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 collagenses, MMP-1, MMP-8, and MMP-13, major morphogenetic products that degrade the fibrillar collagens. MMP-collagenses 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 monocyte/macrophage infiltration. Thus, MMPs may enhance the positive feedback loop of the proinflammatory milieu in atherosclerotic plaques and aneurysmal aortas.

See accompanying article on page 888

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 collagenses. 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-1<sup>−/−</sup>), 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<sup>11,12</sup> or periarticular application of CaCl2 to the descending thoracic aorta<sup>13</sup> induces TAA. Shen et al <sup>9</sup> explored effects of MMP-2 deficiency on aortic pathologies in these 2 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 descending aortic dilation. Of note, although AngII-induced TAA was restricted to the ascending aortic region in C57BL/6 mice, MMP-2 deficiency resulted in profound pathologies in both the ascending and descending regions of the thoracic aorta. 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.<sup>6,9</sup> 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.
deficiency on disruption of ECM turnover toward synthesis versus degradation (Figure). The role of MMP-2 in the synthesis of ECM is currently unclear. Although the proposed mechanism needs to be validated in future study, the findings by Shen et al. suggest that inhibition of MMP-2 may not serve as an applicable therapeutic target for aortic aneurysms. In addition, because many MMPs have been reported in aortic aneurysms, it would be important to determine whether other MMPs are involved in this proposed vascular ECM turnover homeostasis. Administration of doxycycline, a nonspecific MMP inhibitor, to mice either reduced or had no effects on AngII-induced AAA. A prospective clinical trial has also reported that doxycycline has no beneficial effects on the growth of AAA.

Shen et al. propose another mechanism that AngII-induced TAA augmented by MMP-2 deficiency was associated with suppression of transforming growth factor (TGF)-β. TGF-β1 increased in the aorta in response to AngII, which was suppressed by MMP-2 deficiency (Figure). AngII did not change latent TGF-β in wild-type mice, but profoundly increased its expression in MMP-2-deficient mice. However, it is unclear whether these changes were specific to thoracic aorta and also unclear is whether TGF-β1 changed in CaCl2-induced TAA. The evidence suggests conflicting effects of TGF-β on TAA and AAA. Inhibition of TGF-β through injection of neutralizing antibody attenuated aortic root dilation in mice with fibrillin-1C1039G+ mutation, either augmented or reduced TAA in mice with fibrillin-1W522R depending on the pathological stages and augmented both TAA and AAA in AngII-infused mice.

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 models 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 experimental animals and patients, may speed the process of target discovery, establish clinical tools for identifying patients at risk and monitoring changes 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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None.

References


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