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Regulation of Atherogenesis by Chemokine Receptor CCR6

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Abstract

Atherosclerosis is a complex vascular pathology characterized in part by accumulation of innate and adaptive inflammatory cells in arterial plaque. Molecular mediators responsible for inflammatory cell accumulation in plaque include specific members of the chemokine family of leukocyte chemoattractants and their G protein-coupled receptors. Studies using the *ApoE* knockout mouse model have recently implicated chemokine receptor Ccr6 and its ligand Ccl20 as a non-redundant ligand-receptor pair in atherosclerosis, potentially operating at several stages of cell recruitment and on several leukocyte subtypes.

Introduction

Atherosclerosis is an inflammatory disease of large and medium-sized arteries that leads to myocardial infarction and stroke, the leading causes of mortality worldwide (Libby et al. 2011). The earliest stage of atherosclerosis is thought to involve injury to vascular endothelium leading to endothelial dysfunction (Ross 1999, Raines and Ferri 2005). This is followed by accumulation of both innate and adaptive immune cells, including monocytes, macrophages, T cells, B cells, neutrophils and dendritic cells, in the vessel wall, where they differentiate and organize with lipids, smooth muscle cells, platelets, fibroblasts, collagen and glycosaminoglycans (GAG) to form plaque, thereby blocking blood flow to tissue (Galkina and Ley 2009).

With regard to innate immunity, the monocyte-derived macrophage is the most abundant leukocyte subtype in plaque (Weber et al. 2008), and its pathophysiologic importance in atherosclerosis is the best-understood, as shown by selective cell depletion experiments. In particular, in CD11b-diphtheria toxin receptor transgenic mice, in which monocytes and macrophages are both depleted, plaque development is markedly reduced (Stoneman et al. 2007). The importance of adaptive immunity is supported by the ability of total CD4⁺ T cell reconstitution to accelerate atherogenesis in Scid mice (Zhou et al. 2000). Moreover, specific pro-atherogenic antigens and cytokines have been identified (Robertson and Hansson 2006). Lesion progression appears to involve a balance between atherogenic Th1 cells and atheroprotective regulatory T cells (Tregs); the roles for Th2 and Th17 cells remain controversial (Robertson and Hansson 2006, Butcher and Galkina 2011). With regard to humoral immunity, B cells and antibodies to oxidized LDL (oxLDL) have been implicated

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Conflict of interest

The authors have no conflict of interest.

in plaque development. In addition, both direct and immunopathologic effects of infectious agents have also been considered as possible triggers of atherogenesis (Rosenfeld and Campbell 2011).

Given these considerations, how leukocytes traffic to the vessel wall has emerged as an important area of investigation in atherosclerosis research. Among other factors, several chemokines and chemokine receptors have been identified that appear to play important and non-redundant roles. Chemokines are members of a large family of small GAG-binding chemotactic cytokines that signal through specific G protein-coupled chemotactic receptors on the target cell surface to regulate leukocyte trafficking in both homeostasis and inflammation (Murphy et al. 2000). Chemokine receptors implicated in atherogenesis include the inflammatory receptors Ccr2, Ccr5, Cxcr2 and Cx3cr1, the classic homeostatic receptor Ccr7, and most recently Ccr6, which has both inflammatory and homeostatic functions (Koenen and Weber 2011). Like some other homeostatic chemokine receptors, and unlike inflammatory chemokine receptors, Ccr6 has a single chemokine ligand, Ccl20 (also known as macrophage inflammatory protein-3 α [MIP-3 α]) (Schutyser et al. 2003). In this article, we will focus on the role of Ccr6 in atherosclerosis. Analysis of the roles of other chemokines and chemokine receptors implicated in atherosclerosis can be found in several excellent recent reviews (Surmi and Hasty 2010, Koenen and Weber 2011, Weber and Noels 2011).

Cell Types that Express CCR6

CCR6 is expressed on various leukocyte subsets, including immature dendritic cells (iDCs), B cells, T cells (Th17 cells, Tregs), $\gamma\delta$ T cells, NKT cells and neutrophils (Schutyser et al. 2003, Ito et al. 2011). Early after its discovery, CCR6 was found to function in part as a key mediator linking iDCs to adaptive immune responses. In particular, it mediates the proper positioning of iDCs in tissue (Dieu et al. 1998). As iDCs take up antigen, mature and become activated, they downregulate CCR6 and upregulate CCR7. This 'chemokine receptor switch' unmoors the cell from tissue and enables its migration to draining lymph nodes in response to the CCR7 ligands CCL19 and CCL21 expressed on lymphatic endothelial cells (Sallusto et al. 1998, Caux et al. 2000). More recently, CCR6 has received additional attention as an important functional marker of Th17 cells, a subset of CD4⁺ helper T cells important in neutrophil recruitment during bacterial infection and in autoimmunity (Korn et al. 2009). CCR6 was originally not thought to be expressed by monocytes (Schutyser et al. 2003), however there is now substantial evidence that it is. In particular, CCL20 induces chemotaxis of human monocytes *in vitro* and the Ccl20-Ccr6 axis has been implicated in monocyte accumulation in a mouse dermatitis model *in vivo* (Ruth et al. 2003, Le Borgne et al. 2006). Further studies have shown that Ccl20 can induce chemotaxis of purified mouse monocytes *in vitro* and *ex vivo*, and intravenous injection of Ccl20 can induce peripheral blood monocytosis *in vivo* in mice (Wan et al. 2011). Although CCR6 is expressed at low levels by resting monocytes and neutrophils, its expression can be significantly upregulated by stimulation with either IFN γ or TNF α , both of which have been demonstrated to be involved in atherogenesis (Robertson and Hansson 2006). In monocytes, IFN γ treatment has been reported to increase Ccr6 expression by 6-fold at the mRNA level and 2-fold at the protein level; in neutrophils, TNF α induces high levels of CCR6 mRNA expression and there is a further 3 to 5-fold increase when the cells are simultaneously stimulated with TNF α and IFN γ (Wan et al. 2011, Yamashiro et al. 2000). Furthermore, Ccr6 is expressed at similar levels on both M1 and M2 macrophages, which have pro- and anti-inflammatory activity, respectively (Wan et al. 2011, Butcher and Galkina 2012a). Multiple other inflammatory chemokine receptors important in atherosclerosis, including Ccr2, Cx3cr1 and Ccr5, are also expressed on monocytes (Koenen and Weber 2011).

Roles of CCR6 in Immune Responses and Autoimmune Diseases

In considering how CCR6 may function in atherosclerosis, it is worth briefly reviewing its known roles in the immune response and in autoimmune diseases. In mice, genetic inactivation of *Ccr6* results in underdeveloped Peyer's patches, impaired development of M cells and increased T cell content in the intestinal mucosa. Compared with wild type controls, *Ccr6*^{-/-} mice have increased contact hypersensitivity to cutaneous antigens, diminished delayed-type-hypersensitivity, reduced responses in acute graft-versus-host disease and attenuated allergic airway inflammation (Comerford et al. 2010). CCR6 has been linked to several autoimmune diseases, including rheumatoid arthritis (RA), psoriasis, inflammatory bowel disease (IBD) and multiple sclerosis (MS). In affected joints from RA patients, CCR6 is expressed on CD4⁺ T cells from synovium and CCL20 is elevated in synovial fluid (Comerford et al. 2010). In a mouse model of RA it was found that Ccr6⁺ Th17 cells are preferentially recruited to the inflamed joints and Ccr6 antibody treatment can block this process, resulting in substantial clinical improvement (Hirota et al. 2007). Moreover, genetic polymorphism in human *CCR6* is strongly correlated with RA pathology (Stahl et al. 2010); RA is associated with accelerated atherosclerosis (Kitas and Gabriel 2011). In psoriasis, lesional skin expressed significantly higher levels of CCR6 and CCL20 compared with non-lesional skin (Hedrick et al. 2010). In an IL-23 injection model of psoriasis, *Ccr6*^{-/-} mice failed to develop psoriasiform lesions because of failure to recruit CD4⁺ T cells and CD11c⁺CD11b⁺ dendritic cells into the inflammatory sites (Hedrick et al. 2009). In patients with IBD, CCR6⁺ T cells, B cells and iDCs are increased in the lamina propria; in corresponding mouse models both *Ccr6* deficiency and *Ccl20* neutralization reduced colitis, either through altered cytokine balance in the intestine or through inhibition of the recruitment of T and B cells to the gut (Comerford et al. 2010). In MS patients, leukocytes have increased expression of CCL20 and T cells from the cerebrospinal fluid express CCR6. However, studies from different groups using the animal model of MS, experimental autoimmune encephalomyelitis (EAE), have generated contradictory results: EAE has been reported to be inhibited in mice treated with Ccr6 antagonists or *Ccl20* neutralizing antibodies, whereas *Ccr6*^{-/-} mice have been reported to be resistant to EAE in one study but more sensitive in another (Yamazaki et al. 2008, Comerford et al. 2010).

Role of CCR6 in Atherogenesis

In humans, both CCR6 and CCL20 are expressed in atherosclerotic carotid and coronary plaques at increased levels compared with non-atherosclerotic coronary arteries. Also, the circulating level of CCL20 is significantly increased in hypercholesterolemic subjects and the level of CCL20 is much higher in secretomes from atheromatous aorta than from healthy aorta (Yilmaz et al. 2007, Calvayrac et al. 2011). In mice, *Ccr6* and *Ccl20* are also present constitutively in healthy aorta and in atherosclerotic plaque (Wan et al. 2011).

The first evidence that the *Ccl20*-*Ccr6* axis might be functionally important in atherogenesis emerged from experiments in which *Ccr6*^{-/-}*ApoE*^{-/-} mice fed a proatherogenic Western diet were observed to have a 40% reduction in total aortic atherosclerotic lesion area, including the aortic root, compared to *Ccr6*^{+/+}*ApoE*^{-/-} mice (Wan et al. 2011). This is quantitatively comparable to mice deficient in *Ccr2*, *Cx3cr1* and *Ccr5* in the same model. Importantly, the results were obtained using a large number of littermates, minimizing any contribution of environment to the differences found. Further, transplantation of bone marrow from *Ccr6*^{-/-} mice, but not from wild type mice, into *ApoE*^{-/-} mice led to a similar reduction of atherosclerotic lesion burden to levels observed in *Ccr6*^{-/-}*ApoE*^{-/-} mice, suggesting that the pro-atherogenic Ccr6-positive cell type originates in bone marrow.

Histopathologic analysis revealed that resistance to atherosclerosis in *Ccr6*^{-/-}*ApoE*^{-/-} mice was associated with markedly reduced macrophage content in the lesions (Wan et al. 2011).

Moreover, in *Ccr6*^{-/-}*ApoE*^{-/-} mice the absolute total monocyte count in the blood is reduced by approximately 30% compared to control *Ccr6*^{+/+}*ApoE*^{-/-} mice, due to selective reduction of inflammatory Ly6C^{hi} monocytes. This is accompanied by a reciprocal increase of Ly6C^{hi} monocytes in the bone marrow, suggesting that Ccr6 mediates release of inflammatory monocytes from the bone marrow into the blood. The levels of all other leukocyte subsets measured in blood were the same for *Ccr6*^{-/-}*ApoE*^{-/-} and *Ccr6*^{+/+}*ApoE*^{-/-} mice. Moreover, Ccl20 can induce *in vitro* chemotaxis of monocytes from wild type but not from Ccr6 knockout mice, and Ccl20 injection *in vivo* induced monocytosis. Together, these results suggest that Ccr6 modulation of atherosclerosis may at least in part due to Ccr6 function on monocytes, mediating their mobilization into the blood and recruitment into the vessel wall (Figure 1).

There is ample precedent for chemokine control of leukocyte egress from bone marrow. For example, gain-of-function mutations in the chemokine receptor CXCR4 cause WHIM syndrome, a severe combined immunodeficiency disorder of humans characterized in part by myelokathesis, a form of neutropenia that is due to failure of bone marrow release of neutrophils (McDermott et al. 2011). In this regard, it is relevant in future studies to measure Ccl20 levels in bone marrow from *Ccr6*^{-/-}*ApoE*^{-/-} and *Ccr6*^{+/+}*ApoE*^{-/-} mice. CCL20 is expressed mainly by epithelial cells, endothelial cells and keratinocytes, however recent studies have shown that vascular smooth muscle cells, macrophages and Th17 cells can also produce it (Schutyser et al. 2003, Yamazaki et al. 2008, Calvayrac et al. 2011). Interestingly, expression of Ccl20 in the aorta of *Ccr6*^{-/-}*ApoE*^{-/-} mice was reduced by ~80% compared with *Ccr6*^{+/+}*ApoE*^{-/-} mice, whereas serum levels of Ccl20 were similar, suggesting that Ccr6 and Ccl20 may form a local positive feedback loop in the vessel wall (Wan et al. 2011). Stimulation of endothelial cells with the pro-inflammatory cytokines TNF α or IFN γ was able to induce endothelial cell Ccl20 expression *in vitro*. This could promote attraction of circulating Ccr6⁺ monocytes into the subendothelial space where they differentiate into macrophages. Macrophages in this location secrete Ccl20 as well as TNF α , which could further amplify expression of Ccl20 by endothelial cells and promote additional recruitment of inflammatory monocytes into the lesions (Figure 1). This is reminiscent of what has been described for Th17 cells, which are uniformly CCR6 positive and also secrete CCL20, thus forming a positive feedback loop poised to recruit more Th17 cells to an inflammatory site (Yamazaki et al. 2008).

In addition to monocytes, the possible involvement of other Ccr6⁺ leukocyte subsets in atherogenesis must also be considered in the model, including B cells, Th17 cells, neutrophils, dendritic cells, and NKT cells, particularly since depletion of any of these cell types also results in reduced atherogenesis (Weber et al. 2008, Libby et al. 2011). In this regard, a recent paper by Doran et al has addressed the selective role of Ccr6 on B cells in atherogenesis, but obtained results apparently opposite to those of Wan et al described above. In particular, on a normal Chow diet *Ccr6*^{-/-}*ApoE*^{+/+} mice have fewer aortic B cells than *Ccr6*^{+/+}*ApoE*^{+/+} mice, and adoptive transfer of *Ccr6*^{+/+}*ApoE*^{-/-} B cells but not *Ccr6*^{-/-}*ApoE*^{-/-} B cells into μ MT *ApoE*^{-/-} mice (which lack only B cells) on a pro-atherogenic Western diet significantly reduced atherogenesis (Doran et al. 2012). This suggests that Ccr6 is involved in B cell homing to the aorta and B cell-mediated atheroprotection. At the moment, there is no clear experimental reconciliation of the discordant results of the two studies. It is possible simply that Ccr6 plays counterbalancing cell type-specific roles in atherogenesis. However, since mice globally deficient in Ccr6 have reduced atherosclerosis, the phenotypic manifestation of non-B cell Ccr6 deficiency appears to be dominant over B cell-specific Ccr6 deficiency (Wan et al. 2011). Alternatively, since Doran et al transferred a very large number (60×10^6) of Ccr6-deficient or Ccr6-sufficient B cells into B cell deficient μ MT *ApoE*^{-/-} mice, in which Ccr6 was expressed normally on other leukocyte subsets, the apparent protective effect of B cell Ccr6

could be a function of this large cell dose. In addition, since B1 and B2 cells have opposite function in atherogenesis (Kyaw et al 2011), it would be necessary to clarify whether Ccr6 deficiency have altered B cell subtype profile in circulation and how Ccr6-deficient B1 and B2 cells would differently affect atherogenesis.

Th17 cells, a subset of CD4⁺ T cells characterized by the secretion of IL-17A, is another candidate in Ccr6-mediated atherogenesis since CCR6 is expressed on all human Th17 cells and Th17 cells have been found within both mouse and human atherosclerotic plaque (Korn et al 2009, Butcher et al. 2012b). Patients with coronary artery disease have much higher plasma IL-17A levels than healthy controls and the expression of IL-17A in atherosclerotic lesions is also significantly upregulated (Butcher and Galkina, 2011). However, direct experimental tests of the role of Th17 cells or IL-17A in atherogenesis have yielded conflicting results. Blockade of IL-17A *in vivo* by either an adenoviral IL-17RA-construct or by specific antibodies has been reported to inhibit atherogenesis, suggesting IL-17A is proatherogenic; however, *in vivo* administration of IL-17A also reduced atherosclerotic plaque development, indicating that exogenous IL-17A can be atheroprotective (Butcher and Galkina, 2011). Studies with IL-17A-deficient mice also have generated inconsistent results, with one group reporting no difference in plaque burden between *Il17a^{+/+}ApoE^{-/-}* and *Il17a^{-/-}ApoE^{-/-}* mice, a second group reporting that atherosclerosis was significantly increased in *Il17a^{-/-}ApoE^{-/-}* mice compared with *Il17a^{+/+}ApoE^{-/-}* mice, and a third group showing that both deficiency of IL-17A and IL-17RA reduced atherosclerosis in *ApoE^{-/-}* mice (Madhur et al. 2011, Danzaki et al. 2012, Butcher et al. 2012b). Clearly, more studies are needed to clarify the role of IL-17A and Th17 cells in atherosclerosis and in Ccr6-mediated atherogenesis.

Conclusions

This review of recent literature suggests that Ccr6 can be added to the list of chemokine receptors that function as non-redundant mediators of atherogenesis in the *ApoE* knockout mouse model. This list includes both classic inflammatory (Ccr2, Ccr5, Cx3cr1) and classic homeostatic (Ccr7, Cxcr4) chemokine receptors; Ccr6 behaves as a 'dual function' receptor, subserving both inflammatory and homeostatic processes, despite having only one ligand (typical of homeostatic receptors). The relevant Ccr6⁺ cell type appears to be hematopoietic in origin, however its precise identity remains undefined. The evidence for the monocyte/macrophage is indirect whereas the evidence for the B cell is targeted but limited to an adoptive transfer study. With these caveats, the existing data suggest that Ccr6 may mediate both pro-atherogenic (monocyte/macrophage) and atheroprotective (B cell) effects, depending on the cell type. Precise delineation of relevant Ccr6⁺ cell type(s) in the model and their functions will require creation of mice in which Ccr6 is targeted in a cell type-specific manner or adoptive transfer of sorted cell populations stratified by Ccr6 expression. Additional candidates include Th17 cells, Tregs, DCs, neutrophils and NKT cells. The effect of Ccr6 deficiency is quantitatively large in the model, as compared to other immunoregulatory factors previously tested, including other chemokine receptors. The current work on Ccr6 justifies further basic and translational research on its potential roles in diverse forms of vascular disease, including transplant vasculopathy, recurrent plaque growth after balloon angioplasty, vasculitic syndromes, and aneurysms, as well as the suitability of this receptor as a therapeutic target in man.

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Figure 1. A model for the regulation of atherogenesis by Ccr6

Ccr6 controls the release of inflammatory monocytes from the bone marrow into the circulating blood and then their recruitment into atherosclerotic plaque by interacting with its chemokine ligand Ccl20. During atherogenesis, endothelial dysfunction may result in a local increase of Ccl20, which can direct the migration of Ccr6⁺ circulating monocytes into the subendothelial space. Monocyte-derived macrophages are sources of inflammatory cytokines such as TNF α , which can induce endothelial cells to express Ccl20. Also, macrophages themselves are producers of Ccl20. Together, Ccl20 levels increase locally at the vessel wall, attracting more circulating monocytes into plaque, thus promoting atherosclerosis through a positive feedback loop.