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ATHEROSCLEROSIS AND THE PATHOGENESIS OF PLAQUE FORMATION

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Our current understanding of the vascular biology of atherogenesis suggests a pathophysiology that is much more complex than mere lipid storage. The early events in atherosclerosis are triggered by the presence of high levels of atherogenic lipoproteins in the plasma and are mediated by inflammatory factors. The common risk factors for atherosclerosis increase production of reactive oxygen species (ROS) by endothelial, vascular smooth muscle and adventitial cells. ROS initiate processes such as atherogenic lipoprotein oxidation. Oxidized low-density lipoprotein (LDL), remnant lipoprotein (beta-VLDL) and Lp(a) play a critical role in the pro-inflammatory reaction, whereas high-density lipoprotein (HDL), anti-atherogenic lipoproteins, exert anti-inflammatory functions. Endothelial dysfunction is a systemic disorder and a key variable in the pathogenesis of atherosclerosis and its complications. The earliest event in the arterial wall during atherogenesis is the expression of adhesion molecules on the surface of vascular endothelial cells: selectins, VCAM-1... Once adherent, the leukocytes enter the artery wall directed by chemoattractant chemokines such as MCP-1. Oxidized phospholipids, present in oxidized-LDL, have been shown to play a major role in the binding of oxidized-LDL to CD36 and to SR-B1 expressed in macrophages. The lipid and protein moieties of apo B compete to induce the uptake of oxidized-LDL by CD36 and by SR-B1 in macrophages, and their transformation into foam cells. Progression of atheroma involves accumulation of smooth muscle cells that elaborate extracellular matrix macromolecules. The clinically important complications of atheroma usually involve thrombosis. Thrombus formation usually occurs because of a physical disruption of atherosclerotic plaque, resulting from a rupture of the plaque's protective fibrous cap, which permits contact between blood and the highly thrombogenic material located in the lesion's lipid core, such as tissue factor. Interstitial collagen accounts for most of the

tensile strength of the plaque's fibrous cap. The amount of collagen in the lesion's fibrous cap depends upon its rate of biosynthesis stimulated by factors released from platelets (for example, transforming growth factor beta or platelet-derived growth factor), but inhibited by gamma interferon, a product of activated T cells. Degradation by matrix metalloproteinases also influences the level of collagen in the plaque's fibrous cap. Statins and fibrates decrease the risk of plaque disruption.

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