Matrix Metalloproteinase Hypothesis of Plaque Rupture
Players Keep Piling Up But Questions Remain
Prediman K. Shah, MD; Zorina S. Galis, PhD

A rtial thrombosis is generally recognized as the proximate event responsible for most acute ischemic syndromes resulting from atherosclerotic vascular disease.1,2 The majority of such thrombi (60% to 80%) occur at sites of fissure or rupture of a thinned fibrous cap overlying a lipid-rich atherosclerotic lesion with intimal and adventitial inflammation, and the remainder occur over areas of superficial plaque erosion.1–5 The severity of luminal stenosis produced by such lesions before plaque rupture is frequently only mild or moderate, although the plaques tend to be large, and this seeming paradox is mostly because of the outward remodeling of the vessel wall.1,6,7

The precise mechanism(s) responsible for plaque rupture remain to be defined; however, the excessive degradation of the extracellular matrix scaffold has been implicated as one of the major molecular mechanisms in this process. A likely culprit is a family of matrix-degrading metalloproteinases (MMPs) expressed in human atherosclerotic lesions around the lipid core; they generally colocalize with macrophages/foam cells and, to a lesser extent, with smooth muscle cells and endothelial cells.8–11 Further suggesting a role for macrophage MMPs is their association with evidence of collagen breakdown in vitro and in vivo.9,12,13 Increased MMP expression in the cells resident in atherosclerotic plaques has been attributed to lipid ingestion, stimulation by oxidized LDL, cytokines, hemodynamic stress, ligation of CD-40, infection, and increased expression of Tenascin-c.14–21 The MMP family of enzymes includes collagensases (MMP-1 or interstitial collagenase, MMP-8 or neutrophil collagenase, and MMP-13 or collagenase 3), gelatinases (MMP-2 or gelatinase A and MMP-9 or gelatinase B), stromelysins (MMP-3, MMP-10, and MMP-11), membrane-bound MMPs (MT-MMPs 1 through 4) matrilysin (MMP-7), and metalloelastase (MMP-12).

In the present issue of Circulation, Herman et al22 report that MMP-8, also known as the neutrophil collagenase, is also expressed in human atherosclerotic plaques and that it colocalizes with sites of in situ type I collagen cleavage.22 A novel finding is that MMP-8 was found expressed in situ and in vitro by macrophages, smooth muscle cells, and endothelial cells. In vitro expression was induced by stimulation with interleukin-1β and CD-40 ligand, factors that have also been found to induce the expression of other MMPs in vascular cells and macrophages. Interestingly, the authors found that the MMP-8 produced by vascular cells and differentiated macrophages is secreted, as opposed to that produced by neutrophils, which is stored within intracellular granules. This distinctive feature, as well as the difference in the sizes reported for the MMP-8 produced by endothelial cells, smooth muscle cells, macrophages,22 and neutrophils, raise the interesting question of whether these substances represent various processed forms of the same MMP-8 zymogen or distinct variants of the neutrophil MMP-8, which has been previously shown to have alternatively spliced forms.23 On the basis of MMP-8’s rather ubiquitous distribution in the plaques and colocalization with regions that stain immunopositive with an antibody to cleaved collagen, the authors propose that MMP-8 is involved in collagen breakdown and is thus likely a key player in plaque rupture. Their observations are consistent with the currently accepted hypothesis that MMPs contribute to plaque destabilization and rupture. Although much supporting experimental evidence has been gathered from a rather large number of studies of human and experimental atherosclerotic lesions demonstrating the expression and activity of MMPs,9,12 at this point, it is important to assess the current status of this hypothesis with a special emphasis on some of the fundamental questions that still await answers.

A direct causal connection between the matrix-degrading action of MMPs and plaque rupture has yet to be demonstrated. One major obstacle for demonstrating such a relation is the fact that spontaneous plaque rupture with thrombosis has not been convincingly demonstrated in any of the many animal models of atherosclerosis, despite evidence of MMP expression in many of the human and experimental lesions. In fact, Lemaitre et al24 recently reported that overexpression of human interstitial collagenase (MMP-1) in apoE-null mice did not induce plaque rupture and actually resulted in an unexpected reduction of atherosclerosis. Similarly, MMP inhibition in experimental models of arterial injury has been shown to reduce collagen accumulation and neointimal growth, most likely due to inhibition of smooth muscle cell migration from the media. However, one could argue that although some of the animal models of atherosclerosis present many important features of the human lesion, none is yet displaying all the features and, thus, none is yet able to reproduce faithfully the history of the human lesion, includ-

The opinions expressed in this editorial are not necessarily those of the editors or of the American Heart Association.

From the Atherosclerosis Research Center, Division of Cardiology, Cedars Sinai Medical Center, Los Angeles, Calif (P.K.S.), and the Departments of Medicine and Biomedical Engineering, Emory University School of Medicine, Atlanta, Ga (Z.S.G.).

Correspondence to Dr P.K. Shah, Director, Division of Cardiology and Atherosclerosis Research Center, Room 5347, Cedars Sinai Medical Center, 8700 Beverly Blvd, Los Angeles, CA 90048. E-mail shahp@cshs.org

(Circulation 2001;104:1878-1880.)

© 2001 American Heart Association, Inc.

Circulation is available at http://www.circulationaha.org

See p 1899

© 2001 American Heart Association, Inc.
ing the final episode of plaque rupture. These considerations support the notion that although the action of MMPs may be necessary, it is by no means sufficient to destabilize an atherosclerotic lesion.

Because 2 opposite metabolic processes determine the net amount of collagen, it is reasonable to propose that collagen synthesis is also important in determining plaque stability. Net collagen loss and cap thinning may, in fact, also require reduced collagen synthesis in the face of enhanced breakdown. Factors that decrease collagen synthesis and the death of smooth muscle cells, the main cellular source for matrix production, may contribute to such an event. A number of laboratories have, in fact, shown increased smooth muscle cell apoptosis in advanced atherosclerosis. Precise molecular signals and pathways responsible for smooth muscle cell death plaques are not known, although fas ligand and the epidermal growth factor (EGF)-like domain of Tenascin-c produced by macrophages (B.Z. Sharifi, PhD, unpublished observations, 2001) have been implicated.

Knowledge that may prove essential for the development of efficient therapeutic interventions for plaque stabilization relies on the answer to yet other unresolved issues of the MMP hypothesis. First, the identity of MMP(s) most likely to be responsible for weakening the plaque remains elusive, because a large repertoire of MMPs is expressed in human plaques. Because fibrillar collagen types I and III are the major structural components that confer tensile strength to the cap, the activity of enzymes capable of digesting this matrix component is regarded as especially consequential for plaque stability. Interstitial collagens have generally been considered resistant to proteolysis, except when attacked by interstitial collagenases, which cleave the triple helix into one-quarter and three-quarter fragments. These cleaved fragments then disintegrate into fragmented single α-chains, which are subject to further digestion by the gelatinases. Thus, on the basis of the traditional view that only interstitial collagenases can induce the first step in the breakdown of fibrillar collagen, Herman and colleagues propose that besides MMP-1 and MMP-13, which are already associated with the breakdown of interstitial collagen in the fibrous cap, MMP-8 must also be a key contributor. However, it is important to recognize that in addition to the traditional collagenases, the gelatinases MMP-2 and MMP-9 (major products of vascular and inflammatory cells) have also been shown to cleave intact fibrillar collagen, in addition to nonfibrillar and fragmented interstitial collagen and, thus, may be more important for matrix remodeling than previously thought. Relevant to the degradation of plaque collagen are previously reported observations of MMP-2 and MMP-9 overexpression and enzymatic activity within the vulnerable sites of human atheroma. Taken together, these findings can be used to build the hypothesis that gelatinases also participate in the degradation of the plaque’s interstitial collagen, increasing the array of MMPs that may control plaque stability through this mechanism, which further illustrates the complexity of the question regarding the relative contributions of various MMPs.

Another issue essential for potential attempts to inhibit the degrading action of MMPs is to tease out the mechanisms that lead to the in situ activation of the latent zymogens secreted by cells. The study by Herman et al did not investigate mechanisms that may activate the MMP-8 produced by vascular cells and macrophages. Although other MMPs have been shown to be activated by the reactive oxygen species produced by macrophages or activated vascular cells or by the MT-MMPs expressed by these cells, it is unclear if the same factors could lead to the generation of active MMP-8. Previous studies indicate that the activation of the neutrophil MMP-8 requires the action of hypochlorous acid, a product of neutrophils, and of cathepsin G. Although in the absence of neutrophils in vitro and in the plaque the potential source of hypochlorous acid remains unclear, the previous in situ localization of cathepsin S in the lesions reported by the same laboratory offers potential pathways for MMP-8 activation.

Our understanding of factors and pathways leading to plaque rupture and subsequent thrombosis remains incomplete, and the current status of the MMP hypothesis certainly does not provide all the answers. Continued investigation of this critical area in vascular biology is warranted. The application of new investigative tools such as the comparative transcriptional profiling of diseased and nondiseased blood vessels, ruptured and nonruptured plaques, and plaques bearing features of vulnerability versus plaques with a more stable-appearing phenotype may yet identify unique genes and pathways involved in plaque rupture and thrombosis. Even then, the burden of proof will again rely on the development of appropriate models in which we can test options for the “holy grail” of therapeutic inhibition of plaque rupture. So, while the players keep piling up, questions remain.

References


Key Words: Editorials atherosclerosis metalloproteinases inflammation collagen
Matrix Metalloproteinase Hypothesis of Plaque Rupture: Players Keep Piling Up But Questions Remain
Prediman K. Shah and Zorina S. Galis

Circulation. 2001;104:1878-1880

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/104/16/1878

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/