Chemokines in the Pathogenesis of Vascular Disease

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Abstract—Our increasing appreciation of the importance of inflammation in vascular disease has focused attention on the molecules that direct the migration of leukocytes from the blood stream to the vessel wall. In this review, we summarize roles of the chemokines, a family of small secreted proteins that selectively recruit monocytes, neutrophils, and lymphocytes to sites of vascular injury, inflammation, and developing atherosclerosis. Chemokines induce chemotaxis through the activation of G-protein–coupled receptors, and the receptors that a given leukocyte expresses determines the chemokines to which it will respond. Monocyte chemoattractant protein 1 (MCP-1), acting through its receptor CCR2, appears to play an early and important role in the recruitment of monocytes to atherosclerotic lesions and in the formation of intimal hyperplasia after arterial injury. Acute thrombosis is an often fatal complication of atherosclerotic plaque rupture, and recent evidence suggests that MCP-1 contributes to thrombin generation and thrombus formation by generating tissue factor. Because of their critical roles in monocyte recruitment in vascular and nonvascular diseases, MCP-1 and CCR2 have become important therapeutic targets, and efforts are underway to develop potent and specific antagonists of these and related chemokines. (Circ Res. 2004;95:858-866.)

Key Words: chemokine ■ CCR2 ■ vascular ■ atherosclerosis ■ monocyte chemoattractant protein 1

A preponderance of evidence from clinical and experimental studies supports the notion that inflammation plays an important role in a wide range of cardiovascular diseases1-4 and has focused attention on the signals that initiate cellular infiltration of vascular tissues. The chemokines are a family of potent chemotactic cytokines that regulate the trafficking of leukocytes and are rapidly upregulated at sites of vascular inflammation. Here, we review the role of monocyte chemoattractant protein 1 (MCP-1) and related chemokines in regulating the recruitment of monocyte/macrophages to the vessel wall and discuss how these chemokines contribute to the pathophysiology of vascular disease, with an emphasis on atherosclerosis.

Chemokines and Chemokine Receptors

Chemokines (chemotactic cytokines) are small heparin-binding proteins that direct the migration of circulating leukocytes to sites of inflammation or injury.5,6 There are ≈50 human chemokines, which are divided into three major families based on differences in their structure and function. The largest family is known as the CC chemokines because the first two of the four conserved cysteine residues that are characteristic of chemokines are adjacent to each other. CC chemokines tend to attract mononuclear cells and are found at sites of chronic inflammation. The most thoroughly characterized CC chemokine is MCP-1 (also known as CCL2), a potent agonist for monocytes, memory T cells, and basophils.
MCP-1 has been implicated as a key player in the recruitment of monocytes from the blood into early atherosclerotic lesions, the development of intimal hyperplasia after angioplasty, as well as in vasculogenesis and in aspects of thrombosis. Other members of the CC family include RANTES (CCL5), macrophage inflammatory protein 1α (MIP-1α) (CCL3), and MIP-1β (CCL4).

The CXC family of chemokines, of which IL-8 (CXCL8) is the prototypical member, attract polymorphonuclear leukocytes and have been implicated in acute pulmonary inflammation. IL-8 also activates monocytes and may direct their recruitment to vascular lesions. CXC chemokines have a single amino acid residue between the first two canonical transmembrane domains. Thus, unlike other soluble chemokines, it is a type 1 transmembrane protein. In its full-length, FK consists of a soluble chemokine domain fused to a mucin-like stalk and a transmembrane domain. Thus, unlike other soluble chemokines, FK can function as a cell-adhesion receptor that can arrest cells under physiological flow conditions. FK can be cleaved from the cell membrane by tumor necrosis factor-α-converting enzyme and by the metalloprotease ADAM-10 to release a soluble protein. In this soluble form, FK is a potent chemoattractant for monocytes, T cells, and natural killer (NK) cells. Thus, depending on whether it exists as an immobilized protein or a soluble protein, FK can function as a cell-adhesion receptor or as a chemoattractant. FK is expressed in atherosclerotic lesions and has several potential roles in atherogenesis. CXCL16 also has a soluble domain linked to a mucin stalk. CXCL16 is expressed on macrophages and dendritic cells, and, of particular relevance to cardiovascular disease, it has been reported to scavenge oxidized lipids.

Chemokines exert their cellular effects by activating seven-transmembrane–domain G-protein–coupled receptors. Whether a leukocyte responds to a particular chemokine is determined by its complement of chemokine receptors. Chemokine binding activates a signal transduction cascade that involves binding to heparin sulfate proteoglycans. After entering cells, and macrophages in response to oxidized lipids. How MCP-1 is localized on the endothelium is unknown, but may involve binding to heparin sulfate proteoglycans. After entering the subendothelial space, monocytes differentiate into macrophages. The continued ingestion of lipids leads to foam cell formation, and both macrophages and foam cells continue to secrete bioactive molecules, such as growth factors and chemokines, which can recruit and activate additional monocytes.

Figure 1. Monocyte–endothelial cell interactions. Circulating blood monocytes are captured on the endothelium in a multistep process that includes selectin–mediated rolling, firm arrest, spreading, and diapedesis. MCP-1 and other chemokines are synthesized by endothelial cells, smooth muscle cells, and macrophages in response to oxidized lipids. How MCP-1 is localized on the endothelium is unknown, but may involve binding to heparin sulfate proteoglycans. After entering the subendothelial space, monocytes differentiate into macrophages. The continued ingestion of lipids leads to foam cell formation, and both macrophages and foam cells continue to secrete bioactive molecules, such as growth factors and chemokines, which can recruit and activate additional monocytes.

Atherosclerosis

Fatty streaks—the hallmark of early atherosclerotic lesions—are composed of lipid-laden macrophages called foam cells (Figure 1). Studies in swine and nonhuman primates indicate that circulating blood monocytes are the precursors of these foam cells. Several lines of evidence now support the hypothesis that MCP-1 plays a critical role in recruiting these monocytes into early lesions. Early studies reported that MCP-1 is present in macrophage-rich atherosclerotic plaques in humans and primates. Oxidized lipids have long been implicated as mediators of atherosclerosis and foam cell formation. Studies by Cushing et al demonstrated that minimally oxidized low-density lipoproteins (LDLs), but not native LDLs, induced MCP-1 production in vascular wall cells such as endothelial cells and smooth muscle cells. MCP-1 thus emerged as a possible molecular link between oxidized lipoproteins and foam cell recruitment to the vessel wall.

Studies in transgenic mice overexpressing MCP-1 and in mice deficient in MCP-1 or its receptor provided strong evidence that MCP-1 functions in the recruitment of monocytes to atheroma. Thus, overexpression of MCP-1 in specific tissues causes a localized infiltration of monocyte/macrophages. In bone marrow transplantation studies, overexpression of MCP-1 in vessel wall macrophages led to increased foam cell formation and increased atherosclerosis. Deletion of MCP-1 in LDL receptor-null mice attenuated the progression of dietary-induced atherosclerosis. Similar results were reported in MCP-1–null mice expressing human apolipoprotein B.

CCR2 is the only established functional receptor for MCP-1 on hematopoietic cells, and its deletion in apoE-deficient mice afforded significant protection from both macrophage accumulation and atherosclerotic lesion formation in response to a high-fat diet (Figure 2). Similar studies in mice fed a regular chow diet showed that CCR2–/– mice were more resistant to the development of atherosclerosis than wild-type mice. In contrast, mice deficient in CCR5, which is activated by MIP-1α and RANTES but not by MCP-1, were not protected against atherosclerosis. These studies provide strong evidence that activation of CCR2, presumably by MCP-1, contributes to foam cell formation, one of the earliest manifestations of atherosclerosis. It should be noted that CCR2–/– and MCP-1–/– mice have distinct immunologic properties and respond differently to fem-
oral arterial injury. In addition, MCP-3 and MCP-5 activate CCR2. Therefore, it is possible that the results obtained with the CCR2−/− mice may not be solely mediated by MCP-1. Although most work has focused on MCP-1, other chemokines may also play a role. For example, Met-RANTES, a chemokine receptor antagonist that blocks CCR1 and CCR5, significantly reduced lesion progression in atherosclerotic mice.

The importance of inflammation in the later stages of atherosclerosis, especially plaque rupture, has been emphasized in several recent reviews. The traditional view that lesion growth is driven by constant division and migration of smooth muscle cells is being supplanted by models in which cytokines and proteases within lesional inflammatory cells, particularly macrophages, contribute directly to plaque growth and rupture. Underscoring the potential importance of inflammation in atherogenesis is the recent finding that plasma levels of the acute-phase reactant C-reactive protein are a stronger predictor of cardiovascular events than LDL-cholesterol levels. The extent to which chemokines such as MCP-1 contribute to the retention and activation of macrophages in advanced lesions is unclear. However, as an early response gene that is robustly induced in macrophages and vascular wall cells by tumor necrosis factor-α, platelet-derived growth factor, and thrombin, MCP-1 is almost surely present in significant amounts. Through its ability to activate tissue factor, MCP-1 might also contribute to the thrombotic aspects of advanced atherosclerotic lesions. The subsequent elaboration of thrombin would provide potent positive feedback for the local synthesis of additional MCP-1.

Arterial Injury

Chemokines and their receptors have also been implicated in the response of the arterial wall to injury. Animal models of arterial injury are characterized by the development of intimal hyperplasia caused by migration and replication of smooth muscle cells. Intimal hyperplasia is an important component of the atherosclerotic plaque and is thought to be critical to the development of restenosis after coronary artery angioplasty and stenting. Smooth muscle cell chemoattractants and mitogens are key mediators of intimal hyperplasia. The source of these molecules is likely to include the major cells of the arterial wall, such as endothelial cells, smooth muscle cells, and adventitial fibroblasts, as well as the circulation. In addition, leukocytes accumulating at the surface or migrating into injured or atherosclerotic vessels are rich in growth factors and cytokines that can activate smooth muscle cells.

MCP-1 mRNA and antigen are rapidly induced in the arterial media in a variety of normolipemic and hyperlipemic models of arterial injury. The induction of MCP-1 does not always correlate with macrophage accumulation. For example, in balloon and wire injury models of normal rodent arteries, few macrophages are found in the arterial wall. In hypercholesterolemic animals such as cholesterol-fed pigs and rabbits or ApoE−/− mice, however, arterial injury elicits abundant macrophage infiltration. Interestingly, macrophages accumulate abundantly in normal rodent arteries after stenting. Thus, although MCP-1 may recruit macrophages to sites of arterial injury, it might not be sufficient to assure the development of macrophage-rich lesions.

The response to arterial injury appears to be mediated by MCP-1 and CCR2. Antibodies to MCP-1 attenuate intimal hyperplasia in a rat model of carotid artery injury. In addition, a mutant form of MCP-1 with “dominant negative” properties inhibited intimal hyperplasia in a primate model of femoral arterial injury. A CCR2 blocking antibody provided significant protection against in-stent stenosis; the protection was as good as that of an antibody against CD18, which blocks leukocyte adhesion. We recently examined the effects of CCR2 and MCP-1 gene deletions on the development of intimal hyperplasia in mouse models of wire-induced femoral arterial injury. Four weeks after injury, arteries from CCR2−/− mice had substantially smaller (~62%) intimal areas and lower intima/media ratios than CCR2+/+ littermates. Five days after injury, the medial proliferation index was decreased by ~60% in CCR2−/− mice. Interestingly, the effect of MCP-1 deletion was less pronounced, showing ~30% reductions in intimal area and intima/media ratio and no change in the medial proliferation index. These data suggest that MCP-1 and CCR2 deficiencies may have different effects on the arterial wall and raise the possibility that MCP-1 may affect smooth muscle cell migration directly or indirectly. Targeting CCR2 may prove more effective than targeting MCP-1.

As noted, in many animal models used to examine the effect of MCP-1 and CCR2 on intimal hyperplasia, macrophages do not accumulate within the arterial wall. A number of studies, however, have raised the possibility that MCP-1 plays a direct role in activating smooth muscle cells. MCP-1 induced tissue factor, the initiator of coagulation and a critical mediator of arterial thrombosis, in human and rat smooth muscle cells. This induction was dependent on activation of protein kinase C and mobilization of Ca++. MCP-1 also stimulated the expression of intracellular adhesion molecule 1
Chemokines may also directly regulate smooth muscle cell migration. The CCR8 ligand I-30961 and the CCR3 ligand eotaxin69 induce migration of cultured smooth muscle cells in modified Boyden chamber assays. In addition, both the ligands and the receptors are abundant in atherosclerotic plaques and are induced in the arterial media in mouse models of femoral arterial injury. Although the importance of these chemokines in the response to arterial injury or atherosclerosis awaits testing in animal models, these in vitro studies and immunohistochemical analyses raise the possibility that chemokines may be important activators of smooth muscle cells in atherosclerotic or injured vessels.

The importance of chemokines and inflammation in a variety of diseases has sparked intense interest in developing broad-based inhibitors of chemokine activity as therapeutic agents. Several viral proteins, including the myxoma virus M-T7 and the herpes virus M3, bind and inhibit CC and other chemokines ubiquitously. Intravenous infusion of M-T7 markedly reduced intimal hyperplasia in a rabbit model of arterial injury,64 and conditional expression of M3 inhibited intimal hyperplasia after mouse femoral arterial injury.65 Although inhibition of MCP-1 probably accounted for a substantial portion of these effects on intimal hyperplasia, other chemokines may have contributed. In this regard, the chemokine antagonist MET-RANTES reduced neointima formation in Apoe−/− mice62 and atherosclerotic plaque formation in LDLR−/− mice.38 The potential clinical usefulness of chemokine inhibitors dictates that we develop a more comprehensive understanding of the role of chemokines in smooth muscle cell activation and in mediating intimal hyperplasia.

### Arteriogenesis

Arteriogenesis refers to the formation of collateral blood vessels, possibly through enlargement of preexisting vessels, as opposed to angiogenesis, which is the formation of new capillaries.66 Increasing evidence suggests that the recruitment of monocyte/macrophages by MCP-1—dependent mechanisms contributes to arteriogenesis and reperfusion of ischemic tissue. In a rabbit model of hind-limb ischemia, local instillation of MCP-1 increased monocyte/macrophage recruitment, collateral vessel formation, and blood flow to the ischemic tissue.67,68 After ligation of the femoral artery, CCR2−/− mice had impaired distal blood flow and collateral artery formation, as compared with wild-type mice.69 However, this impairment was largely limited to mice on the Balb/c genetic background. Using a similar model, Tang et al (unpublished data, 2004) found that CCR2−/− and wild-type mice on the C57Bl/6 background are indistinguishable in their ability to restore blood flow to the foot and form collaterals after excision of a portion of the proximal femoral artery. Thus, the role of CCR2 in vasculogenesis is not clear. However, these data raise the interesting possibility that MCP-1 acts through a receptor other than CCR2. As noted, there is evidence that vascular smooth muscle cells, which do not express CCR2, express tissue factor in response to MCP-1.53

Few studies in humans have addressed the role of MCP-1/CCR2 in atherosclerosis. However, subjects with hypercholesterolemia tended to express higher levels of CCR2 on monocytes, and CCR2 expression correlated positively with plasma LDL cholesterol levels and inversely with plasma high-density lipoprotein levels.70,71 Furthermore, in postmenopausal women receiving estrogen replacement therapy, which raised high-density lipoprotein cholesterol levels and lowered LDL-cholesterol levels, CCR2 expression on monocytes was reduced.71 These findings suggested that high cholesterol levels increase the sensitivity of monocyte/macrophages to MCP-1, thereby increasing their movement into early atherosclerotic lesions. The subsequent downregulation of CCR2, as monocytes differentiate into macrophages, might serve to retain the cells within the lesion.

A relatively common genetic variant in CCR2 has been identified in which valine at position 64 is changed to isoleucine. Although in vitro studies have failed to reveal significant abnormalities in receptor signaling or MCP-1 binding,72 the 64I mutation is associated with reduced risk of HIV/AIDS,73 pulmonary sarcoidosis,74 and acute renal transplant rejection.75 Information on the 64I mutation and the risk for cardiovascular disease is limited and inconsistent. In healthy subjects with a family history of heart disease, both..
membrane, as a soluble proteins. FK is the only chemokine proteins and, after cleavage at a site(s) near the plasma transmembrane domains and exist as full-length immobilized chemokine-like domain fused to a mucin stalk. Both have capture and the initiation of atherosclerosis.

Evidence for a role for MCP-1 in ischemic heart disease comes from a study of plasma MCP-1 levels in healthy volunteers and patients with acute coronary syndrome. Although the MCP-1 levels overlapped considerably between the two groups, acute coronary syndrome patients with the highest levels of MCP-1 (the top quartile, corresponding to the 90th percentile in the healthy normal population) had a significantly increased risk of death or myocardial infarction over 10 months of follow-up. Although high MCP-1 levels were associated with other traditional risk factors, high levels correlated with poor outcomes, even after adjustment for plasma levels of C-reactive protein. It remains to be established whether these high MCP-1 levels contribute to exacerbation of the disease through continued monocyte/macrophage recruitment and activation or simply reflect the presence of macrophages and other MCP-1-producing cells in established lesions.

Taken together, these studies suggest possible roles for CCR2 and MCP-1 in determining risk for atherosclerosis, myocardial infarction, and left ventricular function, but larger prospective studies will be needed to fully address this important question.

Other Chemokines Implicated in Vascular Disease

At least three other chemokines—IL-8, FK, and CXCL16—have been linked to the development of early atherosclerotic lesions. Perhaps the best characterized of the neutrophil chemoattractants, IL-8 is also a monocyte agonist and is present in macrophage-rich atherosclerotic plaques. In irradiated LDL receptor-deficient mice that were fed an atherogenic diet after receiving bone marrow transplants of cells that either lacked or expressed the murine IL-8 receptor (the homolog of human CXCR2), mice lacking the IL-8 receptor had less accumulation of macrophages and smaller lesions. IL-8 also triggers the arrest of monocytes under flow conditions. This effect did not correlate with chemotaxis or the induction of an intracellular calcium flux and may therefore be mediated by novel signaling pathways. In addition, IL-8-mediated capture of monocytes occurred under physiological conditions and was VLA-4 dependent. These data provide evidence for a potential role of IL-8 in monocyte capture and the initiation of atherosclerosis.

FK and CXCL16 are novel chemokines composed of a chemokine-like domain fused to a mucin stalk. Both have transmembrane domains and exist as full-length immobilized proteins and, after cleavage at a site(s) near the plasma membrane, as a soluble proteins. FK is the only chemokine with three amino acids between the first two cysteine residues and is thus designated CX3CL1 (Figure 3). Full-length transmembrane FK is an efficient cell-adhesion molecule that can capture cells expressing its cognate receptor (CX3CR1) under physiologically relevant flow conditions. In humans, CX3CR1 is expressed on monocytes, NK cells, and CD3+ T cells. CX3CR1 may be preferentially expressed on CD14(CCR2) monocyte/macrophages, which are long-lived resident cells. The notion that CCR2+ monocytes are “inflammatory” and short-lived, whereas CX3CR1+ monocytes are destined to become resident cells, is intriguing and has potentially important therapeutic implications. Soluble FK also activates cells via CX3CR1, one result of which is the induction of integrin-dependent binding to ICAM-1 and VCAM-1. These two forms of FK-mediated cell adhesion may work in concert to capture CX3CR1 positive cells.

FK is present in human atherosclerotic lesions, and McDermott et al have found that the presence of a polymorphism in CX3CR1 (V280M) correlated with protection from coronary artery disease. Haskell et al have made a CX3CR1 knockout mouse and demonstrated a role for FK in organ transplantation. In a heterotopic cardiac allograft model using donor hearts that were mismatched for both MHC class I and class II, CX3CR1 mice rejected the grafts more slowly than wild-type recipients, particularly in the presence of subtherapeutic levels of cyclosporin A. Recently, Lesnik et al demonstrated expression of FK in atherosclerotic lesions in mice and found that, like CCR2+ mice, apoE-deficient CX3CR1 mice were protected against diet-induced atherosclerosis. Similar results were reported by Combadière et al. Further investigation of the V280M polymorphism in CX3CR1 showed that although this single amino acid change had little effect on the binding of soluble FK, it almost completely prevented the...
plasma cell development or localization. CXCL16 is also 
tively by bone marrow stromal cells, suggesting a function in 
cells express CXCR6, and CXCL16 is expressed constitu-
which express high levels of CXCR6. Bone marrow plasma 
cells and CXCR6
CXCL16 may also promote interactions between dendritic 
ceptors of CX3CR1 are being used in phase I/II trials for 
trials as adjuvant treatments for AIDS. Small-molecule inhib-
blocks the binding of MCP-1 to CCR2 is being used in phase 
the efficacy of CCR1 antagonists for the treatment of rheu-
diseases. A central issue in the development of chemokine 
tions would apply to measures of endothelial cell dysfunc-
tion, such as nitric oxide production. It will be interesting to 
possible biomarkers include plasma levels of C-reactive 
correlate well with changes in the coronary arteries. Other 
validated. Advanced imaging techniques seem the most 
markers of disease. Simply put, if we had a safe and potent 
atastic for cardiovascular disease until surrogate markers are developed and 
validated. Advanced imaging techniques seem the most 
prospective candidates, especially if it can be shown that 
changes in peripheral vessels, such as the carotid artery, 
correlate well with changes in the coronary arteries. Other 
possible biomarkers include plasma levels of C-reactive 
protein or MCP-1, if they could be validated as measures of 
vascular inflammation or plaque stability. Similar consider-
ations would apply to measures of endothelial cell dysfunc-
tion, such as nitric oxide production. It will be interesting to 
see to what extent statins exert their anti-inflammatory 
actions by inhibiting the production of MCP-1 and other 
chemokines.

Restenosis may be a more apt target for chemokine 
antagonists than atherosclerosis. The extent of restenosis can 
be quantified at the time of the procedure, and symptomatic 
patients will likely undergo cardiac catheterization. Unlike 
atherosclerosis, which is a slow insidious process, restenosis 
occurs relatively quickly after the procedure. As noted, there

receptor from binding immobilized FK. Thus, FK appears 
to be intimately involved in fatty streak formation.

CXCL16, a chemokine domain fused to a mucin stalk, was 
independently cloned as a scavenger receptor for phosphati-
dylerosine and oxidized lipids and as a chemokine. CXCL16 
is expressed on macrophages and dendritic cells and, at lower levels, on T cells. Like FK, CXCL16 can 
capture cells bearing its cognate receptor, CXCR6, and is 
cleared by the metalloprotease ADAM-10 to release a soluble form that has chemotactic activity. The receptor for 
CXCL16, CXCR6, is expressed on subsets of T cells and NKT cells.

The roles of CXCL16 in vivo are not well understood, but 
recent work has shown that it is present in both human and 
murine atherosclerotic lesions and is upregulated by interferon γ. CXCL16 may thus contribute to atherosclerosis by 
capturing CXCR6 cells and by scavenging oxidized lipids. 
CXCL16 may also promote interactions between dendritic 
cells and CXCR6 T cells, particularly Th1-polarized T cells, 
which express high levels of CXCR6. Bone marrow plasma 
cells express CXCR6, and CXCL16 is expressed constitutively 
by bone marrow stromal cells, suggesting a function in 
plasma cell development or localization. CXCL16 is also 
found in the thymus, suggesting a possible role in the 
development of T cells and/or CXCR6 NKT cells. A more 
complete understanding of the significance of CXCL16/ 
CXCR6 in cardiovascular disease and immune cell development 
awaits further work with mice deficient in either the 
chemokine or its receptor.

**Therapeutics: Where Do We Stand Today?**

Chemokines are important therapeutic targets, and most of 
the initial efforts in this area have been directed toward 
the development of chemokine receptor antagonists. Currently, 
the efficacy of CCR1 antagonists for the treatment of rheu-

Figure 4. Expression of FK in atherosclerosis lesions. Serial sections were cut at 
the level of the aortic valve leaflets and incubated with antibodies. Staining of FK 
is visualized as red and staining of macrophages appears as green. Colocalization of FK 
and macrophages appears as yellow. Movat stain was used to identify smooth 
muscle cells. FK expression was most intense in smooth muscle cells directly 
beneath the lesions macrophages.
is reason to believe that MCP-1–dependent recruitment of macrophages is important in restenosis. The introduction of drug-eluting stents dramatically reduced the incidence of restenosis in recent studies and it remains to be seen whether additional therapeutic modalities, such as chemokine receptor antagonists, will be needed.

In summary, the past few years have witnessed a rapid increase in our understanding of the role of chemokines in the recruitment of leukocytes to sites of inflammation and the importance of inflammation in the pathogenesis of atherosclerosis and other vascular diseases. Most studies have focused on the formation of early lesions. Determining whether chemokine antagonists can stabilize established atherosclerotic plaques or cause them to regress in experimental animals will likely be required before planning of human clinical trials for such antagonists. Human trials will also likely require the validation of novel imaging techniques or biomarkers to quantify lesion size or stability. Given the success in clinical trials for such antagonists, human trials will also likely be required before planning of human clinical trials for such antagonists. Human trials will also likely require the validation of novel imaging techniques or biomarkers to quantify lesion size or stability. Given the success in developing potent chemokine therapeutics, it seems likely that this area will remain a focus for basic and clinical scientists for some time to come.

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