thematic review

Thematic Review Series: The Immune System and Atherogenesis

Molecular mechanisms regulating monocyte recruitment in atherosclerosis

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Abstract **Cardiovascular disease, a progressive disorder characterized by the accumulation of lipids in the artery wall, is a leading cause of death in Western societies. One of the initial events in atherogenesis involves the recruitment of inflammatory cells from the circulation into the developing lesion. Studies during the past decade have underscored the role of inflammatory mediators in disease initiation and progression. Critical progress has been made in our understanding of the complex mechanisms by which monocytes, macrophages, and T-cells accumulate in atherosclerotic plaques. Experimental research has identified several candidate adhesion proteins and chemokines that are critically involved in the recruitment process, and encouraging data provide a mechanistic framework for new therapeutic targets. This review provides an overview of our current understanding of the mechanisms that direct the recruitment of monocytes to, and their retention in, atherosclerotic lesions.**—Quehenberger, O. **Molecular mechanisms regulating monocyte recruitment in atherosclerosis.** ***J. Lipid Res.*** **2005.** 46: **1582–1590.**

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Complications of coronary artery disease are the leading cause of morbidity and mortality in Western societies. Atherosclerosis is a progressive disease characterized by the accumulation and gradual buildup of lipid material in the artery wall. Considerable information gathered about risk factors has proven the multifactorial nature of the disorder, adding to the complexity of available therapeutic options (1). An extensive body of experimental as well as epidemiological evidence established a causal relationship between blood cholesterol and atherosclerosis, and the management of serum cholesterol is the most common medical therapy (2). The identification of the mechanisms of cholesterol biosynthesis and homeostasis led to the subsequent development of statins, now used for the treatment of hypercholesterolemic patients at risk of coronary heart disease (3). Despite their well-documented benefit, the statins do not fully prevent disease progression in all cases, and some patients go on to develop future coronary events.

In recent years, the inflammatory component of atherosclerosis has gained appreciation. Although atherosclerosis was traditionally considered a simple lipid disorder, recent scientific advances revealed another layer of complexity and incorporated inflammation as an important factor in all stages of the disease, from initiation to plaque rupture and associated thrombotic complications. The currently accepted mechanistic model of atherogenesis encompasses both the response-to-injury theory and the oxidation theory (4–6). In agreement with this paradigm, the invasion of the artery wall by leukocytes, primarily macrophages derived from circulating monocytes, is one of the earliest events in atherosclerosis. Although our knowledge of triggering factors is limited, modified LDL retained within the vascular wall may represent a direct or indirect initiating agent for leukocyte recruitment (7, 8).

Infiltrating macrophages contribute in several ways to the local inflammation. Mature macrophages rely on pattern recognition receptors that discriminate between self and nonself to remove selectively modified forms of LDL but not native LDL (9). Although the removal of cytotoxic and proinflammatory LDL particles may initially be atheroprotective, the progressive accumulation of lipid-laden macrophages or foam cells ultimately leads to the formation of atherosclerotic lesions. The secretion of reactive oxygen

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Abbreviations: apoE$^{-/-}$, apolipoprotein E-deficient; CX3CL1, fractalkine; CX3CR1, receptor for fractalkine; EC, endothelial cell; GRO, growth-related oncogene; ICAM-1, intracellular adhesion molecule-1; IL-8, interleukin-8; KC, keratinocyte chemokine; LDLR$^{-/-}$, low density lipoprotein receptor-deficient; MCP-1, monocyte chemoattractant protein-1; MIP, macrophage inflammatory protein; RANTES, regulated on activation normal T-cell expressed and secreted; SMC, smooth muscle cell; SR-A, scavenger receptor A; VCAM-1, vascular cell adhesion molecule-1.

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species by the inflammatory cells may further contribute to the oxidation of LDL retained in the intima. The production of growth factors and cytokines propagates the inflammatory response in an autocrine or paracrine manner, and chemokines facilitate a persistent influx of monocytes. These inflammatory mediators, in addition to oxidized LDL, can stimulate the expression of matrix metalloproteases in macrophages, contributing to lesion remodeling and plaque rupture (10). Furthermore, in their role as antigen-presenting cells, activated macrophages constitute a link between innate and adaptive immunity. The potential role of adaptive immune responses in atherogenesis is pronounced at the early stages and is less clear at later stages of the disease.

This review will briefly highlight the emerging molecular mechanisms that regulate monocyte recruitment into developing lesions and summarize how inflammatory mediators contribute to the pathobiology of atherosclerosis.

ADHESION MOLECULES IN ATHEROSCLEROSIS

Various mediators of inflammation, including adhesion molecules, cytokines, and chemoattractant factors, have been shown to initiate the extravasation of leukocytes. It is well recognized that leukocytes continually interact with the endothelium as part of the immune surveillance. However, the endothelial monolayer of the healthy blood vessel resists firm adhesion of leukocytes, and the initial tethering is reversible. Nevertheless, the transient interactions between the circulating leukocytes and the vessel wall that manifest as rolling along the vascular lining are essential components of the multistep model of the recruitment process (11–13). Tethering and rolling are mediated by the selectin family of adhesion proteins (L-selectin expressed constitutively on almost all leukocytes, P-selectin and E-selectin expressed on the surface of activated endothelium) (14). The major ligands for all three selectins are highly fucosylated and sialylated carbohydrates (15, 16).

The interaction of the selectins with their ligands does not support the firm adhesion that is required for subsequent monocyte extravasation unless the initial attachment is followed by a second event that leads to the engagement of integrins. Monocytes express both the β1 integrin CD49d/CD29 and the β2 integrins CD11a/CD18, CD11b/CD18, and CD11c/CD18 (17–19). The strong attachment of the monocytes to the endothelium is mediated by the interaction of the integrins with a class of ligands that belong to the immunoglobulin superfamily, most notably intracellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) (20). Normally, the integrins are expressed on leukocytes in a state that has low affinity for ligands, and it has become evident that they must undergo activation by a chemokine signal to mediate firm adhesion (21–23).

A substantial body of clinical and experimental evidence indicates that inflammatory processes within the vessel wall are critical events in lesion formation. Both selectins and integrins are highly expressed by the activated endothelium in proximity to atherosclerotic lesions but to a much lesser extent by normal endothelium (24–27). Furthermore, the presence of VCAM-1 and ICAM-1 on the vasculature is associated with increased intimal leukocyte accumulation (28). The most compelling evidence for the participation of adhesion proteins in atherogenic processes comes from studies with genetically altered mice. Systemic deletion of the VCAM-1 gene results in early embryonic lethality, and this approach was unable to confirm independently a role of VCAM-1 in atherosclerosis. However, gene deletion of ICAM-1 resulted in a significant reduction of monocyte recruitment to atherosclerotic lesions in apolipoprotein E-deficient (apoE$^{-/-}$) mice (29). A functional role has also been established for selectins, and the deletion of both E-selectin and P-selectin quantitatively reduced atherosclerosis by ~40% in low density lipoprotein receptor-deficient (LDLR$^{-/-}$) mice (30).

In resting monocytes, most of CD11b/CD18 and CD11c/CD18 is stored in intracellular granules (31). Stimulation of monocytes with inflammatory mediators rapidly mobilizes these integrins to the cell surface, where they become accessible for chemokine-dependent activation to mediate firm adhesion (21, 32). It has been reported that monocytes from patients with hypercholesterolemia display increased adhesion to endothelial cells (ECs) (33). Recently, Han et al. (34) demonstrated a causal link between plasma levels of LDL and integrin expression and showed that monocytes from LDLR$^{-/-}$ mice on a high-fat diet have increased CD11b expression as well as CD11b-dependent adhesion to ECs. Similar results were obtained with normal human monocytes that were exposed to LDL ex vivo. Although LDL stimulated CD11b surface expression, the integrins were not activated, and a chemokine signal was essential to initiate firm adhesion of the monocytes. These findings suggest that in addition to the effects on ECs, lipoproteins may also induce phenotypic changes of circulating monocytes that may be pertinent to the recruitment process.

ROLE OF FRACTALKINE RECEPTOR AND FRACTALKINE IN LEUKOCYTE ADHESION

Recently, a novel integrin-independent pathway for leukocyte adhesion has been described that involves the chemokine fractalkine (CX3CL1 in the standard chemokine nomenclature). Most chemokines are secreted; however, there are two chemokines, CX3CL1 and CXCL16, that are structurally distinct and produced as membrane-bound proteins (35, 36). CX3CL1, the only member of the CX3C family of chemokines, is encoded as a type I transmembrane protein consisting of a chemokine domain that is anchored to the plasma membrane through an extended mucine-rich stalk, followed by a transmembrane-spanning domain and a short cytoplasmic tail (35, 37). CX3CL1 is highly expressed on the inflamed endothelium and has been shown to mediate the rapid adhesion of monocytes, T-lymphocytes, natural killer cells, and dendritic cells (38–41). The adhesion is mediated by strong interaction with

CX3CR1, the receptor for CX3CL1 (38). Like all chemokine receptors, CX3CR1 is a seven-transmembrane domain G-protein-coupled receptor that is expressed predominantly on leukocytes, including monocytes, natural killer cells, and T cells. The CX3CR1-mediated adhesion of leukocytes is resistant to physiologic shear stress and, in contrast to chemotaxis, is independent of G-protein signaling (39, 40). At this time, it is unclear whether CX3CL1 acts alone under in vivo shear stress conditions or whether it cooperates with other tethering molecules, such as VCAM-1, in the recruitment of monocytes (42).

In addition to the adhesive properties, CX3CL1 can be shed from the cell surface either through stimulated or constitutive proteolytic cleavage involving tumor necrosis factor-α-converting enzyme (ADAM17) or the disintegrin-like metalloproteinase ADAM10 (43–45). Soluble CX3CL1 induces intracellular calcium fluxes and chemotaxis in $CX3CR1^{+}$ cells (40). In addition to the intrinsic adhesive properties of membrane-bound CX3CL1, the soluble chemokine has been shown to activate monocyte integrins and enhance the integrin avidity for the ligands ICAM-1 and VCAM-1 (46, 47).

Because of its dual role as an adhesion protein and chemokine, the involvement of CX3CL1 in atherosclerosis has been studied intensively. Lesnik, Haskell, and Charo (48) demonstrated that the expression of CX3CL1 is upregulated in atherosclerotic lesions of $apoE^{-/-}$ mice. A similar strong expression of CX3CL1 was found in human atherosclerotic lesions, localized primarily to macrophages, foam cells, and smooth muscle cells (SMCs) (49–51). CX3CL1 deficiency decreased lesion areas in a site-specific manner at the brachiocephalic artery in both $apoE^{-/-}$ and $LDLR^{-/-}$ mice, but no changes were observed at the aortic root area (52). Similarly, ablation of the CX3CR1 gene proved to be atheroprotective, and the $apoE^{-/-}/CX3CR1^{-/-}$ mice were less susceptible to diet-induced atherosclerosis despite an increase in CX3CL1 expression in lesion areas (48, 53). The $CX3CR1^{-/-}$ mice also showed a significant reduction in macrophage recruitment to the vessel wall, which coincided with the observed decrease in lesion formation. Similar results were reported by Combadiere et al. (53), who in addition noted a substantial accumulation of SMCs and collagen, features closely associated with a stable plaque phenotype.

Two nonsynonymous single-nucleotide polymorphisms were identified that affect codons 249 and 280 of CX3CR1, causing the amino acid changes valine to isoleucine (V249I) and threonine to methionine (T280M) (54). Results from human genetic studies suggested the I249 and M280 alleles as independent risk factors for coronary artery disease (55–57). Functional analysis indicated that the I249 and M280 mutant receptors have impaired adhesive functions and are less efficient at mediating the interaction between monocytes and the injured endothelium (55, 57). Furthermore, Schafer et al. (58) demonstrated the presence of CX3CR1 on platelets and showed that endothelium-bound CX3CL1 activates circulating platelets, promotes P-selectin surface expression, and may thereby contribute to thrombotic events in vascular disorders. Cumulatively, these data are consistent with a critical role of the CX3CR1/CX3CL1 chemokine system in cardiovascular disease.

MONOCYTE CHEMOATTRACTION AND TRANSENDOTHELIAL MIGRATION IN ATHEROSCLEROSIS

It is now clear that the process of extravasation involves not only a range of adhesion molecules but also soluble and immobilized chemokines that both stimulate firm adhesion and guide the adherent monocytes across the endothelium (32). Chemokines consist of a large family of small, secreted chemotactic proteins that have been classified into four subfamilies, C, CC, CXC, and CXXXC, depending on the relative position of the first two cysteines (59). The receptors for chemokines were found to be seven transmembrane-spanning receptors that signal through G-protein interactions (60). Chemokines are produced by virtually all somatic cells, including the cellular constituents of the vessel wall, in response to inflammatory stimuli. The interaction with specific chemokine receptors first causes the arrest of leukocytes rolling along the endothelium through the activation of adhesion receptors. Then, chemokines stimulate the transendothelial migration.

Among the chemokines that are found in atherosclerotic lesions, monocyte chemoattractant protein-1 (MCP-1) has attracted intense interest (61). The formation of the plaque is believed to begin through the accumulation of minimally modified forms of LDL, which become trapped in the extracellular matrix of the subendothelial space and stimulate ECs, SMCs, and macrophages to produce proinflammatory molecules, including MCP-1 (8, 62–64). Additional factors that can augment MCP-1 synthesis by vascular cells include thrombin, inflammatory cytokines, and fluid mechanical forces (65–67). The strong expression of MCP-1 in human and experimental atherosclerosis indicates an active role in monocyte recruitment (63, 68). However, the most compelling evidence for the critical participation of this inflammatory mediator in the initiation and progression of atherosclerotic lesions comes from studies with mice lacking MCP-1 or its receptor, CCR2. Deletion of the MCP-1 gene in atherosclerosis-susceptible $LDLR^{-/-}$ mice or human apoB transgenic mice significantly reduced diet-induced atherosclerosis (69, 70). Similar results were obtained with CCR2-deficient mice. The targeted disruption of the CCR2 gene in $apoE^{-/-}$ mice caused a striking decrease in arterial macrophage accumulation and atherosclerosis (71). Conversely, overexpression of MCP-1 in macrophages achieved by transplantation of bone marrow from mice expressing the MCP-1 transgene increased atherosclerosis in the irradiated hypercholesterolemic recipient mice (72).

Although there is convincing evidence for a nonredundant role of CCR2 and MCP-1 in experimental atherosclerosis, few studies have addressed the involvement of this chemokine system in human atherosclerosis. Han et al. (73) have shown that CCR2 expression is greatly en-

hanced in monocytes from hypercholesterolemic patients compared with normal controls. Increased expression of CCR2 renders the monocytes hyperresponsive to chemotactic stimuli, and it was hypothesized that this may accelerate the rate at which these cells are recruited to diseased aortic segments. CCR2 expression correlated directly with plasma LDL cholesterol levels, and therapies leading to an improvement of the plasma lipids also reduced monocyte CCR2 expression and normalized the functional responses of the monocytes to inflammatory stimuli (74).

Several comprehensive studies have implicated the CXC chemokines growth-related oncogene (GRO)-α/keratinocyte chemokine (KC)/CXCL1 and interleukin-8 (IL-8)/CXCL8 in atherogenesis. The repopulation of LDLR$^{-/-}$ mice with bone marrow deficient in CXCR2, the receptor for both GRO-α/KC/CXCL1 and IL-8/CXCL8, significantly reduced atherosclerosis (75). It was also noted that the macrophage content of the lesions in mice receiving CXCR2-deficient leukocytes was much lower than that in control mice, suggesting a role for CXCR2 in monocyte recruitment. Traditionally, GRO-α and IL-8 have been thought to act predominantly on neutrophils. However, neutrophils are not present in atherosclerotic lesions, and it was unclear how these chemokines could mediate the recruitment of monocytes.

GRO-α and IL-8 exert their effects by binding to either of the closely related receptors CXCR1 and CXCR2. The expression of these receptors has been demonstrated on circulating human blood monocytes, and CXCR2 is present at high levels on mouse macrophages of advanced lesions (75, 76). Furthermore, the ligands IL-8 and GRO-α, expressed on cultured ECs after stimulation with cytokines, have been shown to trigger the firm adhesion of monocytes in vitro in the flow chamber system (77, 78). The important participation of these CXC chemokines in the shear stress-resistant adhesion and recruitment of monocytes was further demonstrated with an ex vivo perfusion model of carotid arteries from apoE$^{-/-}$ mice. Monocyte accumulation to the endothelium of lesion-prone arteries was significantly induced upon preperfusion with KC but not with the mouse homologue of MCP-1 (JE), and the authors concluded that KC selectively triggers very late antigen-4-dependent monocyte recruitment (79).

Although the exact mechanisms at the molecular level remain unclear, the studies described above establish a role for CXCR1/2, IL-8, and GRO-α in monocyte recruitment and possibly the retention and expansion of lesion macrophages. Somewhat of a puzzle is the fact that despite the expression of CXCR1/2, neutrophils are not attracted to atherosclerotic lesions. LDL accumulation and oxidation precede the recruitment of monocytes to the arterial wall (80), and Berliner and colleagues (81, 82) showed that oxidized phospholipids contained in oxidized LDL stimulated specifically the binding of monocytes but not neutrophils to ECs. In addition to IL-8, oxidized phospholipids also induce the expression of the strong monocyte chemoattractant MCP-1 by ECs (83, 84), explaining at least in part the preferential recruitment of monocytes. Interestingly, some types of oxidized phospholipids effectively inhibit the expression of neutrophil binding adhesion molecules on ECs, suggesting a role for the oxidized lipids in regulating the specificity of the leukocyte-endothelium interactions (85).

More recently, leukotrienes have been shown to contribute to monocyte infiltration. Aiello et al. (86) demonstrated that pharmacological inhibition of leukotriene B_4 significantly decreases the development of atherosclerotic lesions in apoE$^{-/-}$ and LDLR$^{-/-}$ mice. In contrast, leukotriene B_4 antagonism had no significant effect on lesion size in MCP-1 null mice, suggesting that MCP-1 and leukotriene B_4 may function through a common mechanism.

OTHER CHEMOKINES IN VASCULAR INFLAMMATION

Several additional chemokines have been implicated in atherosclerosis, but their role in the recruitment of monocytes is less clearly defined, and they may be more important in regulating plaque stability and/or remodeling. The CC chemokines regulated on activation normal T-cell expressed and secreted (RANTES)/CCL5, macrophage inflammatory protein (MIP)-1α/CCL3, and MIP-1β/CCL4 are chemoattractants for both monocytes and T-cells, and they are expressed in atherosclerotic plaques (87, 88). Mice deficient in CCR5, a receptor for RANTES and MIP-1α, were not protected against atherosclerosis (89), but Met-RANTES, a receptor antagonist that blocks both CCR1 and CCR5, markedly reduced atherosclerosis in mice (90). MIP-1α and MIP-1β are typically expressed by T-cells but colocalize with macrophage-rich areas of the plaque (88), suggesting a role in the activation or movement of the macrophages within the inflamed microenvironment.

Eotaxin/CCL11 is a potent chemokine that promotes the migration of eosinophils via the receptor CCR3. A recent study demonstrated the overexpression of eotaxin and CCR3 in human atheroma. However, eosinophils are rarely observed in atherosclerotic lesions, and the expression of CCL11 was not associated with an eosinophilic infiltrate, leading the authors to speculate that it might play a role distinct from eosinophil chemotaxis (91). CCR3 is expressed on SMCs, and eotaxin induces CCR3-dependent SMC migration but not proliferation, at least in vitro (92). The migration of SMCs from the arterial media to the intima is a crucial event in atherogenesis and may also play a role in the development of intimal hyperplasia after arterial injury (93). Because CCL11 is expressed abundantly in the SMC-rich area of atheromata, it may play an important role in regulating SMC migration and associated plaque remodeling. A similar function has also been suggested for the stromal cell-derived factor SDF-1α/CXCL12. It is strongly expressed in human atherosclerotic plaques and is a potent activator for platelets (94). It has also been associated with neointimal formation after arterial injury and may play an instrumental role in regulating the recruitment of circulating SMC progenitors (95). In contrast to the proposed contributions to atherothrombotic disease in response to vascular injury, SDF-1α

may also mediate anti-inflammatory and matrix-stabilizing effects, at least under conditions of unstable angina (96). It is conceivable that the recruitment of circulating progenitor cells is essential for the repair and rejuvenation of arteries after chronic injury, as in native atherosclerosis. Consistent with this idea, infusion of progenitor cells that typically respond to SDF-1α prevented the progression of atherosclerosis in apoE$^{-/-}$ mice (97).

CXCL16, a chemokine with a structure similar to that of CX3CL1, has been detected in murine and human atherosclerotic lesions (98, 99). It may have multiple functions as a chemoattractant, adhesion protein, and scavenger receptor, but its exact role in atherosclerosis remains unclear (98, 100, 101). Additional CXC chemokines, including interferon-γ-inducible protein 10, monokine induced by interferon-γ, and interferon-inducible T-cell α chemoattractant, are detected in human atherosclerotic lesions (102). These chemokines bind to CXCR3, and the colocalization of CXCR3-expressing T-cells suggests that they may serve as chemoattractants and/or activators of T-cells.

FATE OF THE RECRUITED MONOCYTES

Oxidized LDL may contribute to foam cell formation in several ways. First, it may directly stimulate the migration of monocytes into the artery wall (7). Second, it can induce the expression of chemokines (8) as well as that of adhesion proteins by ECs (82, 103). Third, it may be involved directly in the retention of monocytes in the artery wall (104). The induction of monocyte CCR2 expression as outlined above is specific for native LDL. Oxidized LDL very efficiently inhibits CCR2 expression, which may function to retain the recruited monocytes in the lesion (104). Uptake of oxidized LDL is required for the suppression of CCR2 expression, which is mediated by the lipid components of oxidized LDL through the activation of peroxisome proliferator-activated receptor γ (104). Once resident in the arterial intima, the monocytes undergo morphological changes and differentiate into macrophages. Locally produced cytokines and growth factors not only serve to attract and retain the monocytes but also govern the differentiation of the monocytes into mature macrophages (105–107).

Mature macrophages express a range of scavenger receptors, which mediate the unregulated uptake of modified forms of LDL, ultimately leading to foam cell formation (9, 108, 109). Recognition of oxidized LDL by scavenger receptors is mediated, at least in part, by oxidized phospholipids, present either in the lipid phase or covalently attached to the apolipoprotein (110–112). Of the scavenger receptors expressed on macrophages, scavenger receptor A (SR-A) and CD36 appear to be responsible for a quantitatively significant portion of lipid uptake from oxidized LDL. Consistent with this, apoE$^{-/-}$ mice lacking SR-A or CD36 developed significantly less atherosclerosis than control animals (113, 114). Results with macrophages from SR-A/CD36 double knockout mice showed that SR-A and CD36 account for 75–90% of the degradation of oxidized LDL and that other scavenger receptors do not compensate for their absence (115). Cholesterol delivered via the scavenger receptor pathway accumulates in the macrophage and ultimately leads to foam cell formation and plaque progression.

The accumulation of macrophage-derived foam cells may result not only from persistent monocyte recruitment into the artery wall but also from reduced emigration of these cells from the lesion. Relatively little is known about the fate of monocytes once they enter the lesion. Although many of the recruited cells differentiate into macrophages and lipid-laden foam cells, a portion may differentiate into cells with a dendritic cell appearance (116). Dendritic cells have been identified in atherosclerotic plaques and have been implicated in the pathogenesis of the disease (117). Results from a recent study suggested that differentiation into dendritic cells may constitute a pathway for monocyte emigration leading to lesion regression (118). This study shows that the clearance of monocytes from established lesions may occur in part through conversion into migratory dendritic cells when proatherogenic conditions are reversed. Oxidized lipids as found in oxidized LDL impair the capacity of the monocyte-derived cells to clear from the vessel wall. Thus, oxidized lipids not only mediate the recruitment of monocytes both directly and indirectly via the induction of cytokines and chemokines but also may contribute to the retention of the recruited cells in the lesion.

CONCLUDING REMARKS

This review has highlighted some of the inflammatory mediators pertinent to the recruitment process of monocytes in cardiovascular disease. A substantial body of work has demonstrated the complexity of the cascade of cellular and molecular interactions involving adhesion proteins and chemokines that are required for functional leukocyte homing and extravasation to the inflamed tissue. Encouraging results from animal models of diseases characterized by chronic monocyte infiltration indicated that chemokines and their receptors may represent useful therapeutic targets. Pharmacological inhibition of several chemokine systems is currently being evaluated in humans for the treatment of chronic inflammatory disorders, including rheumatoid arthritis and psoriasis. The data reviewed to date demonstrate that it is premature to draw conclusions regarding the efficacy of this treatment. Because of the complexity of the disease, no clinical trials have been organized to evaluate antibody or pharmacological inhibition of predominant chemokine systems associated with human atherosclerosis. Clinical applications of antibody therapy generally are for short treatment periods, and it remains unclear whether this could translate into long-term cardiovascular benefit with persisting plaque regression. Small molecules and pharmacological antagonists for specific chemokines and chemokine receptors are continuously being developed and may prove useful

for intervention in acute and chronic inflammation. Blocking monocyte recruitment to the lesion and simultaneously promoting emigration from the lesion may constitute opportunities for therapeutic intervention to balance the immune response in cardiovascular disease.

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