Matrix Metalloproteinases Are They Antiatherogenic but Proaneurysmal?

Michelle P. Bendeck

The matrix metalloproteinases (MMPs) are a family of enzymes (25 identified to date) that have in common the ability to degrade many molecules of the extracellular matrix. MMP activity can be inhibited by the endogenous tissue inhibitors of metalloproteinases (TIMPs 1 through 4), and the net proteolytic activity within a tissue is a function of the balance of MMPs/TIMPs. Numerous studies have shown that MMPs and TIMPs are expressed during vascular remodeling in the pathological conditions of atherosclerosis, restenosis, and aneurysm formation. Despite this burgeoning knowledge, we are still hampered by an incomplete understanding of the scope and the consequences of MMP/TIMP involvement in the pathogenesis of vascular disease.

In atherosclerosis and restenosis, MMPs are produced by the major cell types inhabiting the plaque, vascular smooth muscle cells (SMCs), and leukocytes of the monocyte/macrophage and lymphocytic lineages. MMP-1, -2, -3, -9, -12, and -13 have been detected in plaques, along with the lytic activity of SMCs. MMP-1, -2, and -4.2 MMPs produced by SMCs clear a path for migration from media to intima by digesting the extracellular matrix, and SMC migration can be inhibited by administration of nonselective MMP inhibitors or transfection of the genes for TIMP-1 or TIMP-2 into the injured vessel wall. MMPs produce abundant amounts of MMPs, which are used to invade through the endothelium and into the atherosclerotic plaque. MMPs are colocalized with macrophages in the core and shoulders of established plaques, areas that are very susceptible to the complications of erosion and rupture. MMPs are also expressed by inflammatory cells found in abdominal aortic aneurysms, and experimental studies using rat and mouse models point to a causal role for the MMPs in the pathogenesis of aneurysm.

A great deal of effort in vascular biology has centered on the hypothesis that inhibiting MMP activity will reduce plaque volume by inhibiting the migration of SMCs and macrophages into the plaque and prevent the later complications of plaque rupture and aneurysm formation. However, the mechanisms of MMP action in complex models of atherosclerosis are largely unknown. With the advent of transgenic technology, better models of atherosclerosis have been developed, including the cholesterol-fed ApoE-null mouse, which is characterized by elevated circulating lipoproteins, and the development of lipid-rich plaques containing inflammatory macrophages and lymphocytes.

In an article published in this issue of Circulation Research, Silence et al have uncovered dual roles of MMPs in the ApoE-null mouse model of atherosclerosis. Surprisingly, they found that deletion of the TIMP-1 gene resulted in reduction of plaque size in the ApoE-null mouse. TIMP-1 inhibits the activity of many MMPs, including the collagenases, gelatinases, and stromelysins. In the absence of the TIMP-1 gene, there was an increase in the number of macrophages present in aortic intimal lesions. The authors postulate that increased MMP activity (predominantly MMP-2), which colocalized with the macrophages, resulted in collagen degradation, thereby reducing plaque size. The reduction in plaque size was evident despite increased lipid accumulation in the lesions of the ApoE-null/TIMP-1–null mice. Unfortunately, the potential for aneurysm formation was substantially elevated in these mice, as evidenced by an increase in the frequency of disruptions in the internal elastic lamina.

The results presented here seemingly contradict a central dogma in atherosclerosis—that increased MMP activity leads to the formation of a thicker neointima. However, we must remember that most of the earlier studies with MMP inhibitors used experimental models where SMC migration was the main, if not the only, determinant of intimal lesion formation. By contrast, a growing body of experimental evidence from murine atherosclerosis models supports the postulate that increased macrophage-derived MMP activity may limit plaque progression. For example, plaque size and collagen content were greater in mice with double knockout of the MMP-3 and ApoE genes, compared to ApoE-null littermate controls. Consistent with this, plaque size, lipid deposition, and collagen content were reduced in ApoE-null mice that overexpressed MMP-1 in the macrophages. Taken together with results from the present study, this suggests that the activity of several plaque MMPs may actually be antiatherogenic. In this light, it is interesting to note that polymorphisms in the human MMP-3 promoter leading to decreased expression of this gene have been correlated with an increased incidence of atherosclerosis. Further work will be necessary to determine the full spectrum of anti- or proatherogenic activities of the many MMPs that are expressed in atherosclerosis. Another caveat is that the previous studies using knockout mice address only plaque progression. By contrast, increasing circulating TIMP-1 levels in the ApoE-null mouse induced the regression of pre-established le-
sions. Thus, the effects of altering the balance of MMPs/TIMPs may differ during the time course of lesion development.

Although the reduction in plaque size seen in the absence of TIMP-1 is potentially beneficial, deletion of TIMP-1 leads to increased degradation of the aortic elastic lamellae and thus may predispose to aneurysmal dilation and rupture. This is probably due to the increase in the amounts and the diversity of the MMPs produced by macrophages and/or to increased MMP activation by reactive oxygen species, nitric oxide, and peroxynitrite formation. In this context, it is interesting to speculate that aneurysm formation may be a case of MMP-mediated outward vessel remodeling gone bad. In the future, it will be important to investigate the potential for plaque rupture in the ApoE-null:TIMP-1–null mouse model. Rosenfeld et al have reported a significant incidence of intraplaque hemorrhage and plaque rupture at very late times during lesion development in the ApoE-null mouse model. In the absence of TIMP-1, the increased clearance of collagen may accelerate the destabilization of the atherosclerotic plaque, leaving it vulnerable to rupture.

Finally, it is important to remember that MMPs and TIMPs have functions beyond their roles in matrix degradation. For example, TIMP-1 is a growth factor for several cell types. In addition, MMPs degrade components of the extracellular matrix that stimulate cell growth and migration, such as collagen and osteopontin. MMPs also disrupt cell-cell interactions by cleaving cadherins or disrupting matrix-integrin associations, leading to apoptosis. Any of these mechanisms could be pertinent to atheroma or aneurysm formation, because they lead to a reduction in cell number.

In conclusion, the data presented in this interesting study highlights the importance of assessing all the potential mechanisms of MMP/TIMP action in the most appropriate experimental models. Clearly the use of transgenic mouse models is extremely informative, but also very complicated. We must take great care to interpret the data in terms of the cell types present in human atherosclerosis, available knowledge of the diversity of MMP/TIMP functions, and the time course of expression and activity of these enzymes. In this way, we can design selective therapies to be administered at the appropriate time and location to prevent the progression and complications of atherosclerosis.

References
22. Deleted in proof.

Key Words: matrix metalloproteinases ■ vascular remodeling ■ aneurysm ■ atherosclerosis
Matrix Metalloproteinases: Are They Antiatherogenic but Proaneurysmal?
Michelle P. Bendeck

Circ Res. 2002;90:836-837
doi: 10.1161/01.RES.0000018141.73992.41

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/90/8/836

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation Research 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 Research is online at:
http://circres.ahajournals.org/subscriptions/