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Divergent Roles of Matrix Metalloproteinase 12 in Abdominal Aortic Aneurysms

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Matrix metalloproteinases (MMPs) are a family of zinc-dependent proteolytic enzymes. In humans, 23 members of MMPs have been identified and 15 of them are observed in the vasculature.[1] MMPs degrade many components of the extracellular matrix (ECM), a vital structure in maintaining the integrity of the aortic wall. Thus, MMPs have generated considerable interest in vascular research, particularly in studies of abdominal aortic aneurysms (AAAs) in which ECM degradation is a prominent pathological feature.

Among MMPs, several preclinical and clinical studies have investigated the roles of MMP12, initially termed macrophage elastase, in AAAs (Table).[2–4] The first report focusing on MMP12 in AAAs was an observational study using human samples.[5] MMP12 was upregulated in aneurysmal tissues and localized with elastin fragmentation in the aortic media. The same group subsequently investigated the role of MMP12 by genetic deletion in AAAs formed after elastase infusion in mice.[4] Since MMP12 is a potent elastase and exerts a critical role in macrophage-mediated ECM degradation, it was hypothesized that genetic deletion of MMP12 would have protective effects on AAA formation. However, MMP12 did not influence elastase-mediated aneurysm development. Meanwhile, another group reported that MMP12 deletion suppressed $CaCl_2$-induced AAAs in mice.[2] The protective effects of MMP12 deletion were also observed in AAAs provoked by simultaneous angiotensin II (AngII) infusion and TGFβ neutralization.[3] Thus, there is inconsistency regarding the impact of MMP12 deletion on development of AAAs. In this issue of *Circulation Research*, an interesting study by Salarian *et al*. serendipitously found deleterious effects of MMP12 deletion on AAA formation,[6] which provided new challenges to understanding the role of MMP12 in AAAs.

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Disclosures

None

The authors manipulated MMP12 in multiple AAA models in mice. First, the authors infused AngII into MMP12 deleted mice. Death due to aortic rupture was observed in 14% of AngII-infused apolipoprotein E deficient (ApoE−/−) mice in the initial week, whereas the compound deficiency of ApoE and MMP12 dramatically increased the death rate to 71%. MMP12 deletion also augmented neutrophil accumulation and NETosis (cell death attributed to neutrophil extracellular traps) in AAAs. The authors replicated these aortic phenotypes in AngII infused C57BL/6J mice expressing a gain-of-function variant of PCSK9 (proprotein convertase subtilisin/kexin type 9) gain-of function mutation to deplete LDL receptors. In addition to augmentation of the death rate and neutrophil accumulation, MMP12 deficiency exacerbated AngII-induced aortic dilatations in the supra-renal abdominal aorta. Of note, the authors also replicated these pathologies in another mouse model in which infrarenal AAAs were induced by a combination of β-aminopropionitrile (BAPN) administration and peri-vascular elastase application. MMP12 deficiency in this model also had augmented AAAs, neutrophil accumulation, and NETosis by MMP12 deletion. Since the primary source of MMP12 is macrophage, the authors deleted the protein in this cell type using Csf1r-Mer-iCre-Mer. Similar to other models used in this study, MMP12 deletion in macrophages promoted AngII-induced aortic rupture and AAA formation in ApoE−/− mice. Given the increase of neutrophil accumulation in AAAs, the authors focused on the complement system as the mechanism of MMP12-mediated AAAs. Coincident with the neutrophil accumulation, C3 was deposited in the aneurysmal tissue. Of interest, administration of IgG-$FH_{1–5}$, an upstream inhibitor of the complement alternative pathway, suppressed aortic rupture and dilatations as well as neutrophil accumulation. These results are compelling evidence that MMP12 deletion has detrimental effects on AAA formation. Interestingly, these findings contradicted previous studies reporting that MMP12 deletion protects against development of AAAs (Table).[2–4] This dimorphism indicates divergent roles of MMP12 in AAA formation. However, the underlying mechanisms by which MMP12 plays protective or harmful effects on AAAs are unclear.

It is of note that divergent roles are also observed in other MMPs. MMP2 and MMP9 are gelatinases that degrade elastin and collagen, major components of the ECM. These MMPs have been the focus of many aneurysmal studies. The amount and activity of these MMPs have been used as criteria to represent the disease severity of AAAs. Nevertheless, the impact of either MMP2 or MMP9 deletion differs among models (Table). Whole-body MMP2 deletion inhibited thoracic and abdominal aortic aneurysms elicited by $CaCl_2$ application. In contrast, MMP2 deletion augmented AngII-induced thoracic aortic aneurysms, but not AAAs, in wild-type mice. $CaCl_2$- or elastase-induced AAAs are inhibited by MMP9 deletion, while MMP9 deletion promotes AngII-induced AAAs in hypercholesterolemic mice. Therefore, not only MMP12, but also MMP2 and MMP9 deletion, have different AAA phenotypes in different models. While MMP12 deletion augments AAA formation in mice,[6] the authors' previous work demonstrated that MMP12 deficiency suppressed medial thickening in aged mice.[7] Given that medial thickening is common in AAAs, this discrepancy indicates dimorphic effects of MMP12 in vascular integrity. Alongside the inconsistency of AAA phenotypes by MMP2 or MMP9 deletion, MMP inhibition is not necessarily protective against AAA formation. Consistent with this

notion, it is worth noting that doxycycline, a non-specific MMP inhibitor, failed to prevent aortic expansion in mouse models and patients with AAAs.[8–11]

Multiple mouse models are available to investigate mechanisms of AAA formation.[12] Of these models, subcutaneous AngII infusion, periaortic $CaCl_2$ application, and intraluminal elastase perfusion (or topical application) are most commonly used. These models mimic facets of human AAAs. However, there are differences in the aortic pathologies that are manifest in these different models. For example, the presence of thrombus is a feature of AngII-induced AAAs, but not those formed after exposure to $CaCl_2$ or intraluminal elastase. The literature is also indicative of different mechanisms of compromising aortic integrity across the mouse models. Since it is not clear what mechanisms are operating within the evolving human aneurysmal tissue, there is considerable merit of in-depth studies of MMPs in each of the mouse models.

In conclusion, the study by Salarian, et al. revealed that MMP12 deletion promotes AAA expansion in selected mouse models.[6] The precise mechanism behind the differences of AAA phenotypes remains unknown. Investigations into which divergent roles of MMPs are mediated in the pathophysiology of AAAs should be encouraged.

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Table.

Divergent effects of MMP2, 9, or 12 deficiency in aortic aneurysm formation

MMP	Model	Aneurysmal Phenotype	Reference
MMP2 −/−	AngII in C57BL/6	TAA ↑ AAA not detected *	Shen, et al.[13]
	$CaCl_2$	TAA ↓ AAA ↓	Shen, et al.[13] Longo, et al.[14]
MMP9 −/−	AngII in ApoE−/−	AAA ↑	Howatt, et al.[15]
	$CaCl_2$	AAA ↓	Longo, et al.[14]
	Elastase	AAA ↓	Pyo, et al.[4]
MMP12 −/−	AngII + TGFβ Ab in C57BL/6J	AAA ↓	Wang, et al.[3]
	$CaCl_2$	AAA ↓	Longo, et al.[2]
	Elastase	AAA ↔	Pyo, et al.[4]
	AngII in ApoE−/−	AAA ↑	Salarian, et al.[6]
	AngII + PCSK9	AAA ↑	
	BAPN + Elastase	AAA ↑	

TAA and AAA indicate thoracic and abdominal aortic aneurysms, respectively.

* C57BL/6J mice have low incidence of AngII-induced AAAs. In C57BL/6J mice with MMP2 deficiency, AAAs were not detected. This result infers that MMP2 deficiency does not augment AngII-induced AAAs in C57BL/6J mice.