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The Genetics and Typical Traits of Thoracic Aortic Aneurysm and Dissection

Jotte Rodrigues Bento,[1] Josephina Meester,[1] Ilse Luyckx,[1,2] Silke Peeters,[1] Aline Verstraeten,[1] and Bart Loeys[1,2]

[1]Centre of Medical Genetics, Antwerp University Hospital, University of Antwerp, Antwerp, Belgium; email: bart.loeys@uantwerpen.be

[2]Department of Human Genetics, Radboud University Medical Center, Nijmegen, The Netherlands

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Abstract

Genetic predisposition and risk factors such as hypertension and smoking can instigate the development of thoracic aortic aneurysm (TAA), which can lead to highly lethal aortic wall dissection and/or rupture. Monogenic defects in multiple genes involved in the elastin-contractile unit and the TGFβ signaling pathway have been associated with TAA in recent years, along with several genetic modifiers and risk-conferring polymorphisms. Advances in omics technology have also provided significant insights into the processes behind aortic wall degeneration: inflammation, epigenetics, vascular smooth muscle phenotype change and depletion, reactive oxygen species generation, mitochondrial dysfunction, and angiotensin signaling dysregulation. These recent advances and findings might pave the way for a therapy that is capable of stopping and perhaps even reversing aneurysm progression.

1. INTRODUCTION

Thoracic aortic aneurysm (TAA) is an insidious condition involving a progressive dilatation of more than 150% of the normal thoracic aortic diameter, with a high risk of sudden death due to dissection or rupture of the vessel wall (57). Risk factors for TAA include hypertension, smoking, male sex, older age, and the presence of a bicuspid aortic valve, and in contrast to aneurysms below the diaphragm (abdominal aortic aneurysm), genetic factors are highly involved (59, 107). Approximately 20% of TAA patients report a positive family history, and on account of extensive gene discovery efforts, approximately 30% of such cases can be explained by monogenic defects in more than 30 different genes (140). Familial TAA can also include additional systemic and dysmorphic features, such as skeletal and other connective tissue manifestations, which are frequently observed in patients suffering from TAA syndromes such as Marfan syndrome (MFS) or Loeys–Dietz syndrome (LDS) (140).

Classical, hypothesis-driven research methods have delivered useful general insights into the pathological processes within the aneurysmal aortic wall. The typical histological findings in TAA are elastic fiber fragmentation and disarray, often with a concomitant loss of vascular smooth muscle cells (VSMCs). The expression of genes involved in structural integrity (e.g., collagens, elastin, fibulins, and integrins) is altered in the aortic tissues of TAA patients, and extracellular matrix (ECM)–related pathways are disrupted (16, 68, 115, 132, 145, 151). Proteolysis of the medial layer is driven predominantly by an imbalance in expression of matrix metalloproteinases (MMPs) and their inhibitors [tissue inhibitors of metalloproteinases (TIMPs)] (71).

Because of its estimated incidence of 6–8 per 100,000 population per year, occurrence at a young age, and devastating complications, TAA dissection ranks as one of the leading causes of death in the young Western population (59, 97). It is therefore important that TAA is discovered in a timely way and followed up, which is complicated by its asymptomatic nature. TAA is often discovered only accidentally during a routine clinical examination, and imaging techniques such as echocardiography, magnetic resonance imaging (MRI), and computed tomography (CT) are currently the only available methods for follow-up—hence the need for more scalable diagnostic methods, such as biomarker detection in routine blood analyses (57).

No established curative therapy currently exists that can stop or even reverse TAA development. Clinical trials regarding the use of antihypertensive drugs (e.g., beta blockers) indicate that progression can be slowed, although the extent of disease outcome amelioration is hardly convincing (36, 58). The mainstay remains elective surgical intervention involving graft replacement of aneurysmal tissue when the aneurysm reaches dangerous dimensions, taking into account the growth rate, family history, and known genotype–phenotype associations regarding risks for dissection (57).

The lack of non-imaging-based diagnostic tools and curative therapy instigated a rapidly evolving amount of research into the genomic, transcriptomic, and proteomic landscape of TAA, facilitated by recent advances in omics techniques. In this review, we discuss the well-established genetic causes and recent discoveries in the field, as well as current insights into the detrimental processes that steer aortic wall degradation.

2. THE GENETICS OF THORACIC AORTIC ANEURYSM

Identification of a genetic cause in patients is important for adequate patient management, as TAA often has genetic underpinnings. The identified monogenic (inherited or de novo) defects typically cause a more severe presentation of aortic disease with early onset (risk of dissection below 55 years of age) and generally show a dominant inheritance pattern, although X-linked and recessive TAA have been described. Moreover, the aggressiveness of vascular disease can vary

greatly depending on the gene and pathogenic variant involved, which makes a molecular diagnosis relevant for clinical decision-making regarding follow-up and elective surgery (57). Family members carrying the disease-causing variant found in the proband can subsequently be identified, and other potential syndromic features associated with specific genes can be recognized and controlled. Furthermore, for several TAA syndromes, genotype–phenotype associations between specific variants, their effects on protein levels, and disease severity have been pinpointed.

TAA is a clinically and genetically heterogeneous disease, and certain factors complicate genetic counseling. Patients with familial or syndromic TAA caused by a specific mutation can display marked inter- and intrafamilial phenotypic variability (e.g., early versus late onset of disease, appearance or absence of syndromic characteristics caused by the mutation, and aggressiveness and dispersion of dilatations and dissections), which seems to indicate that disease modifiers are at play. Consequently, a search for genetic modifiers was initiated and yielded some interesting results in both syndromic and nonsyndromic TAA (6, 74, 130). Disease presentation can also depend on the expression levels of specific genes. Modifying variants in so-called expression quantitative trait loci (eQTLs)—regions in the noncoding genome that are likely involved in gene regulation—have also been described for MFS, either in the neighboring region of the unaffected allele in patients with haploinsufficient mutations or in other genes involved in pathomechanistic pathways (6, 106, 128).

Driven by the assumption that aortic dimensions are a complex trait and that common medium- and low-impact polymorphisms might also influence TAA susceptibility, several genome-wide association studies have been performed in cohorts of sporadic TAA patients, i.e., patients with a nonsyndromic TAA pathology, roughly defined by an absence of a positive family history and an unidentifiable monogenic defect (4, 6, 43, 75). Such frequent causal genetic variation is significantly identifiable only within large cohorts and probably exerts its effect through interplay with environmental triggers or with more than one genetic variant.

In summary, ongoing gene discovery efforts have already uncovered multiple genes in which variants entail risk for TAA and dissection. In a stepwise manner, pathomechanistic pathways are exposed through functional characterization of these disease genes, and most genes with strong causative evidence are involved predominantly in regulating two main processes in the aorta: (*a*) mechanosensing and the contractile response of the elastin-contractile unit (ECU) and (*b*) transforming growth factor beta (TGFβ) signaling. Throughout the following sections, currently known monogenic TAA genes (see **Table 1**), as well as some disease modifiers and frequent variants identified in genome-wide association studies (see **Table 2**), will be discussed within these two processes (for an overview of the known monogenic TAA genes within their respective processes, see **Figure 1**).

2.1. The Elastin-Contractile Unit

The aorta is the central conductance artery that serves as an elastic buffering reservoir to transform the pulsatile, high-pressure blood flow expelled directly from the left ventricle into an even flow through peripheral resistance vessels and organs. To withstand and maintain such high and complex mechanical loads, the aortic wall has an organized architecture of different concentric layers consisting of cells, which are involved predominantly in mechanotransduction and maintenance of the vascular tone, and the ECM, which provides elastic recoil and tensile strength (100). The aorta is lined with a single endothelial cell layer and an adjacent basement membrane, together termed the tunica intima. Separated by a thick elastic lamina, the tunica intima is enclosed by the tunica media or medial layer, which accounts for the greater part of the structure and function of the aorta and consists of alternating concentric layers of VSMCs tethered to elastin sheets (together called lamellar units) with interspersed collagen. The number of lamellar units is linearly related to hemodynamic forces and ranges from 53 to 78 units in the ascending thoracic aorta

Table 1 Monogenic TAA genes

Gene	OMIM	Protein	Function(s)	Detailed function(s)	Syndrome name	IP(s)	Additional phenotypic feature(s)	Reference(s)
TGFβ								
TGFBR1	190181	Transforming growth factor beta receptor 1	TGFβ signaling	TGFβ cell-surface serine/threonine kinase receptor and signal transducer	LDS1	AD	Arterial tortuosity, scoliosis, pectus deformity, joint laxity, translucent skin, easy bruising, hypertelorism, bifid uvula, allergic/inflammatory features	85, 86, 94
TGFBR2	190182	Transforming growth factor beta receptor 2	TGFβ signaling	TGFβ cell-surface protein kinase receptor and signal transducer	LDS2	AD	Same as LDS1	85, 86, 94
SMAD3	603109	SMAD family member 3	TGFβ signaling	Receptor-regulated SMAD, intracellular signal transducer, transcription factor	LDS3	AD	Same as LDS1, strong predisposition for osteoarthritis	85, 86, 94
TGFB2	190220	Transforming growth factor beta 2	TGFβ signaling	Secreted TGFβ ligand	LDS4	AD	Often only mild, more MFS-like features	85, 86, 94
TGFB3	190230	Transforming growth factor beta 3	TGFβ signaling	Secreted TGFβ ligand	LDS5	AD	Same as LDS1, high degree of nonpenetrance	85, 86, 94
SMAD2	601366	SMAD family member 2	TGFβ signaling	Receptor-regulated SMAD, intracellular signal transducer, transcription factor	LDS6	AD	Same as LDS1	99
SMAD6	602931	SMAD family member 6	TGFβ signaling	Negative regulation of TGFβ signaling through inhibition of SMAD4 binding to receptor-activated SMAD proteins	None	AD	Bicuspid aortic valve	91
SKI	164780	v-SKI sarcoma oncogene homolog	TGFβ signaling	Negative regulation of TGFβ signaling through SMAD interaction and repression of TGFβ-responsive genes	Shprintzen–Goldberg syndrome	AD	MFS-like and LDS-like features, developmental delay, craniosynostosis	26
IPO8	605600	Importin 8	TGFβ signaling	Nuclear importer of specific proteins, including SMAD1–4	None	AR	LDS-like and Shprintzen–Goldberg syndrome–like features	138, 152

(*Continued*)

Table 1 (*Continued*)

Gene	OMIM	Protein	Function(s)	Detailed function(s)	Syndrome name	IP(s)	Additional phenotypic feature(s)	Reference(s)
LTBP3	602090	Latent transforming growth factor beta–binding protein 3	TGFβ signaling	Controller of TGFβ signaling by storage of latent-state TGFβ in the ECM	None	AR, AD	Short stature, dental abnormalities, aortic aneurysm in carriers	47
ECU								
FBN1	134797	Fibrillin 1	ECU-ECM, TGFβ signaling	Large ECM glycoprotein in microfibrils, elastogenesis, signaling regulation	MFS	AD	Bone overgrowth, arachnodactyly, joint laxity, scoliosis, pectus deformity, ectopia lentis, mitral valve prolapse	3
MFAP5	601103	Microfibril-associated glycoprotein 2	ECU-ECM, TGFβ signaling	Associated with microfibrils, signaling regulation	None	AD	MFS-like features	7
EFEMP2	604633	Fibulin 4	ECU-ECM, TGFβ signaling	Associated with microfibrils, signaling regulation by LTBP binding, elastogenesis	Autosomal recessive cutis laxa type 1B	AR	Cutis laxa, LDS-like features, arterial tortuosity	20
EMILIN1	130660	Elastin microfibril interfacer 1	ECU-ECM, TGFβ signaling	Associated with elastic fibers, elastogenesis, signaling regulation	None	AD	Increased skin elasticity, neuropathy	13
THSD4	614476	A disintegrin and metalloproteinase with thrombospondin motifs–like protein 6	ECU-ECM, TGFβ signaling	Directly associated with fibrillin 1 and involved in fibrillin 1 microfibril assembly, TGFβ signaling regulation through direct binding	None	AD	Mild MFS-like features	29
ELN	130160	Elastin	ECU-ECM	Elastin sheet component, elastic recoil	None	AD	In the case of gain-of-function mutations (caused predominantly by frameshift mutations in exons 30–34): autosomal dominant cutis laxa with TAA in 30–50% of cases; TAA in the case of duplications and triplications encompassing the *ELN* gene	40, 51

(*Continued*)

Table 1 (*Continued*)

Gene	OMIM	Protein	Function(s)	Detailed function(s)	Syndrome name	IP(s)	Additional phenotypic feature(s)	Reference(s)
TES	606085	Testin	ECU-FA, transcription	Focal adhesion scaffold protein, regulation of transcription in the nucleus	None	AD	NA	79
FLNA	300017	Filamin A	ECU-FA, TGFβ signaling	Large cytoplasmic protein that interacts with integrins and the actin cytoskeleton, signaling regulation through interaction with, e.g., SMAD proteins and ERK	Ehlers–Danlos syndrome, periventricular nodular heterotopia type	XL	Periventricular nodular heterotopia, congenital heart disease (septal defects and patent ductus arteriosus), pulmonary disease, gastrointestinal obstruction, joint hypermobility	15
VSMCs								
MYH11	160745	Smooth muscle myosin heavy-chain isoform 11	ECU-VSMC contraction	Contraction of smooth muscle cells	None	AD	Patent ductus arteriosus	113
ACTA2	102620	Actin alpha 2, smooth muscle	ECU-VSMC contraction	Contraction of smooth muscle cells	In the case of the p.Arg179His missense mutation: smooth muscle dysfunction syndrome	AD	In the case of the p.Arg179His missense mutation: dilatation of large vessels (pulmonary arteries), small vessel infarcts, moyamoya disease, coronary artery disease, patent ductus arteriosus, mydriasis, gastrointestinal malrotation and hyperperistalsis	44
MYLK	600922	Myosin light-chain kinase	ECU-VSMC contraction	Phosphorylation of myosin to facilitate interaction with actin to initiate contraction	None	AD	NA	142
PRKG1	176894	cGMP-dependent protein kinase	ECU-VSMC contraction	Negative regulation of contraction by reducing intracellular calcium and activating myosin light-chain phosphatase	None	AD, gain of function	NA	45
ARIH1	605624	Ariadne RBR E3 ubiquitin protein ligase 1	ECU-nuclear positioning	Ubiquitin ligase involved in myonucleocytoskeletal anchorage and shape	None	AD	Cerebrovascular aneurysm	134

(*Continued*)

Table 1 (*Continued*)

Gene	OMIM	Protein	Function(s)	Detailed function(s)	Syndrome name	IP(s)	Additional phenotypic feature(s)	Reference(s)
ECM								
BGN	301870	Biglycan	ECM component, TGFβ signaling	ECM assembly and maintenance, predominantly in the aortic adventitia; interaction with collagen and elastin; signaling regulation through binding of growth factors	Meester–Loeys syndrome	XL	MFS-like and LDS-like features, decreased penetrance in women	98
LOX	153455	Lysyl oxidase	ECM biogenesis	Cross-linking of ECM components	None	AD	MFS-like features	46
PLOD1	153454	Procollagen-lysine,2-oxoglutarate 5-dioxygenase 1	ECM biogenesis	Lysin hydroxylase, collagen fibril organization and stabilization through cross-linking of collagen	Ehlers-Danlos syndrome, kyphoscoliotic type 1	AR	Hypotonia, kyphoscoliosis, joint hypermobility, skin fragility, ocular features	21
PLOD3	603066	Procollagen-lysine,2-oxoglutarate 5-dioxygenase 3	ECM biogenesis	Lysin hydroxylase, collagen fibril organization and stabilization through cross-linking of collagen	Bone fragility with contractures, arterial rupture, and deafness	AR	Bone fragility, widespread arterial rupture, cerebral aneurysm, deafness	21
FKBP14	614505	FKBP prolyl isomerase 14	ECM biogenesis	Procollagen folding in endoplasmic reticulum	Ehlers–Danlos syndrome, kyphoscoliotic type 2	AD	Hypotonia, kyphoscoliosis, joint hypermobility, hyperelastic skin, motor development delay, myopathy, hearing impairment	21
COL3A1	120180	Collagen type 3 alpha-1 chain	ECM component	Predominant form of collagen in the aortic media	Ehlers–Danlos syndrome, vascular type	AD	Joint hypermobility, fragile and hyperextensible skin, mitral valve prolapse, intracranial aneurysm	21
COL5A1	120215	Collagen type 5 alpha-1 chain	ECM component	Collagen fibrils in aortic media surrounding VSMCs and in basement membrane	Classical Ehlers–Danlos syndrome	AD	Fragile and hyperextensible skin, joint hypermobility, poor wound healing, easy bruising	21

(*Continued*)

Table 1 (*Continued*)

Gene	OMIM	Protein	Function(s)	Detailed function(s)	Syndrome name	IP(s)	Additional phenotypic feature(s)	Reference(s)
COL5A2	120190	Collagen type 5 alpha-2 chain	ECM component	Collagen fibrils in aortic media surrounding VSMCs and in basement membrane	Classical Ehlers–Danlos syndrome	AD	Fragile and hyperextensible skin, joint hypermobility, poor wound healing, easy bruising	21
COL1A1	120150	Collagen type 1 alpha-1 chain	ECM component	Collagen fibrils in all layers of the aorta, adjacent to VSMCs and elastic lamellae	Classical Ehlers–Danlos syndrome; Ehlers–Danlos syndrome, arthrochalasia type	AD	Fragile and hyperextensible skin, severe joint hypermobility, kyphoscoliosis, hypotonia, poor wound healing, easy bruising	21
COL1A2	120160	Collagen type 1 alpha-2 chain	ECM component	Collagen fibrils in all layers of the aorta, adjacent to VSMCs and elastic lamellae	Ehlers–Danlos syndrome, cardiac-valvular type; Ehlers–Danlos syndrome, arthrochalasia type	AD	Mitral and/or aortic valve insufficiency, fragile and hyperextensible skin, severe joint hypermobility, kyphoscoliosis, hypotonia, poor wound healing, easy bruising	21
Other								
FOXE3	601094	Forkhead box E3	Apoptosis, NCC migration, VSMC differentiation	Transcription factor	None	AD	Decreased penetrance in women	72
ABL1	189980	ABL proto-oncogene 1	Signaling	Tyrosine kinase involved in a variety of cellular processes; involved in PTEN, ERK, and mTOR signaling	None	AD, gain of function	Facial dysmorphism, septal defects, pectus excavatum, scoliosis, joint laxity, failure to thrive, gastrointestinal abnormalities, genital anomalies	8, 144
JAG1	601920	Jagged canonical notch ligand 1	Development, VSMC differentiation	Organismal development, regulation of cell fate decisions, epithelial-to-mesenchymal transition induction, VSMC differentiation	Alagille syndrome	AD	Intracranial aneurysm, scoliosis, coarctation of the aorta, tetralogy of Fallot, cholestasis, renal disease, vertebral anomalies	127

(*Continued*)

Table 1 (*Continued*)

Gene	OMIM	Protein	Function(s)	Detailed function(s)	Syndrome name	IP(s)	Additional phenotypic feature(s)	Reference(s)
MAT2A	601468	Methionine adenosyl transferase 2A	Epigenetic regulation	Homeostasis of DNA methylation through synthesis of *S*-adenosyl-L-methionine	None	AD	Bicuspid aortic valve	42
EP300	602700	Histone acetyl-transferase P300	Epigenetic regulation	Histone acetyltransferase activity	Rubinstein–Taybi syndrome	AD	Rubinstein–Taybi syndrome (intellectual disability, facial dysmorphism, broad thumbs/halluces)	90
KCNMA1	600150	Calcium-activated potassium channel subunit alpha 1	Ion channel	Calcium-sensitive potassium channel, controls smooth muscle tone and neuron excitability	Liang–Wang syndrome	AD, p.Gly 375Arg	Polymalformation syndrome (facial dysmorphism, cardiovascular anomalies, gastrointestinal atresia), intellectual disability, developmental delay	81
PKD1/2	601313, 173910	Polycystin 1/2	Ion channel	Intracellular calcium homoeostasis through regulation of calcium channels, cell matrix interactions, and signal transduction	Polycystic kidney disease	AD	Cyst formation in kidneys and liver	117

Abbreviations: AD, autosomal dominant; AR, autosomal recessive; ECM, extracellular matrix; ECU, elastin-contractile unit; FA, focal adhesion; IP, inheritance pattern; LDS, Loeys–Dietz syndrome; MFS, Marfan syndrome; NA, no associated features; NCC, neural crest–derived cell; OMIM, Online Mendelian Inheritance in Man; TAA, thoracic aortic aneurysm; VSMC, vascular smooth muscle cell; XL, X linked.

Table 2 Genes with genome-wide association study single-nucleotide polymorphisms, eQTL findings, and genetic modifiers in TAA

Gene	Association	Reference(s)
ADCK4	Variant p.(Arg63Trp) is associated with milder disease in an MFS cohort.	74
COL4A1	Variant p.(Pro530Ser) is associated with increased disease severity in MFS.	6
ELN	Locus is associated with thoracic aortic dimensions.	120
FBN1	Multiple genome-wide association hits were found in sporadic TAA patient cohorts.	4, 43, 75
FBN1	*Trans*-eQTL in Marfan syndrome patients with haploinsufficient *FBN1* mutations is associated with disease severity.	6, 32, 33
IL1b	Single-nucleotide polymorphism rs16944 is associated with risk for sporadic TAA.	130
IL6	Single-nucleotide polymorphism rs1800795 is associated with risk for sporadic TAA.	130
LRP1	Single-nucleotide polymorphism rs11172113 is associated with decreased risk for sporadic TAA.	43
PRKG1	Locus is associated with MFS severity.	6
TCF7L2	eQTL variants associated with higher TCF7L2 expression are associated with TAA disease risk.	128

Abbreviations: eQTL, expression quantitative trait locus; MFS, Marfan syndrome; TAA, thoracic aortic aneurysm.

(25, 108). A final outer connective tissue layer, again supported by an elastic lamina, is termed the tunica adventitia and contains collagen-secreting myofibroblasts, vasa vasorum, and nerves (67).

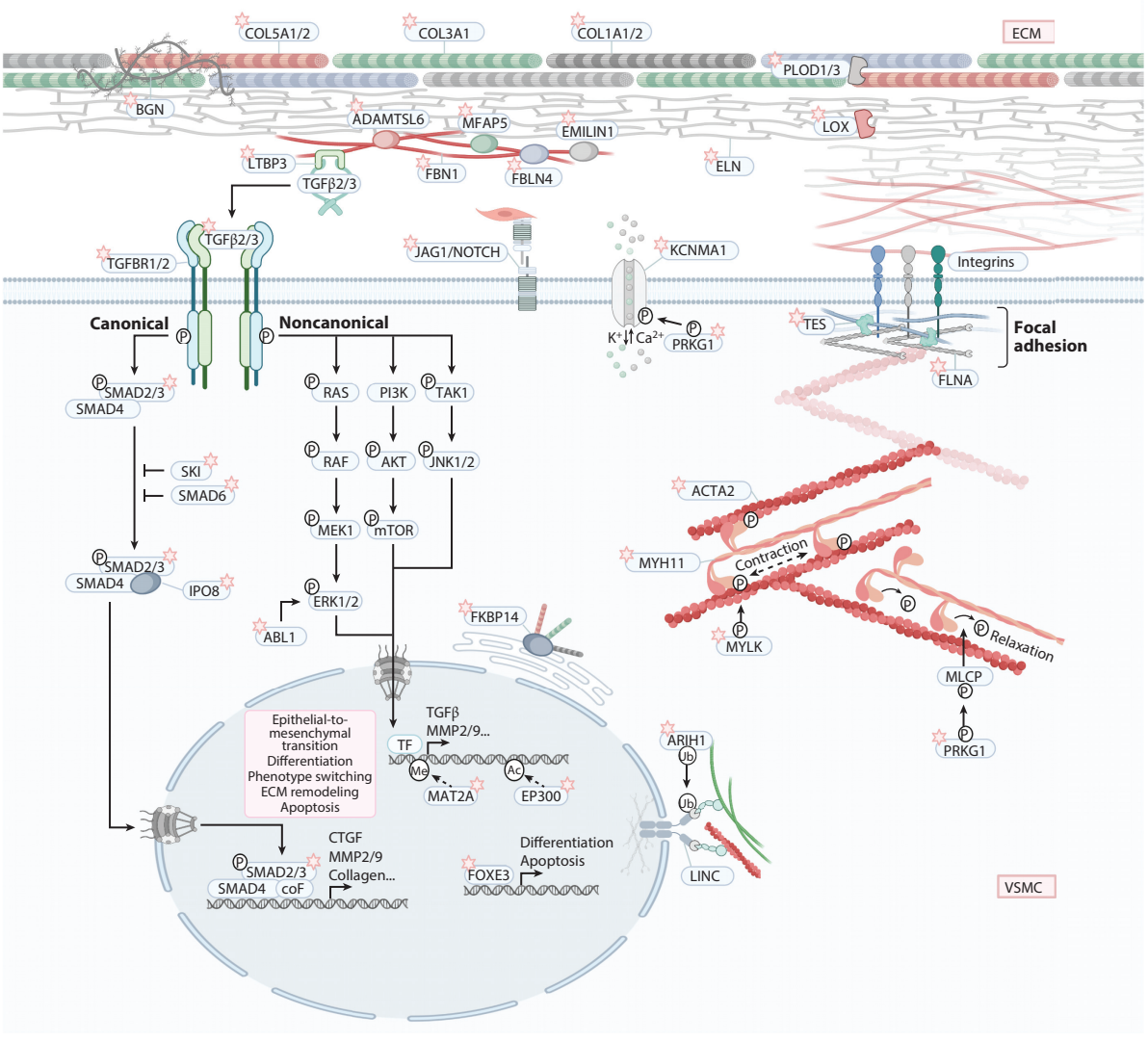
2.1.1. Disruption of the elastin-contractile unit leads to thoracic aortic aneurysm. Because of the functional and structural importance of the tunica media, TAA is often thought to originate there. In fact, multiple TAA-related genes are involved in the ECU, i.e., the connection of the contractile apparatus of VSMCs to elastin fibers, which is essential for mechanosensing and force transmission from the ECM to muscle and vice versa. Elastin sheets in the medial lamellar units are supported by microfibrils consisting of fibrillins, large glycoproteins, and several microfibril-associated glycoproteins (MAGPs) and other proteins [e.g., fibulins (FBLNs) and elastin microfibril interfacer 1 (encoded by *EMILIN1*)] (67). Obliquely positioned elastin microfibril protrusions are connected to the smooth muscle contractile apparatus via membrane-spanning integrins organized in focal adhesions, which are in turn connected to intracellular dense bodies containing actin-anchoring and tethering proteins such as filamin A (encoded by *FLNA*), talin 1 (encoded by *TLN1*), and vinculin (encoded by *VCL*) (62, 67).

2.1.1.1. Elastin, microfibrils, and focal adhesions. Dominant-negative and haploinsufficient genetic defects in fibrillin 1 (encoded by *FBN1*) cause MFS, a syndrome with an estimated prevalence of 1 in 5,000. This connective tissue disorder is, apart from TAA, additionally characterized by skeletal features such as bone overgrowth, joint laxity, pectus excavatum, and scoliosis; ocular features such as ectopia lentis; mitral valve prolapse; and dilatation of the aortic root (22). In some cohort studies, MFS patients with haploinsufficient gene variants in *FBN1* appear to have a more severe aortic phenotype and increased risk for dissections and cardiovascular death, and studies have recently shown that disease severity in such patients can depend on *trans*-eQTLs located in the vicinity of the unaffected allele (6, 32, 33). Multiple genome-wide association studies with nonsyndromic, sporadic TAA patients have noted genome-wide significant hits within the *FBN1* gene, hinting at a common pathway for sporadic TAA and MFS (4, 43, 75).

Similarly, studies have shown that loss-of-function variants in other genes involved in elastin and microfibril homeostasis cause familial TAA, including *MFAP5*, which encodes the fibrillin-associated protein MAGP2; *THSD4*, which encodes the microfibril-associated protein a disintegrin and metalloproteinase with thrombospondin motifs–like protein 6 (ADAMTSL6); the

lysyl oxidase gene *LOX*, which catalyzes the formation of cross-links within elastin lamellae and collagen fibers; and *EFEMP2*, which encodes the ECU component FBLN4 (7, 20, 29, 46, 61). Patients with variants in these genes also sporadically show systemic MFS-like features such as pectus excavatum and mitral valve prolapse, although insufficiently to meet diagnostic criteria for MFS (87).

Intriguingly, mouse models with deletion of the elastin gene (*Eln*) and supravalvular aortic stenosis patients with *ELN* null alleles do not develop aneurysms. Then again, TAA has been described in a rather large proportion (30–50%) of cutis laxa patients with dominant-negative *ELN* frameshift mutations (27, 51, 76). Increased *ELN* gene dosage seems to affect proper aortic function as well, given that patients with duplications (e.g., in the case of the Williams–Beuren region duplication syndrome) or triplications present with aortic dilatations (27). In a recent genome-wide association study, the *ELN* gene locus was the most significantly associated with ascending thoracic aortic dimensions in a cohort of approximately 40,000 participants (120).



(*Caption appears on following page*)

Figure 1 (*Figure appears on preceding page*)

Overview of pathways involved in TAA pathogenesis. Proteins encoded by known monogenic TAA genes are indicated with a red star. (*Top*) The aortic ECM (simplified). Three types of fibril-forming collagens are involved in TAA: COL1A1/2 and COL3A1, which are found in all layers of the aorta, and COL5A1/2, which is found in the media and basement membrane. These collagen types colocalize with several other collagens in the aortic wall as well as with multiple other ECM components, such as the small leucine-rich proteoglycan BGN. ELN is organized into elastic lamellae, supported by microfibrils consisting of large glycoproteins (such as FBN1) and multiple microfibril-associated proteins (such as EMILIN1, FBLN4, MFAP5, and ADAMTSL6). ECM component organization and cross-linking are regulated partly by enzymes such as LOX and the lysyl hydroxylases PLOD1 and PLOD3. The ECM and microfibrils also sequester growth factors such as TGFβ, which is bound to the ECM by latent TGFβ-binding proteins (e.g., LTBP3). (*Bottom*) The intracellular milieu of aortic VSMCs. (*Bottom left*) Upon biomechanical force impulses or enzymatic digestion, TGFβ is released from the latent TGFβ-binding protein and ECM and can bind TGFβ receptors (TGFBR1/2), initiating canonical and various noncanonical signaling cascades. The noncanonical pathways can be positively promoted (e.g., by ABL1), and the canonical pathway with the receptor-activated SMAD proteins SMAD2 and SMAD3 and co-SMAD protein SMAD4 can be inhibited by the proto-oncoprotein SKI and SMAD6. The SMAD2–4 complex is translocated to the nucleus with nuclear IPO8. All TGFβ-controlled pathways in aortic VSMCs ultimately result in the transcription of genes involved in the epithelial-to-mesenchymal transition, differentiation, VSMC phenotype switching, ECM remodeling, and apoptosis. Gene expression can be further influenced by epigenetic mechanisms, including methylation and acetylation by MAT2A-regulated processes and the histone acetylase EP300, respectively. FOXE3 is a transcription factor that is also involved in the differentiation and apoptosis of aortic VSMCs. Lastly, transmembrane JAG1 ligands on neighboring cells can also stimulate the epithelial-to-mesenchymal transition and differentiation, inducing transcription by binding to transmembrane NOTCH ligands. (*Bottom right*) Via integrins, microfibrils connect the ECM to intracellular structural proteins of aortic VSMCs, such as the cytoskeleton and the actin–myosin contractile apparatus, through focal adhesions. Focal adhesions contain structural proteins such as FLNA, which connect integrins to actin, and proteins with dual function (signaling and structure) such as TES. Together with ACTA2 and MYH11, these interconnected structures make up the ECU. The ECU is further connected to the nucleus with the LINC complex, where the ubiquitin ligase ARIH1 is responsible for homeostasis and turnover. VSMC contraction is achieved through the interaction of myosin with actin, which is initiated after the phosphorylation of myosin heads by MYLK. Relaxation is achieved by the dephosphorylation of myosin heads by MLCP, which is activated upon phosphorylation by the protein kinase PRKG1. PRKG1 also regulates intracellular calcium levels by, e.g., controlling the activity of channels such as the calcium-activated potassium channel KCNMA1. The glucose transporter GLUT10 (encoded by *SLC2A10*) is also involved in TAA, as is the endoplasmic reticulum prolyl isomerase FKBP14, which is implicated in correct collagen folding and processing. Abbreviations: Ac, acetylation; ECM, extracellular matrix; ECU, elastin-contractile unit; Me, methylation; P, phosphorylation; TAA, thoracic aortic aneurysm; TF, transcription factor; Ub, ubiquitination; VSMC, vascular smooth muscle cell. Figure adapted from images created with BioRender.com.

FLNA, which connects the ECM-bound cell-surface integrins with intracellular actin, was until recently the only cytoplasmic ECU component that had been linked with TAA (15). That is, functional variants in unassociated focal adhesion scaffolding genes were found to be significantly enriched in a TAA cohort (79). Knockdown of one of the candidate TAA-causing genes *ZYX*, *TES*, and *TLN1* (encoding zyxin, testin, and talin 1, respectively) led to repressed contractility of human aortic VSMCs, and knockout of *Tes* or introduction of a recurrent variant (Tes^{Y249H}) in mice resulted in aortic dilatations (79).

2.1.1.2. The smooth muscle contractile apparatus. At the core of the smooth muscle contractile apparatus, pathogenic variants in VSMC-specific myosin [smooth muscle myosin heavy-chain isoform 11 (*MYH11*)] and actin [smooth muscle actin alpha 2 (*ACTA2*)] genes can be identified in approximately 1% and 14% percent of familial TAA cases, respectively, and cause smooth muscle dysfunction syndromes (44, 113). Cellular findings in the aortic wall include decreased contraction and disarray of VSMCs. Additional clinical features include patent ductus arteriosus, coronary artery disease, stroke, and moyamoya disease. Loss of function of myosin light-chain kinase (encoded by *MYLK*), which is responsible for initiation of the cross-bridge cycle, and gain of function of type I cGMP-dependent protein kinase (encoded by *PRKG1*), a positive regulator of VSMC relaxation, also contribute to familial TAA. Mutation carriers of smooth muscle dysfunction syndromes often suffer acute aortic dissection with little or no preceding enlargement

(45, 142). Worth mentioning is that a disease-modifying locus encompassing *PRKG1* was recently also picked up as a modifier of MFS severity (6).

2.1.1.3. Nuclear positioning. A further indication for the importance of proper VSMC functioning is the recent discovery that impairment of the subcellular localization of the nucleus can severely affect VSMC morphology and cause aneurysmal disease (134). Loss-of-function variants in *ARIH1*, which is responsible for nuclear positioning via homeostasis of the linker of nucleoskeleton and cytoskeleton (LINC) complex, caused TAA and cerebrovascular aneurysm in three separate families. Given that the ECU is intracellularly attached to the nucleus via the LINC complex and that the LINC complex might be involved in mechanosensing via direct gene expression regulation, these findings seem to correspond well with established TAA pathomechanisms (41, 134).

2.1.2. Indirectly related extracellular matrix components are also involved in thoracic aortic aneurysm and its severity. Because the ECU is indirectly connected to other ECM components, such as collagens, one might expect that pathogenic variants in numerous ECM components of the aortic wall might predispose to TAA. Indeed, multiple diagnostic genetic testing panels include a wide variety of collagen and other ECM-related genes based on their expression in the aorta and involvement in other, similar heritable connective tissue disorders, but often without much clinical evidence (124).

Ehlers–Danlos syndrome, characterized by tissue fragility, joint hypermobility, and skin hyperextensibility, currently has 13 subtypes caused by mutations in 20 known ECM genes (95). Vascular Ehlers–Danlos syndrome is the only subtype with prominent vascular involvement, including arterial frailty with a high risk of aneurysm formation or spontaneous rupture, caused by haploinsufficiency or dominant-negative alterations in the *COL3A1* gene (disease course and life expectancy are worse for the latter mutation type) (11, 116). However, life-threatening vascular complications, including aneurysm and dissection, have recently been noted in a proportion of patients with other subtypes, emphasizing the importance of screening for the corresponding genes (the lysyl hydroxylase gene *PLOD1* and the prolyl isomerase gene *FKBP14*, which are important for collagen assembly and cross-linking, and the collagen genes *COL5A1*, *COL5A2*, *COL1A1*, and *COL1A2*) and vascular imaging (21). Moreover, a variant in *COL4A1*, which encodes an important basement membrane constituent in the aorta, cosegregated with increased disease severity in nine MFS individuals (6). Genes encoding other aortic ECM constituents, such as *COL15A1*, *COL3A1*, *COL5A1*, and *COL5A2*, have also popped up as candidate disease modifiers for TAA in general (6, 74). Another confirmed ECM-linked TAA syndrome with MFS- and LDS-like features was described in 2017 as Meester–Loeys syndrome, caused by the X-linked small leucine-rich ECM proteoglycan biglycan (BGN) (98).

2.2. TGFβ Signaling

TGFβ signaling serves pleiotropic, temporally and spatially specific functions in growth, development, cell proliferation and differentiation, tissue homeostasis, and immune function through activation of canonical and noncanonical pathways (73). In vascular development and homeostasis, the TGFβ pathway has a prominent role in regulating processes such as the epithelial-to-mesenchymal transition (see Section 3.1.2), VSMC differentiation, and ECM regulation (39).

TGFβ ligands are secreted by many cell types, noncovalently attached to latency-associated protein (LAP). This complex in turn forms a latent complex with latent TGFβ-binding proteins (LTBPs) that are able to tether to ECM components to regulate TGFβ bioavailability (125). Upon release by either force or proteolytic cleavage, TGFβ can bind the heterotetrameric TGFβ

cell-surface receptor consisting of TGFβ receptor 1 and TGFβ receptor 2 subunits (encoded by *TGFBR1* and *TGFBR2*, respectively). The signal is then transduced by activation of intracellular tyrosine kinases and downstream effectors through phosphorylation (64, 73).

The canonical pathway further operates via two receptor-regulated mothers against decapentaplegic homolog (rSMAD) proteins, SMAD2 and SMAD3, which are cytoplasmic transcription factors that, upon phosphorylation, aggregate into a heterotrimeric complex with SMAD4. This complex subsequently translocates to the nucleus to initiate gene transcription, upregulating ECM-regulating genes such as connective tissue growth factor (CTGF), collagen types 1 and 3, and plasminogen activators that induce MMP expression. In addition, TGFβ can cause various SMAD-independent, noncanonical signaling cascades such as NOTCH, mitogen-activated protein kinase/extracellular signal-regulated kinase (MAPK/ERK), AKT, nuclear factor kappa B (NF-κB), and WNT cascades, thus acting as an alleged master regulator (64, 73, 102).

2.2.1. Disruption of TGFβ pathway components causes thoracic aortic aneurysm. In 2005, Loeys et al. (85) reported a novel MFS-like syndrome caused by pathogenic variants in components of the canonical TGFβ pathway. This TAA syndrome, later termed LDS, is distinguished from MFS by characteristic craniofacial anomalies (such as hypertelorism and a bifid uvula) and cardiovascular features (such as arterial tortuosity). Inflammatory disease (allergies and intestinal inflammation) and cutaneous findings (translucent skin and easy bruising) are also commonly observed, and in addition to aortic root enlargement, aneurysms can be more widespread throughout the arterial tree and tend to dissect at smaller diameters (85, 94). Disease severity varies depending on the gene involved: LDS1–6 are caused by genetic defects in *TGFBR1*, *TGFBR2*, *SMAD3*, *TGFB2*, *TGFB3*, and *SMAD2*, respectively, and present with decreasing severity, which is reflected by the decreasing extent of additional syndromic features, aggressiveness of aneurysm growth, and dissection rate (86). Missense variations in the TGFβ repressor gene *SKI*, an inhibitor of SMAD-induced transcription, cause Shprintzen–Goldberg syndrome, which is characterized by all MFS and LDS features, although with milder aneurysmal disease and additional symptoms such as mental retardation and skeletal muscle hypotonia (26). SMAD6, another inhibitor of TGFβ signaling, also plays a role in the aortopathy of patients with a bicuspid aortic valve (91).

Very recently, another TGFβ-related syndrome with LDS and Shprintzen–Goldberg syndrome overlap was described in 17 patients with biallelic *IPO8* loss-of-function variants (138, 152). *IPO8* encodes a nuclear importin, the specific cargo of which remains largely unknown, although SMAD1–4 have been suggested. Given that this is the most downstream effector implicated in TGFβ-related TAA, one might speculate that *IPO8* might be a promising therapeutic target (138).

A genome-wide association study pointed toward the involvement of a more distantly related gene of the TGFβ pathway [low-density lipoprotein receptor–related protein 1 (*LRP1*)] in the etiology of TAA (43). Although the precise mechanisms remain unknown, a specific single-nucleotide polymorphism in *LRP1* (rs11172113) entails a decreased risk for sporadic TAA. LRP1 [also termed TGFβ receptor type V (TGFβR V)] is a multifunctional but pivotal VSMC cell-surface receptor that has been previously associated with cardiovascular disease (abdominal aortic aneurysm and ischemic stroke). It is involved in VSMC differentiation, maintenance of the contractile phenotype of VSMCs through the modulation of Ca^{2+} signaling, and ECM remodeling through endocytosis of MMP2 and MMP9 (5, 9).

2.2.2. The link between the elastin-contractile apparatus and TGFβ signaling dysregulation. TGFβ signaling is tightly regulated by the ECM and ECU. This functional link stresses the multifaceted role of the ECU and ECM not only as a structural and mechanosensing system but also as a signal-transducing apparatus. The altering force is transduced from ECM fibers via

integrins onto the contractile machinery of VSMCs, which initiates transcription in response to these stimuli. In turn, this results in ECM remodeling and release of ECM-bound TGFβ and other cytokines (62). FBN1 is the best-described tethering protein of the latent complex in the aorta, and it has been hypothesized that MFS is also primarily a TGFβ signalopathy due to *FBN1* variants hindering LTBP-complex binding and regulation (14).

Other ECM constituents with such dual (both structurally and regulatory) functions have been experimentally and clinically associated with TAA and TGFβ dysregulation: The aortic microfibril-associated components ADAMTSL6, EMILIN1, FBLN4, and MFAP5; FLNA; and BGN each participate in the regulation of TGFβ (7, 13, 15, 29, 98, 122, 136). Experimental and clinical proof of the involvement of LTBP proteins themselves in TAA development has also been published: Biallelic variants in *LTBP2* were linked with ocular and other MFS-like features, and patients with biallelic loss of function in *LTBP3* showed widespread aneurysm formation and acute dissections, dental abnormalities, and short stature (47, 70, 101).

3. CELLULAR AND MOLECULAR FEATURES OF THORACIC AORTIC ANEURYSM

TAA progression can be slowed down to some extent by minimizing risk factor exposure, e.g., by reducing blood pressure with antihypertensive drugs and avoiding high-impact physical activity (140). The only curative therapy is structural intervention by preemptive surgery of the thoracic aorta, although in some TAA disorders, aneurysms and dissections can develop at more widespread locations. While preclinical trials for compounds that tackle disease-specific features, such as increased TGFβ signaling (e.g., losartan) and MMP activation (doxycycline), were encouraging, substantial clinical breakthroughs have not been achieved (17, 36, 50). There is thus a great need for new insights into converging pathomechanistic pathways of TAA development where therapeutics could intervene.

Because of the vastly heterogeneous nature of genetics in TAA, exploration of the transcriptomic and proteomic landscape of the diseased aorta to find etiology-transcending mechanisms is very promising. With the advent of novel high-throughput techniques such as RNA sequencing and whole-genome methylation profiling, a deeper understanding will be—and has already been—gained. Single-cell sequencing in particular is vital for investigations of the many different dynamic cell populations that make up the aorta, as well as investigations of possible cell-specific pathological gene expression signatures (119). In the following sections, we discuss established and recently discovered pathological processes in the aortic walls of patients and mice (see **Figure 2**), as well as specific genetic discoveries that corroborate these findings.

3.1. Smooth Muscle Cell Depletion

Depletion of mural VSMCs is a well-characterized event in aortopathies, including abdominal aortic aneurysm, atherosclerosis, and TAA. Its importance in TAA has been corroborated by various transcription studies that described expression signatures of increased apoptosis (68, 80, 132, 145), and recent insights into the cellular composition of the aortic wall obtained with single-cell sequencing further indicated loss of nonimmune cells in patients (80). Aside from apoptosis, failed epithelial-to-mesenchymal transition and migratory events, as well as aberrant phenotype switching, might also contribute to VSMC depletion in TAA.

3.1.1. Apoptosis. Mural VSMC apoptosis disrupts the ECU, which can further increase elastin breaks and ECM deposition, thereby worsening overall aortic wall integrity (18). Both inflammation and TGFβ dysregulation have been put forward as triggers of VSMC apoptosis

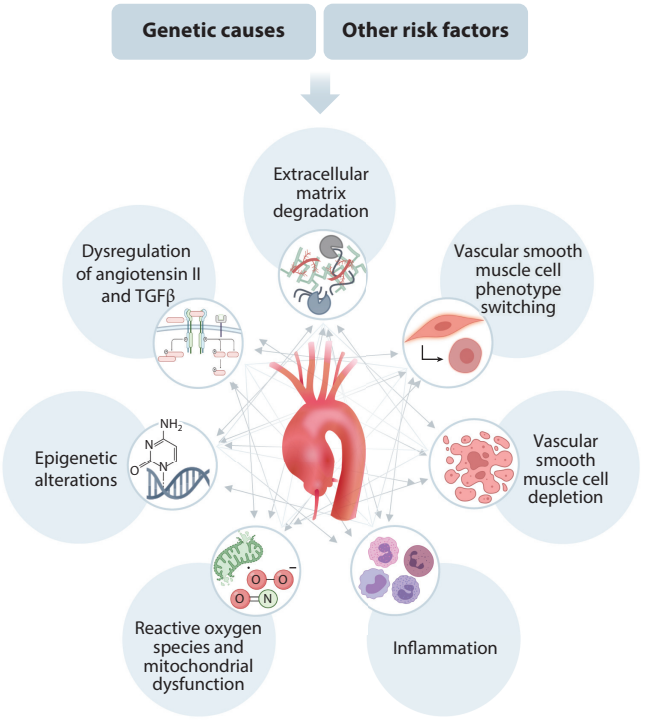


Figure 2

Schematic overview of the cellular and molecular features of thoracic aortic aneurysm. Figure adapted from images created with BioRender.com.

due to colocalization of apoptotic cells in the aortic wall with inflammatory cells and TGFβ overexpression. Apoptosis of mural VSMCs was further associated with increased angiotensin II signaling, shear stress, reactive oxygen species (ROS) formation, and imbalances of pro- and antiapoptotic members of the B cell lymphoma 2 (BCL2) protein family (28, 34, 54).

In a large TAA patient cohort, an eQTL variant that induces overexpression of the *TCF7L2* gene was reported to be associated with disease. TCF7L2 is a transcription factor and distal effector of the WNT pathway, and upregulation of *TCF7L2* induces VSMC apoptosis through repression of the antiapoptotic *BCL2* gene (128). Additional genetic links with apoptosis were recently also uncovered. Dominant pathogenic variants in the DNA-binding domain of the forkhead transcription factor gene *FOXE3* segregated in two families with TAA, and a recently described TAA syndrome that includes skeletal anomalies, congenital heart disease, and failure to thrive is caused by gain-of-function variants in ABL proto-oncogene 1 (*ABL1*) (8, 72, 144). Although the function and role of FOXE3 and ABL1 in the aorta and TAA pathology remain largely elusive, studies have shown that FOXE3 deficiency abrogates apoptosis inhibition in human aortic VSMC and in mice and that augmented ABL1 activity increases apoptosis (72, 150).

3.1.2. Failure of the epithelial-to-mesenchymal transition and neural crest cell migration. Confined areas of the aorta are populated with VSMCs of three different embryonic origins: Second heart field–derived VSMCs line the aortic root, whereas neural crest–derived VSMCs and paraxial plate mesoderm–derived VSMCs are found in the ascending and descending aorta, respectively (93, 119). These VSMCs show lineage-specific signaling, interactions, and responses

to experimental, genetic, and environmental stimuli (including TGFβ-elicited effects), substantiated by the observation that the location of aneurysm formation is not random and often occurs specifically at the borders of regions with VSMCs of different embryological origins (2, 66, 92).

Neural crest–derived cells (NCCs) are epithelial cells that arise at the border of the neural plate during late gastrulation and early neurulation in vertebral development. After the epithelial-to-mesenchymal transition (i.e., mobilization and adoption of a mesenchymal phenotype), NCCs migrate toward specified locations and give rise to a wide variety of cells, including neurons, chondrocytes, ocular endothelium, and VSMCs (93, 139). NCC-like cells are present in adult tissue, although it is undefined whether and (if so) how NCCs migrate and/or differentiate into VSMCs upon injury or hemodynamic changes in later life (1).

The hypothesis that ECU function and aortic homeostasis can also be compromised by impaired NCC migration stems from the following genetic links with ascending TAA development. First, in addition to regulating apoptosis, *FOXE3* appears to be essential for the migration of NCCs in the ascending aorta and their differentiation into adult, contractile VSMCs (72). The average age of presentation is 45 years, which suggests that NCCs potentially have a function in adult aortic homeostasis. Indeed, *FOXE3* expression is absent in adult tissue but is upregulated upon altered hemodynamic forces (72). Likewise, patients with Alagille syndrome, caused by defects in the NOTCH receptor ligand gene *JAG1*, display cardiac malformations and occasionally present with TAA at an average age of 40 years (127). The functioning of JAG1 and NOTCH signaling is vital for induction of the epithelial-to-mesenchymal transition and differentiation of cardiac NCCs into neural crest–derived VSMCs, again indicating that disruption of these processes might be an important but unrecognized hallmark of TAA (139).

3.2. Phenotype Switching of Smooth Muscle Cells

One of the most important findings in single-cell RNA-sequencing studies is that VSMCs in the aortic wall are a highly dynamic cell population distributed in a phenotypic modulation continuum (53). Under certain stimuli, VSMCs can go from a differentiated, quiescent, contractile state to a synthetic, proliferative, remodeling, and migratory state, often characterized by decreased expression of contractile markers along with an increase in VSMC proliferation and synthesis of ECM proteins and elastolytic enzymes. This phenotypic plasticity is a feature that is unique to smooth muscle cells and renders them responsive to vascular injury and altered hemodynamics (111).

Under normal physiological conditions, most VSMCs in the ascending aortic wall have a contractile phenotype. Phenotype switching toward the synthetic state is believed to be a primary driver of aortic disease (118). In MFS mice, synthetic VSMCs are a distinct cell population, found almost exclusively in the aortic media of diseased mice. These altered VSMCs displayed marked downregulation of contractile gene expression and increased expression of collagen and markers of proliferation and adhesion. A temporal investigation of expression changes during the development of these MFS mice further showed that overexpression of Klf4, a marker of VSMC phenotype modulation, had an early and driving function in disease progression (115). In human TAA tissue, KLF4 is also upregulated, and likewise, VSMCs residing in aortic aneurysm tissue samples of sporadic TAA patients are classified into several discrete subtypes, including quiescent contractile, stressed, proliferating, and synthetic VSMCs (37, 80). Intriguingly, an additional VSMC population showed typical markers of monocytic inflammatory cells, indicating that VSMCs could also adopt a macrophage-like phenotype in TAA (80).

Worth mentioning is that further research into the pathological effects of ABL1 gain of function indicated that in these patients, in addition to increased apoptosis, phenotype switching of VSMCs toward a synthetic type was induced, which also suggests genetic involvement in this process (150).

3.3. Altered Epigenetic Signatures

Although epigenetics has been infrequently studied in TAA, evidence of epigenetic disturbances has been accumulating over recent years. For instance, when the VSMC cytoskeleton stability is perturbed in cell models of both LDS and smooth muscle dysfunction syndromes (and thus by intrinsic genetic defects in either the contractile apparatus or TGFβ signaling), the histone deacetylase HDAC9 is activated and forms a repressive complex within the nucleus, situated at gene promotor regions of contractile genes. Inhibition of these events by knockout of *Hdac9* in an MFS mouse model dampened aortic aneurysm growth (82). Among other cardiovascular diseases, variation in the *HDAC9* locus has been associated with intracranial aneurysm and, recently, with aortic calcification and VSMC phenotype modulation in the descending aorta (82, 96). Additionally, HDAC6 deacetylation activity was decreased in human aneurysm samples, and functional studies with HDAC6 and other HDAC proteins proved the importance of these proteins in the control of VSMC and endothelial cell proliferation, ECM deposition, and MMP/TIMP regulation (48).

A genome-wide expression study showed that several HOX genes (*HOXA5*, *HOXB6*, *HOXC6*, and *HOXC8*) were downregulated in samples from TAA patients—an association that had not been made in previous TAA transcriptomic studies (84, 132). Correspondingly, the first-ever genome-wide TAA methylation study found that the promoters and gene bodies of HOX genes (especially *HOXA5*, *HOXB6*, and *HOXC6*) were differentially methylated in aortic samples from patients that underwent repair after type A dissection (84). The HOX transcription factor family controls general proliferation, differentiation, and migration in development and, more specifically, plays a role in VSMC phenotype modulation as well as early cardiovascular development and maintenance at a later age (38, 84).

Genetic evidence of epigenetic involvement in TAA development and progression stems from the observation that loss-of-function variants in *MAT2A* and *EP300* can cause TAA (42, 90). *MAT2A* encodes a methionine adenosyltransferase that participates in the synthesis of *S*-adenosyl-L-methionine (SAM), an enzyme involved in multiple processes, including methylation. Global hypomethylation and dysregulation of other methylation enzymes were previously described in VSMCs that harbored decreased expression of contractile proteins and displayed increased proliferation, further indicating the role of specific epigenetic regulators in TAA development (42). *EP300* encodes a histone acetyltransferase in which genetic defects can cause a congenital disorder characterized by intellectual disability, facial dysmorphism, and TAA. Although the function in the aorta and the link between EP300 dysfunction and aneurysm formation are not clear, the importance of EP300 in VSMC differentiation and vessel formation has recently been demonstrated (114).

Together, these data indicate that aberrant epigenetic regulation might be at the very core of deleterious VSMC phenotype modulation and TAA pathology in general. Notably, Liu et al. (84) used this knowledge to develop a simple, noninvasive blood test based on circulatory cell-free DNA—DNA that is released from apoptotic cells in the blood circulation and contains cell- or disease-specific epigenetic signatures. They were able to detect disease with acceptable sensitivity and specificity (86% and 75%, respectively), thereby opening a new avenue for TAA biomarker development.

3.4. Inflammation

Inflammation is a well-known hallmark of abdominal aortic aneurysm: Medial and adventitial infiltration of a wide range of immune cells and elastolysis and other enzymatic degradation of the ECM are prominent histological characteristics (131). Although TAA is not generally considered

an inflammatory disease, immune infiltrates, uncontrolled cytokine and chemokine signaling, and vascular remodeling in the aortic walls of TAA patients have been described (68, 112, 132, 151). For example, comparative proteomic profiling of TAA tissues from patients with a bicuspid or tricuspid aortic valve revealed that, whereas bicuspid aortic valve–related TAA showed differential regulation of repair processes (due to the altered hemodynamic flow that a bicuspid aortic valve causes), tissues with tricuspid aortic valve disease were distinguished from unaffected samples predominantly by an inflammatory protein expression pattern (69).

Based on multiple transcriptomic studies of aortic wall specimens from TAA animal models and patients, it is hypothesized that an inflammatory cascade is initiated, although the initiating factor remains elusive. Inflammatory cytokines such as interleukin 6 (IL6), IL1β, IL3, and interferon gamma (IFNγ) are upregulated, and inhibitory proteins such as JAK tyrosine kinase—which controls the desensitization and degradation of cytokine receptors—are downregulated in the affected aorta (65, 68, 83, 149). Together with expression of chemotactic proteins [such as monocyte chemoattractant protein 1 (MCP1) and granulocyte–macrophage colony-stimulating factor (GM-CSF)] and transendothelial leukocyte adhesion and migration molecules [such as intercellular adhesion molecule 1 (ICAM1) and vascular cell adhesion molecule 1 (VCAM1)] on endothelial cell surfaces of the adventitial vasa vasorum, an infiltration of leukocytes and monocytes is favored (55, 65, 115, 132). Immunohistochemistry and single-cell RNA sequencing confirm that the number of infiltrating immune cells is much higher in TAA patient samples, and the predominant cell types in these infiltrates are T lymphocytes and macrophages (80, 135). Lymphocytes and macrophages further promote inflammation by producing ROS and secreting tissue-remodeling MMPs (MMP9 secretion by T lymphocytes, stimulated by IFNγ, and MMP12 secretion by macrophages, stimulated by IL3) and through the expression of other cytokines and chemokines, resulting in more medial degradation, which in turn again stimulates chemotaxis (65, 83, 149). Additionally, vascular endothelial growth factor (VEGF), a mediator of angiogenesis and elastolysis, is upregulated in TAA patients, in line with previously observed increased neovascularization in the media and adventitia of human and rat aortae (68, 78, 151).

The role of inflammation in TAA as a disease driver or innocent bystander is still a matter of ongoing debate. Nevertheless, treatment of TAA in rats with the bioactive substance curcumin decreased aneurysm size and elastin disorganization by means of its anti-inflammatory effects—VEGF expression and neovascularization were decreased, and the infiltration of inflammatory cells was inhibited—indicating that the importance of inflammation in TAA progression has been underestimated (78).

Several assumptions regarding the initiating role of aortic inflammation in TAA have been made. TGFβ is known to regulate the immune response by exerting pleiotropic effects on T and B cell differentiation, proliferation, and function (141). It is therefore expected that defective TGFβ signaling (e.g., due to pathogenic variants in the genes described above) initiates inflammatory disease: A *Smad3* knockout mouse model of LDS is characterized by large infiltrates of immune cells in the aortic wall and early mortality due to inflammation, and LDS patients exhibit increased incidence of gastrointestinal inflammation and other inflammatory diseases, such as asthma and eczema (86, 147). On the other hand, infiltrating T cells display monoclonality, and activated dendrocytes are present in the adventitia of patient aortic samples, which might suggest a response to a single unknown antigen (55).

Although inflammation seemingly plays an important role in TAA, there is only limited evidence that variants in genes encoding key inflammatory proteins contribute to the genetic etiology of TAA. Polymorphisms in the interleukin genes *IL6* and *IL1β* have recently been reported as risk alleles for sporadic TAA (130).

3.5. Reactive Oxygen Species and Mitochondrial Dysfunction

ROS molecules are natural by-products of oxygen metabolism and serve as regulators of vascular tone homeostasis, proliferation, cell signaling, and even regulation of VSMC phenotype (10, 129, 133). A proper balance between ROS molecules and antioxidant enzymes is critical, since increased ROS levels are a hallmark of multiple cardiovascular diseases and can cause impaired endothelial function (129).

Upon altered hemodynamic conditions, disruption of ECM-VSMC contractility, and infiltration of immune cells, excessive ROS generation is triggered in TAA. This ROS generation is demonstrated by the increase in ROS protein attack markers in the plasma of MFS patients and the local imbalance between superoxide-producing enzymes and superoxide dismutases in aneurysmal tissues of MFS mice (10, 31, 146).

Several causal molecular mechanisms of ROS imbalance in TAA have been put forward (110, 121). For instance, Oller et al. (110) suggested that constitutive activation of inducible nitric oxide synthase 2 (NOS2), which produces supraphysiological levels of nitric oxide, might be the primary inducer of impaired VSMC contractility and ECM degradation in TAA. Nitric oxide is, among other things, a regulator of smooth muscle contractility, and it is believed to exert its pathological effects at least in part via positive modulation of the relaxant PRKG1 (see Section 2.1.1.2) and activation of MMP9 excretion in VSMCs. Intriguingly, specific inhibition of Nos2 resulted in a quick restoration of the aorta in two TAA mouse models: After three weeks, dilatation was reversed, and elastin and collagen content and integrity were normalized (110). Likewise, pharmacological inhibition as well as knockout of the superoxide-producing NADPH oxidase gene *Nox4* in MFS mice resulted in decreased aneurysm growth, further indicating a role of ROS in TAA. Notably, NOX4 expression and function are strongly induced by TGFβ and vascular injury (30, 63).

Given that mitochondria are essential organelles for ATP and ROS homeostasis because of their role in oxygen metabolization, it is suspected that their dysfunction—and, as a consequence, ROS accumulation—might play a role in TAA pathogenesis, especially due to the high energy requirements for VSMC contraction. Although this hypothesis has not been widely studied, a limited number of studies support it (reviewed in 148). Interestingly, mitochondria-related metabolic function was one of the main dysregulated pathways in a recent RNA-sequencing study of MFS mouse and patient tissues, and single-cell RNA sequencing of aneurysmal tissue derived from sporadic TAA patients showed that mitochondrial genes for oxidative phosphorylation were downregulated in more than half of the detected cell types of the aorta (80, 109). Likewise, a study of a mouse model of TAA found a similar dysregulation of mitochondrial protein expression, which was, according to the authors, attributable to increased TGFβ signaling as a result of ECM disruption (137). Culturing healthy aortic VSMCs on a matrix secreted by FBN1-deficient VSMCs resulted in deterioration of mitochondrial function, further indicating that ECM disruption is indeed a driving factor of mitochondrial dysfunction (109).

A disease-modifying missense variant in *ADCK4*, encoding an important kinase in mitochondrial function and oxidative phosphorylation, seemed to segregate with milder disease in an MFS cohort, further stressing the underexplored role of mitochondria in TAA development (74).

The involvement of mitochondrial dysfunction and (resulting) ROS would indicate that US Food and Drug Administration–approved drugs with antioxidant activity might be a favorable therapy for TAA. Indeed, several such compounds, including resveratrol, have proven beneficial for aneurysm growth in MFS mice and patient cohorts (56, 133). Furthermore, recovery of mitochondrial function in MFS mice through the administration of nicotinamide riboside resulted in a quick reversion of the aneurysm phenotype (109).

3.6. Angiotensin II Signaling

Angiotensin II is not only an effector in systemic blood volume and vascular resistance but also involved in various cell homeostatic processes, and its contribution to aneurysm pathology has been well established in cell and animal models (88, 133). The angiotensin receptors AT1R (a suspected culprit of pathophysiological actions such as proliferation, inflammation, and fibrosis) and AT2R (hypothesized to inhibit AT1R effects through negative feedback loops) were increased in VSMCs in the tunica media of MFS patients (105). Only selective blocking of AT1R in mouse models of TAA resulted in dampening of pathological canonical and noncanonical (specifically ERK) TGFβ signaling and reduced aneurysm progression, independent of blood pressure, indicating that AT1R signaling specifically might be crucial in pathogenesis and might contribute to the increased TGFβ signaling observed in the aortic tissues of most syndromic and nonsyndromic TAA patients (49, 105, 123). Second heart field–derived VSMCs indeed significantly upregulated TGFβ ligand secretion upon angiotensin II stimulation in a mouse model of LDS1. Notably, neural crest–derived VSMCs did not respond with increased TGFβ-ligand secretion upon this stimulus, and intriguingly, in LDS, it is mainly the aortic root, which is lined with second heart field–derived VSMCs, that is involved in TAA (92). The effects of angiotensin II (and, seemingly, TAA disease in general) thus appear to be cell type specific, and not only in VSMCs of different lineages: In MFS mice, knockout of the *At1r* gene either globally or in the endothelium resulted in prolonged survival and reduced medial degeneration with reduced ERK signaling, whereas smooth muscle–specific knockout normalized Erk and Smad2 signaling but did not have an effect on disease outcome (35).

Studies have also shown that angiotensin II elicited a specific increase in ROS production; that is, ROS enhancement by angiotensin II was observed only in the thoracic aortic VSMCs of MFS patients and not in VSMCs of the abdominal aorta. ROS production in turn stimulates *AT1R* expression, thereby creating a positive feedback loop (23, 30). Other evidence indicates that angiotensin II activates MMP2 and MMP9, which could induce further elastolysis and TGFβ release from LTBP (24, 104, 143).

As mentioned above, the current standard of care for TAA patients offers the use of blood pressure–lowering medication such as beta blockers to slow down aneurysm progression by decreasing blood pressure as a risk factor. Sartans, in addition to blood pressure–lowering effects, through AT1R-specific antagonistic properties, also exert TGFβ inhibitory effects, making it an ideal drug for (syndromic) TAA, which is characterized by increased TGFβ signaling. As expected, aneurysm formation and other MFS-related manifestations could be prevented in the MFS mouse model, but in human trials, losartan did not outperform standard beta blockers (36, 50, 77). The latter might, however, be explained by the fact that the trial used a high median dose of beta blocker but a regular dose of losartan; a high dose of losartan might have been needed to reach its TGFβ inhibitory effect. A high dose of irbesartan was also associated with a reduced rate of dilatation in an MFS cohort (103), but to date, no comparison has been made with other sartans or beta blockers.

3.7. Current Limitations

Although transcriptomic studies and the like provide a wealth of new information, the results should often be interpreted with caution. Considerable discrepancies exist between mRNA and protein expression and between expression/cellular patterning and protein function in mice and humans, and reproducibility remains a significant hurdle. Reliable control samples are particularly challenging to acquire: Often, samples are retrieved from organ donors that suffered cardiac arrest or have undergone valve replacement, meaning that hemodynamic changes could have already

influenced aortic integrity and signaling (60). One study used left internal thoracic artery samples as a control, but in contrast to the ascending aorta, which originates from the neural crest, this artery originates from mesodermal lineages (132). Therefore, one could not be entirely certain whether transcriptional differences in this particular study (e.g., for HOX genes, the spatial expression patterning of which is tightly regulated) truly originate from aneurysmal disease. However, continuously mounting experimental data have confirmed previous isolated findings, demonstrated in this example by the additional independent evidence of HOX gene involvement in TAA (84, 132).

Patient samples are often obtained during elective surgery or after dissection, meaning that the disease is already in an advanced stage (68, 115, 132). It has been suggested that pathway regulation differs in early versus late aneurysmal development, supported by the observation in an MFS mouse model that silencing TGFβ signaling with losartan ameliorates further TAA progression but exacerbates the phenotype when given before disease manifestation (19).

4. FUTURE PERSPECTIVES

Owing to technological advances, hypothesis- and family-based study designs pave the way for large-scale hypothesis-free gene discovery approaches, which have already greatly improved the understanding of the genetic foundations of TAA. This review indeed demonstrates that genes and pathways involved in TAA are rapidly being discovered, including ones that have not been associated with TAA before, and that single-gene causes with reduced penetrance as well as common variants that may have subtle disease-modifying effects are being pinpointed as well. Accumulating clinical data also indicate that several syndromes with high variability in phenotype expression can sporadically present with TAA and related vascular complications, although the causal link between the involved genes and TAA is often unclear. For instance, mutations in the gene encoding the alpha subunit of the potassium channel KCNMA1 cause Liang–Wang syndrome, and several patients with severe aortic root aneurysms at a young age have been described (126). TAA is also not uncommon in polycystic kidney disease, caused by variants in the calcium-regulating cell-surface receptor genes *PKD1* and *PKD2* (117, 126). Notwithstanding these many promising insights, a drawback is that the number of genes tested in clinical panels for patients with TAA and the number of characteristics of TAA syndromes increase rapidly, often resulting in an overload of variants of uncertain significance that are diagnostically unclassifiable. From a diagnostic point of view, it is of great relevance that such discovered genes are frequently curated by reviewing evidence of a causal relationship in patients as well as disease models, as was done by Renard et al. (124).

In addition to genetics, insights into the histological, cellular, proteomic, and transcriptomic landscape of the aorta are indispensable for the discovery of common TAA pathomechanisms and new therapeutic avenues. All hallmarks of the aneurysmal aorta described above suggest that, despite different possible molecular causes and starting points, disease pathways converge on the same vicious destructive cascade (see **Figure 2**). All genetic, transcriptomic, and pathomechanistic factors described in this review alter the ability of the aortic wall to withstand and react correctly to mechanical forces (147). A cascade of compensatory mechanotransduction-mediated signaling (including TGFβ), phenotype modulation, and ECM remodeling would be induced, and further matrix destruction would induce inflammatory responses, ROS release, cellular and mitochondrial dysfunction, and apoptosis (64). Intervening in this cascade of events would be paramount for a therapy.

One of the latest hypotheses is that activation of the proinflammatory stimulator of interferon genes (STING), a sensor of cytosolic DNA, might be a leading director in this vicious cycle of

tissue disruption and inflammation. Upon tissue injury and ROS damage, DNA from damaged VSMCs that is released into the VSMC cytosol or engulfed by macrophages can induce a pathway in which STING and its other effectors activate macrophages, directly induce expression of MMP9, and mediate VSMC apoptosis through multiple mechanisms (89). STING and its coeffectors are upregulated in VSMCs in the media and in macrophages or macrophage-like VSMCs in the adventitia, and experimentally induced TAA in a *Sting*-deficient mouse model resulted in marked amelioration of the aortopathy cascade. Treatment of TAA mice with a STING pathway inhibitor also resulted in partial amelioration of the phenotype (89).

The search for more such converging mechanisms and subsequent drug development or repurposing of existing drugs have gained more momentum in recent years. For instance, Hansen et al. (52) computationally pinpointed that the subcellular pathway dysregulation contributing to reduced muscle contractility in an MFS mouse model could—surprisingly—be prevented by intervening in GABA signaling with baclofen, a $GABA_B$ receptor agonist with muscle relaxant properties. Intriguingly, long-term treatment of MFS mice with baclofen resulted in amelioration of the survival and biomechanical function of the aorta by improving VSMC contractility and reducing arterial stiffness, in a manner that is independent of the blood pressure–lowering properties of this compound. In a similar fashion, Caescu et al. (12) discovered that homeodomain-interacting protein kinase 2 (*HIPK2*) overexpression is a driver in aneurysm formation and dissection in both mouse and human MFS and that aneurysmal disease could be delayed by pharmacological interference.

Piece by piece, the puzzle of TAA pathology is being solved. One could perhaps cautiously assume that new, efficient therapeutics for TAA are imminent.

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Errata

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