

Atherothrombosis

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Previously, many viewed atherosclerosis as a bland deposit of lipid trapped in a maze of smooth muscle cells and extracellular matrix. Multiple lines of evidence now point to inflammation as central to all stages of atherosclerosis including plaque development, disruption, and thrombosis. Atherogenesis begins with activation of the endothelium, as shown by surface expression of adhesion molecules that capture blood leukocytes.

Many risk factors augment the expression of pro-inflammatory cytokines by cells involved in atherogenesis. Chemoattractant cytokines promote migration of monocytes into the arterial intima and mature into macrophages when stimulated by other cytokines. These phagocytic cells drive many aspects of subsequent atherosclerotic progression, and also contribute to the propensity of plaques to rupture by production of proteases that weaken the fibrous plaque cap, and to thrombosis by production of tissue factor. Such inflammatory processes provide targets for molecular imaging of atherosclerosis under intense evaluation for application to patients.

Thrombosis provoked by disrupted atheromatous plaques causes most acute coronary events. A disruption of the physical integrity of the collagenous extracellular matrix of the fibrous cap overlying the atheroma's thrombogenic lipid core causes most fatal coronary thrombi. Inflammation critically regulates the stability of human atherosclerotic plaques. Inflammatory cytokines can elicit the expression by macrophages and smooth muscle cells of enzymes that can weaken the extracellular matrix among them, the matrix metalloproteinases (MMPs) and certain cysteinyl elastases that belong to the cathepsin family. In particular MMP interstitial collagenases can attack the usually protease-resistant interstitial collagen molecule that confers most of the biomechanical strength on the plaque's protective fibrous cap. Experiments in genetically-altered mice have proven the importance in vivo of MMP collagenases in determining the plaque's content of collagen, as well as the organization and architecture of the lesion's collagen. Inflammation regulates both the synthesis of collagen and the enzymes involved in its degradation. Lipid-lowering can reduce inflammation, and collagenase expression, and increase collagen content of experimental atheromata. Inflammation also augments fibrinogen levels, and boosts production of the major inhibitor of fibrinolysis, plasminogen activator inhibitor-1. Thus inflammation not only affects the "solid state" of the plaque, but also the "fluid phase" of the blood in a way that not only favors coagulation, but at the same time defeats our endogenous fibrinolytic defenses. Indeed, increasing evidence supports an inextricable intertwining of inflammation and thrombosis.

We can now begin to understand the molecular basis of atherothrombosis, and how dysregulation of inflammation controls clinical manifestations of atherosclerotic plaques. Blood biomarkers of the inflammatory response strongly correlate with outcomes in individuals with or without known atherosclerotic disease. Thus, the growing recognition of the importance of inflammation in atherosclerosis has both theoretical and practical clinical implications. Inflammation in atherosclerosis has now transitioned from being a theory to a practical clinical tool for risk prediction and guiding therapy. The

mastery of the biology of inflammation during atherogenesis – its triggers and effectors – opens new opportunities for the development and evaluation of novel therapeutic interventions.