The specific role of chemokines in atherosclerosis

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Summary
Atherosclerosis is a chronic inflammatory disease that represents the primary cause of heart disease and stroke. The recruitment of inflammatory cells in the intima is an essential step in the development and progression of atherosclerosis. This process is triggered by local production of chemokines and chemokine receptors from activated endothelial cells and inflammatory cells. Various members of the CC chemokine family (e.g. MCP-1/CCL2) as well as CXC family (e.g. IL-8/CCL8, IP-10/CXCL10, SDF-1/CXCL12) and, more recently, fractalkine/CX3CL1 have been implicated in atherosclerosis development. Latest findings in animal models suggest that blocking chemokine/chemokine receptor interactions may serve as a suitable approach to treat atherosclerosis. Likewise, chemokine antagonists that inhibit leukocyte recruitment could particularly be interesting to treat inflammation in response to myocardial infarction, the major consequence of atherosclerosis.

Keywords
Atherosclerosis, chemokines, inflammation, leukocyte recruitment, myocardial infarction

Introduction
Atherosclerosis is an inflammatory disease characterized by arterial lesions containing cholesterol, immune infiltrates, and connective-tissue elements (1–3). It is responsible for the major mortality causes, i.e. ischemic heart disease and cerebrovascular disease. In the initial stages of lesion formation, activation of the endothelium in response to cardiovascular risk factors leads to the expression of chemokines and adhesion molecules (4). This, in turn, leads to monocyte and T-lymphocyte recruitment into the subendothelial space. Within the lesion, proinflammatory cytokines and chemokines, released from endothelial cells, macrophages, or T cells, cause proliferation and migration of smooth muscle cells (SMCs) from the media to the intima. Within the intima, SMCs secrete extracellular matrix components, leading to the accumulation of collagen and proteoglycans, key factors implicated in plaque stability (5). Conversely, the secretion of matrix metalloproteinases by vascular and inflammatory cells degrades matrix components, such as collagen, gelatin, or elastin within atherosclerotic lesions. Depending on the stability of the lesion, the plaque may rupture and induce thrombosis, leading to acute vascular events.

Chemokines and chemokine receptors
Chemokines (chemotactic cytokines) belong to a large superfamily of low-molecular-weight proteins with a highly homologous three-dimensional structure (6). They are divided into four families (CC, CXC, CX3C, XC) based on the configuration of the first two cysteines. Chemokines are known to induce leukocyte migration, growth, and activation through seven transmembrane domain G protein-coupled cell-surface receptors on target cells.

In addition, the biological activity of chemokines has been shown to be critically influenced by their association with glycosaminoglycans (GAGs) (7), tethered to proteoglycans on cell surfaces and in the extracellular matrix. GAGs such as heparin or heparin sulfate are highly sulfated oligosaccharides, which are posttranslationally sulfated by membrane-bound specific enzymes. The GAG interaction is thought to be responsible for the establishment of chemokine gradients over endothelial cells under vascular flow conditions, which is an important step for initial leukocyte recruitment and subsequent migration through the tissue (8).

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Endothelial dysfunction triggers migration of inflammatory cells

Early atherosclerosis is characterized by endothelial dysfunction due to many risk factors. Beyond genetic risk factors, hyperlipidemia, diabetes, hypertension, obesity, and smoking are the main cardiovascular risk factors, which enhance endothelial injury (4, 9). Under normal conditions, endothelial cells inhibit platelet and leukocyte adhesion to the vascular surface. Risk factors may initiate an inflammatory response in the artery wall. Activated endothelial cells switch their molecule expression pattern and, as a consequence, present several types of leukocyte adhesion molecules at their surface and secrete chemotaxant molecules (3, 10). These cellular changes cause leukocyte rolling along the vascular surface and cell adhesion at the site of activation. Endothelial dysfunction occurs preferentially at sites of hemodynamic strain. Leukocytes recruited to the activated endothelium secrete chemokines and cytokines, thus promoting the ongoing chronic inflammatory process at sites. This results in the presence of a large number of inflammatory and immune cells within atherosclerotic lesions.

Chemokines in vascular biology

Chemokines and chemokine receptors involved in atherosclerosis

Chemokines need to bind their coupled receptors on target cells to induce cellular changes. Their receptors constitute a superfamily of 20 members, which possess seven transmembrane loops, coupled with heterotrimeric G proteins (6). The best characterized member of the CC chemokine family, monocyte chemoattractant protein-1 (MCP-1), termed chemokine ligand CCL2 in the systematic nomenclature, was found to be highly expressed in human atherosclerotic lesions (11–13). Other CC family chemokines such as macrophage inflammatory protein-1α (MIP-1α)/CCL3, MIP-1β/CCL4, regulated on activated normal T cell expressed and secreted (RANTES)/CCL5, as well as a number of recently discovered chemokines have also been detected in atherosclerotic lesions (14–16). As we have demonstrated in apolipoprotein E-deficient (ApoE-/-) mice, the progression of atherosclerotic lesions correlates well with an increase of proinflammatory chemokine and chemokine receptor expression within aortas (16). A vast number of studies employing different models of genetic disruption or pharmacological inhibition in mice underscore the crucial role of specific chemokines and their receptors in atherogenesis (summarized in Table 1).

Besides the regulation of leukocyte trafficking during inflammation, chemokines are also involved in the activation of

Table 1: Experimental mouse models showing the implication of chemokines and chemokine receptors in atherosclerosis.

<table>
<thead>
<tr>
<th>Chemokine or chemokine receptor</th>
<th>Experimental mouse model</th>
<th>Effect on atherosclerosis</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CC family</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MCP-1/CCL2</td>
<td>Double KO LDLR-/-, MCP-1-/-</td>
<td>Reduction</td>
<td>(25)</td>
</tr>
<tr>
<td></td>
<td>ApoB overexpressing, MCP-/-</td>
<td>Reduction</td>
<td>(26)</td>
</tr>
<tr>
<td></td>
<td>Transplantation of MCP-1 overexpressing bone marrow in ApoE-/-</td>
<td>Increase</td>
<td>(27)</td>
</tr>
<tr>
<td></td>
<td>Anti-MCP-1 gene therapy in ApoE-/-</td>
<td>Reduction</td>
<td>(28, 29)</td>
</tr>
<tr>
<td>RANTES/CCL5</td>
<td>LDLR-/-, treatment with RANTES antagonist</td>
<td>Reduction</td>
<td>(36)</td>
</tr>
<tr>
<td>CCR1</td>
<td>Transplantation of CCR1-/- bone marrow in LDLR-/-</td>
<td>Increase</td>
<td>(85)</td>
</tr>
<tr>
<td></td>
<td>Double KO ApoE-/-, CCR1-/-</td>
<td>Increase</td>
<td>(41)</td>
</tr>
<tr>
<td>CCR2</td>
<td>Double KO ApoE-/-, CCR2-/-</td>
<td>Reduction</td>
<td>(24)</td>
</tr>
<tr>
<td>CCR5</td>
<td>Double KO ApoE-/-, CCR5-/-, with normal diet</td>
<td>NS</td>
<td>(37)</td>
</tr>
<tr>
<td></td>
<td>Transplantation of CCR5-/- bone marrow in LDLR-/-</td>
<td>NS on lesion extend, but more stable plaques</td>
<td>(38)</td>
</tr>
<tr>
<td></td>
<td>Double KO ApoE-/-, CCR5-/-</td>
<td>Reduction</td>
<td>(41)</td>
</tr>
<tr>
<td><strong>CXC family</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IP-10/CXCL10</td>
<td>Double KO ApoE-/-, IP-10-/-</td>
<td>Reduction</td>
<td>(56)</td>
</tr>
<tr>
<td>SR-PSOX/CXCL16</td>
<td>Double KO LDLR-/-, CXCL16-/-</td>
<td>Reduction</td>
<td>(63)</td>
</tr>
<tr>
<td>CXC2R (mIL-8RH)</td>
<td>Transplantation of mIL-8RH-/- bone marrow in LDLR-/-</td>
<td>Reduction</td>
<td>(51)</td>
</tr>
<tr>
<td>CXC3R</td>
<td>Double KO ApoE-/-, CXC3R-</td>
<td>Reduction (early atherogenesis)</td>
<td>(55)</td>
</tr>
<tr>
<td><strong>CX3C family</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fractalkine/CX3CL1</td>
<td>Double KO ApoE-/- or LDLR-/-, CX3CL1-/-</td>
<td>Reduction</td>
<td>(72)</td>
</tr>
<tr>
<td>CX3CR1</td>
<td>Double KO ApoE-/-, CX3CR1-/-</td>
<td>Reduction</td>
<td>(70, 71)</td>
</tr>
</tbody>
</table>

KO, knockout; NS, not significant.
platelets (17, 18). Platelets are anucleated cellular fragments that circulate in the blood. In addition to their well-recognized role in hemostasis and acute thrombus formation, platelets are also thought to have proinflammatory and growth-regulatory properties that contribute to progression of atherosclerosis (19, 20). Platelet activation releases multiple growth factors and inflammatory mediators, including chemokines, into the microenvironment (21). The most abundant protein secreted by activated platelets is the chemokine platelet factor 4 (PF4/CXCL4). PF4 acts as a chemoattractant for monocytes and promotes their differentiation into macrophages (22). Other platelet-derived chemokines are RANTES, also known to trigger monocyte recruitment, as well as epithelial neutrophil-activating protein 78 (ENA-78/CXCL5) and neutrophil-activating peptide 2 (NAP-2/CXCL7) (23).

In the following, we will discuss in detail the specific role of various members of the CC, CXC and CX3C chemokine family in atherogenesis.

MCP-1 and CCR2

The chemokine MCP-1/CCL2 was found at high expression levels within atherosclerotic lesions and, thus, considered as a key player in monocyte recruitment into the arterial wall (11–13). The predominant cell types within the activated vessel wall, SMCs and monocytes/macrophages, contribute to the overexpression of MCP-1 in the atherosclerotic tissue. Studies in mice in which either MCP-1 or its corresponding receptor CCR2 was genetically deleted revealed its fundamental role in atherogenesis. Deletion of CCR2 prevented the accumulation of macrophages and the formation of high fat diet-induced atherosclerotic lesions in ApoE−/− mice (24). MCP-1 deficiency reduced atherosclerosis development in low density lipoprotein receptor-deficient (LDLR−/−) mice and human apolipoprotein B-expressing transgenic mice (25, 26). On the other hand, transplantation of bone marrow cells overexpressing MCP-1 induced infiltration of donor macrophages in various tissues including aortas and accelerated atherosclerosis in ApoE−/− mice (27). Finally, two different approaches of anti-MCP-1 gene therapy based on a non-functional, CCR2-blocking MCP-1 mutant attenuated atherosclerosis progression (28, 29).

In humans, elevated MCP-1 serum levels were found in patients with coronary artery disease (CAD) or increased coronary risk factors (30). In addition, endothelial activation markers such as soluble adhesion molecules, soluble intercellular adhesion molecule and soluble E-selectin were also increased in these patients. Thus, elevated MCP-1 serum levels might serve as a direct marker of inflammatory activity for those at risk for coronary artery and other atherosclerotic vascular diseases. A polymorphism in the human CCR2 gene has been described that might be associated with increased risk of early myocardial infarction (MI) (Table 2), as demonstrated in two independent reports (31, 32). In a different study, however, no correlation between CCR2 polymorphism and age of the onset of MI was found (33).

Consistent with the crucial role of MCP-1 in atherosclerosis, a genetic variation in the MCP-1 gene (the MCP-1−1−2578G allele) was recently associated with both higher serum MCP-1 levels and higher prevalence of MI (34).

<table>
<thead>
<tr>
<th>Human polymorphism</th>
<th>Correlation with CAD and MI risk</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCP-1−1−2578G allele</td>
<td>Increased risk of MI</td>
<td>(34)</td>
</tr>
<tr>
<td>CCR2−64I</td>
<td>Increased risk of MI</td>
<td>(31, 32)</td>
</tr>
<tr>
<td>CCR5−64I</td>
<td>NS</td>
<td>(33)</td>
</tr>
<tr>
<td>32bp deletion, (delta) CCR5</td>
<td>Reduced risk of MI</td>
<td>(33, 35)</td>
</tr>
</tbody>
</table>

RANTES, CCR1 and CCR5

The expression of CCR1 and CCR5 on various cell types implicated in atherosclerosis such as monocytes/macrophages and T cells suggests a fundamental role for the two receptors in this disease (23). Moreover, the chemokines binding to CCR1 and CCR5, namely RANTES/CCL5, MIP-1α/CCL3 and MIP-1β/CCL4 are present in atherosclerotic lesions (14–16). Polymorphism studies revealed an association between a 32-bp deletion in the human CCR5 gene and reduced risk of early MI (33) as well as severe coronary artery disease (35). Blocking the receptors of the chemokine RANTES with the peptide antagonist Met-RANTES has been shown to inhibit lesion formation and leukocyte infiltration into lesions (36). Moreover, the reduction of lesion size was associated with a more stable plaque phenotype, as shown by increased smooth muscle cell and collagen content and reduced MMP-9 expression. To clarify the exact role of CCR1 and CCR5 in atherosclerosis, several in-vivo studies employing different strategies of chemokine receptor deficiency...
in atherosclerotic mice have been performed. In a first study conducted with ApoE/CCR5 double knockout mice, Kuziel et al. reported that CCR5 does not affect early stages of atherosclerotic lesion formation (37). This unexpected result is in conflict with more recent data obtained with LDLR-/- mice reconstituted with CCR5-deficient bone marrow. Here, CCR5 deficiency was associated with a less inflammatory, more stable plaque phenotype, but had little effects on lesion size (38). The discrepancies might be explained by the different stages of atherosclerosis development analyzed in the two studies. In the same model, CCR1 deficiency in bone marrow cells enhanced inflammation and atherosclerotic lesion development (39). Similarly, deficiency in CCR5 but not CCR1 protected against neointima formation after arterial injury in atherosclerosis-prone mice (40). This attenuation was due to an atheroprotective immune response, mediated via enhanced interleukin (IL)-10 production. To unambiguously clarify the role of CCR1 and CCR5 in atherosclerosis progression, we investigated the impact of chemokine receptor deficiency on advanced atherosclerotic lesion development in ApoE-/- mice. In two independent lines of investigation, we found that CCR5 but not CCR1 deficiency protects from diet-induced atherosclerosis (41). The protective effect was associated with a more stable plaque phenotype, reduced mononuclear cell infiltration, Th1-type immune responses, and increased IL-10 expression. Importantly, the anti-inflammatory cytokine IL-10 was produced by SMCs, as demonstrated by double immunofluorescence. The finding that SMCs are the major source of IL-10 in the ApoE/CCR5 double-knockout model is likely to explain the discrepant results obtained with the CCR5-/ bone marrow transplantation model in LDLR-/- mice (38).

In conclusion, CCR5 and CCR1 have opposite effects in atherosclerotic lesion development. This is somewhat surprising, as both receptors share common ligands. It might be speculated that a chemokine exerts antipodal effects by acting as an activating agonist for one receptor and antagonist for another. In addition, it is conceivable that genetic disruption or pharmacological inhibition of a chemokine receptor not only abolishes the activation of this receptor, but results in alternative activation of other receptors due to altered chemokine binding.

**CCR7**

The homeostatic chemokines CCL19 and CCL21 and their receptor CCR7 play a pivotal role in T-cell and dendritic cell trafficking into lymphoid tissue. New data revealed the involvement of CCL19 and CCL21 in inflammatory responses and T-cell homing in non-lymphoid tissue (42, 43). In a recent study combining different approaches including clinical studies in patients, in-vitro studies and in-vivo experiments in ApoE-/- mice, an implication of these chemokines in CAD was found (44). Increased chemokine expression was found in mouse and human atherosclerotic lesions as well as in plasma of CAD patients. Interestingly, enhanced expression of the corresponding receptor CCR7 was detected in atherosclerotic plaque T cells, whereas circulating T cells from angina patients showed decreased CCR7 expression. This differential expression pattern might reflect redistribution of CCR7+ T cells toward the inflammatory atherosclerotic lesions during plaque progression.

**IL-8 and CXCR2**

Among the members of the CXC chemokine family, interleukin-8/CXCL8 and its corresponding receptor CXCR2 have early been involved in atherosclerosis. Proatherogenic oxidized low-density lipoprotein has been shown to induce IL-8 secretion in primary human peripheral blood monocytes (49). Within atherosclerotic lesions, IL-8 produced by macrophages as well as CXCR2 expression within the intima was found (50, 51). In irradiated LDLR-/- mice reconstituted with bone marrow cells lacking the murine homologue of the IL-8 receptor CXCR2, the lesion size as well as the amount of macrophages within the plaques was reduced (51). Additional experiments indicate that the mouse CXCR2 ligand is central to macrophage accumulation in advanced, but not early atherosclerotic lesion development (52).

**IP-10 and CXCR3**

Interferon (IFN) γ-induced protein of 10 kDa (IP-10), also denoted as CXCL10, is a T-cell chemokine that is constitutively expressed within thymus, spleen and lymph nodes. Its expression, however, can be highly induced by interferons in leukocytes (e.g. monocytes and macrophages) and other cells such as endothelial and SMCs (53). In human atheroma, high expression levels of IP-10 and its two functionally related IFN-γ-inducible CXC chemokines monokine induced by IFN-γ (Mig)/CXCL9 and IFN-inducible T-cell α-chemoattractant (I-TAC)/CXCL11 have been found (54). These three chemokines all bind to the same receptor, CXCR3. Importantly, we have demonstrated that CXCR3 deletion modulates early lesion formation in ApoE-/- mice (55). The observed reduction of lesion formation was associated with an increase of antinflammatory molecules IL-10 and IL-18BP, endothelial nitric oxide synthase and increased amount of Fox3-expressing regulatory T cells. Recently, it has been reported that IP-10 deficiency reduced atherosclerotic lesions in ApoE-/- mice (56). While the overall number of T cells was diminished within the lesions of these mice, the mRNA level of the regulatory T-cell marker Fox3 as well as expression of the regulatory cytokines IL-10 and transforming growth factor (TGF)-β were enhanced. Conversely, the mRNA level of the IP-10-binding chemokine receptor CXCR3 was reduced. In conclusion, the two studies provide evidence for a functional role of CXCL10/CXCR3 signalling in atherosclerosis by modulating the local balance of regulatory and effector T-cell populations.
SDF-1 and CXCR4

Stromal cell-derived factor-1 (SDF-1)/CXCL12 is a potent chemotactic factor for T cells and monocytes, and regulates the recruitment of lymphocytes from the blood flow to the endothelium (57). The chemokine-induced arrest of circulating leukocytes is mediated via integrin-dependent adhesion to intercellular adhesion molecule-1. SDF-1 is highly expressed in SMCs, endothelial cells, and macrophages in human atherosclerotic plaques, but not in normal vessels (18). Although chemokines are known as chemotactic cytokines that activate and direct the migration of leukocytes, new evidence has highlighted an additional role in modulating platelet function. SDF-1 was found to induce platelet aggregation, accompanied by a rise in intracellular calcium (17, 18). Moreover, platelets expressed the corresponding SDF-1 receptor, CXCR4.

Finally, SDF-1 together with eotaxin/CCL11 has recently been shown to induce arterial smooth muscle cell proliferation via activation of metalloproteinase-2 (MMP-2) (58, 59). MMP-2 has been implicated in SMC migration, proliferation and vascular remodelling. By facilitating the migration of vascular SMCs through the internal elastic lamina into the intimal space, MMPs trigger SMC proliferation, thus contributing to plaque formation.

CXCL16

As another member of the CXC family, CXCL16, expressed in dendritic cells, macrophages, and aortic SMCs, has also been detected in atherosclerotic lesions (60, 61). New findings further indicate that CXCL16, also named scavenger receptor SRPSOX, mediates oxidized LDL uptake by macrophages (60, 61). This chemokine is expressed in soluble and transmembrane forms, binds to CXCR6 chemokine receptor, and guides migration of activated T cells. The proinflammatory cytokine IFN-γ enhances CXCL16 expression, as demonstrated in mice and in vitro in human monocytes (61). Interestingly, a recent clinical study revealed that lower plasma levels of CXCL16 are associated with CAD, indicating a potential atheroprotective function for CXCL16 (62). In support of the atheroprotective role of CXCL16, deletion of CXCL16 accelerated atherosclerosis development in LDLR−/− mice (63). This was associated with enhanced macrophage recruitment and enhanced mRNA levels of MCP-1 and tumor necrosis factor-α within the aortic arch.

CX3CCL1

Fractalkine/CXC3CL1, which is the only CX3C chemokine, has also been implicated in the pathology of atherosclerosis. Fractalkine, together with CXCL16, are the only known chemokines expressed in both soluble and transmembrane forms, thus combining chemotactic functions together with receptor/adhesion molecule properties (64). Its transmembrane form is expressed on endothelial cells under stimulation by proinflammatory molecules. In its soluble form, fractalkine is a potent chemotactic agent for monocytes and T cells. First evidence relating fractalkine with atherosclerosis emerged from two epidemiologic studies. A polymorphism in the fractalkine receptor (V249I) was associated with lower risk of CAD, suggesting an implication of this receptor in cardiovascular diseases (65, 66). Conversely, in a more recent study published by Niessner et al., no association of the V249I or T280M polymorphism with the occurrence of CAD was found (67). Here, a protective effect of the T280M polymorphism on acute coronary syndrome was found, whereas V249I appears to have the opposite effect.

In support of its putative role in atherosclerosis, fractalkine has been detected in human atherosclerotic lesions, but not in normal arteries (68, 69). More relevant studies relating fractalkine and atherosclerosis have been performed via genetic disruption of the fractalkine receptor, CX3CR1. ApoE−/− mice deficient in CX3CR1 developed less atherosclerosis compared to controls, most likely by inhibiting monocyte recruitment (70, 71). In a different atherosclerotic mouse model, fractalkine deficiency dramatically reduced the lesion area in the brachiocephalic artery, but not in aortic roots (72). A reduced infiltration of monocytes into the lesions was also observed. In addition to native atherosclerosis, an epidemiologic study conducted with 365 patients undergoing coronary stenting revealed a link between fractalkine receptor polymorphisms and elevated risk of restenosis (73).

Interestingly, two major subsets of monocytes with distinct chemokine receptor patterns have been identified: the first subset expresses CCR2 and CX3CR1, whereas the second, non-classical subset does not express CCR2, but enhanced levels of CX3CR1 (74). In a very recent study, the migration and differentiation properties of these two subsets in ApoE−/− mice have been investigated (75). It was shown that CCR2+ monocytes efficiently accumulated in atherosclerotic plaques, whereas CX3CR1− monocytes were poorly recruited. Although less frequently entering the plaques, CCR2− monocytes were more disposed to differentiate into cells expressing the dendritic cell-associated marker CD11c. Moreover, the two subsets were shown to depend on different chemokine receptors to enter atherosclerotic plaques. CCR5 was selectively upregulated in CX3CR1− monocytes, while CX3CR1+ was not required for plaque entry. By contrast, CCR2+ monocytes employed CX3CR1 together with CCR2 and CCR5. Consistent with these findings, it has been previously reported that a human counterpart of CD14+CD16+ cells also lacks CCR2 while expressing higher levels of CCR5 (76). This unexpected finding might offer new therapeutic approaches based on CX3CR1 antagonists, thus selectively targeting CX3CR1-dependent plaque entry without blocking CCR2-dependent inflammatory responses.

Therapeutic opportunities

Recent findings in animal models suggest that pharmacological inhibition of chemokines may serve as a suitable approach to treat atherosclerosis. In the LDLR−/− mouse model, we could demonstrate that blocking the RANTES receptor with a specific antagonist attenuates atherosclerosis development (36). More recently, the CCR5 and CXCR3 chemokine receptor antagonist TAK-799, originally developed for the treatment of HIV infection, was reported to reduce lesion development in a collagen-induced carotid artery atherosclerosis model (77). The atheroprotective effect was mediated by blocking the influx of IFN-γ secreting Th1 cells.
It is conceivable that blocking chemokine/receptor interactions with specific antagonists or blocking antibodies could be of therapeutic use to reduce inflammatory cell recruitment within atherosclerotic lesions, thus modulating chronic inflammatory processes. However, a major challenge of such a therapeutic approach would be to specifically target atherosclerotic lesions without affecting the general host defence. Atherosclerosis is a chronic inflammatory disease which develops during a long period, but its clinical manifestations appear only at advanced stages of the disease. Thus, potential new therapies must be validated on pre-established lesions.

More interesting in view of a possible clinical application might be the use of chemokine antagonists for secondary prevention of atherosclerosis after arterial injury. Neointima formation in response to arterial injury or during accelerated atherosclerosis involves leukocyte recruitment triggered by chemokines. First experimental studies provide evidence for a therapeutic benefit of chemokine blocking in cardiovascular remodeling. It has been shown that blocking of the MCP-1 receptor CCR2 after stent-induced injury significantly reduced neointima formation in primate arteries (78). In support of these findings, local anti-MCP-1 gene therapy was shown to reduce neointimal hyperplasia in rats and monkeys (79). Finally, in a wire-induced model of arterial injury in mice, blocking the receptor of the chemokine RANTES with an antagonist significantly reduced neointimal plaque area and macrophage infiltration (80). The development of drug-eluting stents for local administration may allow to specifically attenuating neointimal growth, without adverse effects due to systemic administration.

Another suitable application for assessing the efficiency of chemokine antagonists might be the ischemia/reperfusion model. MI, the major consequence of atherosclerosis, is associated with an inflammatory reaction that is a prerequisite for inducing repair mechanisms (81). In animals, the inflammatory response following experimental ischemia was shown to increase if the ischemic tissue was reperfused (82). As observed in the murine MI model, a massive neutrophil and monocyte/macrophage recruitment occurs during reperfusion (82). Neutrophil chemoattractants, such as IL-8/CXCL8, are upregulated in the infarcted area, inducing polymorphonuclear leukocyte infiltration (81). In addition, mononuclear cell chemoattractants, such as MCP-1, MIP-1α and MIP-1β are expressed, leading to monocyte and lymphocyte recruitment in the ischemic area (81, 83). Reducing this inflammatory cell infiltration via selective chemokine antagonists could be an effective therapy to reduce reperfusion damages. Importantly, contrary to atherogenesis, infiltration of inflammatory cells within ischemic tissues is a short-term process. Thus, a major clinical improvement might be achieved by short-term treatment, without potential adverse effects of a systemic long-term therapy. A first study employing genetic MCP-1 disruption as well as an MCP-1 neutralizing antibody, however, suggests an important role for this cytokine in inflammatory responses critical to healing infarct (84). Absence or neutralization of MCP-1 was associated with decreased and delayed myocardial macrophage infiltration, delayed replacement of injured cardiomyocytes with granulation tissue, and down-regulation of both pro- and antiinflammatory cytokines. Thus, the effects of chemokine inhibition should be carefully studied before identifying potential targets for therapeutic intervention.

Conclusions

Chemokines represent an expanding family of small-molecular-weight proteins, responsible for leukocyte trafficking and activation. Within the past years, increasing evidence has highlighted their crucial implication in the pathogenesis of atherosclerosis, and the role of chemokines in MI is subject of ongoing research. These new insights into the role of chemokines in atherosclerosis and acute cardiovascular events not only increase our understanding of this disease, but may also have practical applications in identifying new clinical markers and targeting of novel therapeutic approaches. Indeed, latest findings in animal models suggest that blocking chemokine/receptor interactions may serve as a new therapeutic approach for the treatment of atherosclerosis.

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