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New Insight in Aetiopathogenesis of Aortic Diseases

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Abstract *Background:* Knowledge in the aetiopathogeny of aortic disease helps to characterise aortic lesions better and determine the risk of evolution and therapeutic strategies as well. This article focusses on aneurysms and dissections, and excludes causes related to infection, systemic inflammatory diseases and trauma.
Methods and results: The biomedical literature of the past 10 years has been reviewed here. Aortic diseases are heterogeneous along the aorta as far as their genetic determinants, contribution of smooth muscle cells, inflammation and thrombus formation are concerned. Degradation of extracellular matrix by proteases causing aortic disease is a 'terminal' event, modulated by genetic background, haemodynamic strain, cellular events and thrombus formation. New genetic determinants of aortic disease have been identified. Proteases degrading the aortic wall are derived from a variety of cell types in addition to macrophages, including neutrophils on the luminal thrombus, mesenchymal and endothelial cells in the wall. Smooth muscle cells contribute to aortic wall homeostasis against inflammation and proteolysis. The degradation of the wall is followed by, or paralleled with, a failure of aortic reconstruction.
Conclusions: Aortic diseases are diverse, and involve a multiplicity of biological systems in the vascular wall and at the interface with blood. Future research needs to unravel distinct cellular and molecular mechanisms causing the clinical events, in particular, dissection, expansion of already formed aneurysms and rupture.

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The aorta is made up of an abundant extracellular matrix (ECM) which is responsible for its resistance to arterial flow and pressure. The structural and functional consequences of the weakening of the aortic wall are dilatation, tortuosity, dissection and rupture. Aortic diseases are differently distributed along the aorta, according to their aetiopathogeny. The frequency of abdominal aortic aneurysms (AAAs) is more than 3 times higher than that of thoracic and dissection aneurysms.[1,2] New insights in the role of gene mutations and factors determining the heterogeneity of diseases along the aorta have changed our understanding of the determinants of aortic diseases. Identification of multiple sources of proteases degrading aortic ECM and the role of vascular smooth muscle cells (VSMCs) and endothelial cells provide us with different mechanisms accounting for the multiple aspects of aortic diseases.

Genetic Determinants of Aortic Disease: the Example of Marfan Syndrome

The observation that different individuals in a family have have an aortic disease has prompted the idea that aortic aneurysms and dissections may have strong genetic determinants. A family history is documented in 20% of the cases of thoracic aneurysms[3] and AAAs.[1] Aortic diseases can be associated with multiple characteristic abnormalities in other tissues in a syndromic pattern.[4] There is a gradation of severity of the clinical course of thoracic and abdominal aortic diseases, from sporadic to familial and syndromic cases, with symptoms at younger age, faster aortic dilatation and higher rupture risk in the latter.[1,3] Numerous gene mutations in transgenic mice cause vascular rupture *in utero* because of inadequate vasculogenesis. Genetic syndromes in humans are compatible with embryonic vasculogenesis and allow for survival for two decades of life, although very severe paediatric cases have been reported as well. In thoracic aneurysms and dissections, mutations have been identified in genes encoding for ECM proteins, growth factor receptors and proteins implicated in cell contraction, resulting in inadequate capability of the aortic wall to resist haemodynamic strain.[5]

The Marfan syndrome (MFS) is a prototype for the identification of gene mutations causing aortic disease.[4] It is an autosomal dominant hereditary disorder affecting skeletal, ocular and cardiovascular systems.[4] Recent advances provide insights into the mechanisms by which mutation in a single gene triggers a cascade of molecular, cellular and tissular alterations which ultimately lead to aortic dilation, dissection and rupture. MFS is caused by heterozygous mutations in the gene encoding fibrillin 1, an ECM protein which serves as a template for elastin microfibril formation. Aortic and skeletal features of MFS have been reproduced in mice by mutating the fibrillin 1 gene. Abnormal fibrillin 1 encoded by the mutated allele impairs the formation of microfibrils by non-mutated fibrillin 1, in a dominant-negative pattern. In other words, it is a case of heterozygote disorder in which the function of the normal protein is altered by the abnormal protein. Aortic manifestations in MFS are not entirely explained by abnormal elaboration of the elastin network. Besides, the Williams–Beuren syndrome caused by a micro-deletion in the elastin gene itself is characterised by aortic stenoses, in sharp contrast to MFS.[6] After a cascade of events, fibrillin 1 mutation results in fragmentation of the elastin network by matrix metalloproteinases (MMPs) which are up-regulated in humans and mice with MFS.[7,8] Administration of doxycycline, an inhibitor of MMP, controls aortic expansion and rupture in MFS mice.[8] A direct link between fibrillin 1 gene mutation and MMP-driven proteolysis is suggested by the observation that mutated fibrillin 1 in MFS has an increased susceptibility to proteolysis, and that its fragments up-regulate MMP expression and are powerful chemo-attractants for macrophages.[4] These data provide a model in which a single initial genetic defect triggers a cascade of events organised into a loop which amplifies tissue destruction.

A second mechanism by which fibrillin 1 mutations cause aortic disease in MFS involves the growth factor/cytokine transforming growth factor-beta1 (TGF-beta1). TGF-beta1 protein and signalling are increased in cells from human MFS aortas and in emphysematous lung from fibrillin 1 mutated mice. Enhanced TGF-beta signalling in MFS is thought to increase VSMC apoptosis and impair aortic healing because of hyaluronan up-regulation. TGF-beta signalling is instrumental in aortic dilatation in fibrillin 1 mutated mice, since its blockade, directly by anti-TGF-beta1 neutralising antibody or indirectly by the administration of losartan, an angiotensin II type 1 receptor antagonist, prevents aortic aneurysm formation.[9] The mechanisms by which fibrillin 1 gene mutations up-regulate TGF-beta1 signalling are not fully understood. The fibrillin family is closely related to the latent-TGF-beta-binding protein (LTBP) family, a reservoir of latent (inactive) TGF-beta1, regulating its activation. There are indications that upon mutation, abnormal fibrillin 1 has a low affinity for latent-TGF-beta1 and thus releases excessive amounts.

More than 600 mutations in the fibrillin 1 gene have been identified not only in MFS patients, but also in those with isolated cranial manifestations without aortic disease, or with isolated aortic disease. These mutations affect various functional domains of the fibrillin 1 protein and have various biological consequences.[4] Mutations in genes other than fibrillin 1, encoding proteins which also directly or indirectly regulate TGF-beta activity and signalling, have been identified in patients with aortic disease and/or MFS or related disorders.[4] These mutations result in an increase in TGF-beta1 signalling rather than a loss of function. Mutations in TGF-beta receptors 1 and 2 cause Loyes–Dietz syndrome, in which the ascending aorta dilates to aneurysmal size, with tortuosities, ruptures and dissections.[10] Cases of non-syndromic familial thoracic aneurysms and dissections have also been associated with mutations in TGF-beta receptors 1 and 2. Mutations in the genes encoding fibullin 1 and 4, which regulate TGF-beta activation[4] result in enlargement of the ascending aorta in mice. Mutations in the glucose transporter GLUT10 causing up-regulation of TGF-beta1 are associated with tortuosity of the aorta in mice and humans.[11] These data establish that excessive TGF-beta signalling may result from mutations of a variety of proteins and is linked to thoracic aortic aneurysms and dissections, both syndromic and familial.

Mutations in genes encoding other proteins with no apparent link to TGF-beta signalling have been identified in patients with aortic disease. Collagen III mutations cause

vascular type IV Ehlers—Danlos syndrome. Mutations of genes encoding contractile proteins in VSMC, like the ACTA2 gene encoding smooth muscle cell alpha-actin[12] and the MYH11 gene encoding myosin heavy chain[13] are responsible for familial forms of thoracic aneurysms. Mutations in myosin heavy chain are associated with an up-regulation of pro-inflammatory angiotensin II in the aneurysmal wall and of insulin growth factor. This fact suggests that altered contractile properties may not be the mechanism by which aneurysms form after mutations of myosin heavy chain, in the same manner that a defect in elastin may not be the direct cause of aortic disease in MFS. Rather, despite the diversity of genetic defects, aortic diseases develop through a common pathway represented by elastin destruction by some level of proteolysis, cystic medial necrosis and altered biomechanical properties. In favour of this view, in patients with an aneurysm of the ascending aorta, platelets and prothrombin are activated in proportion to the aortic diameter, independently of the aetiology of aortic dilation, that is, in MFS, aortic valve bicuspidy and degenerative disease.[14]

Proteases in Aortic Disease

The spectrum of proteases found in excess in aortic aneurysms and dissections includes MMPs, cathepsins, chymase and tryptase, neutrophil-derived serine elastase and the enzymes of the plasmid pathway tPA, uPA and plasmin. Some of these proteases may be involved in some level of tissue reconstruction and/or remodelling. However, the main role assigned to proteolysis in aortic diseases, particularly in aneurysms, is ECM destruction. This perception stems from the pioneering work of Dobrin, who showed that *in vitro* perfusion of arteries with elastase or collagenase triggers vessel dilation, elongation and rupture.[15] The instrumental role of proteolysis has been further documented by Michel and co-workers who developed a reproducible animal model of AAA by perfusing rat aortas with elastase *in vivo*.[16] The localisation of the elastase MMP-12 to residual elastin fragments in the media of human AAAs provides strong evidence of ECM-targeting by proteases. In tissues, the proteolytic activity results from a balance between proteases and their physiologic inhibitors. TIMP-2, a broad-spectrum MMP inhibitor, and PAI-1, an inhibitor of tPA and uPA, are less expressed in the wall of AAAs than in athero-occlusive aortic disease,[1] suggesting that ECM destruction is caused by a decrease in inhibitors in addition to an increase in proteases. The role of MMPs and enzymes of the plasmin pathway has been demonstrated using gene and cell transfer to overexpress TIMP-1[17] and PAI-1,[18] and by PAI-1 gene invalidation, thereby shifting protease/antiprotease balances.[19] The overexpression of both TIMP-1 and PAI-1 prevents experimental AAA formation and rupture, and preserves elastin in the media layer by decreasing MMP-9 activity, but through different mechanisms. TIMP-1 overexpression was shown to inhibit directly active MMP-9 on gelatin zymograms,[17] whereas PAI-1 overexpression blocked the activation of (inactive) pro-MMP-9 by blocking tPA and uPA.[18] Inhibition of protease expression by gene invalidation has shown that MMP-3, MMP-9 and MMP-12 drive AAA formation in the elastase model in mice. As a demonstration of its role, polymorphism in MMP-9 predisposes to AAA in humans.[20] At the level of the thoracic aorta doxycycline, an inhibitor of MMP-9 synthesis and activity limits dilatation of the ascending aorta in MFS mice.[8] In humans with MFS, however, levels of MMP-9 and an array of other MMPs in aneurysms of the ascending aorta are low, questioning the role of proteases in this setting.

Diverse Sources of Proteases (Fig. 1)

Mononuclear leucocytes

Once the role of proteases is recognised, particularly in aortic aneurysms, their origin and how their accumulation in the aortic wall are regulated remain important questions. The case of the ascending aorta regarding inflammation as a potential source of proteases is complex and may vary according to its aetiological background. Whether macrophages infiltrate the ascending aorta of MFS patients is debatable. In non-MFS patients with disease on the ascending aorta, T lymphocytes and macrophages have been observed in type A dissection and aneurysms of mixed aetiologies.[21] In AAAs, the relationship between inflammation and protease expression is more documented than in diseases of the ascending aortas. Inflammation driven by auto-immunity has been proposed by Tilson as a mechanism of tissue destruction in AAAs.[22] Activated T and B lymphocytes tend to gather in the adventitia in follicular structures.[23] The pharmacological inhibition of c-Jun kinase, a signalling molecule, causes AAA-regression in a mouse

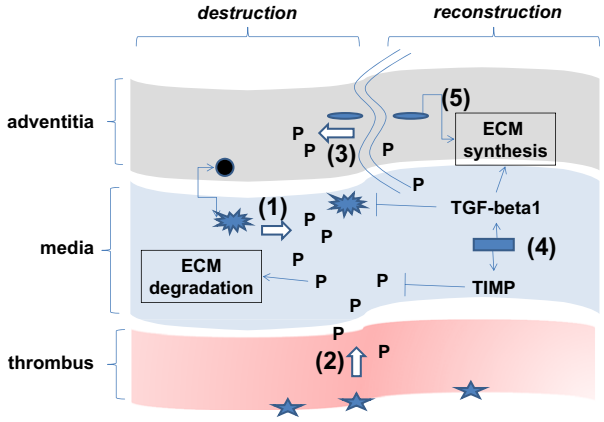

Figure 1 Proposed mechanisms for destruction and reconstruction in the aortic wall. Different sources of proteases. (1) The interplay between lymphocytes and macrophages regulates production of proteases (P). (2) Neutrophils adsorbed at the surface of the luminal thrombus liberate proteases which diffuse centrifugally to the aneurysmal wall, causing ECM destruction and VSMC death (anoïkis). (3) Angiogenesis in the adventitia, spreading to the media, causes influx of leukocytes and concentrates proteases. Fibroblasts in the adventitia may also produce proteases. The three mechanisms may not be active simultaneously in a same type of lesion at the same time of its evolution. (4) VSMCs in the media produce inhibitors of proteases, and TGF-beta1 which, under particular circumstances, triggers ECM production and down-regulates inflammation. (5) Fibroblasts in the adventitia produce ECM.

model, while decreasing wall infiltration by macrophages as well as the aortic MMP-9 content.[24] The higher level of expression of MMP-9 in larger than in smaller AAAs is concordant with the idea that rupture, inflammation and proteolytic burden are closely related. These observations are solid data. However, discriminating the exact role of proteolysis derived from mononuclear leucocytes in aortic disease remains difficult. In fact, recent evidence suggests that mononuclear phagocytes may not be the only cellular source of proteases, let alone the most significant.

Polymorphonuclear neutrophils and thrombus

Michel et al. have shown that the luminal thrombus of AAAs appears to be a reservoir of proteases delivered by neutrophils. It develops over years, but is covered by a thin layer of fresh fibrin which traps neutrophils.[25,26] Its outer aspect is sometimes separated from the aneurysmal wall by a liquid where proteases accumulate.[25] These data support the view that neutrophils adsorbed on the thrombus are major sources of proteases, distributed centrifugally from the thrombus surface to the wall of AAAs. In addition to degrading ECM, neutrophil-derived elastase detaches VSMCs from ECM, causing cell death, a process named anoïkis, thereby contributing to the absence of mesenchymal cell development in the thrombus.[26] In mice, depletion in polymorphonuclear prevents formation of AAA after aortic elastase infusion.[27] In type A dissection in humans, plasma levels of MMP-9 increase as early as 1 h after symptom onset, suggesting that polymorphonuclear degranulation accounts for protease release in this acute context.[28]

Coincident with the work of Michel's group, Schwedenborg and co-workers have documented that the AAA wall covered by the thrombus is thinner, with fewer VSMCs and a more severely injured elastin network than wall areas uncovered by it.[29] These data are concordant with the clinical observations that AAA expansion and risk of rupture are correlated to thrombus size.[30] In chronic type B dissections of the aorta, presence of a thrombus in the circulating false lumen is associated with an increased mortality,[31] another indication that the thrombus modulates evolution of aortic diseases, possibly by trapping neutrophils which deliver proteases to the aortic wall.

Mesenchymal cells and micro-vessels

Mesenchymal cells, for example, VSMCs and fibroblasts, are other potential sources of proteases in aortic disease. Newman and co-workers have observed that, unlike MMP-3 and MMP-9, the MMP-1 collagenase is co-localised with mesenchymal cells in AAA wall.[32] MT1-MMP, a cell membrane-bound MMP instrumental in MMP-2 activation, is localised in VSMCs in AAAs. Mesenchymal cells may be responsible for the destruction of collagen by producing and releasing MMP-1 and by contributing to elastin injury through the activation of MMP-2.

Strikingly, but in line with this view, inflammation (e.g., macrophages and T lymphocytes) is not the prominent feature in rupture edges of AAAs and is less than in non-ruptured areas or walls of the same AAAs. Rather, ruptured areas present significantly increased amounts of immature micro-vessels, with an excess of total and activated MMPs[33] and with cells presenting an immunostaining pattern suggesting fibroblasts. These data need further confirmation, but suggest that micro-vessels and fibroblasts are prominent sources of proteolytic enzymes at sites of rupture in AAAs.

From these observations it appears that aortic lesions are highly heterogeneous with regards to the source of proteases. Presence or absence of a luminal thrombus and formation of rupture modulate the cellular sources of proteases.

Vascular Smooth Muscle Cells and Aneurysm Remodelling (Fig. 1)

The outcome of VSMCs in lesions of the ascending aorta is complex. In (non-atherosclerotic) aneurysms of the ascending aorta, VSMC density may vary according to patient's age and gender and also according to the area of the aneurysm in which quantification is performed.[21] Conversely, depletion of VSMCs in the media is a characteristic of atherosclerotic aortic aneurysms.[1] In AAAs, VSMC death has often been regarded as a bystander effect of wall destruction. Accumulating data support the concept that VSMC disappearance is a permissive factor for AAA formation and expansion, rather than a bystander event. Not only do VSMCs decrease at sites of arterial ECM destruction by inflammation and proteolysis in AAA media, but also in ruptured fibrous caps of atherosclerotic plaques in the intima. In a rat model of AAA, we have shown that addition of VSMCs prevents AAA formation[34] and suspends expansion of already formed AAAs.[35] Another group has shown that delivery of bFGF, a growth factor for VSMCs, prevents formation of experimental AAAs.[36] Several mechanisms explain the fact that addition of VSMCs stops expansion of AAAs. One such mechanism is the making of new ECM by VSMCs.[35] The other is the down-regulation of inflammation and proteolysis in the vicinity of added VSMCs.[34,37] VSMCs exert a paracrine effect that down-regulates effectors of tissue destruction, by producing TIMPs and TGF-beta1. We have established that TGF-beta1 overexpression by endovascular gene transfer stabilises the diameter of expanding AAAs.[38]

In addition to its impact on inflammation and proteolysis, the decrease in the number of VSMCs in AAAs may alter the ability of the diseased aorta to respond to radial stress in an adapted manner. Chronicity and irreversibility of AAAs are consequences of inadequate responses to injury or functionally inadequate healing. VSMCs support vessel wall hypertrophy in response to radial strain in hypertension and during arterialisation of veins grafted into the arterial system in bypass surgery.[39] VSMCs mechanically stimulated *in vitro* produce TGF-beta1, ECM and inhibitors of proteolysis, which contribute to increasing artery wall mass.[40] In sharp contrast to VSMCs, macrophages respond to mechanical stress by producing proteases which degrade ECM. As a result, the effect of wall stress on VSMC-depleted, macrophage-infiltrated AAAs may be wall destruction, rather than a trophic response.

As a consequence of VSMC depletion, the AAA wall tends to heal in a particular manner. Whereas hypertrophic

remodelling in vessels rich in VSMCs is elaborated in the media and intima, AAAs compensate for atrophy by increasing thickness of the adventitia, a process governed by fibroblasts rather than VSMCs. However, in other aetiological backgrounds, the aorta demonstrates robust healing capacities. Clinicians know how the inner medial flap in chronic dissections thickens over time. Whether differences in aortic healing between dissections and AAA are due to differences at the level of the aortic lesion or to differences in patient homeostasis remains undefined. Supporting the latter hypothesis, the poor capabilities of tissues to heal in patients with AAAs expand beyond the aorta, as demonstrated by the increased number of aneurysmal degeneration of venous bypasses in patients with aneurysms.

Topologic Determinants of Aortic Disease (Table 1)

Heterogeneity of aortic disease along the aorta

The distribution of prevalence and causes of aneurysms along the aorta are highly heterogeneous. Of the thoracic aneurysms, 50% are located on the ascending aorta, 10% on the cross and 40% in the descending aorta.[3] There is a gradient of frequency of identified monogenic defects associated with aneurysms, from the ascending to the abdominal segments of the aorta. Atherosclerosis is associated with aneurysms from the aortic arch to its end, but spares the ascending aorta, in which aetiopathogenic backgrounds are haemodynamic factors, aortic valve bicuspidy, monogenic defects and degeneration. The tropism of atherosclerotic aneurysms excluding the ascending aorta is further supported by the observation that smoking and atherosclerotic plaque burden are correlated with dilatation of the thoracic aorta stating from the arch, but not of the ascending aorta. Atherosclerotic aneurysms are at least 3 times more frequent in the abdominal than in the descending thoracic segment of the aorta.

The macroscopic and histological appearance of aneurysms also differs according to their location along the aorta. The luminal aspect of aneurysms in the ascending aorta is essentially free from thrombus, in contrast to more distal aneurysms. The density of VSMCs in the media layer is also different, with a preserved density in the most dilated portion of aneurysms of the ascending aorta in patients with no MFS, and a decreased density in the media of AAAs. In aneurysms of the ascending aorta with tricuspid aortic valves, we have observed that VSMC density is decreased only in the transitional area in comparison with the maximal dilatation zone.[21] In any case, our observation and reports from others suggest that the media of aneurysms of the ascending aorta are re-populated by VSMCs, which is clearly not the case in AAAs.

Lastly, the pattern of micro-vessel infiltration is also different according to the site and cause of the disease. We have observed micro-vessels penetrating into the media layer of aneurysms in the ascending aorta, whereas those in the media of AAAs are observed only in ruptured areas.[21] Others have shown reduction in the number of vasa vasora in aneurysms of the ascending aorta in patients with mutations in smooth muscle cell alpha-actin genes, with possible ischaemia in the media layer. Whether these differences are determined by differences in the pathogenic process or in VSMCs and endothelial cell proliferation/survival according to their localisation along the aorta, needs to be determined. This topographic heterogeneity regarding aneurysms suggests that aetiopathogenic determinants are distributed according to gradients along the aorta.

One first determinant of the heterogeneity of aortic diseases may be the architecture of the aorta. Wolinsky and Glagov have proposed the concept of an elastic lamellar unit as a functional element of the aorta formed by an elastic lamella and VSMCs, and demonstrated correlations between blood pressure, aortic diameter and the number of elastic lamellar units across animal species.[41] The number of elastic lamellae decreases along the aorta, which also becomes thinner and smaller in diameter. The elastin to collagen ratio is constant along the aorta, except in its abdominal segment in which it is decreased. The aorta in acardiac foetuses does not acquire differentiation of its structure from cranial to caudal ends, demonstrating the impact of haemodynamic strain on vascular architecture. Since a minimal number of elastic lamellae needs to be injured for aneurysms to form, the reduced number of elastic lamellae may explain their abdominal tropism.

Haemodynamic strain, which varies along the aorta, may also determine the topology of aortic diseases. Several facts

Table 1 Differences between the ascending and the abdominal aorta

	Ascending aorta	Abdominal aorta	Consequences
Structure			
Elastin lamellae	—	number decreased/diameter	less provisional ECM
elastin/collagen	—	decreased	modified biomechanical properties
Embryonic origin of VSMCs	neurectoderm	mesoderm	differences in responses to TGF-beta
Shear stress	—	decreased	control of inflammation
Thrombus in aneurysms	no	yes	neutrophils adsoption and protease release
VSMCs in aneurysms	?	decreased	homeostasis against inflammation, proteolysis

suggest a relationship between strain and aortic disease. VSMC apoptosis predominates in the convex aspect of the ascending aorta in patients with bicuspid valves, even in the absence of an aneurysm.[42] The observation that patients with limb amputation have a higher prevalence of AAA suggests that asymmetric reflection of the systolic wave during the cardiac cycle causes injury to aortic ECM.[43] Shear stress and resistive conditions may modulate aneurysm formation. In rats, a higher shear stress prevents AAA formation after elastase infusion.[44] The protective effect of shear stress is associated with a shift of the destruction/reconstruction balance in the aortic wall. Macrophage infiltration, MMP-9 and pro-inflammatory reactive oxygen species expression are shut down by shear stress after elastase infusion, whereas VSMC density and expression of heme oxygenase 1[44] are increased. These experimental data are supported by clinical observations. In humans, a polymorphism resulting in a lower level of heme oxygenase expression is associated with a higher prevalence of AAA. The occurrence of AAA is higher in patients with peripheral vascular occlusive disease or spinal cord injury, two conditions in which shear stress is decreased. The lower prevalence of aneurysms in the thoracic segment in which flow resistivity is lower than in the abdominal segment also point to the role shear stress plays in protecting the thoracic aorta from inflammation, proteolysis and VSMC death. VSMC contractile force requires cyclic interactions between smooth muscle cell alpha-actin (encoded by the ACTA2 gene) and beta-myosin heavy chain (encoded by the MYH11 gene). The association of mutations in these two genes with familial thoracic aneurysms and dissections,[12,13] suggests that alterations in VSMC contraction predispose one to disease of the thoracic aorta, which is more mobile during the cardiac cycle than the abdominal aorta.

Another factor gradated along the aorta is the embryonic origin of VSMCs and how they respond to TGF-beta. VSMCs in the proximal end of the aorta originate predominantly from the neural crest, whereas more distally, they are derived from the mesoderm. The VSMC response to TGF-beta1 varies sharply according to their embryonic origin. TGF-beta1 potentiates growth and collagen I production in neural-crest-derived VSMCs (thoracic), whereas it inhibits growth and has no effect on collagen I synthesis in VSMCs from mesodermal origin (abdominal).[45] Mesodermal VSMCs produce more abundant tropo-elastin than neural-crest-derived ones. Since VSMCs are key determinants of aneurysm formation[34] and expansion,[35,44] differences in their survival, proliferation and ECM synthesis in response to a growth factor such as TGF-beta1 are expected to modulate aortic response to inflammation and proteolysis, and haemodynamic strain and be a determinant of the topology of aortic diseases. In return, TGF-beta1 induced in VSMCs exposed to radial strain modulates its growth. TGF-beta1 is a potent regulator of inflammation and proteolysis. Activation of TGF-beta1 signalling seems to be associated to the dilatation of the proximal aorta in MFS mice. In contrast, it is closely related to intimal plaque stability in atherosclerosis, and overexpression of mutated active TGF-beta1 by endovascular gene therapy powerfully inhibits growth of already formed AAAs in rats.[38] We have also documented that pharmacological induction of TGF-beta1 in rat and mouse models of abdominal aneurysms inhibits aortic dilatation, and decreases MMP expression in a culture model of human atherosclerotic AAA (manuscript submitted for publication).

Conclusion

The degradation of ECM by proteases causing aortic disease is a 'terminal' event, determined by the genetic background, VSMC death and growth, inflammation and thrombus formation. Aortic diseases are heterogeneous along the aorta, with regards to their determinants and the contribution of VSMCs, inflammation and thrombus formation. The degradation of the wall is followed by, or paralleled with, a failure of aortic reconstruction. Future research needs to unravel the specificities of very different events, namely diameter and length increase, aortic rupture and dissection, driven by different cellular and molecular mechanisms.

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