Chemokines and atherosclerosis: what Adam Smith has to say about vascular disease

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Chemokines and atherosclerosis

One of the clearest examples of the essential role of chemokines in pathobiology involves atherosclerosis. In broad strokes, the inflammatory model of atherogenesis (2) suggests that insults to endothelial or smooth muscle cells, such as hypercholesterolemia or flow shear stress, stimulate the production of leukocyte chemoattractants that are both displayed on the luminal surface of endothelial cells and also secreted into the subendothelium. When these factors activate their receptors on rolling leukocytes, this induces firm integrin-dependent adhesion to the endothelium, followed by diapedesis into the subendothelium. Among the most important of the migrating cells in this model are monocytes, which differentiate in situ into macrophages and take up cholesterol to become the foam cells of the fatty streak. The target cell specificity of the aptly named monocyte chemoattractant protein-1 (MCP-1) makes this chemokine a superb candidate for the signal that brings circulating monocytes into the vessel wall; MCP-1 attracts monocytes but not neutrophils, and it stimulates the adhesion of monocytes to endothelial cells (3). Mice rendered genetically deficient for MCP-1 or its receptor, CCR2, are protected from atherosclerosis (4–7).

Another ELR-containing CXC chemokine, GRO-α, similarly enhances adhesion to stimulated endothelial cells (13). More recently, Gerszten et al. elegantly demonstrated IL-8’s ability to induce firm arrest of monocytes on endothelial cells under conditions of physiological flow (14). These results strongly suggest that CXCR2 and one or more of its ligands play a role in atherosclerosis. Even so, according to the
Chemokine receptors divide the labor of inflammatory infiltration. A monocyte engaged in selectin-mediated rolling on vascular endothelial cells is depicted as expressing CXCR2 (red) and CCR2 (green). First, interaction of CXCR2 with its ligand IL-8 (red dots attached to glycosaminoglycans [GAG]) leads to up-regulation of α5β1 integrin affinity and firm adhesion. Then, interaction of CCR2 with its ligand MCP-1 (green dots attached to GAG) leads to migratory behavior i.e., diapedesis and entry into the subendothelium. Here, chemokines are shown as being presented to cells in the vascular lumen in the context of endothelial cell surface GAGs.

Specialization and the profusion of chemokines

Besides demonstrating that CXCR2 can be a therapeutic target in atherosclerosis, these results also have important biological implications. One of the enduring puzzles in the chemokine field is the large number of ligands and receptors that seem to have overlapping functions. On the ligand side, there are a dozen chemokines that attract neutrophils, another dozen that attract monocytes, and another dozen that attract T cells. On the receptor side, a single cell can express several chemokine receptors. Why should that be the case if a chemokine receptor is simply needed to get a cell from here to there? It appears now that these homologous proteins have different functions. We have known for some time that ELR-containing CXC chemokines that bind to CXCR2 with similar affinities actually elicit different responses from neutrophils (11, 19). For example, some are more efficient chemoattrac-
tants while others are more efficient inducers of the respiratory burst.

The data from Huo et al. (15) suggest that an analogous division of labor may exist among receptors. Perhaps monocytes require both CXCR2 and CCR2 because the former is more efficiently connected to the adhesion apparatus while the latter communicates more effectively with transmigration machinery. Rather than try to make one receptor do both things, nature has taken a page from The Wealth of Nations in order to increase the efficiency of inflammatory cell infiltration. In the case of atherosclerosis, of course, efficiency is not to be celebrated since it only enhances disease progression. However, the primary function of these cells is to protect us from foreign invaders, and in this context efficient responses should confer a great selective advantage. It will be interesting to see if, in other cases, the specialization of chemokines and chemokine receptors does indeed enhance the opulence of host protection.


