Cytokine Receptor CX3CR-1 and Fractalkine
New Factors in the Atherosclerosis Drama?

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Atherosclerosis is a chronic inflammatory disease of the blood vessel wall that is characterized by the accumulation of mononuclear cells, which are transformed into tissue macrophages/foam cells, and of T cells. The general acceptance of this concept began in the late 1980s and was soon followed by attempts to understand the mechanisms by which the leukocytes were attracted into the arterial wall. A general understanding previously had been achieved, in other inflammatory contexts, of the mechanisms of leukocyte-endothelial interactions in the form of rolling, adhesion, and migration from the blood compartment through the endothelium as a result of the actions of selectins, adhesion molecules, and chemotactic cytokines called chemokines. Chemokines act through a specific family of receptors on leukocytes and other cells to achieve high-affinity binding sites for counter receptors/adhesion molecules on endothelium. They also have potent chemoattractant activity-guiding leukocyte migration through tissues.

Chemokines constitute a large number of structurally related proteins that have been classified into families based on relative positions of cysteine (C) residues. A prototype chemokine is monocyte chemoattractant protein-1 (MCP-1), which has been associated with the pathogenesis of atherosclerosis as discussed below. MCP-1, for example, belongs to the C-C family with adjacent cysteine residues. Fractalkine is a novel, recently discovered chemokine that belongs to the CXXXC (CX3C) family (X represents any amino acid). It exists in a membrane-bound form at the tip of a mucin-like stalk as well as in a soluble form. Fractalkine is particularly interesting for its potential as being pathophysiologically important in atherosclerosis. It not only is a potent chemotactic factor for both monocytes and T cells but also induces firm adhesion of these leukocytes to cells expressing its membrane-bound form. This high-affinity adhesion is mediated, uniquely, by direct binding of fractalkine to its receptor on mononuclear and T cells. Furthermore, fractalkine is robustly expressed at the surface of cytokine-activated (dysfunctional) human endothelial cells.

Chemokines modulate cell adhesion and migration by interacting with members of a family of G protein-coupled receptors, the chemokine receptors (CRs). There are multiple CRs that have some specificity for binding to the chemokines within a specific protein family. The fractalkine receptor is CX3CR1.

Gene polymorphisms at amino acids 249 and 280 of CX3CR1 in humans were reported previously. Amino acid 249 may be either isoleucine (I) or valine (V). Recently, in a group of patients with acute coronary syndromes, homozygosity for V249 CX3CR was associated with increased risk for acute coronary events in comparison to I249 heterozygotes. In this issue of Circulation Research, McDermott et al report the results of a study in which they evaluated the relationships among CX3CR genotypes and the presence of coronary artery disease and the status of endothelial-dependent microvascular dilation in a group of patients undergoing cardiac catheterization. Both the prevalence and severity of coronary artery disease were less in the group that was homozygous for the I249 allele compared with the group that was homozygous for V249. Moreover, endothelial-dependent vasodilator function (as assessed by determining the change in coronary vascular resistance in response to acetylcholine infusion) was also better in the I249 heterozygotes. Endothelial-independent microvascular dilation was similar between the groups. Thus, there is consistency in regard to the apparent protection offered by the presence of the I249 allele in distinct clinical manifestations of coronary artery disease in two separate studies. The mechanisms for the salutary effects are unclear.

Evidence that cytokines are involved in the pathogenesis of atherosclerosis is compelling. Numerous cytokines including MCP-1 have been consistently identified in human lesions, although causality cannot necessarily be inferred. More direct evidence has been obtained from genetic studies in mice. Breeding hypercholesterolemic transgenic or knockout animals with mice in which the gene for certain cytokines or cytokine receptors has been deleted or serve the apparent protection offered by the presence of the I249 allele in distinct clinical manifestations of coronary artery disease. Additional data are obviously needed.

The microvascular endothelial dysfunction that was observed in the patients without the I249 CX3CR-1 polymorphism raises some issues that should be considered. Specifically, what, if any, are the fractalkine/CX3CR-1-dependent interactions of monocytes or T cells with the endothelium of the resistance vasculature and what are the consequences for intracellular signaling in this tissue? Are
there fractalkine/CX3CR effects on the endothelium that are not dependent on leukocyte-endothelial interactions? Additional points are relevant in considering the questions. First, the fractalkine expression in the rat heart endothelium is robustly induced by lipopolysaccharide or cytokines. Sec-
ond, the CX3CR-1 I249 allele is functionally significant and is associated with decreased expression of CX3CR on peripheral blood monocytes and with decreased fractalkine binding.7 Finally, atherosclerosis is not a disease of the microvas-
culature. The endothelial dysfunction in this area associated with the presence of coronary risk factors is not a conse-
quence of the infiltration of leukocytes into the vessel wall. It is caused by the same mechanical or metabolic stresses that result in vasomotor abnormalities and leukocyte recruitment very early in the course of the disease in large arteries. Understanding the underlying mechanisms for this functional abnormality is critically important.

The dysfunction of the endothelium that is necessary but probably not sufficient for the development of atherosclerosis is thought to be a consequence of the presence of excessive intracellular levels of reactive oxygen species (ROS). Many proinflammatory and growth signaling pathways are redox-sensitive and are inactive in a reducing environment. Moreover, ROS can inactivate nitric oxide—one of the most important antioxidant, antiinflammatory vasodilator mole-
cules in the endothelial and other cell types. There is little information available that permits evaluating the roles of fractalkine and CX3CR in the context of this general model.

What are the cellular and metabolic consequences for the cardiovascular system of increased activity of the fractalkine-
CX3CR system? Will the presence of the homozygous state for the V249 allele of CX3CR-1 come to be viewed as a standard cardiovascular risk factor? The tools and general knowledge that are necessary to approach these issues appear to be available. McDermott et al8 have provided a provocative stimulus to proceed. The results may provide new conceptual, diagnostic, and therapeutic approaches to vascular diseases.

References
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