Cells found in atherosclerotic plaques express matrix metalloproteinases (MMPs). Human atheromata contain a broad array of proteases (Table 1) and their endogenous inhibitors. Altered balance between proteinases and their inhibitors may participate in a number of biological processes important in the clinical manifestations of atherosclerosis. For example, matrix remodeling must occur during compensatory enlargement, arterial aneurysm formation, angiogenesis, desquamation of endothelial cells that accompanies superficial erosion, and the weakening of the atherosclerotic plaque’s fibrous cap that presumably renders it prone to rupture and hence thrombosis.

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In this issue of *Arteriosclerosis, Thrombosis, and Vascular Biology*, Choudhary et al confirm the presence of MMP gelatinases and highlight the heterogeneity of MMP distribution in human carotid endarterectomy specimens. They show differential expression of 2 prototypical MMP gelatinases, MMP-2 and -9. Many normal carotid segments contain more MMP-2 than MMP-9. More complex lesions tended to have more MMP-9 than MMP-2. As normal arteries contain substantial medial pro–MMP-2 (the inactive zymogen form; Figure), this finding is expected. Likewise, MMP-9 overexpression in human plaques generally localizes to macrophages, explaining why the more advanced lesions may have disclosed higher levels of this MMP. The sophisticated analysis presented by Choudhary et al may then reflect the cellular content of lesions of different types and in different regions within a given endarterectomy specimen, an issue not addressed in their study.

Whereas gelatinases participate in the latter steps in the degradation of interstitial collagen (the major contributor to the mechanical strength of the fibrous cap of the plaque), the initial and rate-limiting proteolytic attack on collagens I and III requires the action of interstitial collagenases, eg, MMPs 1, 8, and 13—enzymes also overexpressed in human atheromata. Indeed, strong evidence from genetically-altered mice indicates a key role for MMP collagenases in the economy of collagen in the atherosclerotic plaque. Furthermore, non-metalloproteases may participate in regulating aspects of atherogenesis and plaque stability. Non-metallo enzymes implicated in atherogenesis include the cysteinyl elastases (eg, cathepsin S) and serine proteinases (eg, urokinase type plasminogen activator, neutrophil elastase). This plethora of proteinases operating during atherosclerosis presents a daunting palette of targets for therapy, a perplexity compounded by the heterogeneity of protein localization in different plaques and in regions of a given atherosclerotic lesion (Table 1). This multiplicity of enzymes and heterogeneity of expression presents a challenge to the use of MMP inhibitors in the therapy of atherosclerosis (Table 2). The regional dispersion of proteinases in plaques highlights the potential confounding of selective sampling in studies that monitor MMP levels in plaques to gauge therapy. Perhaps more global in vivo assessment of gelatinases or other proteinase activities in atheromata would identify individuals...
with particularly high local levels of proteinase activity and obviate the issue of selective sampling inherent in studies of lesions removed at endarterectomy.11

Ultimately the use of specific proteinase inhibitors to mitigate atherosclerosis and its complications may prove quixotic. Broad spectrum MMP inhibitors have proven too toxic for clinical use. We urgently require much more information regarding which proteinases predominate in the biology of atherosclerosis to guide us to narrower targets. The important difference in the spectrum of MMPs used by mice and humans vitiates the uncritical extrapolation of results obtained in mice to people. Even if we knew the “when” and “which” of proteinases, the most practical and effective manner of reducing proteolytic activities in plaques might not involve direct enzyme inhibitors, rather a more proximal intervention. A broad body of evidence indicates that inflammation regulates protease balance in plaques (Figure). Risk factors associated with atherosclerosis can elicit the expression of proinflammatory cytokines that in turn regulate the levels of a number of proteinases implicated in atherosclerotic plaque biology. Experimental interventions to limit risk factors (eg, decreasing cholesterol levels by either diet or statin treatment) can decrease proteinase activity in vivo.12,13

Today, the most practical approach to limiting the activity of proteinases and their consequent mischievous actions in atheromata would be to reduce the burden of risk factors with accepted and evidence-based strategies. The mechanism by which many of our therapies proven to reduce thrombotic complications of atherosclerosis produce their benefit may indeed result from quelling inflammation and the downstream effector mechanisms of the inflammatory response including MMPs and other proteinases. Thus, while we await a more complete elucidation of the biology of proteinases in human atherogenesis, we can likely effect patient outcomes today by a more concerted effort at controlling risk factors with established measures.

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None.

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Perplexity of Plaque Proteinases
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