Most chemokines (e.g. MCP-1/CCL2, MIP-1 α/CCL3) are induced upon inflammatory stimulation (e.g. TNF α or IL-1) in monocyte/macrophages, endothelial cells and smooth muscles (12), while some chemokines (e.g. SDF-1/CXCL12, MRP-2/CCL9/10) are constitutively produced in lymphoid organs and other tissues (13,14). The inducible chemokines are essential for inducing leukocyte migration into sites of inflammation, while the constitutive chemokines are involved in the development of lymphoid tissues (13,14). Chemokines also have biological functions such as growth-regulatory and angiogenic properties, which are important during the development of the immune system (9). It is well documented that chemokines play a critical role in a variety of inflammatory pathophysiological processes. These include infectious diseases, rheumatoid arthritis, multiple sclerosis, organ transplant rejection, atherosclerosis, diabetes, and cancer metastasis (9-11). It appears that a particular subset of chemokines is expressed and is enhanced in inflamed tissues, indicating that chemokines and chemokine receptors could be useful targets for the development of therapeutic agents, to protect against inflammatory diseases.

CHEMOKINES, ADIPOCYTE FUNCTIONS, AND ADIPOCYTE-RELATED PATHOLOGIES

In several recent reports, adipose tissue was found to be a source of specific chemokines (8,15-17). Constitutive expression of CC chemokines such as MCP-1, macrophage inflammatory protein-1 (MIP-1 α), and IL-8 were detected in human adipocytes (15). These chemokines altered lipid accumulation and leptin secretion by adipocytes (15), supporting the hypothesis that chemokines are important regulators of adipocyte biology. Macrophage inflammatory protein-related protein-2 (MRP-2), a new member of the CC chemokine family, is a potent chemoattractant for monocytes, lymphocytes, neutrophils, and eosinophils (14). We recently confirmed the expression of MRP-2 and its receptor gene in preadipocytes and adipocytes showed that MRP-2 was a potent chemoattractant for preadipocytes (8). MRP-2 suppressed the expression of adipocyte differentiation marker genes such as aP2 and GPDH, suggesting that MRP-2 is one of the key regulators in preadipocyte recruitment and adipocyte differentiation during the development of adipose tissue (8).

It appears that chemokines are directly involved in adipocyte-related pathologies such as insulin resistance and atherosclerosis. For example, MCP-1 is an insulin-responsive gene that affects insulin sensitivity (18). Insulin induced the expression of MCP-1 and its secretion in both TNF α-induced insulin-resistant 3T3-L1 adipocytes and insulin resistant obese mice (*ob/ob*). MCP-1 decreases insulin-stimulated glucose uptake and the expression of adipogenic genes such as LPL, adipsin, GLU-4, aP2, beta3-adrenergic receptor, and peroxisome proliferator-activated receptor gamma (18). These findings raise the possibility that adipocyte-derived chemokines may modulate adipocyte functions, including insulin sensitivity. On the other hand, chemokines play an important role in the development of atherosclerosis, by inducing leukocyte infiltration into the vascular subendothelial area (19). The enhancement of chemokine expression is well documented in atherosclerotic lesions; for example, CC chemokines (e.g. MCP-1, MIP-1 α, Lkn-1) or CXC chemokines (e.g. IL-8) at both the gene and protein levels, were elevated in atherosclerotic lesions (19,20). MCP-1, which is expressed as monocytes/macrophages, endothelial cells, and smooth muscle cells in atherosclerotic leisons, is particularly implicated in the early stages of atherosclerosis (21,22), while MIP-1 α and RANTES, which are expressed as T cells in human plaque, are associated with the advanced atherosclerotic lesions (23). IL-8 receptor CXCR2 was detected in macrophage rich areas of advanced lesions in human and LDLR knockout mice (24). Genetic elimination of MCP-1 or its receptor CCR2 results in a marked decrease in lesional size and the number of macrophages within the lesion in hyperlipidemic mice, LDLR knockout or ApoE deficient mice (25-27). These findings make it possible for chemokines and/or chemokine receptors to become the primary drug targets for the treatment and diagnosis of atherosclerosis.

The circulating inflammatory molecules (e.g. C-reactive protein, IL-6, TNF α etc) in blood are increased in obesity, instilling the idea that obesity may be a low-grade systemic inflammatory condition, which is closely related to insulin resistance state or atherosclerosis (16, 17,28,29). It is likely that chemokines also contribute to the systemic inflammatory milieu in obesity. In a gene-expression profile, obesity-related, macrophages-specific, and inflammatory genes including chemokines (e.g. MCP-1, MIP-1 α), were all upregulated in white adipose tissue of obese mice (16,30). MCP-1 or MRP-2 was upregulated in obese (*db/db*) mice (8,18). Chemokine gene expression and circulating chemokine levels (e.g. MCP-1, IL-8) were elevated in animal or humans with excessive adiposity (16,31). The expression of MCP-1 mRNA was found to be 7.2 times higher in obese

mice than in normal mice. The MCP-1 protein levels in plasma also increased along with the mRNA, as did the population of CD11b-positive monocyte / macrophage and body weight in the obese mice (31). In a previous study from this lab., we also confirmed the enhanced gene expression of MRP-2 in mice fed a high fat diet (32). These results support the idea that an oversecretion of the chemokines by excessive adipocyte in obesity may contribute to pathologies associated with obesity such as atherosclerosis and type II diabetes (28,29).

ADIPOCYTE, MACROPHAGE-LIKE FUNCTION, AND ADIPOSE TISSUE

Preadipocytes/adipocytes secrete a number of pro-inflammatory cytokines and chemokines, as do macrophages. Preadipocytes also exhibit functional features of macrophages such as phagocytosis and microbicidal activity, indicating that preadipocyte/adipocyte and macrophages share similar functional or antigenic properties (33-35). Interestingly, a recent study has shown that preadipocytes can be converted into macrophage *in vivo* (36). The injection of labeled stromal-vascular cells isolated from the mouse in white adipose tissue or 3T3-L1 preadipocyte into the peritoneal cavity of nude mice resulted in the conversion of preadipocytes into macrophages (36). The conversion of preadipocytes into macrophages suggests that adipose tissue may be associated with innate immunity (36). In addition, the phenotypic conversion of preadipocytes into macrophages may provide a clue for the explanation of the potential connection between preadipocytes and atherosclerosis. Preadipocytes may infiltrate into subendothelial lesions where chemokines are abundant and contribute to the development of atherosclerotic lesions (8). In this setting, preadipocytes may play an important role in the development of atherosclerosis, and it may, at least in part, explain why obese people have a higher incidence of atherosclerosis.

It appears that macrophage infiltration into adipose tissue is a characteristic of human obesity (30). The cause of macrophage infiltration into adipose tissue in obesity and its implication is currently unknown. Although not explored in detail, chemokines may be involved in macrophages infiltration. When adiposity increases, adipocyte-derived chemokines induce monocyte infiltration into adipose tissue, and adipocyte-derived MCSF may induce monocyte differentiation, leading to the accumulation of macrophages in adipose tissue (30). The interaction between adipocytes and macrophages through chemokine/cytokine signals may augment the inflammatory reaction in adipose tissue, elevating circulating inflammatory chemokines/cytokines in obesity. In this context, macrophages might modulate adipocyte biology through chemokine/cytokine signaling, and regulate the inflammatory pathway in obesity and obesity-related pathologies (Fig. 3). However, the direction of the causal relationship is unclear, whether obesity causes inflammation or the inflammatory condition causes obesity. Further studies are necessary to address the links among adipocyte/macrophage, inflammation, and obesity.

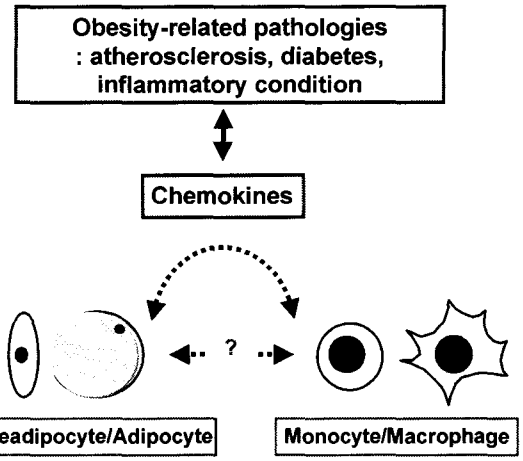

Fig. 3. A link between chemokines and obesity-related pathologies.

CONCLUSIONS

Chemokines are not only involved in the recruitment of leukocytes in the inflammatory processes, but also have a variety of biological functions. Although more studies are needed, it appears that adipocytokines, particularly adipocyte specific chemokines, modulate adipocyte differentiation, metabolism, and other functions. Further studies will be necessary to elucidate the potential role of chemokines in modulating adiposity in animals. It is also important to find out whether the targeting of multiple chemokines/receptors in adipocyte can modulate the systemic inflammatory conditions in obesity and/or the obesity-related pathological processes. As the role of chemokines in adipocyte biology is better understood, chemokines/receptors may become attractive therapeutic targets against obesity and obesity-related pathologies in the near future.

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