Many Faces of Matrix Metalloproteinases in Aortic Aneurysms

Hong Lu, Masanori Aikawa

Accumulating evidence links the remodeling of extracellular matrix (ECM) with vascular diseases. In particular, many studies have established the impact of matrix metalloproteinases (MMPs) in various aspects of vascular biology. Twenty-three MMP family members are classified into 4 groups: (1) archetypal MMPs, (2) matrilysins, (3) gelatinases, and (4) furin-activated MMPs. Archetypal MMPs include 3 collagensases, MMP-1, MMP-8, and MMP-13, major macrophage products that degrade the fibrillar collagens. MMP-collagensases degrade collagen in atherosclerotic lesions and may impair the mechanical stability of the plaques, leading to physical disruption (plaque rupture) and acute thrombotic events. After the initial cleavage by collagenases, gelatinases, MMP-2 and MMP-9, degrade collagen fragments, contributing to plaque instability. In addition, MMP-2, MMP-9, and MMP-12 (metalloelastase) cleave elastin, another major vascular ECM. Evidence has recognized that elastin degradation by MMPs contributes to the pathogenesis of aortic aneurysms. Some cleaved products of ECM are biologically active (matrikines) and promote cell activation and additional monocye/macrophage infiltration. Thus, MMPs may enhance the positive feedback loop of the proinflammatory milieu in atherosclerotic plaques and aneurysmal aortas.

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Thoracic and abdominal aortic aneurysms (TAA and AAA, respectively) typically show signs of elastin degradation, increased collagen, and accumulation of inflammatory cells. Aneurysmal aortas contain high levels of elastolytic MMP-2, MMP-9, and MMP-12. Examining the causal role of each enzyme in vivo typically uses a genetic manipulation and one of the established models of aortic aneurysms, involving systemic infusion of angiotensin II (AngII), or local administration of calcium chloride (CaCl2) or elastase. Several mouse studies demonstrated the role of elastolytic MMPs in aortic aneurysms.

Fibrillar collagens determine mechanical strength and stiffness of the aorta. In late stages of aortic aneurysms, collagen seems to be the only remaining property to support mechanical load in the wall. The paucity of collagen may thus increase the risk of rupture. The role of collagen in the initiation and development of aortic aneurysms, however, remains unclear. Deguchi et al examined the incidence of AAA in AngII-infused mice that express genetically engineered type-I collagen, which is resistant to cleavage by MMP collagensases. Accumulation of uncleavable collagen in these mice accelerated the aneurysm formation, rather than preventing it, seemingly because of increased stiffness and altered collagen fiber orientation in the adventitia, causing the susceptibility to mechanical failure. The role of ECM in vascular disease may depend on the context and be more complex than we have thought. Better understanding of the balance of power between MMPs and ECM in aortic aneurysms may thus provide new insight into the development of new therapies. In this issue of Arteriosclerosis, Thrombosis, and Vascular Biology, Shen et al provide a new link between MMP-2 and ECM in the mechanisms for aortic aneurysms and demonstrate interesting differential roles of MMP-2 in TAA and AAA.

The development of TAA is associated with disruption of aortic structural integrity. Genetic deficiency of MMP-2 led to delayed aortic rupture in mice with diminished expression of fibrillin-1 (fibrillin-1mgR/mgR), a Marfan mouse model with profound aortic root/ascending aortic pathologies; however, attenuation of aortic dilation by MMP-2 deficiency was only significant within 5 weeks of age. In addition to genetic manipulation of fibrillin-1, subcutaneous infusion of AngII or periaortic application of CaCl2 to the descending thoracic aorta induces TAA. Shen et al explored effects of MMP-2 deficiency on aortic pathologies in these mouse models. Although elastin fragmentation is apparent in the diseased aortic region of both mouse models, it is surprising that MMP-2 deficiency augmented AngII-induced TAA, but protected against CaCl2-induced ascending aortic dilation. Of note, although AngII-induced TAA was restricted to the ascending aortic region in C57BL/6 mice, MMP-2 deficiency did not augment AngII-induced AAA in C57BL/6 mice, but reduced CaCl2-induced AAA. AngII promotes MMP-2 production and activity in both thoracic and abdominal aortic regions, which has been proposed as one mechanism of AngII-induced aortic aneurysms. Similarly, CaCl2 application to aortas activates MMP-2. As expected, MMP-2 deficiency ablated effects of AngII or CaCl2-induced MMP-2 productions and diminished total elastase activity. The authors proposed that the differential effects on TAA between AngII and CaCl2, as well as between AngII-induced TAA and AAA reflect differential effects of MMP-2.
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stages21 and augmented both TAA and AAA in AngII-infused
MMP inhibitor, to mice either reduced16 or had no effects on
homeostasis. Administration of doxycycline, a nonspecific
MMPs are involved in this proposed vascular ECM turnover
aneurysms, it would be important to determine whether other
addition, because many MMPs have been reported in aortic
growth of AAA.18

β

whether these changes were specific to thoracic aorta and also
and AAA.19 Inhibition of TGF-
β
on TAA
The evidence suggests conflicting effects of TGF-β on TAA
and AAA.19 Inhibition of TGF-β through injections of neutral-
izing antibody attenuated aortic root dilation in mice with fibrillin-1C1039G/+ mutation.20 either augmented or reduced TAA
in mice with fibrillin-1mutRiseR depending on the pathological stages21 and augmented both TAA and AAA in AngII-infused mice.22

Although exploration of mechanisms in animal models
has not provided consistent results in the roles of MMPs and
TGF-β signaling, we hope the availability of multiple mod-
el will continue to dissect specific causal roles of various
molecules implicated in TAA and AAA. As discussed, many
therapeutic targets for aortic aneurysms, including MMPs,
signaling pathways (eg, TGF-β), and inflammatory mediators,
have emerged. Fuller integrated, multiscale efforts, including
molecular imaging research and systems biology in experi-
mental animals and patients, may speed the process of target
discovery, establish clinical tools for identifying patients at
risk and monitoring in biological processes during
new therapies, and predict the on- and off-target effects of
potential drugs. Aortic aneurysm is a devastating disease.
Despite all the challenges, research efforts to seek more
defined therapies should continue and evolve.

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