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Structure of the Elastin-Contractile Units in the Thoracic Aorta and How Genes that Cause Thoracic Aortic Aneurysms and Dissections Disrupt this Structure

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Abstract

The medial layer of the aorta confers elasticity and strength to the aortic wall and is composed of alternating layers of smooth muscle cells (SMCs) and elastic fibers. The SMC elastin-contractile unit is a structural unit that links the elastin fibers to the SMCs and is characterized by the following: 1. Layers of elastin fibers that are surrounded by microfibrils. 2. Microfibrils that bind to the integrin receptors in focal adhesions on the cell surface of the SMCs. 3. SMC contractile filaments that are linked to the focal adhesions on the inner side of the membrane. The genes that are altered to cause thoracic aortic aneurysms and aortic dissections encode proteins involved in the structure or function of the SMC elastin – contractile unit. Included in this gene list are the genes encoding protein that are structural components of elastin fibers and microfibrils, *FBNI*, *MFAP5*, *ELN*, and *FBLN4*. Also included are genes that are structural proteins in the SMC contractile unit, including *ACTA2*, which encodes SMC-specific α -actin and *MYH11*, which encodes SMC-specific myosin heavy chain, along with *MYLK* and *PRKG1*, which encode kinases that control SMC contraction. Finally, mutations in the gene encoding the protein linking integrin receptors to the contractile filaments, *FLNA*, also cause thoracic aortic disease. Thus, these data suggest that functional SMC elastin-contractile units are important for maintaining the structural integrity of the aorta.

Introduction

The term “arterial aneurysm” was used in the Ebers Papyrus writings of ancient Egyptians in 2000 B.C.¹ Four millennia later, our understanding of the pathophysiology of aortic aneurysm is far more complex than simple enlargement of the vessel diameter. There have been tremendous strides in understanding the pathophysiology, diagnosis, and treatment of this deadly disease. The natural history of an aneurysm involving the root or the ascending thoracic aorta or both (i.e., a fusiform aneurysm) is progressive, asymptomatic enlargement

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over time. In the absence of surgical repair of the aneurysm, the progressive enlargement will lead to an acute ascending or type A aortic dissection. Although medical treatments can slow the enlargement of an aneurysm, the mainstay of treatment is preemptive surgical repair of the thoracic aortic aneurysm (TAA) prior to the occurrence of dissection or rupture. This repair is typically recommended when the aneurysm's diameter reaches 5.0 – 5.5 cm; however, studies on patients presenting with acute type A dissections indicate that up to 60% present with aortic diameters smaller than 5.5 cm.² Therefore, clinical predictors are needed to identify those at risk for TAAD and determine the aortic diameter that justifies the risk of surgical repair of a TAA to prevent acute aortic dissection or rupture. We and others have established that identifying disease-causing mutation in a specific gene can identify who else is at risk for TAAD in the family and predict at what range of aortic diameters a dissection will occur, thereby optimizing the timing of aortic surgery to prevent dissections.^{3, 4}

The aortic wall is composed of three layers. The tunica intima (the innermost layer) is composed of a single layer of endothelial cells and is supported by the internal elastic lamina. The thick tunica media (the middle layer) is composed of over 50 alternating layers of elastic fibers and smooth muscle cells (SMCs). Elastin fibers are composed of a core of elastin surrounded by microfibrils and it is the microfibrils that link to the SMCs through focal adhesions (also called dense plaques) on the cell surface of SMCs. Inside the SMC, the contractile units link to the focal adhesions. The elastin-contractile unit is the functional and structural unit of the tunica media that will be discussed in detail in this review. Finally, the tunica adventitia (the outermost layer) is mainly composed of collagen and contains the vasa vasorum (small arteries that supply nutrients to the medial layer) and autonomic nerves.

The aorta has a unique role in blood flow by acting as an elastic buffering chamber for the heart, termed the Windkessel function. The aorta and some of the proximal large vessels store about 50% of the left ventricular stroke volume during systole. Then, in diastole, the elastic forces of the aortic wall push forward this volume to the peripheral circulation, thus creating a nearly continuous peripheral blood flow. This elastic buffering capacity is due to the elastin in the aortic wall and not due to contraction of the SMCs. If the SMC contraction is pharmacologically inhibited, the elastic recoil of the aorta does not change.

The pathologic changes in the medial layer of a patients with an acute aortic dissection were first described by Babes and Mironescu in 1910,⁵ and the term “cystic medial necrosis” was later coined as the pathological hallmark of TAAD by Erdheim in 1929.⁶ “Cystic medial necrosis” was a misnomer because the pathology associated with TAAD has no cyst formation or overt necrosis. Instead, TAAD is characterized by fragmentation and loss of elastic fibers, accumulation of proteoglycans and loss of SMCs. Some studies have shown hyperplastic cellular remodeling in the aortic media as an aneurysm enlarges, such that there is no reduction of the total number of SMCs in the aorta, but there are often focal areas of SMC loss in the medial layer.⁷ Immunohistochemical studies have shown significantly higher presence of CD3⁺ (a T-cell marker) and CD68⁺ (a monocyte/macrophage marker) in ascending aortic aneurysms compared to normal aortas, but the role of inflammation in the pathogenesis of TAAD has not been firmly established.⁸

In this review, we examine the normal structure of the thoracic aorta and the role of mechanotransduction in development and homeostasis of the aortic wall. In addition, how the gene alterations that predispose to TAAD disrupt components of the elastin-contractile unit will also be discussed.

Smooth muscle cell contractile unit and mechanotransduction

The elastin-contractile unit is both a functional and structural unit in the aortic media, providing direct connection between the SMC and the elastin fibers.⁹ Based on the genes that cause thoracic aortic disease, this interaction is pivotal for maintaining the integrity of the thoracic aortic wall. The elastic fibers are organized in concentric laminae, and the core of elastin (*ELN*) is surrounded by microfibrils. These microfibrils are 10 – 15 nm filaments composed primarily of a large glycoprotein called fibrillin (encoded by *FBN1*, *FBN2* and *FBN3*). There are additional microfibril-associated glycoproteins (MAGPs), including MAGP-1 and MAGP-2 (encoded by *MFAP2* and *MFAP5*, respectively), and elastin microfibril interfacial protein 1 (*EMILIN1*) encoded by *EMILIN1*. These microfibril extensions are organized in an oblique orientation to the elastic fibers, and are attached to the dense plaques in the SMC cell membrane (Figure 1 and 2). The SMCs are longitudinally oriented between the layers of elastic fibers. The intracellular SMC contractile unit, also known as the “actomyosin unit”, is also linked to the dense plaques and this unique configuration is referred to as “elastin-contractile unit”. This unit is uniquely designed to transmit forces to the SMCs as a mechanosensor unit of the aortic wall.^{10–13}

The SMC contractile unit is composed of actin-containing thin filaments and myosin thick filaments, along with regulatory proteins such as tropomyosin. These SMC contractile units interact with the cytoskeleton, which is composed of non-muscle actins, intermediate desmin-containing filaments, and focal adhesions. The actin in the SMC contractile thin filament is the smooth muscle-specific isoform of actin called smooth muscle α -actin (SM α -actin encoded by the *ACTA2* gene). SM α -actin filaments anchor to the focal adhesions (dense plaques) on the cells surface and to cytoplasmic dense bodies. The anchoring proteins, such as talin, vinculin, α -actinin and filamin A, link α -actin of the contractile unit to the integrin receptors in the focal adhesions in the cell membrane. Integrin receptors are composed of α and β subunits, and each $\alpha\beta$ combination has a unique ligand. In the elastin-contractile unit, the integrins link to fibrillin-containing microfibrils. Contractile and cytoskeletal filaments are also anchored to the nuclear membrane through linkage between α -actin and lamin A and other nuclear proteins.¹⁴ This intertwined arrangement of filaments and cellular components is necessary for the mechanotransduction properties of the SMC contractile unit, i.e., the ability to convert mechanical stimulus to biochemical activity. Mechanical stimuli, such as transmural pulse pressure, are transmitted via integrins from the elastin to the intracellular compartment, which can lead to activation of biochemical signal activation and contraction of the contractile unit. Contraction of the SMCs can influence blood flow in small arteries but does not play this role in aorta.^{15, 16} Rather, SMC contraction may function as a mechanosensor in the aorta.

Myosin filaments, also called the thick filaments of the contractile units, consist of a hexameric molecule composed of two myosin heavy chains, two essential light chains, and

two regulatory light chains (RLC). The gene *MYH11* codes for the smooth muscle myosin heavy chain, but there are splice variants of this gene that result in four distinct isoforms. The C-terminal stalks of the myosin heavy chains dimerize to form a long α -helical coiled-coil domain, which is involved in the polymerization to form the thick filaments. The N-terminus harbors the motor domain (MD) and contains both ATP- and actin-binding sites, which together with the light chains form two globular heads that participate in cross bridging with the actin thin filaments and participate in SMC contraction.^{11, 17, 18} In SMCs, mechanical stimuli lead to an influx of calcium, which then binds to calmodulin (CaM). The calcium/CaM complex activates the myosin light chain kinase (encoded by *MYLK*), which in turn phosphorylates the regulatory light chain (RLC) of the myosin complex. RLC phosphorylation activates the actin-dependent ATPase activity of the myosin globular motor head and leads to SMC contraction.

The extracellular matrix has an important and complex function in maintaining the integrity of the aortic wall. Elastin and its associated microfibrils interact with SMCs as described above, but elastin also plays a critical role in regulating the development of the aorta.^{19, 20} The extracellular matrix also contains microfibril-associated proteins, such as fibulin or latent transforming growth factor (TGF)- β 1 binding protein (LTBP), which play an important role in sequestration and regulation of the activity of cytokines, such as TGF- β .^{10, 21} Collagen fibers, primarily type I and III collagen, are also present in the aortic media and contribute to the stiffness of the aorta. Aortic stiffness increases with age but also is increased in individuals with a genetic predisposition to thoracic aortic disease even prior to aneurysm formation.²²

At the cellular and molecular level, the ability of the aortic wall to sense stress via its unique cell-matrix interactions has an important bearing on its structural integrity and development. The aortic wall is constantly exposed to cyclic mechanical loads from pulsatile blood flow, with the ascending aorta exposed to forces delivered by the beating heart. Genetic mutations that affect mechanosensing via the elastin-contractile unit lead to TAAD. Elastin and collagen fibers and the ECM endure the bulk of stress that is exerted on the aortic wall, which is typically 100 to 200 KPa, such that only 3–5 KPa is exerted on the SMCs embedded in the aortic wall. SMCs sense this stress via the elastin-contractile unit and proportionally regulate and remodel the ECM. In essence, the SMCs sense and monitor the mechanical stress of the aortic wall constantly via their contractile thin and thick filaments and integrin receptors and accordingly alter their cytoskeletal structure and the composition of the ECM via various signaling cascades.

How genetic alterations predisposing to thoracic aortic disease disrupt the elastin-contractile unit

Heritable thoracic aortic disease (HTAD) is a spectrum of conditions that lead to a significant predisposition to TAAD. HTAD includes conditions such as Marfan syndrome, a condition inherited in an autosomal dominant manner that predisposes to thoracic aortic disease along with ocular and skeletal manifestations and other systemic features. Loeys-Dietz syndrome, caused by mutations in the transforming growth factor- β type 1 or 2

receptors (*TGFBR1* and *TGFBR2*), is another syndromic cause of HTAD and was originally characterized by a predisposition to aggressive TAAD, MFS skeletal and systemic features, craniostynosis, hypertelorism, cleft lip/bifid uvula, significant arterial tortuosity, and aneurysms and dissections of other arteries.²³ HTAD also includes an inherited predisposition to thoracic aortic disease in the absence of syndromic features, termed familial TAAD. The first case of non-syndromic familial TAAD was published in 1989 describing a family with nine affected members over two generations, without the phenotypic features of MFS or Ehlers Danlos syndrome, or systemic hypertension, and an underlying *TGFBR1* mutation was later identified as the cause of disease in this family.²⁴ Subsequent studies found that up to 20% of patients with TAAD have an affected first degree relative.²⁵ Pedigree analysis shows that familial TAAD most commonly occurs with an autosomal dominant pattern of inheritance, with variable expression with respect to age of presentation, location of aneurysm, and aortic diameter prior to dissection.²⁶ It is critical to emphasize that the distinction between syndromic and nonsyndromic causes of TAAD is a continuum for most of the HTAD genes. That is, the majority of the genes that cause TAAD associated with syndromic features can also lead to autosomal dominant inheritance of TAAD in the absence of syndromic features.

We will focus the remainder of this review on how the mutations in the genes that cause HTAD alter the elastin fibers, the microfibrils, focal adhesions and the SMC contractile unit (Table 1, Figure 2). In other words, all of these genes encode either structural components of the elastin-contractile unit or the kinases involved in activating the SMC contractile response to mechanical forces.

Mutations in Elastin and Components of the Microfibrils

FBN1

Marfan syndrome (MFS) was first described in 1896 by the French pediatrician Antoine Bernard Marfan as a constellation of musculoskeletal findings i.e. arachnodactyly (long and thin digits), dolichostenomelia (elongated limbs), and contracture of multiple joints;²⁷ however, MFS was later found to be associated with multi-organ involvement including skin, eye, pulmonary, and cardiovascular system, which deserves special attention since it affects survival. In 1918 ruptured aortic aneurysm and in 1943 aortic root dilatation and dissection were described as part of MFS.²⁸ In 1949 its pattern of inheritance as an autosomal dominant disease was illustrated.²⁸ In 1986, fibrillin was identified as a component of the ECM microfibrils.²⁹ Around the same time, linkage analyses mapped MFS locus to chromosome 15,³⁰ and a portion of the cDNA encoding fibrillin was cloned³¹ and mapped by *in situ* hybridization to chromosome 15.³² *FBN1* mutations were subsequently identified in MFS patients, including missense mutations, frameshift and nonsense mutations (including those leading to nonsense mediated decay of the message and those that do not), splicing errors, and completed deletion of the *FBN1* gene.^{33, 34} More than 1000 *FBN1* mutations have been identified in patients with MFS and the majority of these mutations are missense mutations.

Fibrillin-1 is a large, 350 kDa, 2871 amino-acid, cysteine-rich glycoprotein and a major component of the elastin associated microfibrils in the aortic media; however, microfibrils

also appear in tissues without elastin (e.g. in zonule of Zinn, the suspensory ligament of the eye that holds the lens in place, or basement membrane).³⁵ Fibrillin is made as a proprotein and cleaved by a furin-like protease as it is secreted from that cell, which is the signal for fibrillin to polymerize into microfibrils.^{36–38} Fibrillin-1 contains 47 epidermal growth factor (EGF)-like motifs interspersed with 7 TGF- β 1 binding protein (TB) motifs and the majority of EGF-like motifs contain a calcium binding sequence (cb-EGF).³⁵ Each EGF-like motif contains 6 cysteine amino acids, which form disulfide bonds, and each TB motif contains 8 cysteine amino acids.

Mutational analysis of *FBN1* has provided unique insight into the biological and physiological role of this complex glycoprotein.^{11, 35} A subset of *FBN1* mutations (frameshift, nonsense mutations leading to decay of the message and gene deletions) are predicted to lead to production of half the normal amount of fibrillin. Fibroblasts explanted from patients with MFS consistently exhibit decreased deposition of fibrillin into the extracellular matrix, regardless of the underlying mutations.^{39, 40} Some mutations disrupt the secondary structure of the EGF-like domains by replacing one of the cysteines and disrupting disulfide pairing,⁴¹ leading to domain misfolding which affects the delivery of fibrillin-1 to the ECM or its assembly into microfibrils.⁴² Study of two *FBN1* missense mutations, C1977Y and C1977R in the cb-EGF domain, cause fibrillin-1 to have increased susceptibility for proteolysis of the mutant fragment, suggesting disruption of these calcium binding EGF-like domains alters fibrillin-1 such that proteases can degrade it more easily.⁴³ Cb-EGF domains also mediate interactions between fibrillin and cells via integrin α V β 3 binding to fibrillin, and interactions amongst monomers favoring lateral packing of microfibrils.^{44, 45}

As described above, fibrillin is a critical component of the elastin-contractile unit and the mutations in *FBN1* either disrupt deposition of fibrillin into microfibrils surrounding the elastin fiber or decrease the amount of fibrillin available to form microfibrils due to haploinsufficiency. Electron microscopy of the developing mouse aorta shows that SMC contractile filaments link through focal adhesions to microfibrils early in development and maintain these connections through adulthood.⁹ A change in the amount or structure of microfibrils due to a *FBN1* mutation is predicted to alter the function of the elastin-contractile unit.

Other genes encoding extracellular matrix components of the elastin-contractile unit

Mutations in genes encoding other extracellular matrix components of the elastin and microfibrils are rare causes of TAAD. Loss of function in *MFAP5* disrupts one of the microfibril associated proteins, MAGP-2.⁴⁶ Mutations in another microfibril associated protein, emilin1, have been recently reported to predispose to thoracic aortic aneurysm but additional families with TAAD due to mutations in *EMILIN1* need to be identified to confirm this finding⁴⁷. Mutations in the gene for elastin itself (*ELN*) cause dominant cutis laxa, and there are reports of these patients developing thoracic aortic aneurysms.⁴⁸ Finally, recessive mutations in a gene for another protein involved in maintenance of elastin, fibulin 4 (*FBLN4*), also cause cutis laxa with aortic aneurysms, along with arterial tortuosity and stenosis.^{49, 50}

Mutations in genes encoding proteins involved in SMC contraction

ACTA2

ACTA2 is the most commonly mutated gene identified to date in familial TAAD, accounting for 12–21% of identified mutations.^{51–53} *ACTA2* encodes the SMC-specific isoform of α -actin, which polymerizes to form the thin filaments of the SMC contractile unit. In SMCs, 40% of the total cellular protein is composed of SMC-specific α -actin. Using genome-wide linkage analysis and candidate gene analysis, a missense mutation in *ACTA2* gene resulting in the amino acid substitution R149C, leading to FTAAD was first described in 2007.⁵³ Subsequent sequencing of the *ACTA2* gene in 97 unrelated TAAD families identified 14 additional families with *ACTA2* mutations.⁵³ Molecular characterization of a disease-causing *ACTA2* variant (p.R258C) indicates that the mutation makes the actin filaments more unstable and susceptible to severing by cofilin.⁵⁴ Additionally, profilin binds more tightly to the mutant actin, which is predicted to increase the pool of monomeric actin in SMCs. Also, myosin moves more slowly across mutant actin filaments. All these observations indicate that the mutant actin will decrease the ability of the SMC to contract in response to pulse pressures.

Familial TAAD secondary to *ACTA2* mutation has unique clinical features.⁵³ In a recent study the clinical features of 277 patients with 41 various *ACTA2* mutations were reported.⁵⁵ The lifetime risk of an aortic event, either dissection or repair, at age 85 years was 76% and mutations disrupting p.R179 or p.R258 were associated with significantly increased risk for aortic events, whereas p.R185Q and p.R118Q mutations showed significantly lower risk of aortic events compared with other mutations. The majority of presenting aortic events in these patients were aortic dissection (88%; 54% type A and 21% type B) with individuals with type B dissections presenting significantly younger than patients with type A dissections. In one third of individuals who experienced type A dissection, dissection occurred at an aortic diameter of less than 5 cm;⁵⁵ which suggest that surgeons should consider offering aortic surgery at aortic diameter smaller than 5 cm in patients with *ACTA2* mutation. In addition to predisposing to thoracic aortic disease, a subset of *ACTA2* mutations leads to early onset coronary artery disease and stroke.^{56, 57}

MYH11

The *MYH11* gene encodes the SMC-specific myosin heavy chain, a major component of the SMC contractile unit.⁵⁸ The report of *MYH11* mutations was in 2006 in two families with FTAAD and patent ductus arteriosus (PDA). The identified *MYH11* mutations were in the C-terminal coiled-coil region of the smooth muscle myosin heavy chain.⁵⁹ Subsequent studies have shown *MYH11* mutation is implicated in 2% of familial TAAD cases.⁵⁸ The phenotypic features associated with *MYH11* mutation are a combination of TAAD and patent ductus arteriosus (PDA).⁵⁸ Disease-causing mutations identified to date are mostly in-frame deletions in the coiled-coiled domain of protein that are predicted to disrupt the ability of the mutant myosin to polymerize into thick filaments. It is important to note that there are rare variants in *MYH11* that do not segregate with disease in families with TAAD.⁶⁰

MYLK

Myosin light chain kinase is a ubiquitously expressed kinase which takes part in phosphorylation of the RLC of the smooth and non-muscle myosin II. RLC phosphorylation increases actin-dependent myosin II ATPase activity, thus initiating SMC contraction.¹⁸ Using a candidate-gene approach, loss of function mutations in myosin light chain kinase encoding (*MYLK*) gene was identified in a small percentage of patients with FTAAD. These mutations are predicted to decrease the phosphorylation of the RLC, and thus decrease SMC contraction. The phenotypic picture secondary to loss of function mutations in *MYLK* is characterized by ascending aortic dissection with minimal enlargement of the aorta, which makes decision about elective surgical repair challenging.⁶¹

PRKG1

PRKG1 encodes the type I cGMP-dependent protein kinase (PKG-1), which controls SMC relaxation. PKG-1 α is the major isoform present in vascular SMCs and is activated by nitric oxide, which stimulates soluble guanylyl cyclase and increases cellular cGMP levels. PKG-1 α is activated upon binding of cGMP and subsequently regulates many cellular systems that lead to relaxation of SMCs, including activation of the regulatory myosin-binding subunit (MYPT) of the phosphatase that dephosphorylates RLC.

Although rare variants are located throughout *PRKG1*, only one variant was identified to cause familial TAAD, pR177Q.⁶² This mutation was identified recurrently in unrelated families with TAAD. The mutation paradoxically increases the activity of PRK-1 α such that it is no longer regulated by cGMP and is constitutively active. The increased kinase activity associated with the PKG-1 α leads to decreased levels of phosphorylated (active) RLC and promotes SMC relaxation. In essence, both loss-of-function mutation in *MYLK* and gain-of-function mutation in *PRKG1* decrease aortic SMC contraction as a result of decreased phosphorylation of the RLC, thus decreasing SMC contraction in response to mechanical stimuli. This *PRKG1* gain-of-function mutation is associated with a relative severe form of FTAAD, with 63% of affected individuals presenting with aortic dissection at mean age of 31 years (range 17–51 years). Affected individuals also have other vascular abnormalities, including aneurysm of the descending thoracic aorta, abdominal aorta, and coronary artery.⁶²

FLNA

FLNA encodes filamin A, a non-muscle actin binding protein, which organizes cytoskeletal actin monofilaments into orthogonal networks, and anchors the actin cytoskeleton to transmembrane integrin molecules. Filamin A plays an important role in cell shape determination and cell signaling. *FLNA* mutations have been detected in human genetic diseases and are also implicated in cancer metastasis.^{14, 63} Proteomic analysis of the aortic media of patients with MFS and bicuspid aortic valve has shown increased filamin A fragmentation providing further evidence for the role of filamin A in maintaining aortic wall integrity.⁶⁴ *FLNA* mutations lead to an X-linked dominant condition called periventricular heterotopia. The phenotype includes brain malformation (periventricular heterotopia) and an Ehlers-Danlos-like phenotype with hyperextensible joints, skin laxity, and risk for thoracic

aortic disease.⁶⁵ It mainly affects female patients and affected women have a high rate of male fetus miscarriage, suggesting affected males die prenatally.⁶⁶

Proposed role of the elastin-contractile unit in other causes of thoracic aortic aneurysms and dissections

In the absence of a predisposing gene mutation, hypertension is the major risk factor for thoracic aortic disease.⁶⁷ In addition, other risk factors for thoracic aortic disease, such as body building, weight lifting and use of cocaine, increase the blood pressure.^{68–70} In these cases, the SMC elastin-contractile unit may not be defective but the forces across the unit will be increased, and thus may activate the same cellular pathways leading to disease.

Mutations in the genes encoding proteins involved in TGF- β canonical signaling predispose to thoracic aortic disease. The mutations in these genes are predicted to decrease TGF- β signaling, leading to the question of the role TGF- β signaling plays in the SMC elastin-contractile unit. Exposure to TGF- β drives differentiation of SMCs, and this differentiation is defined by increased levels of the contractile proteins, including SMC α -actin and smooth muscle myosin heavy chain. We have previously shown that the heterozygous *TGFBR2* mutations identified in patients with thoracic aortic disease lead to decreased expression of these proteins in both SMCs and myofibroblasts.⁷¹ Thus, decreased TGF- β signaling may lead to deficiency of elastin-contractile units in aortic SMCs, thus leading to thoracic aortic disease.

Conclusion

The aortic wall maintains its structure, geometry, and function over decades of an individual's life. As illustrated in this review, any disruption of the elastin-contractile unit by mutations in the genes coding for the proteins that are involved in the structure, maintenance or function of this unit leads to thoracic aortic aneurysms and dissections. Thus, these data suggest that this unit functions as a mechanosensor to maintain aortic structural integrity. If a component of the elastin-contractile mechanosensor is defective, SMC cellular pathways are altered, which lead to thoracic aortic disease. These cellular pathways can lead to increased signaling through the AT1 receptor, increased canonical TGF- β signaling, and increased proteoglycan and metalloprotease production.^{72–74}

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Brief summary

The thoracic aorta is designed to withstand a lifetime of forces due to blood flow from the beating heart. The aorta's thick middle layer is composed of alternating layers of elastic lamellae and smooth muscle cells (SMCs). The elastin and SMCs are connected through the elastin-contractile unit. The genes that are altered to cause thoracic aortic aneurysms and aortic dissections encode proteins involved in the structure or function of the SMC elastin-contractile unit.

Figure 1.

Schematic representations of cross sections of the aorta demonstrating the relationship between the elastin lamellae and the smooth muscle cells (SMCs). A. The elastic lamellae are depicted as the black layers and the SMCs are shown between elastic lamellae. The elastin has oblique extensions that connect with the surface of the SMCs at focal adhesions (also called dense plaques). The SM α -actin filaments attach to the membrane at these focal adhesions and extend obliquely across the cell. The direction of these oblique extensions changes from layer to layer. B. The SMCs are shown in cross section between the elastin lamellae. The elastin extensions to the SMCs are viewed in cross-section at the edge of the elastic lamellae and give the elastin fibers an irregular appearance. Reproduced with permission from Davis EC et al.⁹

Figure 2.

The elastin-contraction unit in smooth muscle cells. The altered genes that predispose to thoracic aortic aneurysms and acute aortic dissections are indicated. The location of the gene indicates where its protein product is located in the elastin-contraction unit.

Table 1

Heritable thoracic aortic disease genes that disrupt the elastin-contractile unit.

Gene	Locus	Altered protein	Role in the elastin-contractile unit	Additional features
Genes encoding elastin or components of microfibrils				
<i>FBN1</i>	15q21.1	Fibrillin-1	The major component of microfibrils	Marfan syndrome
<i>ELN</i>	7q11.23	Elastin	The major protein in elastin fibers	Cutis laxa
<i>MFAP5</i>	12p13.1-p12.3	MAGP-2	Component of microfibrils	Familial TAAD with mild features of the MFS
<i>EMILIN1</i>	2p23.3-p23.2	Emilin-1	Associates elastin fibers to the microfibrillar network	Peripheral neuropathy, arthropathy, increased skin elasticity
<i>FBLN4</i>	11q13.1	Fibulin-4	Associates elastin fibers to the microfibrillar network	Cutis laxa, arterial tortuosity and stenosis
Genes encoding proteins involved in SMC contraction or cytoskeleton				
<i>ACTA2</i>	10q23.3	SMC-specific isoform of α -actin	Monomer polymerized to form the thin filaments of the SMC contractile unit	Familial TAAD; a subset of missense mutations also lead to early onset strokes and coronary artery disease, PDA, and livedo reticularis
<i>MYH11</i>	16p13.11	SMC-specific isoform of myosin heavy chain	Constitutes thick filaments of the SMC contractile unit	Familial TAAD with variable penetrance of PDA
<i>MYLK</i>	3q21.1	Myosin light chain kinase	Phosphorylation of the RLC on the myosin thick filaments	Familial TAAD
<i>PRKG1</i>	10q11.2	Type I cGMP- dependent protein kinase (PKG-1)	Regulates SMC relaxation by activation of the regulatory myosin-binding subunit (MYPT) of the phosphatase that dephosphorylates RLC	Familial TAAD
<i>FLNA</i>	Xq28	Filamin A	Anchors the actin cytoskeleton to transmembrane integrin molecules	Brain malformation (periventricular heterotopia) and an Ehlers-Danlos-like phenotype with hyperextensible joints, skin laxity

ECM= Extracellular matrix, AD= Autosomal Dominant, TAAD= Type A aortic aneurysm or dissection, SMC= Smooth muscle cell, RLC= regulatory light chain