ATTRACTING OF IMMUNE CELLS TO THE VESSEL WALL

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Macrophages are major players in inflammation and innate (i.e., antigen-independent) immune responses. These actions largely depend on their capacity to produce free oxygen radicals, proteases, complement factors, and cytokines. Importantly, the macrophage may also initiate adaptive immune responses by presenting foreign antigens to T-cells. All these activities may be important in atherogenesis. The differentiation from monocyte to macrophage is governed by macrophage colony stimulating factor (M-CSF), a cytokine that is produced not only by macrophages but also by vascular and stromal cells. Lack of M-CSF prevents macrophage differentiation, the consequences of which can be observed in many different organs. Macrophage uptake of modified lipoproteins by way of scavenger receptors is tightly regulated by cytokines.

During the initiation of atherosclerosis, mononuclear leukocytes - monocytes and T-cells, are recruited to the vessel wall across an intact endothelium. This requires activation of the endothelium to express leukocyte adhesion molecules. These cell surface proteins are mainly regulated transcriptionally in a process that involves nuclear factor (NF)-κB, a transcription factor that is transactivated when proinflammatory cytokines ligate their receptors on the endothelial surface. Both E-selectin and 2 imunoglobulin-like adhesion molecules, intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1), can be induced in this way.

VCAM-1 can be induced not only on cytokine stimulation but also in response to other proinflammatory macromolecules. Lipopolysaccharides of Gram-negative bacteria activate NF-κB by ligating toll-like receptors (TLRs), which transduce NF-κB activation through a kinase cascade similar to the one initiated by interleukin-1 (IL-1). In addition, lysophosphatidylcholine and other oxidized phospholipids can induce VCAM-1 expression in endothelial cells. Interestingly, such phospholipid species are generated during lipoprotein oxidation. Their activity may explain the increased adhesive properties of endothelial cells exposed to oxidized LDL (oxLDL). In vivo studies have shown that hypercholesterolemia rapidly leads not only to lipoprotein deposition and oxidation in the intima but also to VCAM-1 expression on the luminal aortic endothelium. This provides a direct link between hypercholesterolemia and inflammatory activation of the vessel wall.

ICAM-1 is induced in endothelial cells through a cytokine-dependent pathway, but its expression is also promoted by hemodynamic stress. The latter seems to be due to activation of the shear stress response element in its promoter. This probably explains the finding of ICAM-1 expression in aortic regions where the endothelium is exposed to variations in shear stress caused by blood flow. It is likely that the disturbed flow encountered during hypertension can increase

ICAM-1 expression. Thus, both hypercholesterolemia and hypertension, 2 major risk factors for atherosclerosis, increase the recruitment of leukocytes to the artery.

Adhesion is a multistep process that starts with leukocyte rolling on the endothelial surface. This is due to selectin ligation, whereas the subsequent firm adhesion depends on interactions between immunoglobulin-like molecules (VCAM-1, ICAM-1, and others) on the endothelium and integrins on the leukocyte surface. Very late-activation antigen-4, a major counter receptor for VCAM-1, is expressed by monocytes and lymphocytes but not by granulocytes. This explains the selective recruitment of mononuclear cells to the arterial intima during early atherosclerosis. Immunopharmacological blockade of ICAM-1 and VCAM-1 has been shown to inhibit fatty streak development. In the classic inflammatory response, adhesion is followed by transmigration of the leukocytes through the endothelial layer and into the intima. This is governed by chemotactic factors produced in the subendothelial layer. Several studies of hypercholesterolemic rabbits and human samples show that the complement cascade is activated subendothelially during hypercholesterolemia. This leads to release of small, proteolytic peptide fragments of complement proteins. Such fragments include C5a, which is strongly chemotactic for monocytes and may be important for the recruitment of these cells to the intima.

Several chemotactic cytokines called chemokines are produced by endothelial cells and intimal macrophages during lesion formation. The best-characterized of these chemokines is monocyte chemotactic protein-1 (MCP-1), which can be induced by complement activation or cytokines and promotes recruitment of monocytes and T cells. MCP-1 is expressed in significant amounts in all stages of atherosclerosis. This demonstrates that chemokine-dependent migration of mononuclear cells into the intima is an important phenomenon in atherogenesis.