

Atherothrombosis and Plaque Rupture

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Thrombosis provoked by disrupted atheromatous plaques causes most acute coronary events. Fragility of the collagenous extracellular matrix of the plaque's fibrous cap predisposes to fatal coronary thrombi. Inflammation critically regulates the stability of atherosclerotic plaques. Inflammatory cytokines can elicit the expression of enzymes that can weaken the extracellular matrix, among them the matrix metalloproteinases (MMPs) and certain cysteinyl elastases. MMP interstitial collagenases can attack the interstitial collagen triple helix that confers most of the biomechanical strength on the plaque's fibrous cap.

Our laboratory described the over-expression of three interstitial collagenases in the atheroma, MMPs 1, 8, and 13. Our recent work in genetically-altered mice has 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. Mice that express a form of interstitial collagen resistant to MMP collagenases accumulate more collagen in their plaques than do wild-type mice. Mice deficient in MMP 13 also show increased collagen accumulation. MMP-14 deficiency in bone-marrow derived cells increases collagen content in plaques, probably in part by limiting activation of pro-MMP13 to the active form. Thus, MMPs regulated by inflammation can control a crucial component of atheroma stability. Molecular imaging strategies may permit the visualization of MMP and cathepsin activity in plaques.

Lipid-lowering can reduce inflammation and collagenase expression, and increase collagen content of experimental atheromata. These data provide mechanistic insight into how lipid-lowering therapies can render plaques less likely to rupture. Macrophages within the plaque characteristically overexpress tissue factor procoagulant, the trigger to thrombosis of disrupted plaques. Inflammatory mediators, notably CD40 ligand (CD154) can elicit tissue factor expression by human macrophages. Lipid-lowering limits tissue factor protein and activity in rabbit atheromata. We can now begin to understand the molecular basis of coronary thrombosis, and how therapeutic interventions can limit inflammation and reinforce the stability and reduce the thrombogenicity of atherosclerotic plaques.