Extracellular Matrix Remodelling and Abdominal Aortic Aneurysm

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Abstract
Aorta is the largest artery in the body. Aortic wall is comprised of an intricate arrangement of extracellular matrix (ECM) structural proteins, primarily collagen and elastin, and layers of vascular smooth muscle cells. This gives the aortic wall the tensile strength to withstand the pressure of blood pumped from the heart during systole, and the elasticity to expand and accommodate the left ventricular stroke volume and to, subsequently, recoil to its original diameter and push the blood forward for systemic perfusion. Aortic aneurysm involves structural degradation of the aortic wall and focal dilatation of the aortic lumen. It is a devastating health problem with no effective treatment. Current management strategies for AAA patients include antihypertensive drugs and surgical repair for severe cases of AAA which are not without limitations and complications. A number of proteases (matrix metalloproteinases, serine and cystein proteases), and their inhibitors (tissue inhibitor of metalloproteinases and cystatin) have been shown to contribute to AAA development and progression. In this review we will summarize the published literature on the role of ECM-regulatory proteins, mainly proteases and their inhibitors, in aortic function and aneurysm formation, with a focus on abdominal aortic aneurysm.

Keywords: Abdominal aortic aneurysm; Vascular matrix; Matrix metalloprotease; Tissue inhibitor of metalloproteinase; Atherosclerosis

Introduction
Aorta, the largest artery in the body, does not merely serve as a conduit to distribute blood from the heart to the body, but plays important roles in multiple aspects of the cardiovascular system, including perfusion of the myocardium and the peripheral tissue, and arterial function [1]. During cardiac systole, aorta expands to store a large proportion of the left ventricular stroke volume while during diastole, recoil of the aortic wall pushes the stored blood forward and into the periphery. This function of the aorta as a ‘mini-pump’ maintains blood flow and pressure throughout the cardiac cycle. The storage capacity of the aorta is directly related to the mechanical properties of the aortic wall. When the aorta becomes stiff, it loses its ability to expand compromising its storage capacity, while loss of its elasticity will reduce its ability to recoil during cardiac diastole and to push forward the blood stored during systole.

Aortic Wall Structure and Composition
Similar to smaller arteries, aortic wall is comprised of three layers, intima, media and adventitia [2,3]. Intima is a single layer of endothelial cells that make up the luminal surface of the aorta. Media is comprised of layers of elastin arranged in fenestrated sheets called ‘lamellae’, collagen fibers, thin layers of proteoglycan-rich extracellular matrix (ECM) and smooth muscle cells (VSMCs) that are embedded in this matrix of structural proteins. Media provides the tensile strength and recoil ability of the aorta. During development, media grows differently in thoracic versus the abdominal aorta. During growth, medial thickness increases by an increase in the number of lamellar units in thoracic aorta, whereas in abdominal aorta each unit widens [4]. In both regions however, a constant aortic diameter-to-medial thickness is maintained which determines wall stress and tension per lamellar unit [5]. Adventitia is the outermost layer of the aortic wall and is comprised primarily of collagen and differentiated from the media by external lamina. Structure of the aortic wall is a major determinant of its function. While the total amount of the main matrix proteins, collagen and elastin, is approximately the same throughout the aorta, thoracic aorta contains more elastin than collagen, whereas more collagen is present in the abdominal aorta than elastin [1,6]. Aortic wall is supplied with a rich network of innervations and vasa vasorum, small blood vessels that supply blood to the adventitia and the outer aortic wall. Vasa vasorum structure is more extensive in the thoracic than the abdominal aorta. Any change in the structure of the aortic wall may result in alterations in the aortic function. Aortic aneurysms result from structural degradation of the aortic wall leading to focal dilation which expands and eventually ruptures. In this review we will summarize the published work on aortic aneurysm with a focus on abdominal aortic aneurysm, and will discuss the contribution of the enzymes and proteins that directly regulate the remodeling of the aortic wall matrix structure. We will also discuss the findings in patients and animal models of aortic aneurysm, and finally will touch on possible treatments for this devastating health condition.

Aortic aneurysm
Aortic aneurysm is defined as a focal dilation of more than 50% of its original diameter. Aortic aneurysm can develop in thoracic or abdominal region of the aorta, each with unique pathology and molecular signatures [5]. Aortic aneurysm is often asymptomatic until it ruptures causing significant morbidity and greater than 80% mortality which accounts for 1-2% of total death in the industrialized countries [7-9]. Other complications of aortic aneurysm include dissection (tearing of the intimal wall with entry of luminal blood into the wall), embolism, or compression of an adjacent structure. Abdominal aortic aneurysm (AAA) is the more prevalent form of aneurysm affecting approximately 6-8% of men aged over 60, compared to thoracic abdominal aneurysm.

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Vascular ECM remodelling in AAA

Vascular ECM is a dynamic structure with continuous turnover whereby existing structural proteins are replaced with newly synthesized proteins. Therefore, any change in the vascular environment can be reflected in the ECM composition that attempts to maintain a homeostatic environment for optimal function. VSMCs have been identified as the main source for ECM proteins [3] that determine the mechanical properties of the arterial wall. Collagen fibres in the aortic wall provides the tensile strength required for the inflation of the wall during cardiac systole without rupture, while elastin lamella underlie the recoil property of the aorta which is essential during cardiac diastole. This elasticity of the aorta is nonlinear which accommodates the increasing pressure without rupture of the aortic wall during systole. Compromised integrity of the vascular ECM can result from impaired synthesis of ECM structural proteins or aberrant proteolysis. The most common cases of aortic aneurysm secondary to impaired ECM synthesis is Marfan syndrome, a genetic disease caused by a mutation in the gene encoding fibrillin-1, a critical component for proper assembly of elastin in the aortic wall. Although abdominal aortic aneurysm has been reported in patients with Marfan syndrome, thoracic aortic dilation and rupture is the most common form of aortopathy in these patients [20,21]. Excellent reviews have been published on thoracic aortic aneurysm [20,22,23], in this review we will focus on the mechanisms that underlie AAA development.

In AAA, the structural degradation of the aortic wall impairs these mechanical properties of the aorta, emphasizing the key role of proteases that have been found to be elevated in the aneurysmal tissue in this process [5,18]. Among the different classes of proteases, matrix metalloproteases (MMPs), serine and cysteine proteases have been found to contribute to aortic aneurysm formation (Table 1).

Matrix metalloproteases and their inhibitors in AAA

| Mouse strain | Aneurysm Model | Phenotype | Ref. |
|--------------|----------------|-----------|------|
| MMP2-/- | CaCl₂, abdominal | Protection against AAA | [46] |
| MMP3-/-ApoE-/- | Cholesterol rich diet | Reduced thoracic and abdominal aneurysm formation (sustained atherosclerotic plaque). | [58] |
| MMP8-/- | Elastase, abdominal | No change in AAA size | [59] |
| MMP9-/- | CaCl₂, thoracic CaCl₂, abdominal Elastase, abdominal | Attenuated TAA Protection against AAA Protection against AAA | [45] [46] |
| MMP12-/- | CaCl₂, abdominal Elastase, abdominal Ang II + anti-TGFβ | Attenuated AAA No change in AAA size Protection against AAA | [45] [46] [56] |
| MMP13-/- | Elastase, abdominal | Reduced AAA aortic dilation | [97] |
| Cathepsin K-/- | Cathepsin K-/ApoE-/- | Elastase, abdominal Ang II + high fat diet | Reduced AAA dilation Unchanged AAA | [66] [64] |
| Cystatin C-/ApoE-/- | Ang II + high fat diet | Exacerbated AAA dilation | [66] |
| MCP4-/- (mast cell protein-4, Chymase) | Elastase, abdominal | Reduced AAA dilation | [66] |
| Pig-/- | CaCl₂, abdominal | Protected against AAA | [70] |
| Timp1-/- | CaCl₂, Thoracic | Exacerbated TAA | [74] |
| Timp1+/ApoE-/- | Cholesterol-rich diet | Enhanced thoracic and abdominal aneurysm formation, (reduced atherosclerotic plaque) | [73] |
| Timp2-/- | CaCl₂, abdominal | Attenuated AAA | [75] |
| Timp3-/- | Ang II infusion | Suprarenal AAA formation | [48] |
| Timp3-/-MMP2-/- | Ang II infusion | Exacerbated AAA dilation | [48] |

Table 1: Summary of abdominal aortic aneurysm formation in protease or TIMP-deficient mouse models. AAA = abdominal aortic aneurysm; ApoE = apolipoprotein E; CaCl₂ = calcium chloride; MCP-4 = mast cell protein-4; MMP = matrix metalloproteinase; plg = plasminogen; TAA = thoracic aortic aneurysm; TIMP = tissue inhibitor of matrix metalloproteinase.
ranging from 21-30 kDa that serve as potent endogenous inhibitors of MMPs through a covalent bond between their N-terminus and the catalytic domain in the activated MMPs [24]. All four TIMPs (TIMP1-4) are found in vertebrates and their expression levels are modulated during tissue remodelling or development [29]. TIMP3 is unique as it is the only TIMP bound to the ECM via its C-terminal domain that provides extra reservoir by prolonging its half life [30] and has a broad inhibitory substrate profile which includes a number of disintegrin and metalloproteinase (ADAMS) [24,31].

In AAA samples from patients, MMP1 and MMP9 mRNA levels were elevated compared to non-aneurysmal aorta [32,33], while MMP1, MMP12 and MT1-MMP proteins levels were also elevated [34]. Among 14 MMPs and 4 TIMPs analyzed in samples of aortic wall from patients with AAA, onlystromelysin-1 (MMP3) and TIMP3 were found to be elevated [35]. MMP12, also known as macrophage elastase, has been reported to be prominently produced by aneurysm-infiltrating macrophages, and localized within the degenerating aortic media of AAA, where it is bound to residual elastic fragments [36].

Differing reports on levels of TIMPs in AAA have been made. Studies on AAA biopsies from patients have shown increased TIMP1 and TIMP2 mRNA levels [32], unaltered TIMP2 [33], and elevated TIMP3 with unaltered TIMP1 and TIMP2 levels [34]. While TIMP1 inhibits a large number of MMPs, it does not inhibit MT1-MMP [37]. TIMP2 is a potent inhibitor of MMP2 and MT1-MMP [38], but in a dose-dependent manner can also activate pro-MMP2 through formation of a trimolecular complex with MT1-MMP [39]. A few studies have utilized the ratio of MMP2 to TIMP2 levels as another index of proteolysis in the ECM [32,40] although this approach does not account for contribution of TIMPs such as TIMP3 and TIMP4 which are also potent inhibitors of MMP2.

It is important to note that the data available from AAA patients are achieved at the late stages of disease, and the patients are often receiving medications that could alter the molecular events in the aortic tissue. Lack of availability of aortic tissue samples during the early stages of AAA is a limiting factor in developing an effective treatment for this disease. Animal models provide a valuable tool to explore and determine the early contributors to disease development and progression with the ultimate aim of preventing the disease or halting its progress.

Experimental models of AAA targeting proteases and their inhibitors

Animal models of AAA have been implemented to recapitulate features of AAA in humans such as adverse ECM remodelling, medial degeneration, inflammation, thrombus formation and rupture. AAA models in rats were reported over 2 decades ago [41] and since then AAA has been generated and studied in different rodent models [42-44], however mouse models have gained dominance over others primarily due to availability of genetically modified mice [18]. Three most common experimental models of AAA include transient intraluminal infusion of elastase (a pancreatic extract) [45], adventitial exposure of a high concentration CaCl2 solution [46], or chronic subcutaneous infusion of a hypertensive dose of Angiotensin II (Ang II) in a hypercholesteremic [47] or normocholesteremic background [48]. Hypercholesteremia in mice is achieved by deficiency of apolipoprotein-E (ApoE) or low density lipoprotein receptor (LDLR) combined with high fat or high cholesterol diet [49-51]. The Ang II infusion model allows for detection of aneurysm throughout the aorta while the elastase infusion and CaCl2 exposure models provide information about regional aortic susceptibility.

The growing list of genetically modified mice with targeted MMPs, proteases, or TIMPs subjected to different models of aortic aneurysm provide valuable insight into the role of these ECM-regulatory proteins in development and progression of AAA (Table 1). In addition to the proteases produced by VSMCs, infiltrating inflammatory cells can contribute to enhanced proteolysis in the aortic wall. Neutrophils generate MMP8, MMP9 [52,53] and MT6-MMP(MMP25) [54], while macrophages produce a number of MMPs including MMP-1, -3, -7,-8, -9 and -12 [55]. Mice deficient in either MMP2 or MMP9 did not develop AAA following CaCl2 treatment [46]. Similarly, MMP9+/- mice showed attenuated TAA induced by CaCl2 despite a significant rise in MMP2 [56]. Reconstitution of wild type macrophages led to the development of AAA in MMP9-/- but not in MMP2-/- mice [46], demonstrating that an interaction between MMP9 produced by macrophages and MMP2 from native VSMCs is required for development of AAA. Deficiency of macrophage-derived MT1-MMP [57] also attenuated CaCl2-induced AAs in mice, indicating that multiple macrophage-derived factors can contribute to AAA formation. MMP3 deficiency reduced frequency of aortic aneurysm formation in hypercholesteremic ApoE-/- mice despite sustained prevalence of atherosclerotic lesions [58]. MMP8 deficiency in mice did not alter the size of elastase-induced AAs, whereas neutrrophil depletion prevented AAA through a mechanism independent from MMP2 and MMP9 pathways [59]. This study demonstrates that additional factors produced by neutrophils (e.g. neutrophil elastase) are essential in AAA formation. Interestingly, deficiency in MMP12 a macromolecules-derived elastase, improved CaCl2-induced AAA [60], but not elastase-induced AAA in mice [45].

Non-MMP cysteine and serine proteases also contribute to the proteolytic degradation of the aortic wall in AAA. Cathespin K, L and S, all cystein proteases have been found in AAA tissues from patients [61,62]. Cathespin S and K are potent elastases that are produced by VSMCs and macrophages in atherosclerotic plaques, and have been found at the site of arterial elastin damage [63]. Cathespin K-deficiency attenuated elastase-induced AAA [64], but not Ang II-induced AAA in ApoE-/- high fat-fed mice [49]. Calpain is another cystein protease that is elevated in response to Ang II in ApoE-deficient atherosclerotic mice, and its pharmacological inhibition reduced AAA in these mice [65]. Cystatin C is an inhibitor of cysteine proteases and is expressed in healthy VSMCs but severely reduced in atherosclerotic plaques as well as aneurysmal tissue from AAA patients [62]. Cystatin C-deficiency exacerbated Ang II-induced AAA in atherosclerotic mice [66].

Among serine proteases, role of chymesases and plasminogen activators have been studied in AAA. Chymesases are mast-cell restricted serine proteases that have been shown to activate MMP9 in AAA patients [67]. Deficiency in MCP4 (mast cell protease 4) but not MCP5 reduced AAA formation up to 8 weeks after elastase infusion [68]. Plasminogen binds to the ECM and upon conversion to plasmin, by tissue or urokinase plasminogen activator (uPA or tPA), degrades multiple ECM proteins through activation of collagenases. In addition, tPA can release degradate neutrophils and release neutrophil MMPs and elastase [69]. Plasminogen-deficiency attenuated CaCl2-induced AAA in mice through reduced trans-ECM migration of macrophages and decreased MMP9 activation [70]. Moreover, deficiency in uPA, but not tPA, abrogated aortic aneurysm formation in hypercholesteremic ApoE-deficient mice through inhibiting activation of MMP3, MMP9 and MMP13 [71]. Interestingly, in a recent study it was reported that tobacco smoke exposure exacerbates AAA independent of elastase activity but possibly through recruiting leukocytes [72].

TIMP1 was the first TIMP whose role in aortic aneurysm was
examined. In a hypercholesteremic mice, TIMP1 deficiency led to increased incidence of aortic aneurysm but reduced formation of atherosclerotic plaque lesions [73]. Consistently, a CaCl₂ model of TAA showed more severe aneurysm progression in TIMP1⁻/⁻ mice with continual dilatation of the aorta up to 8 weeks after CaCl₂ treatment, whereas in parallel wildtype mice aortic dilatation plateaued by 4 weeks [74]. TIMP2-deficiency however proved to be beneficial in a CaCl₂ model of AAA [75]. This beneficial effect was attributed to reduced conversion of pro-MMP2 (72 kDa) to its cleaved (64 kDa). Role of TIMP3 in aortic aneurysm has been reported recently in a model of Ang II infusion in the absence of any metabolic phenotypes. Infusion of TIMP3⁻/⁻ mice with a hypertensive dose of Ang II resulted in a suppressed hypertensive response [76], but development of AAA after 4 weeks of Ang II infusion, whereas wildtype mice, that had increased TIMP3 levels in the abdominal aorta, did not exhibit AAA [48], suggesting a protective function of TIMP3 in this process (Figure 1). Although elevated MMP2 activation was detected in the abdominal aorta after 2 weeks of Ang II infusion, ablation of MMP2 in TIMP3⁻/⁻ mice exacerbated AAA dilatation and increased the rate of aortic rupture, primarily due to heightened inflammation. Treatment with a broad spectrum MMP inhibitor (PD166793) prevented AAA formation in TIMP3⁻/⁻ and TIMP3⁻/⁻/MMP2⁻/⁻ mice [48].

Figure 1: Lack of TIMP3 increases susceptibility to AAA in the absence of metabolic syndrome. A) representative images of mouse aorta showing that 4 weeks of Ang II infusion (1.5 mg/Kg/day) resulted in AAA formation in TIMP3⁻/⁻ but not in WT mice. (Modified from [48]). B) TIMP3⁻/⁻-Ang II mice exhibited 18% mortality due to aortic rupture in the suprarenal region where aneurysm was detected. C) Different morphologies of AAA in TIMP3⁻/⁻-Ang II mice. D) Schematic of molecular events leading to AAA in the absence of TIMP3.
Overall, these studies demonstrate that distinct molecular mechanisms are involved in different models of aortic aneurysm, and while it was once believed that generally a reduction in MMPs and increase in TIMPs would provide beneficial effects, it is important to acknowledge that the interaction between these molecules is quite complex and deserves detailed investigation in different AAA models.

Aortic aneurysm occurs independently from hypertension and atherosclerosis

Although it was initially believed that AAA was the consequence of advanced atherosclerosis [77], it has become increasingly evident that there is no causal link between atherosclerosis and AAA [12]. While age, gender and body surface area have been found to be major determinants of aortic dimensions, aortic atherosclerotic plaques were weakly associated with aortic dilatation risk factors [78]. Tromso study reported that among the 6446 men and women studied, consistent dose-response relationship was not found between atherosclerosis and abdominal aortic diameter, suggesting that atherosclerosis is not the causal event in AAA development but perhaps occurs in parallel or secondary to aeurysmal dilatation [79]. Consistently, therapies against atherosclerosis have not been effective in treating AAA in humans [10,80]. Animal studies have been in agreement with these findings as a clear dissociation between atherosclerotic lesions and aortic aneurysm formation has been reported [58,73,81]. MMP3−/−/ApoE−/− mice (on cholesterol-rich diet) showed reduced frequency of aortic aneurysm formation despite sustained prevalence of atherosclerotic lesions compared to ApoE−/− mice [58]. Conversely, hypercholesterolemic TIMP1−/−/ApoE−/− mice showed increased incidence of aortic aneurysm but reduced formation of atherosclerotic plaque lesions [73].

Hypertension is another co-morbidity but independent from AAA development. Ang II-mediated AAA formation in ApoE−/− and LDLR−/− mice was independent of the blood pressure as suppression of hypertension (by hydralazin administration) did not prevent AAA or atherosclerosis in these mice [51]. Recently, we reported that despite the suppressed Ang II-induced hypertension in TIMP3−/− mice, these mice develop AAA after 4 weeks of Ang II infusion while WT mice did not [48]. Overall, sufficient evidence indicate ECM degradation and as the central and initiating event in development of AAA, while co-morbidities such as atherosclerosis and hypertension may or may not be present with AAA.

Doxycycline, a potential treatment for aortic aneurysm

Over that past few decades a number of drugs have been used to treat AAA, however the search continues. Beta-receptor blockers, angiotensin-converting enzyme (ACE) inhibitors and statins have not shown consistent beneficial effects in patients [10,82]. Inhibition of c-Jun N terminal kinase (JNK) prevented formation of aneurysm in a CaCl2 model of AAA [83], however clinical efficacy of this approach remains to be determined. Doxycycline, a member of the tetracycline antibiotic group commonly used to treat infections, has been shown to exert beneficial effects and has been approved by FDA as an MMP-inhibitor in periodontal diseases [85,86]. Doxycycline has been shown to exert beneficial effects in a number of animal studies including the elastase-infusion model of AAA in rats [87,88] and mice [45], CaCl2-induced AAs in mice [89], and in AngII-infused hypercholesteremic mice where it markedly reduced the rate of development of AAA, aortic diameter and aortic rupture without altering atherosclerotic plaque formation [90,91]. However, a recent study reported that doxycycline treatment did not prevent progression of established AAA in hypercholesteremic mice [92].

Reports on the beneficial effects of doxycycline treatment in AAA patients appear promising in controlling AAA expansion, although not its regression. Prolonged administration of doxycycline was well tolerated by AAA patients [93]. A randomized trial in patients awaiting open AAA repair showed that 2 weeks of doxycycline treatment reduced inflammation in AAA biopsies [94], while a randomized trial in patients who underwent endovascular AAA repair showed that doxycycline reduced circulating levels of MMPs which were suggested to be a marker of endograft failure [95]. Currently two larger randomised trials are examining the efficacy of doxycycline in patients with small AAAs, with one of these studies expected to report in 2014 [10]. Since non-MMP proteases have also been shown to contribute to AAA development and progression, incorporation of other protease inhibitors with doxycycline could result in synergistic beneficial effects.

Conclusion

Aortic aneurysm remains a major health burden which due to it asymptomatic nature often is undetected until it ruptures causing devastating morbidity and mortality. AAA results from structural degradation of the aortic wall due to uncontrolled proteolysis. Protease inhibitors such as doxycycline appear to be a promising treatment for AAA although it remains to be determined whether doxycycline can reverse aortic dilation in AAA patients. In addition, since non-MMP proteases also contribute to AAA development and progression, a combination-therapy incorporating other protease inhibitors with doxycycline could convey synergistic beneficial effects.

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