Killing Two Birds With One Stone
Targeting Chemokine Receptors in Atherosclerosis and HIV Infection

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The recruitment of mononuclear cells into the arterial wall is a hallmark of atherosclerotic lesion formation. It has been widely acknowledged that the infiltration with monocytes is instrumental in the initiation and progression of atherosclerosis and that this inflammatory process is also driven or sustained by a T helper type 1 (Th1) lymphocyte-mediated immune response. Among other proinflammatory cytokines, an abundance of chemokines has been detected in atherosclerotic lesions and has been crucially implicated in directing the recruitment of monocytes and T cells into the lesions. Notably, genetic deletion or transfer of constructs encoding antagonistic mutants has revealed the essential contribution of certain chemokines and their receptors to lesion formation and macrophage infiltration in atherosclerosis-prone mice, eg, for the prototypic MCP-1 and its receptors CCR2 and for the fractalkine receptor CX3CR. Moreover, the CCR1 and CCR5 ligand RANTES and the CX3C ligands Mig and IP-10 have been found in atherosclerotic lesions. CCR5 and CXCR3 are index chemokine receptors primarily expressed on Th1 T cells guiding their migration to sites of inflammation. Although it has become apparent that the involvement of multiple chemokines is more reflective of the robustness and complexity of the recruitment signal required rather than the redundancy of the system, the precise role of these chemokines and their receptors in atherosclerosis has remained elusive until very recently. In addition, it has been questioned whether the involvement of these chemokines corresponds to a specific recruitment of different mononuclear cell types.

See page 2642

The global blockade of the RANTES receptors CCR1, CCR3, and CCR5 using the peptide antagonist Met-RANTES has been shown to reduce atherosclerotic lesion formation and macrophage infiltration. A 32-bp deletion in the CCR5 gene (CCR5Δ32) results in a nonfunctional receptor, and individuals that are homozygous for this deletion are resistant to infection with HIV. Findings that this deletion in the CCR5 sequence is associated with a reduced incidence in early myocardial infarction and lower susceptibility to severe coronary artery disease have strongly inferred a specific role for CCR5 in atherogenesis. On the other hand, attenuating transplant arteriopathy, complete deletion of the CCR5 gene failed to protect against spontaneous atherosclerosis in apolipoprotein E–deficient mice, whereas diet-induced atherosclerosis was not studied. More recently, deficiency in CXCR3 has been shown to reduce diet-induced atherosclerotic lesion formation in the thoraco-abdominal aorta but not in the aortic root of apolipoprotein E–deficient mice, implying a differential local contribution complementary to CCR2.

The nonpeptide small molecule CCR5 antagonist TAK-779 was developed for the treatment of HIV infection by inhibiting HIV entry via CCR5. This small molecule compound has also been shown to target CXCR3 and to block the influx of CCR5- and CXCR3-positive Th1-type T cells into inflamed joints in a model of collagen-induced arthritis. The study by van Wanrooij et al in this issue of Arteriosclerosis, Thrombosis, and Vascular Biology makes adept use of TAK-779 to explore the role of CCR5 and CXCR3 expressed on Th1 cells in atherosclerosis. Treatment with this CCR5 antagonist markedly reduced the formation of accelerated carotid lesions and diet-induced plaques of the aortic root in LDL receptor–deficient mice. Although not formally shown for aortic plaques, TAK-779 resulted in a dramatic and selective decrease in T cell infiltration and a near complete abrogation of the Th1-specific IFN-γ expression. The remarkable reduction of Th1 cell influx attributable to retention in the spleen underscores the concept of atherosclerosis as a Th1-mediated disease and at the same time provides a novel option for intervention. Given the marked upregulation of CCR5 but not CXCR3 and its ligands, it is conceivable that CCR5 exerts a more dominant role than CXCR3 in lesion formation or alternatively that TAK-779 primarily serves as a CCR5 antagonist. This would also be supported by recent data that in contrast to TAK-779, the genetic deletion of CXCR3 did not attenuate the development of lesions at the aortic root. The pivotal role of CCR5 in atherosclerosis is corroborated by findings that genetic deletion of CCR5 imparts a marked reduction of accelerated and diet-induced lesion formation in apolipoprotein E–deficient mice (Weber, Mach, Luckow et al, unpublished data, 2005). In contrast to treatment with TAK-779, life-time absence of CCR5 did not only inhibit lesional T cell content and Th1 cytokine expression but also macrophage infiltration. Indeed, TAK-779 inhibited spreading and migration of both Th1 cells and monocytes on activated endothelium in flow, suggesting that effects of TAK-779 on low levels of monocyte CCR5 may be compensated by other chemokine receptors in the model used by van Wanrooij et al. Together, these data help to dissect the importance of CCR5 in the immunopathogen-
esis of atherosclerosis and indicate a striking parallel to its role as a coreceptor for HIV infection.

The inhibition of T cell influx but not macrophage recruitment into atherosclerotic lesions with TAK-779 is in accordance with a recent report that genetic deletion of CXCR3 reduced the infiltration with T cells but not macrophages into atherosclerotic lesions of apolipoprotein E–deficient mice. Conversely, using CCR2-deficient mice in the same model confirmed a differential role of CCR2 mediating macrophage but not T cell infiltration into atherosclerotic lesions. Similarly, the deletion of CCR3 produced a marked decrease in macrophage infiltration, without affecting T cell content in atherosclerotic lesions. Taken together, a more differentiated picture emerges in which CCR2 and CX3CR preferentially recruit monocytes/macrophages in atherosclerosis, whereas CXCR3 and CCR5 rather recruit T cells, in particular of the Th1 subtype (Figure). In addition, a life-time absence of CCR5 may attenuate macrophage recruitment. The chemokine receptor repertoire for selective recruitment of other mononuclear cell subset, eg, regulatory T cells or Th2 cells, which exert protective effects in atherosclerosis, remains to be determined, but may involve CCR4 characteristic of Th2 cells.

Of particular note to appreciate the clinical importance of this study are recent data providing solid evidence for an association between the treatment with HIV protease inhibitors and an increased mortality from acute coronary events and atherosclerosis in HIV-infected patients. The administration of this class of drugs does not only entail a pronounced dyslipidemia with elevated total serum cholesterol and triglyceride levels in HIV-positive patients but also exerts direct cytotoxic effect on endothelial cells. Together with the emerging resistance of HIV strains to several groups of protease inhibitors, this imposes severe limitations to an optimal treatment. On the other hand, growing evidence indicates that HIV infection per se may directly contribute to subclinical atherosclerotic disease and myocardial infarction, eg, by inducing endothelial dysfunction in correlation with the viral load. It may be speculated and subject to further investigation whether the interaction/internalization of HIV and CCR5 or HIV-infection of mononuclear cells expressing CCR5 may promote proatherogenic effects. In consequence, treatment with TAK-779 may constitute a promising approach for a combined inhibition of HIV entry into CCR5-expressing target cells and attenuation of atherosclerotic lesion formation in HIV-infected patients treated with protease inhibitors. In terms of clinical application, this may turn out to be a more feasible strategy for HIV entry inhibition than treatment with large peptide antagonists, which do not offer the advantages of small molecule compounds or have not been evaluated for their capacity to attenuate atherosclerosis. An atheroprotective potential may also be investigated for maraviroc, a novel small molecule CCR5 antagonist, recently shown to be an efficacious short-term monotherapy reducing viral load in HIV patients in the absence of CXCR4-using virus.

In an interesting parallel to the abundance and yet specific functions of chemokine receptors involved in atherosclerosis, a wide range of 7 transmembrane coreceptors of CD4 for HIV entry has been identified among members of this family, including CCR3, CCR5, CCR8, CXCR4, and several orphan receptors. However, 2 receptors CCR5 and CXCR4 function as the primary receptors of HIV in macrophages. Interestingly, the absence of CXCR4 or the transfer of a CXCR4 antagonist has also been shown to abrogate neointimal hyperplasia after arterial injury in atherosclerosis-prone mice. Whereas the molecular mimicry of viral chemokine receptors may facilitate infected mononuclear cells to be driven into atherosclerotic lesions, the striking overlap between the functional involvement of CCR5 and CXCR4 in cell entry of distinct HIV strains and vascular lesion formation may allow for combined strategies to block HIV infection and atherosclerosis specifically tailored to the clinical context. For instance, antagonists could be selected for CCR5- versus CXCR4-using strains, and native atherosclerosis involving macrophage recruitment versus neointimal...
hyperplasia, eg, after stent implantation, involving recruitment of smooth muscle progenitor cells (Figure). This may harbor the promise to further improve the treatment of HIV patients with increased incidence of cardiovascular disease associated with the previous use of therapies including protease inhibitors or at advanced age.

References


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