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Matrix Metalloproteinases and Descending Aortic Aneurysms: Parity, Disparity, and Switch

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Abstract

Central to the pathologic changes in developing aortic aneurysms are alterations in the abundance and activity of proteases, of which the most important for aneurysm production comprise the matrix metalloproteinase (MMP) family. In this review, literature demonstrating the role of MMPs in the development of aortic aneurysms is presented, with emphasis on the parity and disparity between the thoracic and abdominal aorta. Furthermore, the role of embryologic cellular origins and evidence of phenotypic switch will be addressed in terms of how this process alters MMP production during aneurysm development.

Introduction

Between 1982 and 2002, the incidence of thoracic aortic aneurysms (TAA) doubled.^{1,2} Current projections indicate that the number of individuals 65 years and older will double by the year 2030.^{3,4} These data suggest that aneurysm incidence will also increase dramatically at rates higher than current projections (**Figure 1**).^{1,2,5} Furthermore, the advent of computed tomography and 2-dimensional echocardiography has led to increased recognition of supra- and infradiaphragmatic aortic dilatations.²

The most common etiology of TAAs is related to idiopathic degeneration of the aortic vascular extracellular matrix (ECM). Other etiologies include genetic disorders such as Marfan syndrome, and congenital cardiovascular malformations such as a bicuspid aortic valve.⁶⁻⁸ Although invasive and noninvasive treatment options exist for timely repair of aortic aneurysms, the complication rate remains high, and neither approach is aimed directly at the underlying cellular and molecular mechanisms responsible for this devastating disease. The central theme of pathogenesis involves degeneration and loss of structural integrity of the aortic media and to a lesser extent, the adventitia. Central to these pathologic changes are alterations in the abundance and activity of proteases, of which the most important for aneurysm production comprise the matrix metalloproteinase (MMP) family.⁹

Recently it has been postulated that variations exist between the thoracic and abdominal aorta.¹⁰ Disparities in genetic, anatomic, mechanical, and environmental pathways have

been described in various studies, thereby demonstrating potentially significant regional heterogeneity.¹⁰ Furthermore, recent data suggests that resident cells within the aorta may undergo phenotypic changes during the process of aortic dilatation.^{8,11,12} Better knowledge of these cellular events that lead to aneurysm formation may elucidate novel treatment options for this condition including region specific gene therapy and targeted pharmacologic treatments.

This review presents literature, demonstrating the role of matrix metalloproteinases (MMPs) in the development of aortic aneurysms, with emphasis on the parity and disparity between the thoracic and abdominal aorta. Furthermore, the role of embryologic cellular origins and evidence of phenotypic switch will be addressed in terms of how this process alters MMP production during aneurysm development.

Parity: matrix metalloproteinases and aortic aneurysm formation

Aneurysmal disease of the aorta has been a focus of investigations utilizing various animal models to reveal the peculiar interplay between MMPs in the formation of aortic aneurysms. Both agonists and antagonists, the MMPs and their inhibitors, the TIMPs, play an important role in aortic aneurysms of the thoracic and the abdominal aorta. Symmetrical pathways, i.e. the parity in the development of aneurysms in both the descending thoracic and the abdominal aorta are discussed below.

Matrix Metalloproteinases (MMPs)—The role of proteolysis in cardiovascular disease has been well documented.¹³ With regard to aneurysms of the aorta, vessel dilatation is caused by lysis of elements of the extracellular matrix (ECM), primarily elastin and collagen, in the aortic media and adventitia, thereby weakening the vessel wall.¹³ The MMPs constitute a family of over 25 extracellular and transmembrane enzymes, and the stoichiometric balance between these MMPs and their antagonists, the tissue inhibitors of metalloproteinases (TIMPs) are instrumental in the pathogenesis of aortic aneurysm disease (**Table 1**).¹⁴ They have an important role in the homeostasis of connective tissue.¹⁵ MMPs are synthesized by a variety of cell types, are secreted as pro-MMPs and can be activated by a number of proteinases including other MMPs. MMPs are divided into subclasses based upon substrate specificity, such as gelatinases, elastases, and collagenases.¹⁶

Members of the gelatinase subclass, MMP-2 and MMP-9, have demonstrated an ability to degrade denatured fibrillar collagen (gelatin), elastin, and native Types IV, V, and VII collagen along with other ECM components.¹⁷ MMP-2, or gelatinase A, is constitutively expressed by smooth muscle cells (SMCs) and fibroblasts of the aortic media and also displays interstitial collagenase capabilities, cleaving Type I collagen which comprises approximately 60% of the collagen content of the aorta.¹⁸⁻²⁰ MMP-9, or gelatinase B may be produced by inflammatory cells such as neutrophils and macrophages,²¹ and also, as discussed below, by resident aortic cells under certain conditions.²² The importance of MMP-9 in both dTAA and AAA development has been further supported in murine models where aneurysm induction was inhibited in MMP-9 knockout mice.^{21,23}

Another important MMP, the membrane-associated matrix metalloproteinase, MMP-14 or MT1-MMP, has been shown to be markedly elevated and may play a central role in

orchestrating elastolytic processes, both in the development of dTAAs and AAAs.^{12,24} Utilizing a murine model of dTAA, we have previously demonstrated that MT1-MMP activity was correlated with the time-dependent change in thoracic aortic diameter, suggesting that MT1-MMP may be required for aortic dilatation.¹² Specifically, the results suggest a multifunctional role for MT1-MMP in dTAA development that is defined through two phases of expression and activity. The first phase defines a role for MT1-MMP early in aneurysm development, when its primary function involves the activation of MMP-2. The second phase defines a role for MT1-MMP as a protease, modifying the cell-matrix interface and resulting both in further ECM destruction and the release of numerous ECM-bound matrixines and signaling molecules which continue to drive aneurysm formation. To investigate the role of MT1-MMP in AAA formation, a recent study utilized a murine bone-marrow transplant model, in which wild-type mice were transplanted with MT1-MMP deleted marrow.²⁴ Subsequent CaCl₂ induced aneurysm formation to the abdominal aortic surface was almost completely prevented, however, AAA formation could be reconstituted when MT1-MMP macrophages were infused into these recipients. These results therefore implicate MT1-MMP as a turnkey mediator of TAA and AAA formation and as such, suggest that targeting this protease may have significant therapeutic implications.

Other MMPs, such as collagenases (MMP-1, 8, 13), have also been implicated in the basic pathophysiology of aortic aneurysm formation. All three have been found in much larger quantities and with increased activity in aortic aneurysms.²⁵⁻²⁸ The primary elastase involved in the progression of aneurysm disease is MMP-12. This MMP has been shown to co-localize to residual elastic fiber fragments in aneurysmal tissue. Its deficiency is associated with attenuation of experimental aortic aneurysm formation.²⁹ In other models, TAA formation was reduced in mice deficient of the stromelysin MMP-3, and elevated MMP-3 activity has been confirmed in extracts from atherosclerotic aortas.³⁰ Compared to the other two stromelysins, MMP-10 and MMP-11, MMP-3 contributes to plaque destabilization and promotes TAA formation by degrading the elastic lamina, and therefore plays an important role in aneurysm formation. MMP-3 was shown to degrade type IV collagen, fibronectin, laminin, proteoglycan core protein, and type IX collagen.¹⁵

Tissue Inhibitors of Metalloproteinases (TIMPs)—MMPs are tightly regulated at transcriptional and translational levels. Perhaps the most important source of the post-translational regulation of MMPs are the four endogenously produced MMP antagonists, the TIMPs. Of these, the most important TIMP within the aorta is TIMP-1. Presently, there is no clear evidence that TIMP-4 plays a significant role in aneurysm development and studies investigating TIMP-3 are sparse.³¹ An increase in TIMP-3, but not TIMP-1 or TIMP-2 was observed in human AAA tissue specimen and was correlated with a reduction in aortic SMCs.³² Aortic SMCs, however, constitutively express TIMP-1 and TIMP-2,^{33,34} and TIMP-1 has been demonstrated to inhibit most MMPs, especially MMP-9.³⁵ In both AAAs and dTAAs, the absence of TIMP-1 has been shown to potentiate formation. The function of TIMP-2 is more complex in that, although it can inhibit MMP-2 and MMP-9, TIMP-2 also activates MMP-2 through an activation complex which involves MT1-MMP.³⁶ Thus, it is not surprising that no consistent trend in the relationship between TIMP-2 expression and either dTAA or AAA formation has been demonstrated. However, a compelling study by

Xiong and coworkers demonstrated that AAA growth in TIMP-2 knockout mice was inhibited; a counter-intuitive result to the removal of an endogenous MMP inhibitor that suggested that the MT1-MMP-dependent activation of MMP-2 was essential for aneurysm formation.³⁶

Some aneurysm studies have evaluated the ratio of MMP-2 to TIMP-2.³⁷⁻⁴⁰ In dTAA specimens, an increase in the MMP-2/TIMP-2 ratio has been observed,³⁷ while that of AAA samples has remained unchanged from control aortic tissue.³⁸⁻⁴⁰ This represents one of many transcriptional responses to aneurysm initiating stimuli, which differ in the thoracic and abdominal aorta, implying differences in the proteolytic and inhibitory signatures between the thoracic and abdominal aorta. However, the parity, or common theme with both AAAs and dTAAs, is the central role, played by the stoichiometric balance between MMPs and TIMPs on aortic ECM degradation.

Disparity: aortic regional heterogeneity

While aneurysmal disease of the peripheral vasculature and abdominal aorta have been a focus of intense investigation, definitive studies regarding the pathogenesis of TAAs have been elusive and historically restricted to descriptive case series reports. Likely reasons for a relative paucity of mechanistic and translational studies focused on TAAs are 2-fold. First, a long held assumption was that the thoracic and abdominal aorta was similar in terms of the molecular and cellular pathways which mediate ECM remodeling. However, the thoracic and abdominal aorta is distinctly different from an embryologic and structural standpoint,^{41,42} and therefore an equivalent biophysical stimulus may cause distinctly different cellular and extracellular responses. Second, it was assumed that the initiation and progression of aneurysms in the thoracic and abdominal aorta would follow a similar natural history and clinical course, but it is becoming recognized that diverse and disparate vascular remodeling processes occur within these different aortic compartments. The presence of regional heterogeneity between the thoracic and abdominal aorta has gained considerable interest, and was a subject of a recent review.¹⁰ In the following paragraphs we summarize the disparity between developments of aneurysmal disease in dTAAs versus AAAs.

Genetic differences—The genetic contribution to aneurysm disease in the thoracic and abdominal aorta has been well studied. Approximately 20% of TAAs are attributed to some form of genetic syndrome.⁴³ Specifically, mutations in key TGF- β signaling pathway components are invariably associated with vascular pathology. These are directly implicated with genetic disorders and development of TAA, such as Marfan syndrome, Marfan syndrome type 2, Ehlers-Danlos Syndrome Type IV, familial TAAs and dissections, and Loeys-Dietz syndrome.⁴⁴⁻⁴⁶ In AAA, on the other hand, the genetic predisposition reported in 12-19% of AAA patients has not yet been traced to particular mutations, but coincides with a family history of a first-degree relative with aneurysm disease.⁴⁷⁻⁴⁹ The varying contributions of genetic influences on TAA versus AAA development support the premise that the two are unique pathophysiologic entities. Furthermore, heterogeneity between the thoracic and abdominal aortic regions was shown to arise during embryogenesis.⁵⁰ Neural crest cell precursors to the thoracic aorta and mesodermal ancestors of the abdominal aorta

have demonstrated unique responses to various cytokines and growth factors, DNA synthesis and contractility^{41,51, 52}

Anatomic, mechanical, and environmental differences—In the thoracic as well as abdominal segments of the aorta, aneurysm formation is attributed to degradative remodeling of the medial ECM and SMC loss.⁵³ Differences with regard to avascular and vascular zones have been described in murine models.⁵⁴ This principle remains true in humans and provides a clear distinction between the thoracic and abdominal aorta. Variations in vascular penetration of the aortic media layer have been shown between the mostly vascular thoracic media versus the avascular abdominal aortic media.⁵⁴ Therefore, differences in oxygen, nutrient, and growth factor delivery to the cells of the thoracic and abdominal aortic media exists with subsequent risk of medial degeneration and aneurysm formation, further underlining the concept of spatial heterogeneity within the aorta.⁵⁵

Previous investigations utilizing human tissue specimens harvested from aneurysms showed that the strength of TAA samples was roughly twice that of AAA samples underscoring the mechanical heterogeneity of these two regions.⁵⁶⁻⁵⁹ Furthermore, the disease of atherosclerotic plaque deposition affects the aorta differently above and below the diaphragm^{60,61}, with preferential growth of atherosclerotic plaque in the abdominal aorta being attributed to variations in flow and shear stress in that region.⁶² Although some TAAs are associated with atherosclerotic disease, many occur in the complete absence of plaque deposition.⁶³ Thus, the thoracic aorta appears more resistant to plaque formation supporting a disparate pathophysiologic mechanism for TAA development.

Differences in MMP activation and stoichiometry—Significant differences exist regarding proteinase systems within these aortic regions. The contribution of MMP-2 to dTAAs is somewhat controversial. While studies of ascending TAAs have shown clear increases in MMP-2,³¹ studies focusing upon degenerative dTAAs have failed to show an increase in MMP-2 compared to normal aorta.^{64,65} dTAAs associated with atherosclerosis, on the other hand, have demonstrated increased MMP-2 activity.^{37,66} Increasing age has been associated with elevated MMP-2 levels in the thoracic aorta and therefore, the lack of use of age-matched controls may have obscured the impact of MMP-2 on TAAs.⁶⁷ A murine model of dTAA development reported elevations in MMP-2 as early as 72 hours after aneurysm induction with return to baseline by 2 weeks,⁶⁸ suggesting a role for MMP-2 in early dTAA growth that perhaps has not been captured in human tissue samples harvested at the time of aneurysm repair. Additionally, a study by Jones and colleagues demonstrated early activation of MMP-2 at 2 weeks post dTAA induction in a murine model.⁶⁹ In AAAs the data is more definitive that MMP-2 is instrumental to aneurysm development. Tissue samples harvested at the time of aneurysm repair have consistently shown increased MMP-2 expression and activity^{33,40,70} due to amplified production by native SMCs.^{20,71-73} More interestingly, Freestone et al., demonstrated that aneurysms less than 5.5 cm had greater MMP-2 activity than larger aneurysms and proposed that early AAA growth is directed by MMP-2.⁷⁴ The vital role of MMP-2 in AAA formation has been corroborated in a murine model of AAA where aneurysms could not be induced in MMP-2 knock-out mice.²¹ Therefore, elevated MMP-2 activity is required for AAA growth, but may or may not

influence TAA development, representing an emerging concept in aortic heterogeneity. The inflammatory infiltrate accompanying atherosclerotic plaque deposition may increase MMP-2 transcriptional activity in AAAs and atherosclerotic dTAAs.³⁷

With regard to MMP-9, a consistent elevation in AAA tissue was documented in various studies^{34,40,75} and was attributed to macrophage infiltration into the aortic media and adventitia.^{76,77} This was confirmed by other studies that documented a regional variation of MMP-9 in stimulated rodent aortas, with production greater in the abdominal aorta compared with the thoracic aorta.^{35,78,79} Trends in MMP-9 expression have also been identified with regard to aneurysm size such that aneurysms between 5 and 7 cm in diameter have more MMP-9 than those either larger or smaller.^{74,80} This evidence suggests a role for MMP-9 in aneurysm progression, perhaps to a point where additional proteases or hemodynamic factors become the driving force in AAA growth and rupture.⁸⁰ Confirmation of the macrophage as the primary source of MMP-9 in AAA was achieved when MMP-9 knock-out mice were infused with wild-type macrophages and subsequent restoration of AAA growth was documented.²¹ However, in murine studies of dTAA, a significant inflammatory infiltrate has not been identified. MMP-9 was shown to be produced by endogenous cells following CaCl₂-induced TAA formation.⁸¹ Ideally, a comprehensive understanding of the activity of these enzymes in thoracic versus abdominal aneurysm disease will allow development of therapies which target site-specific, divergent pathways to slow or halt aneurysm growth.

Switch: Cellular phenotype changes during disease development

Multiple cell types, including smooth muscle cells (SMCs), fibroblasts, and inflammatory cells, populate the wall of an aortic aneurysm. Each of these cell types is capable of producing proteases. Although in previous studies, inflammatory cells have been implicated as the major source of MMPs in aneurysm development in AAAs^{65,82}, recent publications utilizing animal and human tissue of dTAAs have shown that changes in MMP abundance can also arise as a result of increased production by endogenous aortic cellular constituents.⁸³⁻⁸⁶ Specifically, while it has been demonstrated that endogenous fibroblasts produce MMP-9 during early aortic dilatation,⁸⁴ further degeneration of the aortic elastic architecture was found to occur concomitantly with the emergence of a population of fibroblast-derived myofibroblasts, which co-localize with MMP-9.⁸ Moreover, upon isolation of aortic fibroblasts from control and TAA-induced mice, it was determined that the TAA-induced fibroblasts had undergone a significant phenotypic change during TAA formation, resulting in an enhanced proteolytic gene expression profile, including in increases in MMP-9 expression.⁸³ Similarly another study demonstrated significant co-localization of MT1-MMP with DDR2-positive cells (fibroblasts or myofibroblasts) within the thoracic aortic wall. These investigations have resulted in the postulate that constituent aortic cellular phenotypic switch occurs during the pathogenesis of aortic dilatation.

Previous clinical and experimental aneurysm investigations have demonstrated significant changes in aortic structure and composition in the developing TAA. These changes include alterations in collagen deposition, changes in cellular content characterized by loss of medial SMCs, and alterations in aortic transcriptional profiles, in the absence of a significant

inflammatory infiltrate.^{11,87} It is therefore likely, that changes in endogenous cellular constituents play a significant role in mediating TAA formation and progression.⁸³ Within the normal aorta, the predominant cell type within the tunica media is the SMC with a minority of fibroblasts. Thus, under normal conditions, primary synthetic and metabolic pathways are likely regulated by smooth muscle cells. However, in direct contradistinction to the normal aorta, in TAAs, the loss of SMCs is supplanted by fibroblasts that possess a unique protein signature. Primary cultures of fibroblasts harvested from aortic aneurysms have demonstrated increased growth rate characteristics, increased release of proteolytic enzymes, and expression of contractile proteins such as alpha smooth muscle actin.⁸⁸ The protein expression and synthesis patterns of this expanded fibroblast population within the aneurysm is consistent with switching to a myofibroblast phenotype, which is commonly found in pathological remodeling.⁸⁸ These observations would suggest that fibroblast proliferation and switching to a myofibroblast phenotype is an important cellular event in TAA progression. A previous study demonstrated significant transcriptional changes in TAA fibroblasts compared with normal aortic fibroblasts.⁸³ This suggested enhanced degradation and remodeling of the vascular ECM during TAA development, in part, because of altered fibroblast function. Furthermore, when isolated fibroblasts were challenged by treatment with relevant biological stimuli, differential transcriptional responses were observed between normal and TAA fibroblasts, suggesting that intracellular signaling pathways in the TAA fibroblasts may be altered, and thus may respond differently to equivalent stimuli.⁸³ Taken together, the study supports the hypothesis that aortic fibroblasts undergo a stable phenotypic transformation during TAA development, and that these changes in gene expression may alter normal fibroblast function and contribute to TAA formation and progression.

Additional work has established that vascular SMCs have the ability to undergo profound changes in phenotype in response to changes in their extracellular environment in both animal models and human subjects. This includes coordinated repression of SMC marker genes and induction of MMPs in response to inflammatory mediators. Specifically, repression of SM22 α , SMC α -actin, and myosin heavy chain in concert with increased MMP-2, MMP-3, and MMP-9 expression as seen in patients with atherosclerosis.^{89,90}

Furthermore, in a mouse model of Marfan syndrome, utilizing defective fibrillin-1 encoding, phenotypic vascular smooth muscle cell alterations were found in early vascular lesions, preceding elastolysis.⁹¹ These alterations of vascular smooth muscle cells were accompanied by changes in the synthetic repertoire including vast expressions of MMP-9 within the aortic wall of fibrillin-1 deficient mice. Based on this, it was speculated that deficiencies in cell-matrix connections contribute to various disease processes and that therapeutic strategies aimed at modulation of cellular phenotype may preclude or delay aortic disease.

Murine TAA models have demonstrated attenuated aneurysm growth in MMP-9 knockout mice at four weeks post-induction, and MMP-9 abundance in wild-type mice beginning 2 weeks post-induction.^{22,68} MMP-9 levels remained elevated throughout aneurysm growth. Interestingly, immunohistochemical staining has localized MMP-9 to mesenchymal cells of the aortic media and adventitia that have undergone a phenotypic switch with increased

synthetic activity.^{22,76} In the healthy aorta these cells do not produce MMP-9, and such a shift in transcriptional activity has previously been attributed to alterations in cell-cell and cell-matrix interactions,⁹² suggesting that ECM remodeling may precede and actually help initiate MMP-9 production in the TAA. It is currently unclear whether a similar process occurs within the atherosclerotic AAA, where MMP-9, important for aneurysm progression, is possibly derived from inflammatory cells.

The different cellular sources of MMP-9 in TAA versus AAA have substantiated a major point in the argument favoring aortic regional heterogeneity with regard to aneurysm disease. A hypothesis of AAA formation can be constructed from the prevalence of atherosclerotic plaque leading to macrophage infiltration with consequent MMP-9 production and surrounding matrix degradation. In contrast, in dTAAs, MMP-9 expression by native, phenotypically altered mesenchymal constituent cells may drive aneurysm formation (**Figure 2**).

Clinical studies

In humans, homogenized aortic extracts and smooth muscle cell cultures from patients with AAAs have been studied and early immunohistochemical staining techniques identified various MMPs (MMP-1, 2, 3, 9) and TIMPs in the wall of the aneurysms.⁹³ Fontaine *et al.* identified MMP-9 release from the polymorph nuclear lymphocytes present in aneurysm thrombus, with high levels of both MMP-2 and MMP-9 in the liquid interface between the thrombus and aneurysm wall, indicating a potential significant etiopathologic relationship between the presence of the thrombus that commonly layers and accumulates in a developing aneurysm and further expansion of the aneurysm.⁹⁴ These findings are in concert with previous animal investigations corroborating that MMP-9 from inflammatory cells in the abdominal aorta cause continued growth of AAA.

Multiple studies in humans have also examined the relationship between MMP production and aneurysm size and progression to rupture. Freestone and colleagues documented increased MMP-2 zymographic activity in smaller aneurysms of 4.0 to 5.5 cm in diameter, with increased MMP-9 activity occurring in larger aneurysms. From these findings the authors postulated differential roles of the gelatinases in aneurysm expansion and rupture.⁸² McMillan *et al.* examined the MMP-9 mRNA levels in aneurysms of varying sizes and found a fourfold elevation in MMP-9 mRNA in aneurysms 5.0 to 6.9 cm in diameter compared to smaller or larger sizes and suggested that the tendency for medium sized aneurysms to expand is related to increase MMP activity, with expansion at larger sizes owing to the effects of other proteases or to diameter-dependent mechanical stress.⁹⁵ Petersen and associates also identified relative increases in MMP-2 and MMP-9 mRNA levels in medium-sized aneurysms, with dramatic increases in MMP-9 in mediumsized aneurysms that went on to rupture.⁹⁶ Therefore, a clear, measurable relationship between the extent of aortic MMP activity, especially MMP-9, and temporal stage of aneurysm expansion exists. TIMP expression in a human study of ascending thoracic and abdominal aortic aneurysms was also found to corroborate previous animal studies. In this study, differences were seen in expression of MMP-9 and TIMP-1 with regard to their source from inflammatory cells in AAAs versus SMCs in TAAs.⁹⁷ Taken together, these findings are in

concert with MMP-2, MMP-9, and TIMP-1 involvements in animal models, as presented in the previous paragraphs.

Currently, only non-specific MMP inhibition is being explored clinically to limit aneurysm growth mainly utilizing tetracyclines and statins that have shown promising results.⁹⁸⁻¹⁰⁰ Both doxycycline and statin therapy was associated with decreased MMP levels and less expansion rates in patients with small AAAs. However, to date, most clinical studies are being conducted in the setting of AAAs and clinical investigations in dTAAs are sparse.

Future Studies and Directions

Future studies should be aimed to address the sequence of four main questions with regard to descending aortic aneurysms. First, diagnosis of aneurysms should entail sensitive biomarkers, such as blood chemical assays of MMPs for example, which would increase the positive predictive value of a more expensive imaging request, such as a computertomography. While TIMP-potentiating strategies are currently not being used clinically to limit aneurysm disease, plasma quantification of TIMPs, especially relative to MMP abundance may prove useful in predicting the presence and activity of aortic aneurysm disease. Presently, most nonsymptomatic aneurysms are discovered incidentally, when patients undergo imaging for other reasons.

Secondly, when aortic aneurysms are identified, the maximal diameter remains the indication for repair. However, more precise indicators for operative or endovascular intervention are warranted as small aneurysms may rupture earlier than other larger aneurysms. Many investigators have studied aneurysm wall specimen, collected at the time of surgical repair to examine structural and biochemical alterations. While informative, this tissue can only provide a snapshot of the histologic transformations and enzymatic activity occurring at that current stage disease. Newer studies have therefore also measured elevations of MMPs in plasma.^{101,102} Therefore, investigations involving circulating biomarkers, as promoted by a recent systematic review¹⁰³, or involve advanced quantitative imaging with specific antibodies to tissue MMPs, as are ongoing in our laboratories, could have important potential for identifying patients who need urgent surgery versus safe nonoperative follow-up.

Thirdly, treatment regimens of aneurysms include open surgery versus endovascular approach. In the future, the development of agents that target MMP cassettes, specific for different aneurysm types and locations, may demonstrate to be beneficial in modifying aneurysm formation. This may also reduce potential side effects associated with global MMP inhibition, as their use in other disease processes such as osteoarthritis was associated with high rates of musculoskeletal toxicity.¹⁰⁴ Specifically, MMP inhibitors could be delivered systemically or regionally as part of a drug-eluting endovascular stent graft to directly limit aortic remodeling and potentially increase the long-term success of endografting.

Lastly, the incessant follow-up of patients after aortic aneurysm interventions remains important especially following endovascular treatments with respect to endoleaks. As demonstrated in a previous study¹⁰⁵, post-intervention measurements of MMPs or other

cytokines and systemic biomarkers could help to assess effective aneurysm exclusion versus endoleakage.

Conclusions

This review has sought to summarize the protease homeostasis during development of aneurysmal disease of the aorta, define some of the common and disparate properties in the descending thoracic and abdominal aortic segments as they pertain to aneurysm development, and emphasize the presence of changes in endogenous cellular constituents that play a significant role in mediating aortic aneurysm development. The following list, in adjunct to **Figure 2**, summarizes the specific and overall findings, respectively, which propose dTAA and AAA development and growth:

Common properties in the descending aorta during aneurysmal development:

- Elevated levels of MMP-2, MMP-9, and MMP-14 (MT1-MMP) play a central role in orchestrating elastolytic processes, both in the development of dTAAs and AAAs.
- The absence of TIMP-1 potentiates formation of both dTAAs and AAAs.

Disparate properties in the descending aorta during aneurysmal development:

- In dTAAs, loss of smooth muscle cells is supplanted by fibroblasts.
- With increased growth rate characteristics and increased release of proteolytic enzymes in the thoracic aorta, a phenotypic switch from fibroblasts to myofibroblasts occurs.
- Increased release of MMP-9 from mesenchymal cells of the thoracic aorta causes continued growth of dTAAs.
- Increased release of MMP-9 from inflammatory cells in the abdominal aorta causes continued growth of AAA.

Additional research into these regional distinctions with respect to phenotype switch and identification of site production of proteases during disease development may reveal new noninvasive interventional options targeting specific molecular and cellular mechanisms occurring differentially within the thoracic and abdominal aorta, that are responsible for this devastating disease.

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Figure 1. Projected Incidence of Aneurysm Development

Previous work demonstrated that the incidence of TAA development had doubled between 1982 and 2002.^{1,2,6} Based on that data, TAA incidence has been projected to continue to increase within the population through 2050 (triangles; red line). However, when considering factors such as the aging “baby boomer” generation and new advancements in noninvasive imaging techniques, these trends in TAA incidence may be grossly under represented, and may in fact increase at a sharper rate (circles; dashed blue line). Accordingly, further diagnostic and therapeutic advancements are a critical need. TAA; thoracic aortic aneurysm

Figure 2. Summary illustration of parity and disparity in addition to cellular phenotype switch in descending aortic aneurysms.

Table 1

MMPs and TIMPs in development of abdominal and descending thoracic aneurysms

MMP/TIMP	TAA	AAA	References
MMP-1 (Collagenase)	Equivocal	Elevated	25
MMP-2	Equivocal (Elevated Early?)	Elevated	19, 64, 65
MMP-3 (Collagenase-3)	Elevated	Elevated	30, 6
MMP-8	No Change	Elevated	26
MMP-9	Elevated < AAA (Aneurysm Induction)	Elevated (Aneurysm Growth)	21, 22
MMP-10	No Change	No Change	6
MMP-11	No Change	No Change	6
MMP-12	Unknown	Elevated	29
MMP-13	No change	Elevated	28
MMP-14 (MT1-MMP)	Elevated	Elevated	12, 24
TIMP-1	Decreased	Decreased	32, 35
TIMP-2	No Change	Decreased	33, 34
TIMP-3	Unknown	Elevated	32

MMP: Matrix Metalloproteinase; TIMP: Tissue Inhibitor of Metalloproteinase; TAA: Thoracic Aortic Aneurysm; AAA: Abdominal Aortic Aneurysm