Published in final edited form as:

Curr Probl Surg. 2017 March ; 54(3): 95–155. doi:10.1067/j.cpsurg.2017.01.001.

Molecular pathogenesis of genetic and sporadic aortic aneurysms and dissections

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Introduction

The aorta is the largest artery and can be divided into several segments (Fig 1). The diaphragm divides the aorta into the thoracic and abdominal aorta. The thoracic aorta extends from the heart to the diaphragm and comprises the following 3 segments: the ascending thoracic aorta, the aortic arch, and the descending thoracic aorta. The ascending aorta originates at the aortic root, comprising the aortic valve and sinuses of Valsalva from which the coronary artery ostia arise, and ends just proximal to the origin of the innominate artery. The transverse aortic arch is the segment from which the innominate, left common carotid, and left subclavian arteries arise. The descending thoracic aorta extends from just beyond the origin of the left subclavian artery to the diaphragm. Below the diaphragm, the abdominal aorta is divided into suprarenal and infrarenal segments.

Aortic aneurysms and dissections (AAD) are common diseases that can cause aortic rupture and other life-threatening complications. Aortic aneurysm occurs when the progressive weakening of the aortic wall causes the aorta to enlarge to a diameter of at least 1.5 times greater than normal (Fig 2A). Aortic dissection occurs when a tear forms within the aortic wall and causes blood to flow between the layers, thereby separating them and creating a false lumen with a severely weakened outer aortic wall (Fig 2B). Aneurysms and dissections may involve one or more aortic segments and are named accordingly. Thoracoabdominal aortic aneurysms are those that extend through the diaphragm, involving the descending thoracic aorta and the abdominal aorta in continuity.

The incidence of thoracic AAD (TAAD) is estimated to be 9-16 cases per 100,000 individuals per year,^{1,2} with more cases occurring in men than in women (16.3 vs 9.1 cases per 100,000 individuals per year for men and women, respectively).² Of all TAADs, 60% involve the aortic root, ascending aorta, or both; 10% involve the aortic arch; 40% involve

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the descending thoracic aorta; and 10% involve the thoracoabdominal aorta.³ Thoracic aortic dissection (TAD) is estimated to occur at a rate of 3 cases per 100,000 individuals per year.^{4–7} The prevalence of infrarenal abdominal aortic aneurysms (AAA) is estimated to be between 2.2% and 5% in men older than 55 years of age.^{3,8,9}

AAD are highly lethal conditions that often necessitate surgical treatment. Operative treatment generally involves replacing the diseased segment with a prosthetic graft by using an open surgical, endovascular, or hybrid approach. Despite significant improvements in the surgical treatment of AAD, they cause more than 10,000 deaths in the United States each year. Although AAD are a leading cause of death in people 55 years of age or older,^{10,11} AAD are also a significant cause of morbidity and mortality in children and young adults.¹² Recent reports indicate that the mortality rate of acute TAAD is 16%.² AAD are particularly lethal when they involve the ascending aorta. The current incidence of in-hospital death is 24% for patients presenting with acute ascending aortic dissection (ie, DeBakey type I or II dissection and Stanford type A dissection).¹³

From an etiologic standpoint, TAAD can be classified as either genetically triggered or sporadic. Less than 30% of all TAAD cases are genetically triggered, whereas more than 70% are sporadic.^{14–16} Genetically triggered TAAD are caused by mutations in genes encoding proteins such as smooth muscle (SM) contractile proteins,¹⁷ extracellular matrix (ECM) proteins, and proteins involved in transforming growth factor beta (TGF- β) signaling.^{18,19} Sporadic TAAD are mainly associated with risk factors such as aging,^{16,20–24} male sex,^{21,25} smoking,^{20,22,23,26,27} and hypertension.^{21,24,27–29} Sporadic TAAD and AAA share similarities in risk factors and in pathogenesis. In both genetically triggered and sporadic AAD, the upregulation of common pathways such as reactive oxygen species (ROS) production and stress signaling activation can cause SM cell (SMC) dysfunction and death, ECM destruction, and aortic inflammation, which all contribute to the progression of these diseases.

Although surgical approaches for treating AAD have become more advanced and less invasive, an urgent need remains for new medical approaches that prevent disease progression. Although a few drugs, such as beta-blockers and angiotensin II receptor antagonists, can slow disease progression in some patients with genetically triggered aortopathy, no medications are widely effective in preventing or halting the disease. A better understanding of the molecular mechanisms underlying AAD initiation, progression, and rupture is important for developing effective medications to treat these diseases. In this review, we summarize the major progress that has been made in our understanding of the pathogenesis underlying genetically triggered and sporadic forms of AAD.

Normal structure and function of the aorta

Histology of the aortic wall

The aortic wall is composed of 3 layers (Fig 3A): a thin inner layer (the intima), a thick medial layer (the media), and a thin outer layer (the tunica adventitia). The intima is lined with a monolayer of endothelial cells that not only separates the aortic wall from circulating blood but also regulates vascular functions.³⁰

The media is composed of SMCs within an ECM of elastic fibers, collagen, adhesive proteins (eg, laminin and fibronectin), and proteoglycans. The aortic media is critical in controlling aortic biomechanical functions, including elasticity and compliance (ie, the ability to distend and recoil), tensile stiffness (ie, changes in stress associated with changes in strain), and tensile strength (ie, maximum stress sustained without failure). Elastic fibers contribute to aortic compliance, whereas collagen fibers contribute to stiffness and strength.³¹

The aortic adventitia contains cells such as fibroblasts and adipocytes, ECM containing collagen and elastin, vasa vasorum and lymphatics, and perivascular nerves. The aortic adventitia not only provides nourishment to the aortic wall, but it is also an important gateway for inflammatory cell infiltration into the aortic wall. Recent studies have shown that the adventitia contains abundant stem cell or progenitor cell niches. Furthermore, a growing body of evidence supports a critical role of the adventitia in vascular injury, repair, inflammation, and remodeling.³²

The lamellar unit, elastin-contractile unit, and mechanotransduction

The lamellar unit—The lamellar unit is the basic structural and functional unit of the aortic media. Each lamellar unit is composed of SMCs sandwiched between 2 layers of elastic fibers and surrounded by collagen bundles (Fig 3B). The connection between the SMCs and the surrounding ECM is important for maintaining the integrity of aortic structure and function.

The elastin-contractile unit—The elastin-contractile unit (Fig 4) is a unique configuration of elastic fibers, focal adhesions or dense plaques in the membrane, and contractile filaments inside the cell. The elastin-contractile unit³³ transmits forces from the elastic fibers to the SMCs and serves as a mechanosensor unit of the aortic wall.^{31,34}

Elastic fibers.—The elastic fibers (Fig 4) are organized as a core of elastin surrounded by microfibrils that are composed of fibrillin, microfibril-associated glycoproteins (MAGPs), elastin microfibril interfacial protein 1 (EMILIN1), fibulins, and other glycoproteins. Under normal conditions, elastin molecules are synthesized in SMCs and deposited into the ECM, where they are aligned and cross-linked to form elastic fibers. Elastin is believed to have a half-life of approximately 50 years in humans; most of the body's elastic fibers are produced before adulthood.^{31,34,35}

Focal adhesions or dense plaques.—Focal adhesions or dense plaques (Fig 4) on the SMC membrane contain integrin receptors composed of α and β subunits. Dense plaques connect to the fibrillin-containing microfibrils in elastin fibers.^{33,36} The connection of dense plaques in the SMC membrane to the fibrillins in elastic fibers contributes to the stability of elastic fibers.^{36,37} Dense plaques connect to the α -actin filaments in the contractile unit through actin linkage proteins or intracellular anchoring proteins, which are composed primarily of talin, vinculin, α -actinin, and filamin A.

SMC contractile unit.—A SMC contractile unit (Fig 4) is composed of actin-containing thin filaments and myosin-containing thick filaments, along with regulatory proteins. The

thin filaments are composed of SM α -actin and regulatory proteins, including tropomyosin. Myosin thick filaments are composed of myosin heavy chains, essential light chains, and regulatory light chains. The signaling-induced phosphorylation of the regulatory light chains induces the formation of a cross-bridge between actin and myosin filaments, as well as the motion of the actin thin filaments, resulting in SMC contraction. The SMC contractile units are connected with cell membrane, cytoskeletal filaments, dense bodies, and nuclei. This arrangement of filaments intertwined with cellular components is necessary for the mechanotransduction properties of the SMC contractile unit.³¹ SMC contractile force requires SM α -actin assembly in the thin filaments³⁸ and SM α -actin polymerization in the subcortical region.³⁹

Mechanotransduction—The contractile activity of SMCs is fundamental to aortic functions.³¹ Mechanical stimuli, such as transmural pulse pressure, are transmitted from the elastic fiber, through the focal adhesions or dense plaques in the membrane, through the anchoring proteins or actin linkage proteins, and to the contractile unit, leading to the activation of SMC contraction (Fig 4).³¹ Mechanical signals also induce the influx of calcium; calcium then binds to calmodulin to form the calcium-calmodulin complex that leads to the activation of the myosin light chain kinase (MYLK), phosphorylation of the regulatory light chains in the myosin complex, and activation of actin-dependent ATPase activity in the myosin globular motor head, leading to SMC contraction.

Heterogeneity of the aorta in different segments

The heterogeneity of aortic structure—Aortic segments differ in structure and function.^{40–42} The ascending aorta is where the pressure is the highest and the thickness of the aortic media is the greatest. The aortic media becomes thinner as the aorta descends into the abdomen. The aortic root and ascending aorta are composed of an elastic wall that contains multiple elastic lamina and SMCs.⁴⁰ The abundance of elastin in these segments contributes to the distensible properties of the aorta that are essential for responding to blood volume and pressure changes and withstanding the pulsatile force during the cardiac cycle.⁴³ The blood velocity in the descending thoracic aorta is substantially decreased when compared to that in the ascending aorta and aortic arch. Likewise, the extracellular components in the descending thoracic aorta differ greatly from those in the ascending aorta.^{44,45}

The heterogeneity of aortic SMC origin—Heterogeneity in the origin of aortic SMCs has also been observed among aortic segments. SMCs in the ascending aorta are derived from neural crest cells,^{46,47} whereas SMCs in the descending thoracic aorta are derived from the somitic mesoderm.⁴⁸ There is abundant evidence showing that vascular SMCs with different embryonic origins have distinct gene expression profiles and characteristics.^{49–51} It has been suggested that the embryonic origin of vascular SMCs may play a role in their response to changes in the environment.^{49,50} Interestingly, a study recently showed that vascular SMCs from the ascending and descending thoracic aorta displayed distinct differences in migratory properties and contractile activity in embryonic mice; however, in adult mice, these functions were indistinguishable between the 2 domains.⁵¹ Thus, it

remains to be determined whether the embryonic origin of SMCs dictates their phenotype and response to the environment in the adult vascular wall.^{40,47}

Genetic TAAD

Proper aortic function requires the intact structure of the elastin-contraction unit, as well as the efficient signaling that controls the function of aortic cells. Defects in these structural and functional components result in compromised aortic homeostasis, rendering the aorta vulnerable to failure.³¹ A growing body of evidence supports a new theory that altered cell-matrix connections in the contraction-elastin unit play an important role in the development of TAAD.^{17,36,52–55} Genetic TAAD are associated with mutations in genes encoding proteins that control the structure and function of the elastin-contraction unit (Fig 4) and signaling pathway proteins (eg, TGF- β (Fig 5)) that control the maturation and functions of aortic cells.

Mutations affecting the function of the SMC contraction unit

SM α -actin gene (ACTA2)—*ACTA2* encodes SMC-specific isoform of α -actin, a key component in the thin filaments of the SMC contraction unit. Mutations in *ACTA2*^{38,56–58} are the primary cause of familial TAAD.^{58,59} Aortic tissues from affected individuals show medial degeneration with focal areas of SMC proliferation, hyperplasia, and disarray.³⁸ *ACTA2* mutations interfere with actin filament assembly³⁸ and compromise actin filament movement and SMC contraction.³⁹ *ACTA2* mutations also affect actin polymerization,^{39,60} resulting in unstable actin that is susceptible to severing by cofilin.³⁹ In addition, *ACTA2* mutants have abnormal mitochondrial morphology, altered thermos stability, and a reduced ability to grow under stress conditions.⁶¹

Myosin heavy chain 11 gene (MYH11)—*MYH11* encodes SMC-specific myosin heavy chain 11 (MYH11), a major component of the thick filaments of the SMC contraction unit. Heterozygous mutations in *MYH11* have been identified in patients with nonsyndromic familial TAAD.^{62–64} The phenotypic features associated with *MYH11* mutations include TAAD and patent ductus arteriosus.^{62,63} Mutations in *MYH11* are predicted to prevent myosin from polymerizing into thick filaments, resulting in altered force generation.⁶⁵ Mutations in *MYH11* also cause changes in the phenotype of SMCs, such as reduced expression of SMC contraction proteins, increased proliferation and dedifferentiation of SMCs, and altered focal adhesions.⁶⁵ In addition, *MYH11* mutations compromise the stress or injury response and increase vulnerability to intramural damage.⁶⁶

Myosin light chain kinase gene (MYLK)—*MYLK* encodes MYLK, which phosphorylates and activates myosin regulatory light chain, leading to an increase in actin-dependent myosin II ATPase activity and the initiation of SMC contraction.⁶⁷ Loss-of-function mutations in the *MYLK* gene have been identified in a small percentage of patients with familial TAAD.⁶⁸ *MYLK* mutations are predicted to decrease myosin regulatory light chain phosphorylation and activation, leading to compromised SMC contraction.⁶⁸ Mice with SMC-specific *Mylk* deletion showed altered gene expression and medial degeneration in the aortic wall.⁶⁸

Type I cGMP-dependent protein kinase gene (PRKG1)—*PRKG1* encodes the type I cGMP-dependent protein kinase (PKG-1), which induces the activation of myosin light chain phosphatase. This leads to the dephosphorylation and inactivation of myosin regulatory light chain, thus promoting SMC relaxation. A gain-of-function mutation in the *PRKG1* gene has been identified in patients with familial TAAD and has been associated with severe aortic dissection in the descending thoracic aorta.⁶⁹ In patients with the gain-of-function mutation in *PRKG1*, PKG-1 is constitutively active, even in the absence of cGMP, leading to decreased phosphorylation of the myosin regulatory light chain, which is predicted to reduce SMC contraction.⁶⁹

Filamin A gene (FLNA)—*FLNA* encodes filamin A, a large actin-binding protein that polymerizes cytoskeletal actin and anchors the actin cytoskeleton to transmembrane integrin molecules. These steps are important for maintaining cell shape and contraction.⁷⁰ A loss-of-function mutation in the *FLNA* gene, located on the X chromosome, results in an X-linked dominant condition that is characterized by brain malformation (periventricular heterotopia) and an Ehlers-Danlos–like phenotype, as well as an increased risk of thoracic aortic disease.⁷¹

Together, these study findings have supported the notion that defective contractile function contributes to the pathogenesis of TAAD,^{38,39,56} highlighting the importance of SMC contractile function in preserving aortic structure and preventing TAAD development.¹⁷

Mutations affecting elastic fiber and collagen components

Fibrillin-1 gene (FBN1)—*FBN1* encodes fibrillin-1, a 350-kDa cysteine-rich glycoprotein that is the major protein in microfibrils. Fibrillin-1 connects elastic fibers to dense plaques in the SMC membrane^{72,73}; this connection is important for mechanotransduction and the stability of elastic fibers.^{36,37}

FBN1 mutations cause Marfan syndrome.—Mutations in *FBN1* have been identified in Marfan syndrome,^{74,75} a heritable autosomal-dominant disorder. More than 1000 *FBN1* mutations have been identified in patients with Marfan syndrome, including missense mutations, nonsense mutations, splicing errors, and complete deletion of the *FBN1* gene.^{76,77}

FBN1 mutations result in reduced fibrillin-1 protein levels.—Mutational analysis of *FBN1* has provided unique insight into the biologic and physiological role of fibrillin-1.⁷⁸ Frameshift and nonsense mutations in *FBN1* result in gene deletions that are predicted to decrease the normal amount of fibrillin-1 protein production by half.⁷⁹ *FBN1* mutations also cause fibrillin misfolding, impaired secretion, and disorganized elastin structure and assembly into microfibrils, rendering fibrillin-1 to proteolysis-mediated degradation.^{80,81} Fibroblasts explanted from patients with Marfan syndrome consistently show decreased deposition of fibrillin into the ECM, regardless of the underlying mutations.^{82,83}

FBN1 mutations result in SMC dysfunction, phenotype alteration, and aortic destruction.—Mutations in *FBN1* cause reduced SMC contraction⁵³ that probably results from the disrupted connection between elastic fibers and SMCs and the compromised

function of the elastin-contractile unit.³¹ Loss of fibrillin-1 alters SMC phenotype and induces ECM remodeling.^{36,84} Furthermore, mutations in *FBN1* increase matrix metalloproteinase (MMP) activity and elastic fiber destruction.⁵³ As a consequence, the aorta exhibits markedly abnormal SMC and elastic properties that lead to progressively increased dilatation.

FBN1 mutations result in altered TGF- β signaling.—Fibrillin-1 binds to latent TGF- β -binding protein (LTBP) and sequesters TGF- β in the ECM, thereby inhibiting TGF- β signaling.^{85–87} Mutations in *FBN1* and fibrillin-1 deficiency alter the matrix sequestration of the latent TGF- β complex, leading to the uncontrolled release of active TGF- β from the ECM and enhanced TGF- β signaling.^{88–90} In a mouse model of Marfan syndrome, mice that lack LTBP have reduced aortic destruction and improved survival, suggesting the involvement of TGF- β signaling in aortic disease progression.⁹¹

Activation of noncanonical TGF- β signaling causes aortic destruction in Marfan syndrome.—Evidence has indicated that the role of TGF- β signaling in aortic disease progression is complex. Both SMAD-dependent canonical and SMAD-independent noncanonical TGF- β signaling pathways (including the extracellular signal-regulated kinase [ERK]1/2 pathway and the Jun N-terminal kinase [JNK] pathway) (Fig 5) have been shown to be increased in mice with Marfan syndrome.^{92,93} However, recent studies have suggested that only the noncanonical TGF- β signaling ERK1/2 and JNK pathways cause aortic destruction and drive the development of aortic disease in mice with Marfan syndrome.^{92,93}

Angiotensin II type 1 receptor signaling is involved in aortic destruction in Marfan syndrome.—Angiotensin signaling has receptor-specific effects on disease progression in mice with Marfan syndrome. Deficiency of angiotensin II type 2 receptor (AT2R) was shown to accelerate aortic destruction,⁹⁴ whereas the selective angiotensin II type 1 receptor (AT1R) blocker (ARB) losartan^{90,94,95} abrogated aneurysm progression in mice with Marfan syndrome, suggesting a protective role of AT2R signaling and a destructive role of AT1R signaling in the aorta of these mice. Notably, AT2R signaling was shown to attenuate aortic aneurysm formation in mice through ERK antagonism.⁹⁴

Mutations in other genes encoding proteins in elastic fibers—Loss-of-function mutations in *FBN2* (encoding fibrillin-2),⁹⁶ *MFAP5* (encoding microfibril-associated glycoprotein 2 [MAGP2]),⁹⁷ and *EMILIN1* (encoding elastin microfibril interfacer 1)⁹⁸ also predispose individuals to TAAD. Mutations in the elastin-encoding gene *ELN* cause rare dominant cutis laxa, and aortic dilatation and rupture can develop in some patients.⁹⁹

Fibulin-4 gene (FBLN4)—Fibulin-4 is an ECM protein that binds to elastin and promotes elastic fiber formation. Mutations in the gene encoding fibulin-4 also cause aortic aneurysms with arterial tortuosity and stenosis.^{100–102} Fibulin-4 deficiency in mice results in ascending thoracic aortic aneurysm (TAA) with perturbations of vascular homeostasis and aortic valve abnormalities.¹⁰³ Mice with SMC-specific fibulin-4 deficiency develop ascending TAA. The aortic wall of these mice does not fully differentiate, featuring an immature SMC phenotype, reduced expression of SMC-specific contractile genes, medial degeneration, and focal SMC proliferation.¹⁰⁴

Lysyl oxidase gene (LOX)—Lysyl oxidase (LOX), a copper-dependent amine oxidase that oxidizes lysine residues in elastin and collagen to form covalent cross-links, is an important enzyme in elastic fiber assembly and stabilization.¹⁰⁵ Recently, mutations in *LOX* that cause LOX deficiency or reduce LOX activity have been identified in patients with familial TAAD.^{106,107} Individuals with *LOX* variants have enlargement of the aortic root and ascending aorta and associated aortic dissections.¹⁰⁶ Transgenic mice heterozygous for the mutated human allele of *LOX* have fragmented elastic lamellae, whereas mice homozygous for the mutated human allele die shortly after parturition from ascending TAA.¹⁰⁷ These findings suggest a critical role of LOX in maintaining aortic wall integrity and indicate the importance of *LOX* mutations in the development of genetic TAAD.

Collagen gene (COL)—Mutations in *COL* are associated with Ehlers-Danlos syndrome. Mutations in *COL3A1*^{108,109} encoding collagen III, *COL5A1*¹¹⁰ encoding collagen V, and *COL1A2*¹¹¹ encoding collagen I have been identified in Ehlers-Danlos syndrome patients with TAAD.

Mutations affecting TGF- β signaling

TGF- β (Fig 5) plays a critical role in the regulation of cell growth, differentiation, and development in a wide range of biologic systems. Gene mutations affecting several signaling molecules in this pathway, including ligands, receptors, and downstream transcriptional factor SMAD, have been shown to cause TAAD.

TGF- β receptor genes (TGFB1 and TGFB2)—Mutations in *TGFB1* and *TGFB2* genes are associated with Loeys-Dietz syndrome and other TAAD. Mutations in the *TGFB* genes *TGFB1* and *TGFB2* have been identified in patients who have Loeys-Dietz syndrome^{112–114} and phenotypic overlap with Marfan syndrome,^{113,115} and in patients with familial TAAD.^{113,116} The phenotype of transgenic mice with mutations in either *Tgfb1* or *Tgfb2* recapitulates the Loeys-Dietz syndrome phenotype.¹¹⁷

TGF- β ligand genes (TGFB2 and TGFB3)—Loss-of-function mutations in *TGFB2* cause syndromic TAAD with the phenotype of Loeys-Dietz syndrome or with mild systemic features of Marfan syndrome.^{114,118} Mutations in the *TGFB3* gene also cause syndromic TAAD.¹¹⁹ Mice deficient in *Tgfb2* develop aortic aneurysm.¹¹⁴ Paradoxical upregulation of TGF- β signaling has been observed in aortic tissues from patients with mutations in *TGFB2* or *TGFB3*.^{114,119}

SMAD3 gene (SMAD3)—Mutations in *SMAD3* cause syndromic familial TAAD.^{120–122} Mice with *Smad3* deletion develop progressive aortic aneurysms¹²³ and have elevated levels of granulocyte-macrophage colony-stimulating factor, which may contribute to the development of aortic aneurysms.¹²³ Recently, the SMC-specific deletion of *Smad4* in mice was shown to promote aortic aneurysm.¹²⁴ Paradoxically, *SMAD3* mutations lead to increased aortic expression of SMAD3 and other key proteins in the TGF- β pathway.¹²⁰

Critical role of TGF- β signaling in aortic wall homeostasis—Several lines of evidence from mice suggest that TGF- β signaling protects against AAD development. Mice

deficient in *Tgfb2*,¹¹⁴ *Smad3*,¹²³ or *Smad4*¹²⁴ develop aortic aneurysm. In addition, the SMC-specific deletion of *Tgfb2* in postnatal mice impairs aortic wall homeostasis¹²⁵ and causes severe TAAD.^{125,126} Furthermore, aortas and explanted SMCs from patients with *TGFBR2* mutations show decreased expression of contractile proteins, as well as compromised expression of contractile genes in response to TGF- β stimulation.¹²⁷ Moreover, fibroblasts explanted from patients with *TGFBR2* mutations fail to transform to mature myofibroblasts with TGF- β stimulation.¹²⁷ Thus, it has been proposed that TGF- β signaling promotes aortic wall homeostasis^{125,127} and that mutations in this pathway cause AAD formation.

Activation of TGF- β signaling in aortas from patients with gene mutations affecting TGF- β signaling—Paradoxically, aortic tissues from patients with mutations in *TGFBR1* or *TGFBR2*,^{112,128} *TGFB2* or *TGFB3*,^{114,119} or *SMAD3*¹²⁰ have consistently shown enhanced TGF- β signaling, as indicated by the upregulation of SMAD2 or SMAD3 and the increased production of TGF- β target genes such as collagen and connective tissue growth factor (CTGF). The mechanisms underlying this paradoxical elevation in TGF- β signaling are not completely understood. It is possible that decreased expression of TGF- β target genes leads to a secondary increase in TGF- β signaling.

Mutations in other genes

Forkhead transcription factor 3 gene (FOXE3)—Exome sequencing of families with TAAD has identified mutations in the *FOXE3* gene that encodes the forkhead transcription factor FOXE3.¹²⁹ Mice deficient for *Foxe3* had a reduced number of aortic SMCs during development and increased rates of SMC apoptosis and aortic rupture in a model of transverse aortic constriction-induced TAAD. These phenotypes can be rescued by deleting the *p53* gene or by inhibiting p53 with an inhibitor.¹²⁹ Thus, FOXE3 may be important for aortic development and the stress response. Mutations in *FOXE3* predispose individuals to TAAD.¹²⁹

Methionine adenosyltransferase IIa gene (MAT2A)—Methionine adenosyltransferases (MATs) are the key enzymes involved in the production of S-adenosylmethionine, the principal methyl donor in cells. A loss-of-function mutation in *MAT2A* has been identified in patients with TAAD.¹³⁰ The knockdown of *mat2a* in zebrafish was shown to disrupt cardiovascular development.¹³⁰ These study findings suggest that loss-of-function mutations in *MAT2A* may cause TAAD.

MMP-17 gene (MMP17)—MMP-17/MT4-MMP is a membrane-bound MMP that is essential for vascular SMC maturation and function in the arterial vessel wall.^{131,132} A missense mutation in the *MMP17* gene that prevents its expression has been identified in patients with genetic TAAD.¹³² Loss of function of MMP-17 in mice results in dysfunctional vascular SMCs and altered ECM in the vessel wall, leading to increased susceptibility to angiotensin II-induced TAA.¹³²

Etiology of sporadic AAD

Sporadic AAD, including sporadic TAAD and AAA, are more common than genetically triggered TAAD and often occur in older patient populations.^{16,21,24} Sporadic AAD occur more frequently in men than in women.^{21,25} Risk factors for sporadic AAD include cigarette smoking,^{20,22,23,26,27} hypertension,^{21,24,27–29} and aging.^{16,20–24} More than 80% of all AAD cases and more than 70% of TAAD cases are sporadic.^{14–16} Understanding the risk factors and pathogenesis of sporadic AAD may provide opportunities for developing targets for the primary prevention of AAD.

Effect of age

Sporadic TAAD^{16,21,24} and AAA^{20,22,23} often occur in older patient populations. Aging is associated with changes in aortic structure and function that compromise the ability of the aorta to respond to biomechanical stress, predisposing these individuals to aortic destruction and dilatation. In people without known aortic disease, the descending thoracic aorta shows an age-related increase in fragility and susceptibility to permanent dilation after pressure distention.¹³³ In older mice¹³⁴ and monkeys,¹³⁵ the aorta shows ECM disarray and stiffness, which are believed to contribute to TAA development.^{134,135} Aortic stiffness increases aortic wall stress, damage, and inflammation that precedes AAD growth.¹³⁶

Effect of sex

Sex is a major determinant of sporadic TAAD^{21,25} and AAA²³; the ratio of men to women who have sporadic AAD is 2:1.²⁵ Although the incidence of AAA is higher in men,²⁴ the prognosis of AAA is worse in women than in men.¹³⁷ The mechanisms responsible for this difference between men and women are not well understood. It has been suggested that testosterone may play a role in promoting AAD development. Testosterone administration in neonatal female mice increases hydrogen peroxide generation and promotes angiotensin II–induced AAD.¹³⁸ Testosterone upregulates AT1R, which may mediate the effects of testosterone in promoting AAD development.^{138,139}

Genetic contributions

Recent studies have indicated that genetic variants contribute to sporadic AAD. Rare copy number variants in genes that regulate SMC adhesion and contractility have been identified in patients with sporadic TAAD.¹⁴⁰ In addition, common genetic variants in *FBNI* have been found in patients with sporadic TAAD.^{141,142} Genetic polymorphisms in several genes have been studied in patients with AAA. A recent meta-analysis showed that polymorphisms in genes such as *LRPI* (low-density lipoprotein [LDL] receptor–related protein 1), *APOA1* (apolipoprotein A), *IL6R* (interleukin 6 receptor), *MMP3*, *AT1R* (angiotensin II type I receptor), and *ACE* (angiotensin-converting enzyme) were associated with AAA.¹⁴³ By performing the Sanger sequencing of all coding exons and exon-intron boundaries of the genes associated with genetic TAAD, van de Lijstgaarden and colleagues¹⁴⁴ found potential pathogenic variants of *COL3A* and *MYH11* of patients with familial AAA (with at least 1 first-degree relative with an aortic aneurysm) and a pathogenic variant in *TGFBR2* in patients with sporadic AAA.

Hypertension

Hypertension is a risk factor for sporadic TAA,^{7,21,24,28,145} TAD,²⁷ and AAA²³ and is also associated with an increased rate of mortality from TAA.²⁹ In mice, prolonged angiotensin II infusion produces aortic aneurysms in both the thoracic and the abdominal aorta.^{146–149} The effects of hypertension on the development of aortic disease are attributed, in part, to the mechanical effects of elevated blood pressure on the aortic wall. In an ex vivo study of aortas from patients with TAA, the mean circumferential wall stress was shown to increase linearly with increased intraluminal pressure and aortic diameter.¹⁵⁰ It has been suggested that elevated systolic pressure significantly affects the structure and function of the aortic wall, thereby increasing aortic wall stress¹⁵¹ and promoting aortic dilatation.

Cigarette smoking

Smoking is a major risk factor for the development and progression of TAAD^{21,27} and AAA.^{20,22,23,26,27} Smoking is also a risk factor for aortic dissection.²⁷ Several experimental studies in mice have shown that cigarette smoke exposure augments AAA induced by angiotensin II infusion or elastase perfusion.^{152,153} Smoking-induced effects have been attributed for alterations in aortic SMCs and in the inflammatory response.^{154,155} In patients with AAA, the cessation of cigarette smoke exposure did not produce an immediate decrease in aortic expansion,¹⁵⁴ suggesting that the effects of cigarette smoking on the aortic wall may be long term.

Inflammatory diseases

AAD occur in several inflammatory diseases. Takayasu's arteritis, a chronic inflammatory disease, is the most striking arteritis that affects the aorta.¹⁵⁶ In patients with Takayasu's arteritis, aortic dilatation and aneurysm formation¹⁵⁷ can occur in the ascending aorta^{158,159} and aortic arch.¹⁵⁶ Significant T-cell infiltration has been observed in the aorta of these patients.¹⁶⁰ Because of the inflammatory process caused by Takayasu's arteritis, severe narrowing, or even occlusion of the entire aorta and large arteries can develop in these patients. Another inflammatory disease that affects the aorta is giant-cell arteritis, which typically affects the temporal or cranial arteries but can also affect the aorta^{161–164} with serious outcomes.¹⁶⁵ In addition, ankylosing spondylitis¹⁶⁶ and psoriasis¹⁶⁷ have been shown to be associated with ascending aortic aneurysms and AAA, respectively. Interestingly, a recent population-based case-control study showed that asthma is associated with AAA and rupture.¹⁶⁸ In mouse models of AAA induced by angiotensin II and calcium chloride, the simultaneous induction of allergic inflammation in the lung increased aortic macrophage and mast cell infiltration, promoted SMC loss, and aggravated aortic enlargement.¹⁶⁹ These findings suggest a potential association between allergic inflammation and AAD development.

Dyslipidemia and atherosclerosis

Ample evidence has shown that dyslipidemia and atherosclerosis are closely associated with the development of sporadic AAD.

Atherosclerosis in AAA—AAA are associated with the occurrence of cardiovascular events,¹⁷⁰ atherosclerotic risk factors,²³ carotid atherosclerosis and stenosis,^{20,22,26} and coronary artery disease.²² High LDL levels, low high-density lipoprotein (HDL) levels, and a high LDL/HDL ratio are common in patients with AAA.^{20,23,27,171} Furthermore, there is direct evidence showing the presence of atherosclerosis in patients with AAA. Atherosclerosis is associated with significantly increased aortic diameter and wall thickness.¹⁷¹

Atherosclerosis in sporadic TAAD—Atherosclerosis is also associated with sporadic TAAD and has been detected in the descending thoracic^{21,25} and thoracoabdominal aorta.¹⁷² One study showed that atherosclerosis risk factors and aortic atherosclerotic plaque are weakly associated with distal aortic dilatation, suggesting that atherosclerosis plays a minor role in aortic dilatation.²¹ However, other studies have shown that atherosclerosis in these distal segments is associated with aortic enlargement, suggesting that atherosclerosis is the predominant etiology of aneurysms in the descending thoracic aorta and thoracoabdominal aorta.^{25,172}

Compared to descending TAA, ascending TAA have a lower incidence of grossly detectable atherosclerosis (9% in ascending TAA vs 88% in descending TAA).^{21,25} Although atherosclerosis is often not obvious in sporadic ascending TAAD on gross examination, histologic analysis has shown the presence of atherosclerosis in most cases.¹⁷³ Advanced atherosclerosis (ie, denoted by the presence of atherosclerotic plaque with intraplaque hemorrhage, calcification, and intima hyperplasia) is present in more than 35% of sporadic ascending TAA cases and is associated with increased degeneration of the aortic media characterized by SMC depletion, elastic fiber destruction, and fibrotic remodeling.¹⁷³ A recent study showed that increased cholesterol level is also associated with an increased rate of mortality from TAA.²⁹

Role of atherosclerosis in sporadic AAD progression—Although studies in humans have shown an association of dyslipidemia and atherosclerosis with AAD incidence, the cause-effect relationship between atherosclerosis formation and aneurysm initiation and progression is less clear. It has been suggested that atherosclerosis may not be a causal event in AAA but, rather, develops in parallel with or secondary to aneurysmal dilatation.¹⁷⁴ However, evidence from animal studies supports a role of dyslipidemia and atherosclerosis in the development of sporadic AAD. In mice, a high-fat diet produces hypercholesterolemia¹⁷⁵ and progressively augments the incidence of angiotensin II–induced AAA^{175,176} in apolipoprotein E–deficient (*ApoE*^{−/−}) mice in a time-dependent manner.¹⁷⁶ Reducing plasma levels of lipoproteins containing apolipoprotein B attenuates angiotensin II–induced AAA formation in *ApoE*^{−/−} mice.¹⁷⁵ Furthermore, increasing plasma levels of HDL reduces angiotensin II–induced AAA formation in *ApoE*^{−/−} mice or calcium chloride–induced AAA formation in C57BL/6 mice,¹⁷⁷ presumably by reducing the activation of ERK1/2 and matrix remodeling.¹⁷⁷ Thus, atherosclerosis may promote aortic destruction and disease progression in sporadic AAD.

Obesity and AAD—Body mass index has been associated with the incidence of TAA²⁸ and AAA¹⁷⁸ and the rate of mortality from TAA.²⁹ Animal studies have shown that obesity

induced by a high-fat diet increases macrophage accumulation in periaortic adipose tissue and enhances angiotensin II-induced AAA formation,¹⁷⁶ supporting the potential link between obesity and aortic disease.

Diabetes

Although thoracic and abdominal aortic diseases have different clinical profiles,²⁸ they both have a negative association with the incidence of diabetes.

Negative association between diabetes and sporadic TAAD—Consistently, diabetes has been shown to be associated with a reduced incidence of TAA, dissection, and rupture.^{179–182} Evidence from a community screening of 30,412 individuals has suggested that diabetes is not significantly associated with TAA.²⁷ A recent study based on nationwide hospital discharge or inpatient data showed that TAAD among individuals diagnosed with diabetes occurred in 9.7 per 10,000, compared to 15.6 per 10,000 among all hospital discharges.¹⁷⁹ The prevalence of diabetes has been reported to be lower in patients with TAAD (13%) than in general population controls (22%).¹⁷⁹ Furthermore, study findings have indicated that aneurysms in patients with diabetes are less likely to develop TAD and rupture.^{182–184}

Negative association between diabetes and AAA—Diabetes has also been negatively associated with AAA.²² In a recent systematic review of 17 population studies, the prevalence of AAA in individuals with diabetes was estimated to be lower than that in individuals without diabetes.¹⁸⁵ Another meta-analysis of data from 19 studies of a total of 9777 patients confirmed that diabetes is associated with slower AAA growth.¹⁸⁶ Thus, clinical observations have consistently shown a negative association between diabetes and the development, growth, and rupture of thoracic and abdominal aortic diseases.

The effects of diabetes on aortic structure—An important question remaining is, what are the mechanisms underlying the negative association between diabetes and thoracic and abdominal aortic diseases? Furthermore, what are the protective factors that could potentially be targeted for the prevention and treatment of sporadic aortic diseases? Interestingly, Golledge and colleagues¹⁸⁷ found that aortic tissues from diabetic patients have decreased MMP-2 and MMP-9 activity. Furthermore, in vitro analysis showed that aortic tissue lysate from diabetic patients prevented monocyte activation¹⁸⁷ and that glycated type I collagen lattices prevented monocyte activation and MMP and interleukin (IL)-6 secretion. The authors concluded that the cross-linking of type I collagen by glycation may inhibit inflammatory cell activation and MMP production, thus preventing excessive proteolysis.¹⁸⁷

The effects of antidiabetic medication on AAD progression—Evidence has indicated that antidiabetic medications may have protective effects against thoracic and abdominal aortic diseases. Hsu and colleagues¹⁸⁸ compared the use of antidiabetic medications between 4468 diabetic patients with aortic disease and 4468 matched diabetic patients without aortic disease. The use of metformin, sulfonylurea, or thiazolidinediones was found to be associated with a lower risk of developing aortic disease. The effects of

metformin and sulfonylurea on the risk of developing aortic disease were dose-dependent. In another study of 58 patients, metformin use was negatively associated with AAA enlargement.¹⁸⁹ In experimental models, metformin^{189,190} and rosiglitazone¹⁹¹ prevented elastin reduction, SMC destruction, and inflammatory cell infiltration in the aortic media and suppressed AAD formation and progression. Thus, AAD suppression in diabetes may be attributable to concurrent antidiabetic therapy.

Changes in aortic cells in AAD

The aortic wall is highly dynamic, performing sophisticated biomechanical functions to provide suitable compliance and adequate strength in response to hemodynamic changes. Dysregulation and destruction of the cellular and extracellular components of the aortic wall result in progressive SMC depletion, ECM destruction, and inflammation, which are pathologic changes that commonly lead to aortic aneurysm, dissection, and rupture (Fig 6).

SMC injury and death in AAD

SMC apoptosis in AAD—One of the key histopathologic features of AAD is progressive SMC depletion and aortic medial degeneration.¹⁹² A growing body of evidence has suggested that SMC injury and death contribute to medial degeneration during AAD development. SMC apoptosis occurs not only in the genetic form of AAD but also in sporadic AAD. SMC apoptosis, as evidenced by the presence of cells positive for terminal deoxynucleotidyl transferase dUTP nick end labeling and by the activation of caspase-mediated apoptotic pathways, has been detected in the aortas of patients with Marfan syndrome^{193,194} and in those of patients with sporadic TAA or TAD.^{195–198} The presence of apoptotic cells is also a prominent feature in the aortic wall of patients with AAA.^{199–201}

Role of SMC apoptosis in aortic destruction and AAD development—Apoptosis has been suggested to play a major role in SMC depletion during AAD development. Animal studies have shown that caspase inhibitors diminished apoptosis and inflammation in the aortic media and prevented aneurysm progression in both *ApoE*^{−/−} mice challenged with angiotensin II²⁰² and mice with Marfan syndrome.²⁰³ Using a mouse model of inducible vascular SMC-specific apoptosis in *ApoE*^{−/−} mice, Clarke and colleagues²⁰⁴ showed that vascular SMC apoptosis promoted elastic lamina breaks and abnormal matrix deposition, leading to medial degeneration and medial expansion. These findings support a critical role of SMC apoptosis in aortic destruction and AAD development.

Signaling pathways affecting SMC apoptosis in AAD development—Several pathways and factors have been shown to affect AAD development by regulating SMC apoptosis. Mechanical stretch induces endoplasmic reticulum (ER) stress and apoptosis that contribute to TAAD formation.¹⁹⁸ Factors such as aldosterone,²⁰⁵ proinflammatory S100A12 protein,²⁰⁶ and mast cell-produced chymase and tryptase²⁰⁷ induce aortic SMC apoptosis and aneurysm formation. Signaling pathways such as TGF- β ,¹⁹⁴ protein kinase C,²⁰⁸ and p53²⁰⁹ are also involved in promoting SMC apoptosis during AAD development. In contrast, the elevation of HDL level inhibits angiotensin II-induced apoptosis and protects the aorta.¹⁷⁷ AKT2 has also been shown to protect the aorta, in part, by inhibiting apoptosis.

²¹⁰ When challenged with angiotensin II, *Akt2*-deficient mice showed profound apoptotic cell death in the aortic media and developed AAD.²¹⁰

Necroptosis in AAD development—Interestingly, a recent study showed that the activation of necroptosis, a programmed necrosis pathway, contributes to AAA. Receptor-interacting protein kinase 3 (RIP3) is a key regulator in promoting necroptosis. In mice, adenoviral overexpression of *Rip3* was sufficient to trigger SMC necroptosis, whereas deficiency in *Rip3* prevented SMC necrosis, inflammation, and AAA formation.²¹¹ Thus, SMC death contributes to aortic weakening and dilatation, dissection, and rupture.

Alteration of SMC phenotype in AAD

SMC phenotype changes—SMCs possess remarkable plasticity. Differentiated SMCs express SMC-specific contractile proteins and have characteristic myocyte morphology and contractile properties. Under conditions such as inflammation and injury, vascular SMCs can lose their contractile phenotype²¹² and exhibit phenotypes resembling those of inflammatory cells, fibroblasts, or osteogenic cells^{213–217}—a phenomenon termed phenotypic switching (Fig 7). Although SMC phenotypic switching allows vessel growth, repair, and adaptation to the environment, it can also lead to vascular dysfunction and maladaptive remodeling.^{213–216}

Heterogeneity of SMC phenotype in AAD—The alteration of SMC phenotype is a critical event in AAD pathology. However, the phenotypes of SMCs vary significantly in different pathogeneses (eg, genetic vs sporadic), in different focal areas (eg, degeneration vs compensational hyperplasia or proliferation), and at different disease stages. SMC phenotype alterations can be characterized either by increased expression of SMC genes and ECM proteins or by decreased expression of SMC genes and ECM proteins. Regardless of whether the expression of SMC genes is increased or decreased, the feature of increased expression of inflammatory and destructive factors such as MMPs is often observed in these dedifferentiated SMCs.

SMC phenotype with increased expression of SMC and ECM proteins in AAD

—A recent study showed that aortic SMCs in patients with Marfan syndrome have an altered phenotype characterized by the increased expression of contractile proteins, actin stress fibers, focal adhesion components, and collagen I, leading to increased cellular and ECM stiffness.⁸⁴ A study in a mouse model of Marfan syndrome also showed that SMCs retained the expression of vascular SMC markers but had increased expression of matrix elements and MMP-9, and the SMC phenotypic alteration preceded elastolysis.³⁶ It has been suggested that the TGF- β pathway may be involved in this type of phenotypic switch, given that the pharmacologic inhibition of the TGF- β pathway reduced alterations in gene expression.⁸⁴

SMC phenotype alteration with decreased expression of SMC proteins and increased expression of inflammatory proteins in AAD—The SMC phenotype characterized by the reduced expression of SMC genes (eg, genes encoding SM22- α and SM α -actin) and the increased expression of inflammatory genes (eg, *MMP-2* and *MMP-9*) has also been observed in aortas from patients with genetic and sporadic AAD.^{127,218,219}

SMCs in the aortas of patients with *TGFBR2* mutations showed decreased expression of contractile proteins.¹²⁷ SMC phenotype modulation characterized by decreased SMC proteins and increased MMPs has been observed in aortas from patients with sporadic TAA.^{218,219} In a study of an elastase-induced model of AAA, SMC phenotypic modulation was observed as an early event during the development of AAA.²¹⁸

Hyperplastic cellular remodeling—Hyperplastic cellular remodeling of the media has been observed in patients with ascending TAA.²²⁰ SMCs in the aortic media from patients with *MYH11* mutations also showed phenotypic alterations, including SMC disarray and focal SMC hyperplasia.⁶³

Factors involved in SMC phenotype alteration in AAD—An important question that remains is, what triggers SMC phenotypic changes in AAD? In a mouse model of angiotensin II–induced AAD, findings have indicated that increased peak wall stress induces a synthetic phenotype by increasing the production of ROS and the expression of CTGF.²¹⁹ In addition, bone marrow–derived monocyte chemotactic protein 1 has been shown to be involved in the reduction of contractile protein levels and in the induction of MMP expression.²²¹ Kruppel-like factor 4 (KLF4) is a key transcription factor involved in inflammatory responses after vascular injury or disease. It has been shown that KLF4 binds to SMC gene promoters, suppresses SMC gene expression, and induces SMC phenotype alterations.^{222,223} Furthermore, KLF4 inhibition reduces SMC phenotypic switching and prevents angiotensin II–induced AAD development.²²³ Interestingly, a recent study showed that RNA editing controls messenger RNA (mRNA) splicing, which is an important mechanism underlying SMC phenotypic switching.²²⁴ Whether this mechanism is involved in SMC phenotype switching in AAD remains to be determined.

Thus, phenotypic changes in SMCs occur in both genetic and sporadic AAD. The dedifferentiation and phenotypic modulation of SMCs can cause SMC dysfunction, loss of a functional SMC population, and matrix remodeling—all of which contribute to aortic degeneration and biomechanical failure.⁸⁴

Endothelial cell dysfunction in AAD

Endothelial cells play a fundamental role in controlling blood flow and blood pressure by regulating SMC functions. Endothelial cells also maintain aortic homeostasis by providing barrier functions and preventing inflammation and thrombosis. Endothelial dysfunction is known to be involved in the initiation of many cardiovascular diseases.

Protective role of endothelial cells against AAD—Evidence has indicated that intact endothelial functions are required for protecting the aorta against AAD. The endothelial-specific deletion of C-type natriuretic peptide, a fundamental factor that modulates vascular tone, leads to hypertension and aneurysm formation.²²⁵ In addition, the endothelial-specific deficiency of phosphoinositide 3-kinase-C2α (PI3K-C2α), an upstream kinase of the AKT pathway, impairs vascular barrier function and increases susceptibility to angiotensin II–induced AAD formation.²²⁶ Interestingly, a recent study showed that endothelial cells participate in aortic repair.²²⁷ In a rat xenograft model, the endovascular transplantation of

endothelial cells in the aorta prevents AAA formation and stabilizes AAA.²²⁷ Rather than directly participating in aortic repair, the transplanted endothelial cells promote aortic repair through paracrine mechanisms and the recruitment of resident vascular cells, leading to the reconstitution of new aortic wall rich in SMCs and ECM.²²⁷

Endothelial dysfunction in AAD development—In pathologic conditions, abnormal activation of endothelial cells may have destructive effects in the aorta. The endothelial-specific deficiency of the AT1R receptor attenuates the formation of angiotensin II-induced aortic aneurysms in mice,²²⁸ suggesting that endothelial cells may transduce angiotensin II signals and mediate angiotensin II-induced AAD formation. Evidence has also indicated that endothelial dysfunction promotes AAD development. Endothelial cell-specific ROS production induced by endothelium-specific NOX2 overexpression increases susceptibility to angiotensin II-induced aortic dissection in mice.²²⁹ The aortas from these mice show increased adhesion molecule-1 expression, inflammatory cell infiltration, and MMP activity.²²⁹ By releasing cyclophilin A, endothelial cells induce the activation of the ERK1/2 pathway and ROS production in SMCs, thereby increasing susceptibility to angiotensin II-induced AAD formation.²²⁹ Finally, it has been shown that the immunosuppressive drug azathioprine reduces aneurysm progression through the inhibition of Ras-related C3 botulinum toxin substrate 1 (Rac1) and c-Jun N-terminal kinase (JNK) in endothelial cells.²³⁰

These findings illustrate a pivotal role of endothelial cells and endothelial cell-derived factors in protecting the aorta against AAD formation. Dysregulation of endothelial functions may contribute to increased susceptibility to stress-induced aortic destruction.

Activation of fibroblasts and myofibroblasts in AAD

Activation of myofibroblasts in AAD—Myofibroblasts are specialized cells that have a more contractile phenotype and produce more ECM proteins than fibroblasts. They can be derived from multiple cells such as fibroblasts, bone marrow cells, mesenchymal cells, epithelial cells, and endothelial cells.^{231,232} Myofibroblasts are activated in response to stress and tissue injury and contribute to tissue repair and structural integrity, as well as fibrotic remodeling.^{232–236}

Recent studies have drawn attention to the possible role of myofibroblasts in aortic diseases.²³⁷ Activated myofibroblasts have been found in aortic tissues in human TAA²³⁸ and AAA.²³⁹ In a calcium chloride-induced rodent model of TAA, Jones and colleagues²⁴⁰ observed a time-dependent increase in the number of fibroblasts and fibroblast-derived myofibroblasts in the aortic wall. In a transverse aortic constriction mouse model, Kuang and colleagues²⁴¹ reported that biomechanical pressure induced significant adventitial hyperplasia, which was accompanied by an increase in myofibroblast accumulation and collagen production.²⁴¹

Potential roles of myofibroblasts in aortic wall homeostasis and destruction—

The precise roles of myofibroblasts in regulating aortic structure and function during the different stages of AAD development remain to be determined. Myofibroblasts can be activated in response to mechanical stress^{241,242} and injury.²⁴⁰ These cells can proliferate rapidly, migrate to the injured area, contract, and produce large amounts of ECM proteins,

thereby maintaining the structural integrity of tissues. By producing reparative growth factors, myofibroblasts can participate in tissue repair.^{233,237} After acute aortic injury, the quick, substantial increase in myofibroblasts and ECM proteins may increase aortic strength and prevent aortic rupture, thus playing a protective role.

However, myofibroblasts can also produce proinflammatory cytokines, activate inflammatory cells, and induce MMP production and activation,^{233,234,236,237} thus promoting aortic inflammation and destruction. Additionally, by driving inflammatory responses and producing collagens, these cells are key players in maladaptive fibrotic remodeling,^{233,234,236,237} which can progress to aortic dysfunction and, ultimately, to aortic biomechanical failure. Thus, myofibroblasts may represent a compensatory response that maintains aortic structural integrity during acute injury, but their concurrent participation in ECM proteolysis and collagen deposition promotes vascular fibrotic remodeling, leading to aortic failure. Therefore, precise and timely control of myofibroblast activation and inactivation is critical for maintaining aortic homeostasis.

Regulation of myofibroblast activation in AAD—Myofibroblasts can be derived from the transdifferentiation of fibroblasts and mesenchymal cells. In addition, myofibroblasts can be derived from epithelial and endothelial cells through the epithelial-to-mesenchymal transition and endothelial-to-mesenchymal transition (EMT), respectively.^{231,232} Several signaling pathways and factors, including TGF- β , angiotensin II, CTGF, platelet-derived growth factor, endothelin-1, Wnt/*Wingless*, and yes-associated protein 1, have been linked to the activation and maintenance of myofibroblasts and fibrotic remodeling.²³⁵ Altered TGF- β signaling is a key feature in AAD development in both genetically triggered and sporadic AAD. Fibroblasts explanted from patients with *TGFBR2* mutations fail to transform into mature myofibroblasts when stimulated with TGF- β ,¹²⁷ suggesting that deficient TGF- β signaling can result in impaired myofibroblast activation in AAD. Angiotensin II signaling is also involved in myofibroblast activation in pressure-induced aortic remodeling. Blocking angiotensin II signaling with losartan, an AT1R antagonist, partially prevented pressure-induced myofibroblast activation, collagen accumulation, adventitial hyperplasia, and aortic dilatation.²⁴¹

Despite the critical importance of myofibroblasts in aortic diseases, our understanding of aortic myofibroblasts, fibroblasts, and fibrotic remodeling in aortic homeostasis is limited. Improving our understanding of the regulation of myofibroblast activation and inactivation may help to develop therapies designed to manipulate these cells, thereby promoting their beneficial effects during acute injury but preventing their detrimental effects on aortic disease progression.

Stem cells and aortic repair

Aortic degeneration can result from a combination of excessive destruction and insufficient repair. When cells are injured, they release signals that trigger stem cell-mediated reparative responses. Stem cells proliferate and self-renew, differentiate into other cell types, and secrete factors to create a favorable microenvironment, thus promoting tissue repair or regeneration and maintaining tissue homeostasis. Insufficient tissue repair can cause

sustained chronic inflammation that triggers further injury and tissue destruction. Stem cells play an important role in the repair and regeneration of various cardiovascular tissues.^{243–246}

Activation of stem cells in AAD—Activation of stem cells has been seen in patients with AAD. Circulating endothelial progenitor cells are increased in patients with ascending TAA²⁴⁷ and in those with AAA.²⁴⁸ Moreover, significant amounts of mesenchymal cells have been detected in the aortic tissue of patients with TAA, TAD,²⁴⁹ and AAA.²⁵⁰

Mesenchymal stem cell–based therapy in AAD—Mesenchymal stem cells (MSCs) are promising candidates for cell therapy. Bone marrow–derived MSCs (BM-MSCs) and adipose-derived MSCs can be readily isolated and expanded in vitro and are therefore suitable for allogeneic cell-based therapy.²⁵¹ The therapeutic effects of BM-MSCs in AAD have been tested extensively in animal models.^{252–258} These studies have shown that BM-MSC therapy—administered directly to the aortic adventitial surface²⁵³ by endovascular seeding²⁵⁴ or via intravenous injection^{255,256,258}—reduced aortic destruction, decreased inflammation, and attenuated AAD development. Recent studies have shown that adipose tissue–derived MSCs have similar effects.^{259–261}

Mechanisms of stem cell–mediated protection—MSCs exert their protective effects through several mechanisms. When co-cultured with SMCs, MSCs promote the secretion of elastin from SMCs.²⁶² In addition, MSC treatment can inhibit the activation of proinflammatory cells and the secretion of proinflammatory factors, and reduce the production and activity of MMPs.^{253,257,263} These effects prevent aortic inflammation and destruction. In a recent study, MSCs activated anti-inflammatory cells such as M2 macrophages and T regulatory (T_{reg}) cells and inhibited proinflammatory cells such as neutrophils.²⁶¹

Regulation of stem cells in AAD—Stem cells receive signals from surrounding cells such as vascular and inflammatory cells.²⁶⁴ The communication and dynamic interplay among these cells are important in determining the fate and function of stem cells. Identifying the factors and signaling pathways involved in regulating stem cell recruitment, survival, proliferation, growth factor production, and differentiation in the aortic wall is important. Understanding the regulation of stem cell–mediated aortic repair and remodeling will be a critical step toward designing strategies to promote aortic repair and prevent adverse remodeling.

Inflammatory cells and inflammatory components

Inflammatory cells actively participate in tissue injury, repair, and remodeling. After tissue injury, inflammatory cells undergo significant phenotypic and functional changes. They play critical roles in the clearance of tissue debris, the initiation and maintenance of tissue repair and regeneration, and the resolution of inflammation. These steps require communication and interaction between inflammatory cells and aortic cells (eg, endothelial cells, SMCs, fibroblasts or myofibroblasts, and stem or progenitor cells). Dysregulation of inflammatory cell functions can lead to the insufficient clearance of damaged tissues, impaired tissue repair and regeneration, deficient anti-inflammatory responses and inflammation resolution,

and the uncontrolled production of inflammatory mediators and growth factors. These things ultimately add to tissue injury and contribute to maladaptive fibrotic remodeling. A variety of inflammatory cells accumulate in TAAD and AAA tissue,^{265–269} including lymphocytes, macrophages, mast cells, and neutrophils. Each cell type has unique features and functions in the aorta (Fig 8).

T lymphocytes (T cells) in AAD

Activation of T cells in AAD—T cells are a heterogeneous group of lymphocytes with diverse classifications and functions. The major types of T cells are CD4⁺ cells and CD8⁺ cells. CD8⁺ cells perform cell-mediated cytotoxicity,²⁷⁰ whereas CD4⁺ cells regulate immune responses.²⁷¹ A significant amount of CD4⁺ cells has been observed in aortas from patients with TAAD^{220,272,273} and AAA.^{265,268,274,275} Direct evidence supports a critical role of CD4⁺ cells in the development of AAD. Xiong and colleagues²⁷⁶ showed that aneurysm formation was attenuated in a mouse model of AAD when mice were deficient in CD4⁺ cells. Furthermore, CD4⁺ cells were shown to exacerbate disease progression by producing cytokines and MMPs and by promoting aortic inflammation and destruction.²⁷⁶

CD4⁺ T cells can be classified according to the unique profile of cytokines, transcription factors, cell markers, secreted products, and effector actions that they induce.^{271,277–280} Classifications of CD4⁺ T cells include T effector (T_{eff}) cells and T helper (Th) cells, which can be further classified as T-helper 1 lymphocytes (Th1),²⁷⁷ T-helper 2 lymphocytes (Th2),²⁷⁷ T-helper 17 lymphocytes (Th17),²⁷⁸ and T_{reg} cells.²⁷⁹

Th1 and Th2 in AAD—Th1 cells are proinflammatory, proatherogenic cells that are involved in several chronic inflammatory disorders.^{271,280} Th1 cells are activated by IL-12, which activates signal transducer and activator of transcription 4 (STAT4) and T-bet pathways, stimulates Th1 differentiation, and induces the expression of proinflammatory cytokines including interferon gamma (IFN- γ) and tumor necrosis factor- α (TNF- α). In turn, these cytokines activate inflammatory cells such as macrophages that can produce additional IL-12 and further promote Th1 activation.^{271,280} Th2 cells can be induced by IL-4, IL-13, or both, which activate STAT6 and GATA-binding protein 3 (GATA-3) transcription factors to stimulate Th2 differentiation and the production of IL-4, IL-5, and IL-13. Th2 cells have complex roles in the regulation of inflammation, repair, and regeneration. When Th2 cells are dysregulated, they participate in the pathogenesis of several allergic and fibrotic disorders.^{271,277,280,281}

Activation of Th1 and Th2 in AAD.—Several complexities have been observed regarding the presence of Th1 and Th2 cells in AAD tissues and their roles in AAD development. Increased expression of the Th1 cytokine IFN- γ and the usually undetectable Th2 cytokines has been observed in ascending TAA tissues.²⁸² In addition, Th1 immune responses have been positively correlated with aortic remodeling and the intimal expansion of TAA.²²⁰ Moreover, Th1 cells were found to be abundant in aneurysmal tissue from patients with AAA.²⁶⁸ However, a different study has shown that levels of Th1-related cytokines (particularly IFN- γ) were decreased and that Th2 cytokine levels were increased in human AAA tissues.²⁷⁴

Role of Th1 and Th2 in AAD development.—Th2 cells have been implicated in aneurysm development^{283,284}; this has been supported by studies showing that the inhibition of the Th2 cytokine IL-4²⁸³ or IL-5²⁸⁴ reduces aortic destruction and AAD formation. However, the role of Th1 in AAD development may be more complex than that of Th2. In a mouse model of calcium chloride-induced AAA, the deletion of the gene encoding Th1 cytokine IFN- γ attenuated MMP expression and aneurysm formation, indicating a destructive role of IFN- γ in matrix remodeling and AAA development.²⁷⁶ Interestingly, in an aorta transplantation experiment, profound aortic aneurysm formation was observed in recipient mice deficient in IFN- γ receptor or IFN- γ signaling. The blockade of IL-4 prevented aortic aneurysm formation in these mice.²⁸³ These studies illustrate the complex role of Th1 in AAD development and highlight the importance of the Th1/Th2 balance in matrix remodeling and aortic aneurysm formation.^{283,285}

Th17 cells in AAD—Th17 cells are an important proinflammatory cell type stimulated by IL-1, IL-6, and IL-23, which activate retinoic acid receptor-related orphan receptor γ t and STAT3 to induce Th17 differentiation and the secretion of IL-17 and IL-23. These cytokines, in turn, promote the infiltration and activation of macrophages and are involved in several inflammatory diseases.^{278,286–288} The levels of Th17 cytokines IL-17 and IL-23 were also found to be significantly increased in aortic tissues of patients with AAA.²⁵⁷ A growing body of evidence has indicated an important role of Th17 cells in promoting aortic inflammation and aneurysmal disease development. Inhibition of the Th17 cytokine IL-17 or IL-23 by genetic deletion²⁵⁷ reduced cytokine production and inflammatory cell infiltration in the aorta and attenuated aneurysm development in an elastase perfusion-induced experimental model. Moreover, the inhibition of the Th17 inducer IL-6 attenuated angiotensin II-induced AAD development.²⁸⁹ A recent study showed that inhibiting the IL-17A inflammatory response with digoxin reduced aortic disease development and increased survival in a mouse model of AAD.²⁹⁰ Finally, giving mice MSCs has been shown to decrease IL-17 production and reduce aortic dilation.²⁵⁷ These studies support a destructive role of the Th17 response in AAD development.

T_{reg} cells in AAD—T_{reg} cells are a unique subclass of CD4⁺ T cells that function as anti-inflammatory cells.^{279,291,292} T_{reg} cells are activated by IL-2 and TGF- β , which stimulate the forkhead box P3 (FOXP3) pathway to produce IL-10 and TGF- β . T_{reg} cells prevent further inflammation and tissue damage by limiting the activation of proinflammatory cells and by inhibiting the secretion of proinflammatory cytokines such as TNF- α and IFN- γ .^{279,291,292} T_{reg} cells also play a critical role in promoting tissue repair.^{279,291,292} Reduced T_{reg} cell population size and impaired T_{reg} cell function have been implicated in chronic inflammation^{279,291,292} and have also been observed in aortas from patients with AAA.^{293,294} Furthermore, evidence supports a protective role of T_{reg} cells against AAD formation. Ait-Oufella and colleagues²⁹⁵ showed that depleting T_{reg} cells increased the inflammatory response and significantly enhanced susceptibility to AAD formation and rupture in a mouse model of AAD. In contrast, the reconstitution of T_{reg} cells in T_{reg}-deficient mice limited inflammation and tissue damage and attenuated aortic aneurysm, dissection, and rupture in a mouse model of AAD.^{293,295}

T cells play critical roles in inflammation, either as proinflammatory cells or antiinflammatory cells. In chronic inflammatory processes such as AAD, the imbalance between the proinflammatory and anti-inflammatory responses leads to chronic inflammation, progressive tissue destruction, and AAD development.

Monocytes and macrophages

Activation of macrophages in AAD—Macrophages are important components in the inflammatory response.^{296–299} The macrophage is a predominant cell type in the aorta of patients with TAAD^{273,300,301} and AAA^{302,303} and in mice with AAD.^{304,305} Because of their role in producing proinflammatory factors such as IL-6, TNF- α , and MMPs^{306–308} and in promoting inflammation, macrophages have been implicated in the development of AAD.

M1 and M2 populations—Macrophages display plasticity and have the ability to polarize to various phenotypes, such as the classically activated (M1) phenotype or the alternatively activated (M2) phenotype. M1 macrophages produce proinflammatory cytokines and initiate tissue destruction, whereas M2 macrophages promote inflammation resolution and tissue repair.^{296–299} M1 macrophages can be activated by proinflammatory cytokines including IFN- γ , lipopolysaccharides, and TNF- α , which activate the STAT1-, nuclear factor- κ B (NF κ B)-, and IRF5-mediated induction of the M1 phenotype. Through the production of proteolytic enzymes and proinflammatory mediators, M1 macrophages promote tissue inflammation and damage. The markers for M1 macrophages include inducible nitric oxide synthase; proinflammatory TNF- α , IL-1 β , IL-6, and IL-23; and cell surface proteins such as CD80 and CD86, which are associated with antigen presentation.^{296–299} M2 macrophages are activated by IL-4 or IL-13, which antagonize IFN- γ to promote the STAT6- and peroxisome proliferator-activated receptor γ (PPAR γ)-mediated induction of the M2 phenotype.^{298,299} M2 macrophages produce anti-inflammatory cytokines including IL-10 and promote tissue repair and healing.^{298,299} M2 macrophages also have unique markers such as mannose receptor, arginase I, CD206, and CD163. The M1/M2 balance is vital to the outcomes of sustained inflammation vs inflammation resolution and of tissue injury vs repair.

M1 and M2 macrophages in AAD—Both M1 and M2 cells are present in human AAA tissue^{303,309} and in mouse AAD tissue.³⁰⁵ A high M1/M2 ratio with predominantly M1 cells has been observed in AAA.³¹⁰ Recent study findings have indicated that the M1/M2 imbalance is critical for aneurysm formation,^{310–313} and the manipulation of the M1 and M2 cell populations may affect AAD progression. Elastin-derived peptides, which act as proinflammatory mediators, induce M1 polarization. The neutralization of elastin-derived peptides was shown to attenuate aortic dilation. Importantly, the injection of M2-polarized macrophages reduced aortic dilation after aneurysm induction.³¹⁰ In addition, the inhibition of Notch³¹¹ and STAT3³¹² signaling was shown to decrease the M1/M2 ratio and reduce aneurysm formation. Furthermore, administering D-series resolvins in mice increased M2 macrophage polarization, decreased the levels of proinflammatory cytokines, and inhibited AAA formation in a model of elastase infusion-induced AAA.³¹³ Thus, these findings support that targeting the M1/M2 imbalance by reducing the M1 response and inducing the

M2 response may be a useful therapeutic approach to reducing chronic inflammation and tissue destruction in AAA.^{310,313}

Monocytes in AAD—Monocytes give rise to macrophages. In patients with AAA, circulating monocytes were shown to enhance adhesion to the endothelial cell wall and increase MMP-9 production.³¹⁴ Circulating monocytes have been suggested to contribute to the development of AAA.³¹⁵ Monocytes or macrophages are recruited to sites of injury by numerous chemokines, including monocyte chemoattractant protein (MCP)-1, IL-8, and TNF- α .²⁹⁶ One of the main sources promoting the attraction or chemotaxis of monocytes to the aortic wall may be the presence of aortic ECM breakdown products, such as the peptide sequence VGVAPG found in elastin.³¹⁶ Blocking the VGVAPG sequence with a monoclonal antibody reduces monocyte or macrophage recruitment and limits additional ECM breakdown.^{317,318}

Neutrophils

Activation of neutrophils in AAD—Neutrophils are an important population of inflammatory cells that not only comprises key effectors of acute inflammation but also contributes to chronic inflammation.^{319,320} By interacting with innate and adaptive immune cells³¹⁹ and releasing proteolytic enzymes and reactive intermediates,³²⁰ neutrophils contribute to immune responses, tissue injury, and repair.^{319,320} A significant increase in neutrophil infiltration has been observed in aortas from patients with TAA, TAD,³⁰¹ and AAA.^{321–323} Neutrophils are also abundant in the aorta of experimental mouse models of AAD.^{324–327}

Role of neutrophils in AAD development—Neutrophils play a significant role in AAD development. Neutrophil depletion by anti-neutrophil antibody³²⁸ or by anti-granulocyte-differentiation antigen-1 (anti-Gr-1) antibody³²⁶ significantly decreased the incidence of AAD in an experimental mouse model of AAD. Furthermore, preventing neutrophil recruitment to the aortic wall alleviated elastase-induced experimental AAA.³²⁵

Mechanisms of neutrophil-mediated aortic destruction—Neutrophils may promote aortic inflammation and destruction through several mechanisms. They produce destructive proteases such as MMPs^{326,328} and elastase- and neutrophil-derived proteases.³²⁷ In addition, neutrophils release cytokines such as IL-6³²⁹ and also express chemokines such as C-X-C motif ligand 1 (CXCL1) and their receptors, including chemokine receptor type 2 (CXCR2),^{303,329} which are important in inducing inflammation.

Neutrophil extracellular traps in AAD—Neutrophils extrude molecular lattices of chromatin and granular materials that are termed neutrophil extracellular traps (NETs).³³⁰ NETs stimulate inflammatory cells and amplify inflammation.³³¹ In addition, they promote vasculopathy and inflammasome activation.^{332,333} Interestingly, a recent study has shown that NETs are significantly increased in elastase-induced AAA.³²⁷ Furthermore, breaking NETs with DNaseI suppresses elastase-induced AAA,³²⁷ suggesting that NETs are involved in AAD development. The NETs contain cathelicidin-related antimicrobial peptide and self-

DNA, which recruit dendritic cells and induce the production of inflammatory factors, leading to AAA formation.³²⁷

Regulation of neutrophil activation in AAD—Several factors are involved in the recruitment of neutrophils to the aortic wall. Dipeptidyl peptidase I (a protease critical for the activation of neutrophil elastase),³²⁵ CXCL1, and CXCR2³²⁹ are involved in local neutrophil recruitment in AAD. Deficiency in these factors by loss-of-function mutations or neutralization of these factors with antibodies diminishes neutrophil infiltration and reduces aneurysm formation and rupture in a mouse model of AAD.^{325,329} Diminished catalase expression and activity and increased oxidative stress in neutrophils are also responsible for neutrophil infiltration in AAA.³³⁴

Mast cells

Mast cells are a major inflammatory cell type involved in immediate hypersensitivity and chronic allergic reactions such as asthma and allergies.³³⁵ Through the rapid release of vasoactive mediators, mast cells regulate vascular permeability and recruit various inflammatory cells, initiating an acute inflammatory response.³³⁶ Evidence has indicated that mast cells also participate in chronic inflammation and tissue destruction in cardiovascular diseases.³³⁷ The granular content in mast cells includes heparin, histamine, and several enzymes (eg, tryptase, chymase, carboxypeptidase, and cathepsin G).³³⁸ Activated mast cells can cause cell apoptosis, matrix degradation, and inflammatory infiltration through the release of growth factors, histamine, chemokines, and proteases such as the mast cell–specific proteases chymase and tryptase.³³⁷

Role of mast cells in AAD development—Mast cells have been found in the aortic media and adventitia from patients with TAA, TAD,³⁰¹ and AAA.^{269,339,340} Mast cells were also found in the aorta in mouse models of aneurysm formation.^{341–343} Mast cell–deficient mice showed reduced aortic elastic lamina degradation, inflammation, SMC apoptosis, and attenuated aneurysm formation.³⁴¹ Reconstitution of these mice with bone marrow–derived mast cells from wild-type mice resulted in increased susceptibility to AAA formation.³⁴¹ Furthermore, the inhibition of mast cells with the degranulation inhibitor tranilast attenuated AAA development in mice.²⁶⁹ It has been suggested that chymase³⁴² and tryptase³⁴³ in mast cells have critical roles in MMP activation, ECM destruction, and SMC apoptosis, and thus promote AAA formation.³⁴⁴ Mast cell stabilizing agents and histamine receptor blockers may be effective therapeutic approaches in preventing the development and growth of AAA.³³⁸

Extracellular matrix

The ECM is a dynamic noncellular component of the aorta that provides structural support and controls the plasticity and strength of the aortic wall. The ECM also actively regulates cellular functions. ECM proteins bind to adhesion receptors (eg, integrins) on the cell membrane to mediate matrix and cell attachments and transduce biomechanical signals into cells. ECM proteins also bind to soluble growth factors (eg, TGF- β) and control their signaling in a spatially patterned and regulated fashion. The ECM gives rise to stem cell

niches that host and reserve stem cells for tissue repair and regeneration. Although the ECM is constantly undergoing degradation and biosynthesis, abnormal degradation of ECM components can release bioactive fragments that serve as signaling molecules and actively affect cell functions.^{345–347} Thus, the integrity of the ECM is critical in maintaining aortic structure and function.

ECM degradation in AAD

Intact elastic fibers are vital for aortic structure and function. Elastic fiber fragmentation and depletion reduce aortic resilience that causes aortic dilatation.^{348,349} In addition, loss of elastic fiber integrity can decrease the undulation of collagen fibers, leading to decreased extensibility and increased stiffness of the aortic wall.³⁵⁰ Aortic dilatation and stiffness are characteristic of aortic disease.^{52,351} Additionally, functional elastic fibers contribute to the contractile phenotype of SMCs.^{352,353} Thus, the destruction of elastic fibers may result in aortic contractile dysfunction. Furthermore, microfibrils sequester latent TGF- β and inhibit TGF- β signaling. Elastic fiber damage can result in the release of TGF- β , leading to the overactivation of TGF- β signaling and SMC dysfunction.^{354,355}

In contrast to elastic fibers, collagen fibers in the aorta have a short half-life.³⁵⁶ Appropriately regulated collagen turnover is critical for the aorta to adapt to altered hemodynamics or to respond to injury.^{357,358} Degradation or loss of collagen fiber integrity decreases aortic strength, rendering the aortic wall prone to rupture.

As discussed earlier, mutations in various genes encoding ECM proteins can cause genetically triggered AAD. However, in both genetic and sporadic aortic diseases, the excessive production of proteases that degrade elastic and collagen fibers can cause matrix destruction, leading to AAD formation.^{359,360} MMPs and cathepsins, which are involved in proteolysis, are the major classes of extracellular proteases affected in AAD.

Activation of MMPs in AAD

Matrix metalloproteinases—MMPs are a large family of Zn²⁺-dependent proteolytic proteases that are produced by endothelial cells, SMCs, fibroblasts, and inflammatory cells in the aortic wall.^{361,362} MMPs not only degrade ECM proteins and control ECM homeostasis,³⁶² but they also regulate signal transduction.^{363,364} The activities of MMPs are regulated through transcription, zymogen activation, and inhibition by endogenous inhibitors.^{362–364} When the balance between MMP production or activation and inhibition is disrupted and favors MMP activation, ECM turnover is accelerated.^{363,364}

Destructive role of MMP-9 in AAD—Elevated MMP-9 production and activity have been consistently seen in the aortas of patients with Marfan syndrome,^{365,366} TAA,^{367–369} and AAA.^{370,371} The gene-targeted disruption of MMP-9 in mice suppresses aortic destruction and TAA and AAA formation^{326,372–374} in models of aortic disease induced by elastase or angiotensin II infusion. Furthermore, the inhibition of MMP-9 activity with MMP inhibitors reduces AAD formation.^{326,375} Several inflammatory factors such as IL-6³⁰⁶ and TNF- α ³⁰⁸ trigger AAD development by upregulating MMP-9. Doxycycline³⁷⁶ or cytokine antibodies such as TNF- α ³⁰⁸ reduce AAD development through the downregulation of

MMP-9. Thus, evidence from animal studies has indicated that MMP-9 is an important protease involved in aortic destruction and AAD formation. Other MMPs that may also be involved in TAA development are MMP-14 and MMP-19, which have increased expression in aortic tissues from patients with TAA.³⁷⁷

Dual role of MMP-2 in AAD—A recent meta-analysis of 8 studies (including a total of 106 patients and 30 controls) showed no change in MMP-2 levels among aortas from patients with TAA, although MMP-2 levels were higher in patients with TAA and bicuspid aortic valve (BAV) than in patients with TAA and tricuspid aortic valve.³⁶⁸ We observed reduced MMP-2 levels in the tissues of patients with chronic TAD.³⁶⁹ In contrast, MMP-2 has been reported to be upregulated in patients with AAA³⁷⁸ and has been suggested to have a dual role in AAD development. MMP-2 may contribute to AAD development in Marfan syndrome, as indicated by the finding that MMP-2 deficiency in mice with Marfan syndrome attenuated aortic destruction.^{53,93} Interestingly, a recent study showed that MMP-2 deficiency in mice suppressed angiotensin II–induced elastin and collagen production, thus increasing the severity of TAA.³⁷⁹ However, MMP-2–deficient mice were also shown to be protected against calcium chloride–induced ECM degradation and TAA formation. These findings suggest that MMP-2 has both protective (via ECM synthesis) and destructive (via ECM degradation) functions that affect aortic structure and AAD development.

Membrane-type MMPs—Membrane-type MMPs (MT-MMPs) form a subgroup of the MMP family. Because of their unique location in the cell membrane, MT-MMPs not only control matrix remodeling but also regulate cellular functions (eg, cell migration) and signaling activation (eg, Notch signaling). MT-MMPs are involved in various processes such as angiogenesis and inflammatory responses.^{380,381} The aortic expression of MT1-MMP, the most studied MT-MMP,^{380,381} was shown to be elevated in mouse models of AAA³⁰⁷ and TAA.³⁸² In a mouse model of calcium chloride–induced AAA, chimeric mice with MT1-MMP^{−/−} bone marrow cells had reduced aneurysm formation, and macrophage infiltration was unaffected. However, the infusion of MT1-MMP^{+/+} macrophages into chimeric mice with MT1-MMP^{−/−} bone marrow cells induced AAA formation.³⁰⁷ Thus, MT1-MMP regulates macrophage proteolytic activity and plays an important role in aortic destruction and disease progression.³⁰⁷ In contrast to MT1-MMP, MMP-17/MT4-MMP has a protective role against AAD development. A missense mutation (R373H) in *MMP17* causes inherited TAAD in humans.¹³² MMP-17 cleaves osteopontin, which is required for SMC maturation during aortic wall development. MMP-17 loss of function in mice was shown to result in dysfunctional vascular SMCs and altered ECM in the vessel wall, leading to increased susceptibility to angiotensin II–induced TAA.¹³²

Tissue inhibitors of metalloproteinases—The tissue inhibitors of metalloproteinase (TIMP) family, which includes TIMP-1 to TIMP-4, are endogenous MMP inhibitors.^{361–363,383} Tissue MMP activity is determined by the balance of MMP and TIMP activation. A recent meta-analysis showed the significant induction of MMP-9 and reduction of TIMP-1 and TIMP-2 protein expression in human TAA tissues that in turn led to the elevation of MMP-9/TIMP-1 and MMP-9/TIMP-2 ratios.³⁶⁸ An imbalanced MMP and TIMP ratio was

also observed in AAA tissues.³⁸⁴ Evidence supports a protective role of TIMPs against AAD development. *Timp-1* deficiency in *ApoE*^{-/-} mice increased atherogenic diet-induced atherosclerosis and promoted gelatinolytic activity, elastic lamellae degradation, and aortic destruction.^{385,386} Similar findings were observed in a model of calcium chloride-induced TAA.³⁷³ TIMP-3 deficiency also led to elevated proteolytic activities and inflammation and resulted in exacerbated aneurysm and aortic rupture in a mouse model of angiotensin II-induced AAA.³⁸⁷ Notably, the aortic diseases in these mouse models can be reversed by MMP inhibitors.^{373,387} These studies support critical roles of TIMP-1 and TIMP-3 in limiting MMP activity and highlight the importance of a low MMP to TIMP ratio in preventing aortic aneurysm formation, expansion, and rupture.

The role of cathepsins in AAD—Evidence has indicated that cathepsin L (CatL) and K (CatK) are involved in AAD development. Deficiency of *Ctsl*^{β88} or *Catk*³⁸⁹ in mice significantly reduced aortic inflammation, elastin fragmentation, and the elastase perfusion-induced formation of AAAs. Cathepsin K has also been shown to cause medial SMC apoptosis in AAA.³⁸⁹

Proteoglycans and proteoglycan degradation enzymes

Syndecan-1—Syndecans are a family of TM heparan sulfate proteoglycans that are composed of a core protein and attached glycosaminoglycan chains. Through the glycosaminoglycan chains, syndecans can interact with a variety of extracellular molecules (eg, growth factors and cytokines) and regulate cell functions. Syndecans are involved in a variety of processes such as ECM assembly, tissue repair, and anti-inflammation.³⁹⁰ Syndecan-1, encoded by the *SDC1* gene, has been shown to be important for maintaining aortic integrity. Protease activity, elastin degradation, and inflammatory cell infiltration were increased in mice deficient for *Sdc1*, and elastase- or angiotensin II-induced AAA formation was exacerbated.³⁹¹ Syndecan-1 and syndecan-4 can be cleaved by MMPs^{392,393} and a disintegrin and metalloproteinase with thrombospondin motifs 4 (ADAMTS-4).³⁹⁴ Although this process has not been examined in the context of AAD, the possibility remains that activated MMPs and ADAMTS-4 may cleave and degrade syndecans in AAD, thereby inhibiting the protective actions of syndecans in the aortic structure.

Biglycan—Biglycan has tissue-specific affinities to structural components, and thus plays a crucial role in maintaining tissue integrity. Biglycan also acts as a signaling molecule that binds to its receptors and regulates cell functions.³⁹⁵ Decreased levels of biglycan have been observed in human AAA tissues.³⁹⁶ Furthermore, biglycan deficiency causes spontaneous aortic dissection and rupture in mice,³⁹⁷ indicating an essential role of biglycan in maintaining aortic wall integrity. Consistent with these findings, a recent study showed that loss-of-function mutations in the X-linked biglycan gene cause a severe early-onset syndromic form of TAAD.³⁹⁸ Thus, biglycan is important in maintaining aortic integrity, and genetic defects that alter its function or degradation may play a role in the pathogenesis of aortic dissection and rupture.

ADAMTS proteins in AAD—The ADAMTS family of extracellular proteinases has been shown to be involved in ECM turnover.³⁹⁹ ADAMTS-1 and ADAMTS-4 are particularly

well-studied members of this family.⁴⁰⁰ ADAMTS-4 promotes ECM turnover by digesting proteoglycans including aggrecan, versican, decorin, and biglycan, and ECM proteins such as fibronectin.^{401,402} ADAMTS-1 digests versican⁴⁰³ and also inhibits cell proliferation by sequestering growth factors.⁴⁰⁴ The expression of ADAMTS-1,^{367,405,406} ADAMTS-4,⁴⁰⁵ ADAMTS-5, and ADAMTS-16⁴⁰⁶ has been shown to be increased in human TAA tissues. In human TAA tissues, ADAMTS-1 and ADAMTS-4 were identified in vascular SMCs and macrophages, concomitant with the degradation of versican, which is the main proteoglycan substrate of ADAMTS proteinases in the aorta.⁴⁰⁵ Given the activities of ADAMTS proteinases in ECM degradation, they may play a role in promoting aortic destruction during TAA development.

Plasmin, plasminogen, and plasminogen activators and thrombosis

The plasmin-plasminogen system plays a key role in modulating hemostasis, thrombosis, and inflammation. Plasmin is generated from plasminogen by tissue-type plasminogen activator (t-PA) and urokinase-type PA (u-PA). The major inhibitor of the plasmin-plasminogen system is PA inhibitor-1 (PAI-1). Apart from its key role in fibrinolysis, plasmin also functions as a powerful activator of MMPs,^{407–410} directly activating MMP-1 and MMP-3 and thereby inducing the activation of MMP-9.⁴⁰⁷ The plasmin-plasminogen system also plays a central role in the inflammatory response.⁴¹¹

Plasmin, plasminogen, and PAs in AAD—Significantly increased levels of t-PA and u-PA have been observed in aneurysmal tissues from patients with TAAD^{412,413} and AAA.⁴¹⁴ Furthermore, u-PA expression is increased in mice challenged with angiotensin II infusion.⁴¹⁵ Several studies have suggested that the plasmin-plasminogen system is essential for the progression of AAD development. The deletion of *t-PA* or *u-PA* in mice prevented medial destruction and aneurysm formation in experimental models of TAA and AAA.^{416–418} Plasminogen deficiency also reduced the formation of AAA in mice by reducing plasmin-dependent MMP activation and inflammation.⁴¹⁹ However, another study showed that the deletion of *u-PA* in bone marrow-derived cells impaired thrombus resolution in the aortic wall and increased aortic rupture in an angiotensin II-induced mouse model of AAA.⁴²⁰ These studies have indicated that u-PA has potentially paradoxical roles in the development of AAD vs aneurysm rupture.⁴²¹

PAI-1 in AAD—PAI-1 expression is increased in the aortic media of TAA tissues⁴¹³ but is decreased in AAA tissues.⁴²² Interestingly, the deficiency of *Pai-1* in mice resulted in increased MMP-2 levels and promoted aneurysm formation.⁴²³ Conversely, the overexpression of PAI-1 in mice provided protection against aneurysm formation.⁴²⁴ Furthermore, PAI-1 overexpression in SMCs protected SMCs from plasmin-induced detachment and death.⁴¹³ These findings suggest that PAI-1 has a protective role against aortic destruction and AAD development.

Platelet and prothrombin activation in AAD—Platelets are required for hemostasis but can also contribute to excessive thrombosis and inflammation. Platelet activation in plasma has been observed in patients with large ascending TAA⁴²⁵ and AAA.⁴²⁶ Significant platelet activation was observed in the luminal thrombus.⁴²⁶ In a rat model, the inhibition of

platelets with inhibitors limited aortic aneurysm expansion, suggesting that platelet activation may enhance AAA development.^{426–428} The effect of platelet inhibitors on AAD progression has been examined in clinical studies, which is discussed in the medical treatment section.

Signaling pathways and cellular stress

The complex and precise regulation of aortic function and homeostasis involves highly coordinated actions of different aortic cells and the ECM. The aortic cells sense biomechanical and biologic signals and respond by adapting structurally and functionally through highly coordinated signaling pathways. Dysregulation of signaling pathways results in aortic dysfunction, aortic injury, uncontrolled aortic inflammation, and maladaptive remodeling, leading to aortic destruction and biomechanical failure. Elucidating the regulation of signaling pathways in aortic homeostasis and understanding the dysregulation of signaling pathways during AAD development will help us to identify novel targets for the treatment of AAD. Here, we focus on a few major pathways that are important in aortic homeostasis and AAD development.

TGF- β signaling

TGF- β signaling occurs through distinct pathways (Fig 5). The canonical TGF- β signaling pathway involves receptor phosphorylation and the subsequent activation of SMAD2/3, which binds to SMAD4 and forms a complex that binds to the promoters of target genes. In the noncanonical pathways, the TGF- β receptor complex transmits signals through other pathways such as ERK1/2, JNK, and p38 mitogen-activated protein kinase (MAPK) pathways, which induce the production and release of MMP-2, MMP-9, MMP-13, and PA, thereby causing ECM disruption.

Protective role of TGF- β signaling in aortic homeostasis—The role of TGF- β in regulating aortic structure and function and the underlying molecular mechanisms of this regulation have proven to be complex. A more detailed discussion of this subject is available in another review.⁴²⁹ Numerous studies have supported a beneficial role of TGF- β signaling in aortic homeostasis. Loss-of-function mutations in the genes encoding TGF- β ligands TGFB2 and TGFB3,^{114,118,119} receptors TGFBR1 and TGFBR2,^{112,113,115,116} and target transcription factor SMAD3^{120–122} are associated with genetically triggered TAAD. In mice, the deletion of or loss-of-function mutations in genes that encode TGFB2,¹¹⁴ TGFBR1, TGFBR2,^{117,125,126} SMAD3,¹²³ or SMAD4¹²⁴ causes aortic destruction and AAD development. In a mouse model of angiotensin II-induced sporadic AAD, TGF- β signaling can be activated by angiotensin II. Systemically inhibiting TGF- β with neutralizing antibody enhanced inflammatory cell activation and MMP-12 activity and promoted AAD formation, dissection, and rupture.^{430,431} The results of these studies have clearly identified a protective role for TGF- β in preserving aortic integrity and homeostasis.

Mechanisms underlying the protective role of TGF- β signaling—TGF- β has a critical and fundamental role in the maturation and function of SMCs and in aortic development. Aortic tissue and explanted SMCs from patients with *TGFBR2* mutations

show reduced basal and TGF- β -induced expression of contractile proteins in SMCs and reduced transformation of fibroblasts into myofibroblasts,¹²⁷ an important process in the postnatal aortic injury response and aortic homeostasis. Postnatal deletion of *Tgfb2* in the SMCs of mice altered SMC gene expression and caused severe AAD,^{125,126} suggesting that TGF- β is critical in regulating SMC functions and maintaining aortic wall homeostasis.

Destructive role of TGF- β signaling in AAD—TGF- β signaling has also been shown to have dimorphic effects on AAD formation. In a mouse model of Marfan syndrome, *Ltbp-3* deficiency was associated with impaired TGF- β signaling, less aortic destruction, and greater survival,⁹¹ suggesting that TGF- β signaling is involved in aortic disease progression. It has also been shown that TGF- β is protective during the early stages of aortic development but is destructive at later stages.⁹⁵

Mechanisms underlying the dimorphic roles of TGF- β signaling in AAD—One possible explanation for the dual roles of TGF- β in AAD is that TGF- β exerts protective and destructive effects through different pathways.⁹² Originally, only the canonical SMAD4-dependent TGF- β pathway was evaluated in aneurysmal disease. However, a recent study showed upregulation of both the canonical SMAD4-dependent and the noncanonical ERK1/2 and JNK pathways in mice with Marfan syndrome. *Smad4* deficiency exacerbated aortic disease and caused premature death in mice with Marfan syndrome. In contrast, inhibiting ERK1/2 activation or JNK pathways ameliorated aortic dilation.⁹² Thus, it has been proposed that activation of the noncanonical TGF- β signaling ERK and JNK pathways drives aortic destruction and disease in mice with Marfan syndrome.^{92,93,95}

Upregulation of TGF- β signaling in AAD—Paradoxically, increased TGF- β signaling has been consistently shown in aortic tissue from patients with familial TAAD,⁸⁹ Marfan syndrome,^{88–90} or with mutations in *TGFB2*, *TGFB3*,^{114,119} *TGFBR*,^{112,128} or *SMAD3*.¹²⁰ A recent study showed evidence of dysregulated TGF- β signaling in aortic tissue from patients with mutations in *ACTA2* and *MYH11*.⁴³² Canonical and noncanonical TGF- β signaling and target gene expression have also been shown to be upregulated in mice with AAD.⁹² The mechanisms underlying this paradoxical elevation are not completely understood. Evidence has indicated that deficiency or dysregulation in canonical TGF- β signaling causes the compensational elevation of TGF- β production,¹¹⁸ which, through the noncanonical pathway, causes aortic destruction and disease development.⁹²

Angiotensin II signaling

The renin-angiotensin system is critically involved in regulating normal cardiovascular homeostasis. However, excessive stimulation of angiotensin II signaling promotes vascular destruction and dysfunction that contributes to a range of cardiovascular diseases. Angiotensin II is the most potent trigger of AAD formation, and it is widely used in experimental AAD models. Angiotensin II-mediated aortic dissection may occur independent of blood pressure changes.²⁸⁹ Angiotensin II has 2 distinct receptors, AT1R and AT2R, which counter-regulate each other and have opposite effects on vascular function (Fig 9).

Destructive role of AT1R in AAD—AT1R has been suggested to have a destructive role in promoting AAD development. A polymorphism in *AT1R* was associated with AAA in clinical studies.⁴³³ In addition, mice deficient in *At1r* were protected from angiotensin II-induced aneurysm formation.^{228,434} Treating mice with the ARB losartan, which selectively blocks AT1R, abrogated aneurysm progression in mice with Marfan syndrome⁹⁰ and partially prevented pressure-induced TAA in a transverse aortic constriction mouse model.²⁴¹ AT1R may promote AAD formation through multiple mechanisms. It has been shown that blocking AT1R with losartan reduced angiotensin II-induced vascular inflammation and macrophage accumulation.²⁴¹ Interestingly, AT1R deficiency in bone marrow-derived cells or in SMCs had no effect on ascending aneurysm formation, whereas AT1R deficiency in endothelial cells attenuated angiotensin II-induced TAA formation,²²⁸ indicating the importance of endothelial cells and endothelial-specific AT1R in aneurysm formation. Angiotensin II activates several signaling pathways such as the rho-kinase pathway that induces proteolysis and apoptosis, both of which are important activities associated with AAA. Fasudil, a rho-kinase inhibitor, attenuates angiotensin II-induced AAA in *ApoE*^{-/-} mice by inhibiting apoptosis and proteolysis.⁴³⁵

Protective role of AT2R in AAD—In contrast to AT1R, AT2R has a protective role against AAD development. Deletion of *Agt2r*, the gene encoding AT2R, accelerated the aberrant growth and rupture of the aorta in a mouse model of Marfan syndrome.⁹⁴ In addition, signaling through AT2R attenuates aortic aneurysm formation in mice through ERK antagonism.⁹⁴

Notch signaling

Notch signaling regulates cell-fate determination during development and maintains adult tissue homeostasis. Notch ligands include the delta-like (eg, DLL1, DLL3, and DLL4) and jagged (eg, JAG1 and JAG2) protein families. Notch receptors are transmembrane proteins composed of functional extracellular, transmembrane, and intracellular domains. Upon ligand binding, the Notch intracellular domain is cleaved by γ -secretase, released from the membrane, and translocated into the nucleus, where it associates with the CSL (CBF1/Su[H]/Lag-1) transcription factor complex, thus activating Notch target genes such as the hairy and enhancer of split-1 (*HES*) and the hairy-related family of transcriptional repressors (*HRT*).⁴³⁶

Mutations of NOTCH1 in BAV disease—BAV is the most common congenital heart malformation, and it is associated with significant abnormalities in the left ventricular outflow tract and thoracic aorta. Recent studies suggest that Notch signaling regulates proper valve and outflow tract development.⁴³⁷ Notch signaling also appears to be important for inhibiting calcification.⁴³⁸ Loss-of-function mutations in *NOTCH1* have been identified in patients with BAV and aortic valve calcification.^{438–441} *NOTCH1* mutations cause early-stage developmental defects in the aortic valve and, at later stages, unsuppressed calcium deposition that leads to progressive aortic valve disease.⁴³⁸

Protective role of Notch signaling in the aortic valve and aorta—Mechanistically, the Notch signaling pathway suppresses the production of runt-related transcription factor 2

(RUNX2), a transcription factor critical for osteoblast cell differentiation, bone formation, and tissue calcification.⁴³⁸ The NOTCH1 signaling target HRT directly interacts with RUNX2 and represses RUNX2 transcriptional activity. It has been proposed that loss of Notch signaling results in the overactivation of RUNX2-mediated osteoblast cell differentiation and tissue calcification, leading to valve calcification. Notch signaling is also a key pathway in promoting EMT, a process that is important for tissue development and repair. Recently, Kostina and colleagues⁴⁴² showed that Notch-dependent EMT was attenuated in patients with aortic aneurysm and BAV. Aortic endothelial cells from patients with aortic aneurysm and BAV had downregulated Notch signaling and failed to activate EMT in response to different Notch ligands.

Dysregulation of Notch signaling in sporadic TAAD—Notch signaling exhibits a complex pattern in sporadic TAA and TAD tissues.⁴⁴³ Notch signaling is impaired in SMCs of the aortic media but is activated in stem cells, fibroblasts, and macrophages of sporadic TAAD tissues.

Destructive role of Notch signaling in AAA—Although Notch signaling is protective against TAAD in BAV, it plays a destructive role in the abdominal aorta. Inhibiting Notch signaling by gene deletion of *Notch1* in mice reduces macrophage-mediated inflammation and AAA formation.⁴⁴⁴ In addition, blocking the Notch signaling pathway inhibits vascular inflammation⁴⁴⁵ and AAD progression.^{311,444,446}

Thus, Notch signaling has multiple functions in different cells in the aortic wall and may have both protective and destructive roles in AAD development. Further studies are needed to discern the various tissue-specific roles that Notch signaling plays in aortic homeostasis and disease development.

Other signaling pathways

β -Arrestin-2— β -Arrestin-2 is a multifunctional scaffolding protein that binds G-protein-coupled receptors such as AT1R and regulates numerous G-protein-coupled receptor-dependent and independent signaling pathways during physiological and pathophysiological processes. Recent studies have shown that *β arr2* deficiency attenuates aortic aneurysm development in mouse models of Marfan syndrome⁴⁴⁷ and angiotensin II-induced AAA.⁴⁴⁸ The inhibition of disease development was attributed to the reduced aortic expression of MMP-2, MMP-9,⁴⁴⁷ and cyclooxygenase-2, and decreased inflammatory cell infiltration.⁴⁴⁸ These studies suggest that β -arrestin-2 is another player in promoting aortic destruction and AAD formation.⁴⁴⁸

Endothelin-1—Endothelin-1 has a role in aortic disease. In *ApoE*^{-/-} mice, the selective overexpression of endothelin-1 in endothelial cells increased atherosclerosis and induced AAA development. This process was associated with increased ROS production, monocyte or macrophage infiltration, and MMP-2 activity in CD4⁺ T cells.⁴⁴⁹

Aldosterone and mineralocorticoid receptor signaling—Through the induction of inflammation, ROS production, and fibrosis, aldosterone and mineralocorticoid receptor signaling can have detrimental effects on the cardiovascular system.^{450,451} A recent study

described a potential role of aldosterone in the pathogenesis of aortic aneurysm in mice.²⁰⁵ Administering aldosterone promoted salt-induced elastin degradation, SMC degeneration and apoptosis, inflammatory cell infiltration, and AAA and TAA formation and rupture in an age-dependent manner. These findings imply a role for the mineralocorticoid receptor in promoting aortic aneurysm development.

Kinin B₂ receptor (B₂R)—Activation of the kallikrein-kinin system, which signals through bradykinin B₁ and B₂ receptors, has both beneficial and deleterious effects on cardiovascular functions.⁴⁵² Interestingly, a recent study has indicated that the activation of B₂R signaling promotes aortic rupture.⁴⁵³ In a mouse model of angiotensin II-induced AAD, a B₂R antagonist inhibited aortic rupture, whereas a B₂R agonist promoted it. Administering a B₂R antagonist reduced the expression of the angiotensin II-induced SMC inflammatory phenotype, inflammatory cell activation, and MMP-2 and MMP-9 activation. This study's findings suggest that B₂R signaling may promote a SMC inflammatory phenotype switch, aortic inflammation, and MMP production, leading to aortic destruction.

Apelin—Through its receptor, apelin induces vasodilation by releasing nitric oxide bioavailability from endothelial cells.⁴⁵⁴ Chun and colleagues⁴⁵⁵ showed that apelin induced nitric oxide production and inhibited angiotensin II-induced gene expression in SMCs, and it attenuated atherosclerosis and AAA in *ApoE*^{-/-} mice.

LDL receptor-related protein 1—LDL receptor-related protein 1 (LRP1) is a member of a family of structurally related transmembrane proteins (which also includes LRP2, LDL receptor, and very low-density lipoprotein receptor) that participate in a wide range of physiological processes, including lipid metabolism and cardiovascular functions.⁴⁵⁶ Recent studies have indicated that LRP1 has a protective role against AAD.^{457,458} In mice, *Lrp1* deficiency in vascular SMCs results in disruption of the elastic layer, SMC proliferation, and aneurysm formation.^{457,459} Inactivation of LRP1 in vascular SMCs increases elastic fiber fragmentation, which is associated with increased production of high-temperature requirement factor A1, a secreted serine protease involved in ECM degradation and elastogenesis inhibition.⁴⁶⁰

Kinase pathways and the inflammasome cascade

AKT signaling—The AKT kinase pathway regulates many cellular functions, including survival, proliferation, migration, cell growth, and metabolism; thus, this pathway plays diverse yet critical roles in the cardiovascular system. AKT2 has recently been shown to protect the aorta against AAD development.²¹⁰ *Akt2*-deficient mice had abnormal elastic fibers and reduced medial thickness in the aortic wall. When challenged with angiotensin II, these mice developed aortic aneurysm, dissection, and rupture with features similar to those seen in humans, in both thoracic and abdominal segments. Aortas from these mice had profound aortic apoptosis and increased MMP production and inflammation. AKT2 was downregulated in aortic tissues from patients with sporadic TAAD. These results suggest that AKT2 maintains aortic integrity and protects the aorta against AAD formation by preventing aortic apoptosis and tissue destruction.²¹⁰ Consistent with the protective role of AKT, the deletion of genes encoding upstream kinases of the AKT pathway, such as

integrin-linked kinase,⁴⁶¹ PI3K-C2 α ,²²⁶ and PI3K- δ ,⁴⁶² also results in aortic destruction and AAD formation.

ERK, JNK, and p38 mitogen-activated protein kinase pathways—The MAPK pathways include ERK, JNK, and p38 pathways. These pathways are activated by inflammatory cytokines and extracellular stresses, as well as by intracellular stress such as ROS and ER stress. They are involved in many stress responses, including apoptosis and inflammation. The JNK pathway is activated in the aortic wall of mice with Marfan syndrome. Inhibiting the JNK1 pathway abolishes aortic destruction in these mice, which suggests that JNK is involved in aortic destruction and disease progression.⁹² JNK has been shown to promote abnormal ECM degradation and AAA development.⁴⁶³ The ERK pathway is also activated in mice with Marfan syndrome⁹² and is likewise involved in aortic destruction and disease progression.⁹² Numerous studies have shown that ERK is critically involved in MMP activation, aortic destruction, and AAD development.^{93,464–467} Finally, p38 MAPK is also activated in mice with Marfan syndrome and promotes SMAD2/3 activation.⁴⁶⁸ p38 has been shown to potentiate MMP activation,⁴⁶⁶ indicating its potential role in aortic destruction.

Protein kinase C—Protein kinase C (PKC) regulates numerous cellular responses, including gene expression, protein secretion, cell proliferation, and the inflammatory response. It has been shown that PKC production is increased in ascending aortic aneurysms excised from patients with BAV.⁴⁶⁹ Elevated PKC- δ production has been shown to contribute to aneurysm pathogenesis by stimulating apoptosis and inflammatory signaling.^{208,470}

NLRP3–caspase 1 inflammasome cascade—Inflammasomes are intracellular multiprotein complexes that are activated by various cell-stress signals^{471,472} and function as molecular platforms to mediate the activation of caspases and amplify inflammatory and stress responses.^{473,474} Recently, a study showed that the inflammasome is activated by mitochondrial oxidative stress in macrophages, leading to the development of angiotensin II–induced aortic aneurysm.⁴⁷⁵ Enhanced caspase activity was also shown to contribute to aortic wall remodeling and early aneurysm development in a mouse model of Marfan syndrome.²⁰³

Transcription factors

Peroxisome proliferator–activated receptor gamma—PPAR γ is a ligand-activated nuclear receptor that regulates glucose and lipid metabolism, maintains endothelial function, and inhibits inflammation. Jones and colleagues¹⁹¹ showed that treating mice with the PPAR γ activator rosiglitazone inhibited the angiotensin II–induced upregulation of AT1R and the inflammatory response and prevented aortic dilatation and fatal rupture. These findings suggest that PPAR γ protects against AAD development.

Nuclear factor- κ B—NF κ B is a transcription factor that promotes the expression of inflammatory genes. Deficiency in the gene encoding MYD88, an upstream signaling molecule of NF κ B, in bone marrow-derived cells inhibited angiotensin II–induced AAA

formation, independent of signaling through Toll-like receptors 2 and 4,⁴⁷⁶ suggesting the involvement of NF κ B in aneurysm formation.

Kruppel-like factor 4—KLF4 is a transcription factor that functions as both a repressor and an activator of transcription.⁴⁷⁷ KLF4 is essential for normal homeostasis and inflammation.^{477,478} Salmon and colleagues²²³ showed that KLF4 expression is increased in aortic SMCs in human and mouse aortic aneurysms. KLF4 binds to promoters of SMC genes and is involved in downregulating SMC gene expression. Deletion of *Klf4* in SMCs reduced SMC gene suppression, elastin degradation, inflammation, and aneurysm formation in a mouse model of aortic disease induced by elastase infusion and angiotensin II infusion.²²³ These findings suggest that KLF4 plays a critical role in aneurysm formation.

MicroRNA

MicroRNAs (miRNAs) are small, noncoding RNAs that, by inducing mRNA degradation and translational repression, posttranscriptionally silence target mRNAs (Fig 10).^{479–481} Several miRNAs have been studied in aortic disease (for details, see the review by Raffort and colleagues⁴⁸²). The altered expression of miRNAs in TAA tissues has been reported and was shown to be associated with aortic enlargement and MMP activation.⁴⁸³

MiR-29b—MiR-29b targets cell survival pathways, such as AKT signaling, and ECM proteins. MiR-29b has also been shown to induce apoptosis. MiR-29b levels were increased in the ascending aorta of mice with Marfan syndrome, and blocking miR-29b with antisense oligonucleotides prevented aortic wall apoptosis, ECM deficiencies, and aneurysm development in these mice.⁴⁸⁴ The overexpression of miR-29b augmented AAA expansion and increased the likelihood of aortic rupture.⁴⁸⁵ Thus, miR-29b promotes aortic destruction and rupture.^{484,485}

MiR-195—MiR-195 also targets ECM proteins, including collagens, proteoglycans, elastin, and proteins associated with elastic microfibrils. MiR-195 was differentially expressed in the aortas of *ApoE*^{−/−} mice with angiotensin II–induced AAA. Although silencing miR-195 had no effect on aortic dilation, it resulted in greater elastin expression, suggesting that miR-195 may reduce elastin production and contribute to the pathogenesis of aortic aneurysmal disease.⁴⁸⁶

MiR-205/MiR-712—MiR-205/miR-712 targets TIMP-3 and promotes MMP activity.⁴⁸⁷ MiR-205/miR-712 expression was shown to be increased in human AAA tissues and in the aneurysmal tissues of mice with angiotensin II–induced AAA. MiR-205/miR-712 reduces TIMP-3 expression and increases MMP activity in the aortic wall. Silencing miR-205/miR-712 in mice significantly decreased angiotensin II–induced MMP activity and inflammation and prevented AAA development.⁴⁸⁷

MiR-24—MiR-24 inhibits endothelial cell apoptosis and vascular inflammation.⁴⁸⁸ Maegdefessel and colleagues⁴⁸⁸ showed that, by targeting a proinflammatory chitinase-3-like and protein 1, miR-24 inhibited macrophage activation and the inflammatory response and attenuated AAA progression in mice.

Reactive oxygen species (ROS)

At low concentrations, ROS regulate signaling pathways and play important roles in various cell functions. However, the overproduction or accumulation of ROS causes cellular stress and is lethal to cells, thereby contributing to tissue dysfunction, inflammation, and destruction in patients with cardiovascular disease. In cardiovascular physiology and pathophysiology, the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase complex constitutes a major source of ROS in cells.⁴⁸⁹

Increased ROS production in AAD—The expression of ROS-generating NADPH oxidase and p22phox is elevated in aortic tissues from patients with TAA, particularly in areas where monocytes or macrophages have accumulated.⁴⁹⁰ Metallothionein, a metal-binding protein that protects against heavy metal and oxidant damage,⁴⁹¹ is dysregulated in ascending aortic SMCs of patients with BAV.⁴⁹² ROS production is also increased in aortic tissues from patients with AAA.^{493,494}

Role of ROS in AAD development—Numerous studies have established the role of ROS in the pathogenesis of AAD.⁴⁹³ Reducing ROS generation in mice by inhibiting NADPH oxidase with the inhibitor apocynin⁴⁹⁵ or by inhibiting cytochrome P450 by gene deletion⁴⁹⁶ prevented aneurysm formation in mouse models of AAD. Additionally, promoting ROS removal by administering the antioxidant enzyme catalase or by overexpressing catalase in SMCs decreased SMC apoptosis, aortic inflammation, and aneurysm formation in a model of calcium chloride-induced AAA.⁴⁹⁷ In contrast, inducing ROS generation in endothelial cells in mice by overexpressing NADPH oxidase NOX2 increased aortic inflammatory cell infiltration and enhanced angiotensin II-mediated aortic dissection.²²⁹ Furthermore, several triggers such as iron overload³⁰² and cyclophilin A production⁴⁹⁸ in the aorta contribute to AAA development by causing vascular oxidative stress. ROS promote aortic destruction by inducing aortic inflammation, MMP production,^{302,498} and SMC apoptosis⁴⁹⁴ during AAD development.

Interestingly, a recent study showed that systemic *Nox2* deficiency reduced the level of ROS in AAA lesions but promoted AAA development in mice.⁴⁹⁹ This study illustrates the complex role of NADPH oxidases and ROS in AAD development.

ER stress (unfolded protein response)

The cells of the aortic wall are constantly exposed to various stress-triggering factors such as hemodynamic disturbance, inflammatory factors, metabolic stress, and ROS. These factors can cause intracellular stress that interferes with normal cellular function. Protein folding in the ER is particularly vulnerable because stress can interfere with the complicated processes of concomitant glycosylation, disulfide bond formation, and membrane insertion. Protein misfolding, also called ER stress, not only causes protein dysfunction but also triggers signal-transduction events. These signaling events can amplify stress in a way that provokes an inflammatory response,^{500–503} causing cellular dysfunction and even cell death.^{500–503}

ER stress in AAD—In a mouse model of aortic injury induced by the inhibition of LOX with inhibitor 3-aminopropionitrile fumarate, the expression of ER stress markers ATF4 and

CHOP was induced. *Chop* deficiency reduced SMC apoptosis, inflammation, and AAD formation in mice.¹⁹⁸ Additionally, the overexpression of SM *Myh11* was shown to cause ER stress, which induced the autophagic degradation of thick filament-associated proteins.⁵⁰⁴

Medical treatment and drug development

A large number of therapeutic drugs has been tested in animal models of AAD. These drugs reduce aortic destruction and AAD development by targeting signaling pathways, inflammatory factors, and MMPs. Several of these drugs have also been examined in association studies or randomized trials in patients with AAD. The medical treatment of thoracic^{505–509} and abdominal^{510–513} AAD has been extensively reviewed in the literature.

β -Blockers

β -Blocker use in TAAD— β -Blockers have been the first-line medication for patients with Marfan syndrome and thoracic TAAD. Early studies showed that the β -blocker propranolol decreased aortic dilatation and mortality in patients with Marfan syndrome.⁵¹⁴ However, its effect was not confirmed in later studies; large meta-analyses did not show the beneficial effects of β -blockers on the reduction of aortic dissection or mortality in patients with Marfan syndrome⁵¹⁵ or chronic type B aortic dissection.⁵¹⁶ Despite the limited evidence supporting their efficacy, β -blockers are still routinely provided to patients with Marfan syndrome and other causes of TAAD to prevent the progression of aortic disease.⁵⁰⁹

β -Blocker use in AAA—Early studies in rodents suggested that β -blockers may slow the progression of AAA. In later, large-scale randomized controlled trials (RCT), no significant reduction in AAA expansion was observed in patients receiving β -blockers.^{511,513,517} However, β -blockers may have a beneficial effect in patients with AAA during surgical repair. It has been shown that patients receiving β -blockers around the time of surgery have a reduced incidence of nonfatal myocardial infarction.⁵¹⁸

ACE inhibitors

ACE inhibitor use in TAAD—ACE inhibitors limit the production of angiotensin II and thus reduce signaling through both AT1R and AT2R. Clinical studies have shown that the ACE inhibitors enalapril and perindopril reduce aortic stiffness and aortic root diameter in patients with Marfan syndrome.^{519,520} However, in a recent study in mice with Marfan syndrome, enalapril was less effective than losartan (an AT1R blocker) in reducing aortic enlargement.⁹⁴

ACE inhibitor use in AAA—Animal studies have yielded promising results on the use of ACE inhibitors to treat AAA. ACE inhibitors (eg, captopril, lisinopril, and enalapril) attenuated elastin degradation and disease development in an elastase infusion-induced AAA model.⁵²¹ However, the results from human studies have been conflicting. Associated studies have shown that patients taking ACE inhibitors had a reduced need for surgery⁵²² and a lower risk of rupture.⁵²³ In contrast, a prospective cohort study showed an association between ACE inhibitor use and increased AAA expansion in patients with small AAAs.⁵²⁴

In a recent RCT, ACE inhibitor use effectively lowered systolic blood pressure but had no effect on AAA growth.⁵²⁵

Angiotensin receptor blockers

ARBs selectively inhibit AT1R but have no effect on AT2R.

ARB use in TAAD—Losartan, the best-studied ARB, has been shown to prevent aneurysm progression in a mouse model of Marfan syndrome.^{90,94} The effect was attributed to the reduction of TGF- β signaling and ERK activation.^{90,94} In small, prospective cohort studies, losartan slowed aortic root dilation in pediatric patients with Marfan syndrome.^{526,527} Furthermore, in a multicenter RCT of 233 adult patients, losartan treatment reduced aortic dilatation.⁵²⁸ Several trials are currently ongoing to further evaluate and compare the effects of losartan and β -blockers and their additive effects on disease progression in patients with Marfan syndrome.^{529–531} The use of ARBs in other genetic TAADs has been tested in mouse models. Recent studies have shown that losartan treatment ablates aortic aneurysms in mice with Loeys-Dietz syndrome.^{117,532} Additionally, in a transverse aortic constriction mouse model, losartan treatment significantly blocked pressure-induced vascular inflammation.²⁴¹ These preliminary studies suggest that ARBs may have beneficial effects in treating genetically triggered and sporadic TAAD.

ARB use in AAA—Conflicting results have been reported regarding the use of ARBs in treating AAA. Although losartan completely inhibited angiotensin II-induced AAAs in *ApoE*^{-/-} mice,⁵³³ another study showed that losartan had no significant effect on aneurysm formation in an elastase-induced model of AAA.⁵²¹ These disparate results may be related to differences in the disease process in these different models. However, in a population-based case-control study, the protective effect of ARBs was not observed in patients with AAA.⁵²³ The efficacy of ARBs in limiting AAA growth is currently being studied in 2 randomized trials.⁵³⁴

Calcium channel blockers

Although calcium channel blockers (CCBs) are prescribed to patients with Marfan syndrome to prevent aneurysm progression,⁵³⁵ limited data are available on the efficacy and safety of their use for this condition. A small RCT showed that the use of perindopril, verapamil, and atenolol all reduced peripheral and central systolic pressure,⁵³⁶ but only atenolol delayed aortic expansion in patients with Marfan syndrome. However, in a recent study in mice, Doyle and colleagues⁵³⁵ observed unexpectedly that amlodipine and verapamil promoted aortic destruction and rupture in the aorta of mice with Marfan syndrome. In addition, patients with Marfan syndrome and other forms of inherited TAA who were taking CCBs had an increased risk of aortic dissection and need for aortic surgery compared with patients taking other antihypertensive agents.⁵³⁵ Further studies are needed to confirm this finding. For the time being, it is suggested that the use of CCBs warrants caution in patients with inherited TAAD.

Statins

Independent of their cholesterol-lowering effects, 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) reduce inflammation and protect the vascular wall.^{537,538} Because they are relatively well tolerated for long-term use, statins may be useful for the treatment of aortic diseases.

Statin use in TAAD—In a mouse model of Marfan syndrome, statins were shown to preserve aortic structure and attenuate aortic root dilation.⁵³⁹ Moreover, several clinical studies have indicated that statin use was consistently associated with improved long-term outcomes in patients with TAA.^{540–543}

Statin use in AAA—In a mouse model of elastase-induced AAA, statins have been shown to reduce MMP-9 production, decrease macrophage activation,^{544–547} and suppress AAA growth.⁵⁴⁷ In several clinical studies, statin use was associated with reduced AAA expansion, need for surgery, or incidence of rupture.^{541,548–550} However, other studies have not confirmed these findings.^{551,552} Conflicting results were reported in a recent review of 8 observational studies comprising a total of 4466 patients.⁵⁵³ One large trial is currently underway to examine the efficacy of statin use in limiting AAA growth (NCT01756833).⁵⁵⁴

Doxycycline

Doxycycline use in TAAD—The antibiotic doxycycline is a potent MMP inhibitor.⁵⁵⁵ Doxycycline has been shown to inhibit the production and activity of MMP-2 and MMP-9, reduce elastin degradation, and delay aneurysm rupture in mice with Marfan syndrome.^{93,376,556} Moreover, doxycycline and losartan have a synergistic effect on preventing the development of TAA in mice with Marfan syndrome.⁵⁵⁷ Additionally, long-term treatment with doxycycline prevented the development of spontaneous aortic lesions in a mouse model of vascular Ehlers-Danlos syndrome.⁵⁵⁸ However, no clinical data are available on its efficacy in patients with TAA.

Doxycycline use in AAA—In mouse models of AAA, doxycycline inhibited aneurysm development and progression.⁵¹¹ In preoperative patients with AAA, a short-term, 2-week regimen of doxycycline decreased inflammation in the aortic wall.⁵⁵⁹ In patients after endovascular AAA repair, doxycycline reduced circulating levels of MMPs.⁵⁶⁰ However, in a recent clinical trial, an 18-month regimen of doxycycline therapy did not reduce aneurysm growth or the need for AAA repair.⁵⁶¹ Therefore, the beneficial effects of long-term doxycycline use for treating AAA remain to be determined.^{511–513,562} The efficacy of doxycycline in treating AAA is currently being evaluated in an ongoing clinical trial (NCT01756833).

Platelet inhibitors

Large thrombi containing significant amounts of inflammatory cells and increased levels of MMPs are often seen in descending TAAD and in AAA. Thrombus size has been shown to correlate with aneurysm growth in AAA.⁵⁶³ Thus, antiplatelet therapy has been studied for treating aortic diseases.

Platelet inhibitor use in AAA—In a mouse model of AAA, aspirin and clopidogrel reduced aortic inflammation, tissue destruction, and aneurysm rupture.⁴²⁸ A retrospective cohort study showed that aspirin use was associated with reduced AAA progression.⁵⁶⁴ Moreover, the use of aspirin or P2Y₁₂ inhibitors has been associated with a reduced rate of death among patients with AAA.⁴²⁸ In a study of the potential mechanisms underlying the benefits of aspirin therapy, Bailey and colleagues⁵⁶⁵ showed that aspirin therapy in patients was associated with enhanced fibrinolysis and less compact fibrin networks. In a meta-analysis of a few trials, the use of aspirin was associated with lower expansion rates and less need for later surgical repair in patients with larger AAA (> 35 mm).⁵⁶⁴ A clinical trial examining the efficacy of the antiplatelet agent ticagrelor in limiting AAA growth is currently underway (NCT02070653).

Experimental drugs for AAD treatment

A large number of therapeutic drugs has been tested in animal models for use in reducing AAD development.

Anti-inflammatory agents—Infliximab, a US Food and Drug Administration-approved TNF- α antagonist, has been shown to inhibit aneurysm growth in mice.³⁰⁸ Anakinra, an IL-1 β antagonist, attenuated elastase-induced TAA formation in mice.⁵⁶⁶ Anakinra is currently being studied in a large clinical trial to determine its effects on atherosclerotic diseases (NCT02007252).⁵⁶⁷ The immunosuppressive drug azathioprine has been shown to reduce angiotensin II-induced inflammation and aneurysm progression in mice.²³⁰ Using an innovative experimental approach, investigators have injected nanoparticles containing the MMP inhibitor batimastat; they found that this approach prevented the progression of calcium chloride-induced AAAs in mice.⁵⁶⁸

Targeting other signaling pathways—In mice, the JNK inhibitor SP600125,⁴⁶³ the rho-kinase inhibitor fasudil,⁴³⁵ the rapamycin inhibitor everolimus,⁵⁶⁹ and the adenosine 2A receptor agonist⁵⁷⁰ have been shown to reduce aortic destruction, decrease inflammation, and attenuate AAD formation.

Conclusions

In the last decade, tremendous progress has been made toward improving our understanding of the molecular pathogenesis of AAD. The aortic wall is highly dynamic, performing sophisticated biomechanical functions to provide suitable compliance and adequate strength in response to hemodynamic changes. This requires the highly coordinated actions of different aortic cells and the ECM. Aortic function and homeostasis rely on intact cellular and extracellular proteins, as well as efficient signaling and communication among these components. Genetic defects in these structural components (eg, SMC contractile proteins and elastic microfibrils) or in their signaling pathways (eg, TGF- β signaling) cause aortic dysfunction and destruction. In the case of sporadic AAD, clinical risk factors for disease development (eg, smoking and hypertension) cause biologic insults, either directly or indirectly, that interfere with normal signaling and result in cell dysfunction. Both genetic defects and risk factors, through various shared stress pathways, disturb aortic homeostasis,

cause SMC dysfunction and loss, promote ECM destruction, and induce uncontrolled inflammation and maladaptive fibrotic remodeling, leading to aortic aneurysm, dissection, and rupture.

Importantly, our improved understanding of the molecular pathogenesis of AAD has led to the development of new strategies for treating AAD. Several drugs have been tested that target signaling pathways (eg, with the AT1R blocker losartan), suppress inflammation (eg, with statins), or inhibit destructive proteases (eg, with doxycycline as an MMP inhibitor). These drugs have shown promising results from preclinical and early clinical studies and may be used to prevent aortic destruction and slow disease progression. However, larger scale and better controlled clinical studies are needed to confirm their efficacy, test combination therapy, and define the best suitable patient groups for each medical regimen. Future research focused on uncovering the precise regulation of aortic injury, repair, and remodeling will further improve our understanding of the disease process and facilitate the development of new drugs to treat these highly lethal diseases.

Acknowledgments

We gratefully acknowledge Scott A. Weldon, MA, CMI, for creating illustrations; and Nicole Stancel, PhD, ELS, and Rebecca Bartow, PhD, at the Texas Heart Institute for editorial support.

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Fig. 1. Aortic segments. The aorta comprises the ascending thoracic aorta, aortic arch, descending thoracic aorta, suprarenal aorta, and infrarenal aorta. The diaphragm divides the aorta into the thoracic and abdominal aorta. (Color version of figure is available online.)

Fig. 2.

Aortic aneurysms and dissections. (A) Aortic aneurysm occurs when the progressive weakening of the aortic wall causes the aorta to enlarge to a diameter of at least 1.5 times greater than normal. (B) Aortic dissection occurs when a tear forms within the aortic wall and causes blood to flow between the layers, thereby creating a false lumen. (Color version of figure is available online.)

Fig. 3. Structure of the aortic wall. (A) The aortic wall is composed of a thin inner layer (the intima), a thick medial layer (the media), and a thin outer layer (the tunica adventitia). (B) The lamellar unit is composed of smooth muscle cells (SMCs) sandwiched between 2 layers of elastic fibers and surrounded by collagen bundles. (Color version of figure is available online.)

Fig. 4.

The elastin-contraction unit and mutations affecting aortic contractile function. The elastin-contraction unit is a unique configuration of elastic fibers, focal adhesions or dense plaques in the membrane, and contractile filaments inside the SMCs. The elastic fibers are organized as a core of elastin surrounded by microfibrils that are composed of fibrillin, microfibril-associated glycoproteins (MAGPs), elastin microfibril interfacial protein 1 (EMILIN1), fibulins, and other glycoproteins. An SMC contractile unit is composed of actin-containing thin filaments and myosin-containing thick filaments, along with regulatory proteins. Mechanical stimuli are transmitted from the elastic fiber, through the focal adhesions or dense plaques in the membrane, through the anchoring proteins or actin linkage proteins, and to the contractile unit, leading to the activation of SMC contraction. Genetic thoracic aortic aneurysms and dissections (TAAD) are associated with mutations in genes encoding proteins that control the structure and function of the elastin-contraction unit. These proteins include SM α -actin, myosin heavy chain 11 (MYH11), myosin light chain kinase (MYLK), filamin A, fibrillin-1, microfibril-associated glycoprotein 2 (MAGP2), EMILIN1, and lysyl oxidase (LOX). (Color version of figure is available online.)

Fig. 5. Transforming growth factor β (TGF- β) signaling in aortic aneurysms and dissections (AAD). TGF- β ligands are produced as a large latent TGF- β complex consisting of mature TGF- β , latency-associated peptide (LAP), and a latent TGF- β -binding protein (LTBP). TGF- β activates canonical and noncanonical signaling pathways. In the canonical pathway, TGF- β binds and induces heteromeric complex formation between TGF- β type I (T β RI) and type II (T β RII) receptors, leading to T β RI phosphorylation. T β RI, in turn, phosphorylates and activates downstream transcription factors such as SMADs (ie, R-SMADs, SMAD2, and SMAD3). SMADs translocate to the nucleus, where they bind to the promoters of target

genes and transactivate their gene expression. The canonical TGF- β signaling pathway promotes aortic development and maintains aortic wall homeostasis. Mutations in genes encoding TGF- β ligands, receptors, and downstream transcription factor SMAD cause TAAD. In the noncanonical pathways, the activated TGF- β receptor complex transmits signals through other pathways, such as TGF- β -activated kinase 1 (TAK1), p38 mitogen-activated protein kinase (p38 MAPK), extracellular signal-regulated kinase (ERK), JUN N-terminal kinase (JNK), and nuclear factor- κ B (NF- κ B). The noncanonical TGF- β pathways promote aortic destruction and AAD development. (Color version of figure is available online.)

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Fig. 6.

Common pathologic changes in aortic aneurysms and dissections (AAD). The common pathologic features of AAD are aortic degeneration, which is characterized by aortic smooth muscle cell (SMC) death and loss; elastic fiber destruction and depletion; and aortic inflammation. Aortic degeneration weakens the aortic wall, leading to the development of aortic aneurysm, dissection, and rupture. (Color version of figure is available online.)

Fig. 7.

Smooth muscle cell (SMC) phenotype changes in aortic aneurysms and dissections (AAD). SMCs possess remarkable plasticity. Differentiated SMCs express SMC-specific contractile proteins and have characteristic myocyte morphology and contractile properties. In differentiated contractile SMCs, transcription factors myocardin and serum response factor (SRF) bind to the CArG motif in the promoters of SMC genes and induce the expression of SMC-specific contractile proteins. Under conditions such as inflammation and injury, SMCs can lose their contractile phenotype and exhibit phenotypes resembling those of inflammatory cells, fibroblasts, or osteogenic cells—a phenomenon termed phenotypic switching. In dedifferentiated SMCs, transcription factors such as Kruppel-like factor 4 (KLF4) inhibit myocardin or SRF-mediated SMC gene expression, thereby inducing SMC phenotype alterations. Several pathways such as those involving angiotensin II (Ang II),

transforming growth factor β (TGF- β), connective tissue growth factor (CTGF), platelet-derived growth factor (PDGF), interleukin 6 (IL-6), and reactive oxygen species (ROS) have a role in promoting the SMC phenotype switch. (Color version of figure is available online.)

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Fig. 8.

Inflammatory cells in aortic aneurysms and dissections (AAD). In AAD, a variety of inflammatory cells accumulates, including lymphocytes, macrophages, mast cells, and neutrophils. Inflammatory cells actively participate in tissue injury, repair, and remodeling in AAD. After tissue injury, inflammatory cells infiltrate the aortic wall, clear tissue debris, and initiate tissue repair and regeneration. Once the tissues are repaired, inflammatory cells are removed and the inflammation is resolved. Insufficient clearance of damaged tissues, deficient tissue repair and regeneration, and impaired anti-inflammatory responses and

inflammation resolution can lead to sustained inflammation with uncontrolled production of destructive inflammatory mediators and growth factors, which aggravate tissue injury and contribute to maladaptive fibrotic remodeling. (Color version of figure is available online.)

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Fig. 9.

Angiotensin II signaling in aortic aneurysms and dissections (AAD). Angiotensin II (shown as Ang II) has 2 distinct receptors, AT1R and AT2R, which counter-regulate each other and have opposite effects on vascular function. The angiotensin system is critically involved in regulating the structure and function of aortic cells and in maintaining aortic homeostasis. However, excessive stimulation of angiotensin II signaling via AT1R activates several pathways involving rho or rho-associated protein kinase (ROCK), NFκB, ERK1/2, JNK, and p38 and induces NADPH oxidase activation and reactive oxygen species production. These signaling events promote aortic cell dysfunction, inflammation, and fibrotic remodeling,

leading to aortic destruction and the formation and progression of AAD. (Color version of figure is available online.)

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Fig. 10.

MicroRNAs (miRNAs) in aortic aneurysms and dissections (AAD). MiRNAs are small, noncoding RNAs that, by inducing mRNA degradation and translational repression, posttranscriptionally silence target mRNAs. MiRNA genes are transcribed by RNA polymerase II (Pol II). The precursor primary miRNA (pri-miRNA) is cleaved by the RNase III Drosha and DiGeorge syndrome critical region 8 (DGCR8) to form a hairpin-shaped precursor miRNA (pre-miRNA). The pre-miRNA is exported from the nucleus into the cytoplasm, where it is further cleaved by the RNase III enzyme Dicer, yielding an imperfect

miRNA-miRNA* duplex. MiRNA is then incorporated into the RNA-induced silencing complex (RISC). Association of a miRNA with its mRNA targets results in degradation and translational inhibition of the target mRNAs. Stress conditions can influence miRNA biogenesis at multiple levels. Competing endogenous RNAs (ceRNAs) bind and sequester miRNAs, preventing them from binding to their mRNA targets and thereby regulating miRNA activity. Several miRNAs that target the extracellular matrix or tissue inhibitor of matrix metalloproteinase-3 (TIMP-3) have been implicated in aortic disease. lncRNA, long noncoding RNA; m⁷G, 7-methylguanosine (a modified form of guanosine attached to the 5' ends of mRNAs); ORF, open reading frame. (Modified with permission from van Rooij E and Olson EN. MicroRNA therapeutics for cardiovascular disease: opportunities and obstacles. *Nat Rev Drug Discov*. 2012;11:860-72.) (Color version of figure is available online.)