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Therapies for Thoracic Aortic Aneurysms and Acute Aortic Dissections:

Old Controversies and New Opportunities

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Abstract

Thoracic aortic aneurysms that progress to acute aortic dissections are often fatal. Thoracic aneurysms have been managed with treatment with β-adrenergic blocking agents (β-blockers) and routine surveillance imaging, followed by surgical repair of the aneurysm when the risk of dissection exceeds the risk for repair. Thus, there is a window to initiate therapies to slow aortic enlargement and delay or ideally negate the need for surgical repair of the aneurysm to prevent a dissection. Mouse models of Marfan syndrome—a monogenic disorder predisposing to thoracic aortic disease—have been used extensively to identify such therapies. The initial fi that TGFβ (transformation growth factor-β) signaling was increased in the aortic media of a Marfan syndrome mouse model and that its inhibition via TGFβ neutralization or At1r (Ang II [angiotensin II] type I receptor) antagonism prevented aneurysm development was generally viewed as a groundbreaking discovery that could be translated into the first cure of thoracic aortic disease. However, several large randomized trials of pediatric and adult patients with Marfan syndrome have subsequently yielded no evidence that At1r antagonism by losartan slows aortic enlargement more effectively than conventional treatment with β-blockers. Subsequent studies in mouse models have begun to resolve the complex molecular pathophysiology underlying onset and progression of aortic disease and have emphasized the need to preserve TGFβ signaling to prevent aneurysm formation. This review describes critical experiments that have influenced the evolution of our understanding of thoracic aortic disease, in addition to discussing old controversies and identifying new therapeutic opportunities.

Keywords

aneurysm; aneurysm; dissecting; aorta; Marfan syndrome; therapeutics

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Disclosures

None.

Aortic aneurysms involving the aortic root and proximal ascending aorta are generally the result of constant biomechanical forces from pulsatile blood flow from the heart associated with structural weakening of the aortic wall caused by genetic lesions and environmental factors. The natural history of thoracic aortic aneurysms is that they progressively enlarge, and over time, this enlargement increases the risk for an acute ascending (Stanford type A) aortic dissection. An aortic dissection occurs when a tear in the inner layer of the aortic wall allows blood to fl w from the lumen into the wall of the aorta, forming a false lumen. Population-based studies have determined that up to half of individuals affected with a type A dissection die before reaching the hospital and that the mortality and morbidity remains high even after emergent surgical repair of the ascending aorta.[1,2] These deaths because of dissection can be avoided if aneurysms are diagnosed and monitored and if surgical repair of aneurysmal segments of the aorta is performed to prevent type A dissections. Surgical repair of the aorta is pursued when vessel dilation reaches approximately twice the normal diameter (5.0–5.5 cm).[3] The diameter of the aortic aneurysm is the major criterion for surgical repair, but this size can vary based on the underlying cause of the disease, the rate of growth of the aorta, the status of the aortic valve, symptomatology, and the presence of other cardiovascular disease. Because thoracic aortic enlargement is present in the majority of patients before an acute dissection, there is a window to initiate therapies to slow aortic enlargement and delay or ideally negate the need for surgical repair of the aneurysm to prevent a dissection.

Thoracic Aortic Disease Risk Factors and Current Therapy

Hypertension is the major risk factor for thoracic aortic disease.[5–7] Other factors that heighten biomechanical forces of the pulsatile blood (eg, pregnancy, cocaine abuse, body-building weightlifting) also increase the risk for thoracic aortic disease. Genetic predisposition is the second major risk factor. Up to 20% of individuals presenting with an aneurysm or dissection have single-gene mutations that confer a high risk for disease development with or without additional systemic features.[8,9] More than 15 genes have been thus far identified that harbor highly penetrant mutations predisposing to thoracic aortic disease.[10] The most common congenital heart defect—a bicuspid aortic valve—increases the risk for the disease.[11] Additionally, the risk for developing thoracic aortic disease also increases with age, and more men than women are affected. Interestingly, recent data indicate that diabetes mellitus protects from thoracic aortic aneurysms and dissections.[12–14] The majority of families with an inherited predisposition for thoracic aortic disease have no associated syndromic features.[8] One widely studied exception is Marfan syndrome (MFS), in which the risk for thoracic aortic aneurysms and dissections is associated with additional abnormalities in the eyes, heart, and musculoskeletal system. MFS results from mutations in *FBN1* that interfere with fibrillin-1–dependent ECM (extracellular matrix) assembly of functional microfibrils and elastic fibers.[15]

Thoracic aortic aneurysms and dissection are associated with degenerative pathological changes in the medial layer of aortic wall.[16] The aorta has 3 histologically distinct layers: the intima, composed of a single layer of endothelial cells attached to a basal lamina; the media, containing >50 alternating layers of elastic fibers and smooth muscle cells (SMCs) in humans; and the adventitia, made up of a loose connective tissue, fibroblasts, and vasa

vasorum (Figure 1). Thoracic aortic disease is associated with genetic alterations believed to primarily impair the contractile function of the SMCs in the medial layer, thus disrupting the proper response to the hemodynamic load constantly imposed on the aortic wall. Among others, major histopathologic findings include fragmentation and loss of elastic fibers, fewer SMCs, and excessive accumulation of collagen (vascular fibrosis) and proteoglycans (Figure 1).[17,18] These same histopathologic changes of the medial layer also occur with normal aging but to a less degree and later than in individuals with thoracic aortic disease.

β-Adrenergic blockade (β-blockers) has traditionally been the treatment of choice for thoracic aortic disease.[3] The effectiveness of β-blockers in preventing aortic dissection was originally demonstrated >70 years ago, when it was determined that turkeys eating sweet pea (*Lathyrus odoratus*) seeds, which contain the lysyl oxidase inhibitor, β-aminopropionitrile, die of acute aortic dissections.[19,20] As β-blocker therapy reduces the rate of change in central aortic pressure with respect to time, treatment with the β-blocker propanol dramatically decreased deaths from dissection in β-aminopropionitrile–fed turkeys.[21] Based, in part, on these data, an open-label, randomized β-blocker treatment trial was pursued in patients with MFS, which showed that propranolol decreased the rate of growth of the aortic root and reduced aortic complications.[22] Additional studies interrogating β-blocker therapy to prevent aortic growth and events in patients with MFS have yielded mixed results.[23–25]

Losartan Controversy

Two mouse models of MFS (*Fbn1*$^{mgR/mgR}$ and *Fbn1*$^{C1039/+}$ mice) have been widely used for ≈2 decades to identify molecular pathways associated with onset and progression of thoracic aortic disease. *Fbn1*$^{mgR/mgR}$ mice produce significantly less fibrillin-1 than wild-type animals and rapidly form thoracic aortic aneurysms that dissect and rupture within the first 6 to 8 months of postnatal life.[26] *Fbn1*$^{C1039/+}$ mice instead produce equal amounts of normal and mutant fibrillin-1 and slowly develop thoracic aortic aneurysms that rarely progress to dissection.[27] The initial finding that TGFβ (transformation growth factor-β) signaling was increased in the aortic media of *Fbn1*$^{C1039G/+}$ mice and that its inhibition via TGFβ neutralization or At1r (Ang II [angiotensin II] type I receptor) antagonism prevented aneurysm development was generally viewed as a groundbreaking discovery that could be translated into the first cure of a heritable thoracic aortic disease.[27] However, several large randomized trials of pediatric and adult patients with MFS have subsequently yielded no evidence that At1r antagonism by losartan slows aortic enlargement more effectively than conventional treatment with β-blockers (Table 1).[28–31] Several explanations have been invoked to reconcile this discrepancy between experimental findings and clinical trials; among others, they include differences in drug dosing and mode of administration, as well as stage of the disease and genetic variability of the cohorts studied.[32,33] The presence of 2 At1rs in rodents (At1ar and At1br) and only 1 in humans (AT1R) could potentially be another factor accounting for the diverse outcome of losartan treatment in the 2 species.

A role for TGFβ signaling in thoracic aortic disease was further emphasized when additional mutations predisposing to thoracic aortic disease were identified that disrupt proteins involved in canonical TGFβ signaling.[36–39] A paradox also emerged in the field because mutations in these genes decrease rather than increase TGFβ signaling.[36–39] It should be

noted that clinical evidence supporting a TGFβ-driven mechanism of aneurysm formation was largely based on staining of phosphorylated Smad proteins in end-stage diseased aortas.[38,39] Below, we discuss studies using mouse models of thoracic aortic disease that have begun to resolve the complex molecular pathophysiology underlying onset and progression of arterial disease, in addition to emphasizing the need to preserve early TGFβ signaling to prevent aneurysm formation.

Initial Evidence Suggesting Excessive TGFβ Signaling Drives Thoracic Aortic Enlargement

TGFβ1, TGFβ2, and TGFβ3 (hereafter collectively referred to as TGFβ) are multifunctional signaling molecules that orchestrate a large variety of physiological processes, including SMC differentiation and ECM assembly and remodeling, in a context-specific manner.[40] TGFβ signals through receptor-induced phosphorylation of Smad2/3 proteins followed by formation, nuclear translocation, and binding of activated Smad2/3:Smad4 complexes to specific DNA targets in association with transcriptional activators or repressors (Figure 2). TGFβ can also signal through non-Smad (noncanonical) pathways, including those mediated by MAPKs (mitogen-activated protein kinases) that can transduce Ang II stimuli as well; additionally, TGFβ and Ang II pathways can interact with each other to modulate vascular tone and SMC phenotype (Figure 2).[4,41] Work by Habashi et al[27] originally showed that either TGFβ inhibition by a neutralizing antibody or At1r blockade by losartan prevented onset of thoracic aortic disease in *Fbn1*$^{C1039/+}$ mice. The authors interpreted these findings to indicate that aneurysm formation in MFS is the result of excessive TGFβ synthesis stimulated by heightened At1r signaling and compounded by uncontrolled activation of latent TGFβ improperly released from a fibrillin-1–deficient ECM.[27] Several lines of indirect evidence supported a causal relationship between TGFβ hyperactivity and aortic aneurysm onset. First, in vitro binding assays implied that fibrillin-1 can modulate TGFβ bioavailability through interaction with LTBPs (latent TGFβ-binding proteins) that bind and sequester the inactive (C-pro-domain associated) ligand in the ECM (Figure 2).[42] TGFβ hyperactivity was also reported in the diseased aortas of patients with heritable forms of thoracic aortic disease caused by mutations in genes encoding proteins not involved in modulating TGFβ bioavailability, such as fibulin-4 and the smooth muscle-specific isofoms of α-actin and myosin heavy chain.[43–45] Surprisingly, TGFβ hyperactivity was also reported in the diseased aortas of patients and mice with heterozygous loss-of-function mutations in genes encoding components of canonical TGFβ signaling pathway, such as ligands, receptors, and signal transducers.[38,39] Lastly, aneurysmal tissue and SMC cultures derived from patients with MFS had been shown to contain abnormally high levels of phosphorylated Smad2 due in part to TGFβ-independent epigenetic upregulation of the corresponding gene.[46] Hence, the proposal has been made of grouping together these genetically and clinically distinct disease under the rubric of TGFβ signalopathies, thus implying the possible use of a common anti-TGFβ pharmacotherapy.[47] It was, therefore, surprising when Holm et al[48] reported that aortic disease was dramatically augmented in *Fbn1*$^{C1039G/+}$ mice haploinsufficient for the obligatory TGFβ and BMP (bone morphogenetic protein) signal transducer Smad4.[48] Nonetheless, the authors concluded that TGFβ signaling through noncanonical signaling pathways is the predominant driver of

aneurysm formation in MFS because inhibition of Erk1/2 (extracellular signal–regulated kinase) or Jnk1 (Jun N-terminal kinase) mitigated arterial disease in *Fbn1*$^{C1039G/+}$ and *Fbn1*$^{C1039G/+}$;*Smad4*$^{-/-}$ mice, respectively.[48]

Emerging Evidence of an Alternative Role of TGFβ Signaling in Thoracic Aortic Disease

More recent studies of genetically engineered mice have substantially revised the original proposal of Habashi et al[27] that placed TGFβ central to the development of thoracic aortic disease. Neutralization of TGFβ signaling starting at postnatal day 16 in *Fbn1*$^{mgR/mgR}$ mice was in fact found to accelerate rather than mitigate aneurysm formation, thus leading to earlier dissection and death of these MFS mice.[49] Similarly, the studies by Li et al[50], Hu et al[51], and Wei et al[52] have independently demonstrated that genetic inhibition of TGFβ signaling via postnatal *Tgfbr2* gene inactivation in SMCs of newborn *Fbn1*$^{C1039G/+}$ mice worsened rather than mitigated thoracic aortic disease, as originally reported.[27] Surprisingly, phosphorylated Smad2 and Erk1/2 levels were not increased in the dilating aortas of young *Fbn1*$^{C1039G/+}$ mice.[52] The additional finding that SMC-specific *Tgfbr2* inactivation in young wild-type mice promoted aneurysm formation and dissection has demonstrated that TGFβ signaling is required for postnatal aortic growth and homeostasis.[50,51] TGFβ2 is likely to be the signaling molecule required for normal development of the aorta because haploinsufficiency of this ligand causes thoracic aortic aneurysm in both humans and mice.[39,53] *Tgfbr2* inactivation has been casually related to perturbed SMC contractility, IGF1 (insulin-like growth factor) production by adventitial fibroblasts, and altered paracrine cross talk between the medial and outer compartments of the vessel wall.[50] Of note, inhibition of mTOR (mammalian target of rapamycin) signaling eliminated the risk of dissection in mice with *Tgfbr2* inactivation by restoring SMC differentiation and quiescence. By demonstrating that TGFβ signaling protects from thoracic aortic disease in MFS and wild-type mice, these genetic studies have called into question the proposed use of anti-TGFβ therapies as a common treatment of thoracic aortic aneurysms, particularly when it applies to the pediatric population.[47]

Differences in selectivity or efficacy of genetic versus serological TGFβ blockade were advocated to reconcile the opposite outcomes of the earlier and more recent studies of thoracic aortic disease in *Fbn1*$^{C1039G/+}$ mice.[50] However, this explanation has been refuted by the finding that either TGFβ neutralization in either the newborn *Fbn1*$^{mgR/mgR}$ mice or adult wild-type mice infused with Ang II increased aneurysm severity.[49,54] Furthermore, the opposite effects of neonatal TGFβ neutralization (detrimental) and neonatal losartan treatment (beneficial) on arterial disease progression in *Fbn1*$^{mgR/mgR}$ mice disproved the original postulate that TGFβ acts as a mediator of At1r hyperactivity in promoting aneurysm formation.[49] The additional finding that starting TGFβ neutralization soon after completion of vascular growth (postnatal day 45) decreased the rate of aortic enlargement and improved median survival of *Fbn1*$^{mgR/mgR}$ mice implied a pathogenic role for TGFβ signaling later in aneurysm progression.[49] As it should always be the case, genetic experiments are still needed to independently corroborate the pharmacological evidence suggesting that TGFβ

hyperactivity is a secondary driver of maladaptive tissue remodeling in advanced stages of thoracic aortic disease in MFS.

The proposed dual, contextual role of TGFβ signaling during thoracic aortic disease progression resembles what happens in the many types of cancer, in which TGFβ acts as tumor suppressor in the early stages of a malignancy and as a prometastatic factor at later stages of the disease.[55] Recent work using non–small-cell lung carcinoma as a model system has implicated Smad2 inhibition by molecular chaperone CCT6A (chaperonin containing TCP1 subunit 6A) in switching TGFβ-stimulated gene expression to a prometastatic program.[56] Similar stage-specific mechanisms may diversify TGFβ action in thoracic aortic disease. For example, prevention of aneurysmal dissection and premature death of *Fbn1*$^{mgR/mgR}$ mice lacking Ltbp3 might be accounted for by selective association of this ECM protein with the TGFβ isotype(s) responsible for detrimental signaling driving late stages of thoracic aortic disease.[57] Conversely, association of Ltbp3 with a disease-preventing TGFβ (most likely TGFβ2[39]) might be responsible for aortic disease in human and mice with Ltbp3 deficiency.[57,58] Alternatively, this epistatic effect might reflect an unsuspected involvement of Ltbp3 in ECM assembly and vascular homeostasis, similar to the role Ltbp4 plays in lung elastogenesis.[59] This alternative explanation is in line with the distribution of *LTBP3* mutations predisposing to thoracic aortic disease in protein domains other than the one that binds pro-TGFβ dimers.[58] Neonatal deletion of each of the 3 TGFβ isotypes in MFS mice before and after aneurysm formation is expected to validate this hypothetical mechanism. Similar experiments could also test the potential involvement of TGFβ receptors and transducers in signal diversification. Irrespectively, it is clear from all these studies that TGFβ hyperactivity is a secondary driver of thoracic aortic disease, largely associated with promoting and sustaining maladaptive vessel wall remodeling.

Emerging Ang II Controversies

Although it is well established that augmented Ang II signaling is a prominent determinant of both thoracic and abdominal aortic aneurysm development,[4,60–62] there are also significant differences and emerging controversies about the source of increased Ang II signaling in various mouse models of aneurysms. Current evidence suggests that different mechanisms increase Ang II signaling in various genetic forms of thoracic aortic disease. For example, Ang II signaling is potentiated by upregulating angiotensin-converting enzyme levels in the aorta of mice with SMC-specific loss of fibulin-4 (*Fbln4*^{SMKO} mice). In contrast, NFκB (nuclear factor kappa-light-chain-enhancer of activated B cells)-dependent At1ar overexpression potentiates Ang II signaling in mice deficient for smooth muscle α-actin (*Acta2*$^{-/-}$ mice).[63,64] It would be interesting to determine whether these 2 mechanisms reflect the distinct nature of the genetic lesion driving aneurysm formation (ECM versus contractile unit impairment). Another unresolved important issue is how angiotensin-converting enzyme augmentation translates into a narrow postnatal window of losartan sensitivity in the dilated aorta of *Fbln4*^{SMKO} mice.[63]

The recent finding that genetic inactivation of At1ar in *Fbn1*$^{C1039G/+}$ mice does not mitigate aneurysm formation has raised the intriguing possibility that losartan might exert its therapeutic effects independently of the targeted receptor.[65] Based on losartan inactivation

by NOS (NO synthase) inhibition and eNOS (endothelial NOS) protection from aneurysm formation in *Fbn1*$^{C1039G/+}$ mice,[66] Sellers at al[65] have concluded that endothelial NO release may mediate this losartan off-target effect, thus implying a significant role of endothelial dysfunction in aneurysm progression. In contrast to these findings, mitigated aneurysm formation in *Fbn1*$^{mgR/mgR}$ mice with either germ line or endothelial At1ar inactivation has implied that receptor signaling is a prominent arterial disease determinant likely to perturb normal intima-to-media communication.[67] At2r (angiotensin II type II receptor) role in thoracic aneurysm formation is also controversial. On one hand, *Fbn1*$^{C1039G/+}$ mice lacking At2r have a significantly reduced response to losartan, suggesting that the beneficial effect of At1r antagonism is, in part, mediated by shunting Ang II activity through protective At2r signaling.[68] On the other hand, the comparable aortic phenotypes of losartan-treated *Fbn1*$^{C1039G/+}$ mice with or without At1ar have excluded the predicted shift toward At2r signaling in the latter group of mutant animals.[65] Furthermore, thoracic aortic disease pathology was not reversed after short-term treatment of *Fbn1*$^{C1039G/+}$ mice with the At2r agonist C21.[69] Because At1ar antibodies are unavailable to monitor receptor dynamics during aneurysm formation and growth, combinatorial deletions of angiotensin receptor genes in mice treated with various receptor agonists and antagonists should eventually resolve these discrepancies.

Other Pathogenic Pathways and Potential New Therapies for Thoracic Aortic Disease

The above studies, together with an evergrowing list of treatments reported to modify thoracic aortic disease in MFS mice (Table 1), clearly indicate that arterial disease involves the gradual stratification of stress-stimulated interactions among different cell types and multiple regulatory pathways, of which At1r- and TGFβ-signaling pathways are an important subset.[70,71] It follows that combinatorial drug treatments are likely to be required to more effectively slow down aneurysm progression or even prevent disease onset. Below are discussed a few examples of potential new treatments identified by studies of thoracic aortic disease in mouse models of MFS.

Inhibition of NOS, specifically Nos2, has recently emerged as an attractive therapeutic strategy against both syndromic and nonsyndromic forms of thoracic aortic disease. A combination of genetic and pharmacological approaches has causally connected thoracic aneurysm development with augmented Nos2 activity in the media of *Fbn1*$^{C1039G/+}$ mice.[66] Phenotypic similarities between these and Adamts1 (a disintegrin and metalloproteinase with thrombospondin motifs 1)-deficient mice were interpreted to suggest that a decrease of the metalloproteinase in the MFS aorta may lead to excessive accumulation of its substrates with the result of stimulating Nos2 through Akt and NFκB signaling and of promoting Mmp9 (matrix metalloproteinase-9)-driven medial degeneration through NO overactivation. In support of this disease model, elevated Nos2 and decreased Adamts1 levels were also noted in aneurysmal specimens from patients with MFS. NO involvement in MFS pathogenesis should be confirmed using the more severe mouse model of the disease (*Fbn1*$^{mgR/mgR}$ mouse) because improved survival is a more informative surrogate parameter of thoracic aortic disease severity than modifications in the rate of aortic dilation and in the

degree of aortic tissue degeneration. As an illustrative example of this point, genetic disruption of IL6 (interleukin 6)-STAT3 (signal transducer and activator of transcription 3) signaling in *Fbn1*$^{mgR/mgR}$ mice was reported to decrease vascular fibrosis and Mmp9-mediated elastin degradation (2 key histopathologic evidence of arterial disease) without improving animal survival.[72] Because a gain-of-function mutation in the type I cGMP (cyclic guanosine monophosphate)-activated protein kinase—an NO target in SMCs—causes thoracic aortic disease by decreasing SMC contractility,[73] it would also be informative to determine whether disruption of the contractile unit is associated with dysregulated NO signaling in other mouse models of thoracic aortic disease.

Epigenetic analyses of *Fbn1*$^{C1039G/+}$ mice has potentially expanded the therapeutic options for thoracic aortic disease in MFS and related diseases. It has recently been shown that the methyltransferase EZH2 (enhancer of zeste homolog 2) is responsible for inhibiting Smad3-binding sites to the first intron of the gene coding for SM22α—an early marker of SMC differentiation.[74] Importantly, targeting the chromatin modifier with a small molecule inhibitor restored expression of the contractile protein and alleviated arterial pathology in *Fbn1*$^{C1039G/+}$ mice. The same investigators have subsequently identified the same epigenetic pathway promoting SMC dysfunction because of pathogenic variants in 2 other genes causative for thoracic aortic disease.[75] They have also connected this pathway with the assembly of an HDAC9-MALAT1-BRG1 (histone deacetylase 9-metastasis associated lung adenocarcinoma transcript 1-Brahma-related gene 1)–repressing complex on the promoters of genes encoding contractile proteins.[75] Together, these studies support the possibility of using chromatin modifying factors as therapeutic targets in thoracic aortic disease resulting from various etiologies. Additionally, Fischbein et al[76] have found that increased expression of miR29b—a regulator of apoptosis and ECM remodeling—contributes to aneurysm onset and progression, as evidenced by the ability of miR29b blockade to significantly reduce aneurysm development. Although promising, development of pharmacotherapies that target either of these epigenetic programs exclusively in the dilating aorta needs to first resolve the notorious problems associated with site-specific delivery of such therapeutics.

A recent preclinical study in MFS mice has called into question a class of medications currently prescribed for some patients with MFS. In spite of limited clinical data about drug efficacy and safety in MFS, calcium channel blockers are usually given to afflicted individuals who are intolerant to β-blockers under the assumption that the drug would lower stress on the aortic wall during cardiac systole. Experimental and clinical data have led to conclude that calcium channel blockers aggravate thoracic aortic disease in *Fbn1*$^{C1039G/+}$ mice and increase aneurysmal growth and risk of dissection in patients with MFS.[77] The investigators have also reported that the deleterious effect of calcium channel blockers in MFS mice involves PKCβ (protein kinase C beta)-mediated Erk1/2 activation and that an antihypertensive drug (hydralazine) that inhibits activation of this pathway prevented aneurysm formation. Independent experimental confirmation of this important finding is needed, along with thorough clinical evaluation of all causes of thoracic aortic disease that might be negatively affected by treatment with this common antihypertensive drug.

Closing Remarks and Future Perspectives

By addressing old and new controversies, the studies discussed in this review have highlighted the molecular complexity of thoracic aortic disease onset and progression and consequently the significant challenges we still face to identify suitable new treatments. Although the losartan experience has cast some doubt on using experimental mice as a reliable model of human thoracic aortic disease, several new insights into cardiovascular disease gathered from the study of MFS mice make them the best experimental model currently available.[53,66,77,78] Induced pluripotent stem cells derived from patients with MFS and differentiated into vascular SMC have recently been used as an alternative model to interrogate thoracic aortic disease mechanisms.[79] These studies have corroborated and extended prior in vivo findings of TGFβ's pathological connection with MMP-driven maladaptive ECM remodeling and MAPK p38's contribution to arterial disease independent of TGFβ.[49,80] However, a major limitation of this in vitro model system is the lack of paracrine stress/regulatory stimuli from intima and adventitial cells that are involved in progression of thoracic aortic disease.[50,65,67]

In closing, we would like to offer a few suggestions for research directions that could be pursued to advance our understanding of thoracic aortic disease and that may eventually lead to better, evidence-based treatments. Although by necessity these suggestions reflect our own biases, we nonetheless offer them to stimulate a conversation among interested scientists and clinicians. The first and most important lesson we have learned from recent studies of thoracic aortic disease largely performed with MFS mice is that the notion of a common anti-TGFβ therapy for MFS and thoracic aortic disease in general is unwarranted, particularly in pediatric patients. In this respect, it would be productive to standardize and increase the number of surrogate markers for thoracic aortic disease progression so as to more rigorously compare data on varying treatments in different mouse models. Moreover, biomechanical analyses should be integral part of aortic disease characterization under different genetic lesions and pharmacological interventions. This suggestion stems from having recognized for many years that although patients with MFS have increased aortic stiffness particularly evident in individuals <40 years of age,[81] the data have been conflicted as to whether this stiffness is beneficial or not in terms aortic growth and risk for dissection. Despite the anti-inflammatory effects of Atr2, Ang II has an established role in driving fibrosis, including aortic stiffness associated with hypertension, and these fibrotic actions are linked to activation of TGFβ signaling.[82] Therefore, it is surprising that a recent follow-up study of the largest clinical trial assessing losartan versus atenolol in patients with MFS found that treatment with atenolol >3 years decreased baseline aortic root stiffness, whereas losartan did not.[29,83] This study also found that patients with MFS with higher baseline stiffness measurements had the fastest rate of growth of the aortic root. Although these results favor the use of β-blockers over Atr1 inhibition to prevent aortic growth in patients with MFS, it remains unclear why an Atr1 blocker failed to block aortic stiffness. Additionally, although lower aortic root stiffness was associated with slower growth rates of the root, how this impacts risk for aortic dissection is unknown. In other words, decreasing the aortic stiffness may decrease growth rates but increase the risk for dissection or rupture

because aortic fibrosis could potentially prevent these events. Biomechanical analyses in relevant mouse models should be used to address such questions.

The ultimate goal for any treatment for thoracic aortic disease is to prevent acute aortic dissections and its associated mortality and morbidity. Prophylactic aortic surgery to prevent aortic dissections is based largely on aortic dimensions >5 to 5.5 cm.[84] However, almost half of individuals presenting with acute ascending aortic dissections have aortic diameters <5.5 cm.[92] These findings emphasize the need to improve our understanding of the molecular pathways triggering dissections independent of aneurysm formation and identify therapeutics that block not just aortic enlargement but also acute aortic dissections. As illustrated in Table 2, the majority of preclinical trials have used *Fbn1*$^{C1039/+}$ mice, which develop aneurysms by 12 months of age but rarely progresses to dissection. Going forward, the more severe mouse model of the disease (*Fbn1*$^{mgR/mgR}$ mice) should be used for preclinical trials because it more faithfully replicates the natural history of thoracic aneurysm progression to dissection observed in individuals diagnosed with MFS.

Finally, the combination of computational and experimental approaches should be more extensively applied to the study of thoracic aortic disease pathophysiology. Although a few recent reports have included proteomic and transcriptomic profiles of aortic tissues from patients with MFS and mice,[67,74,93] none of them has used this information to computationally model the dynamics of rewiring networks of molecular signals during aneurysm progression to dissection. Computational methods can also be used to identify druggable nodes within disease-associated molecular networks, as exemplified by the successful identification of a new drug treatment for inflammatory bowel disease.[94] Our last suggestion is, therefore, to prioritize such computational studies according to standardized clinical and experimental surrogate readouts of thoracic aortic disease progression.

Although significant progress has been made during the past 20 years in our understanding of the molecular pathogenesis of thoracic aortic aneurysm, there are still limited therapeutic options to delay disease progression and none to prevent it. Therefore, it is imperative to build on the knowledge gained from the previous studies by improving our experimental tools and clinical analyses, as well as by fostering cross-communication between the bench and bedside. Hopefully, global collaborative efforts, like the recently revived GenTAC Alliance, will help move with the standardization. In addition, patient support organizations, like the Marfan Foundation, and John Ritter Foundation, and international patient registries, like the Montalcino Aortic Consortium[95–97] and BAV (bicuspid aortic valve) Consortium, [11,98] are poised to approach individuals with thoracic aortic disease for further clinical trials to prevent or delay disease progression.

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Nonstandard Abbreviations and Acronyms

Ang II	angiotensin II
At1r	angiotensin II type I receptor
At2r	angiotensin II type II receptor
ECM	extracellular matrix
eNOS	endothelial NO synthase
LTBP	latent transforming growth factor-β–binding protein
MAPK	mitogen-activated protein kinase
MFS	Marfan syndrome
NOS	NO synthase
SMC	smooth muscle cell
TGFβ	transforming growth factor-β

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Highlights

- Thoracic aneurysms have been managed with treatment with β-adrenergic blocking agents (β-blockers) and routine surveillance imaging, followed by surgical repair of the aneurysm when the risk of dissection exceeds the risk for repair. Thus, there is a window to initiate therapies to slow aortic enlargement and delay or ideally negate the need for surgical repair of the aneurysm to prevent a dissection.
- Mouse models of Marfan syndrome—a monogenic disorder predisposing to thoracic aortic disease—have been used extensively to identify such therapies.
- Initial experiments suggested that TGFβ (transformation growth factor-β) signaling was increased in the aortic media of a Marfan syndrome mouse model and that its inhibition via TGFβ neutralization or At1r (Ang II [angiotensin II] type I receptor) antagonism prevented aneurysm development.
- Subsequent studies in mouse models have begun to resolve the complex molecular pathophysiology underlying onset and progression of aortic disease and have emphasized the need to preserve TGFβ signaling to prevent aneurysm formation.
- This review describes critical experiments that have influenced the evolution of our understanding of the molecular pathogenesis of this disease and discusses the controversies and identifies new therapeutic opportunities.

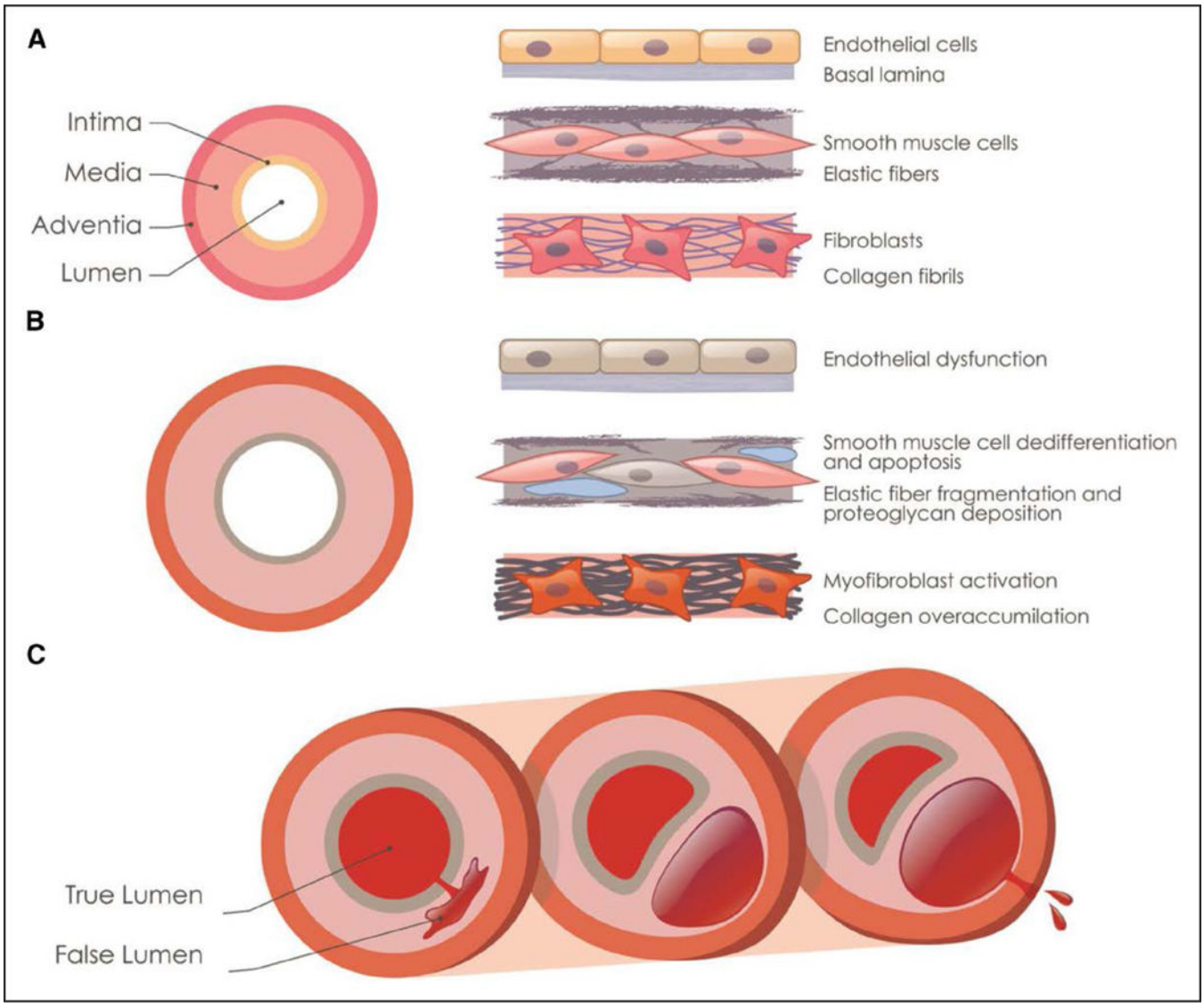

Figure 1.

Pathology and progression of thoracic aortic aneurysms and dissections. A, Schematic illustration of the cellular and ECM (extracellular matrix) components in the 3 layers of the thoracic aorta. **B**, Cellular and ECM changes associated with aneurysm progression are illustrated, including endothelial dysfunction, elastin fiber fragmentation and loss, increased proteoglycan accumulation (blue), and smooth muscle cell loss (gray cell). **C**, Illustration of an acute aortic dissection because of a tear in intimal layer, progressing through the medial layer to form a false lumen and rupturing from the false lumen through the adventitial layer.

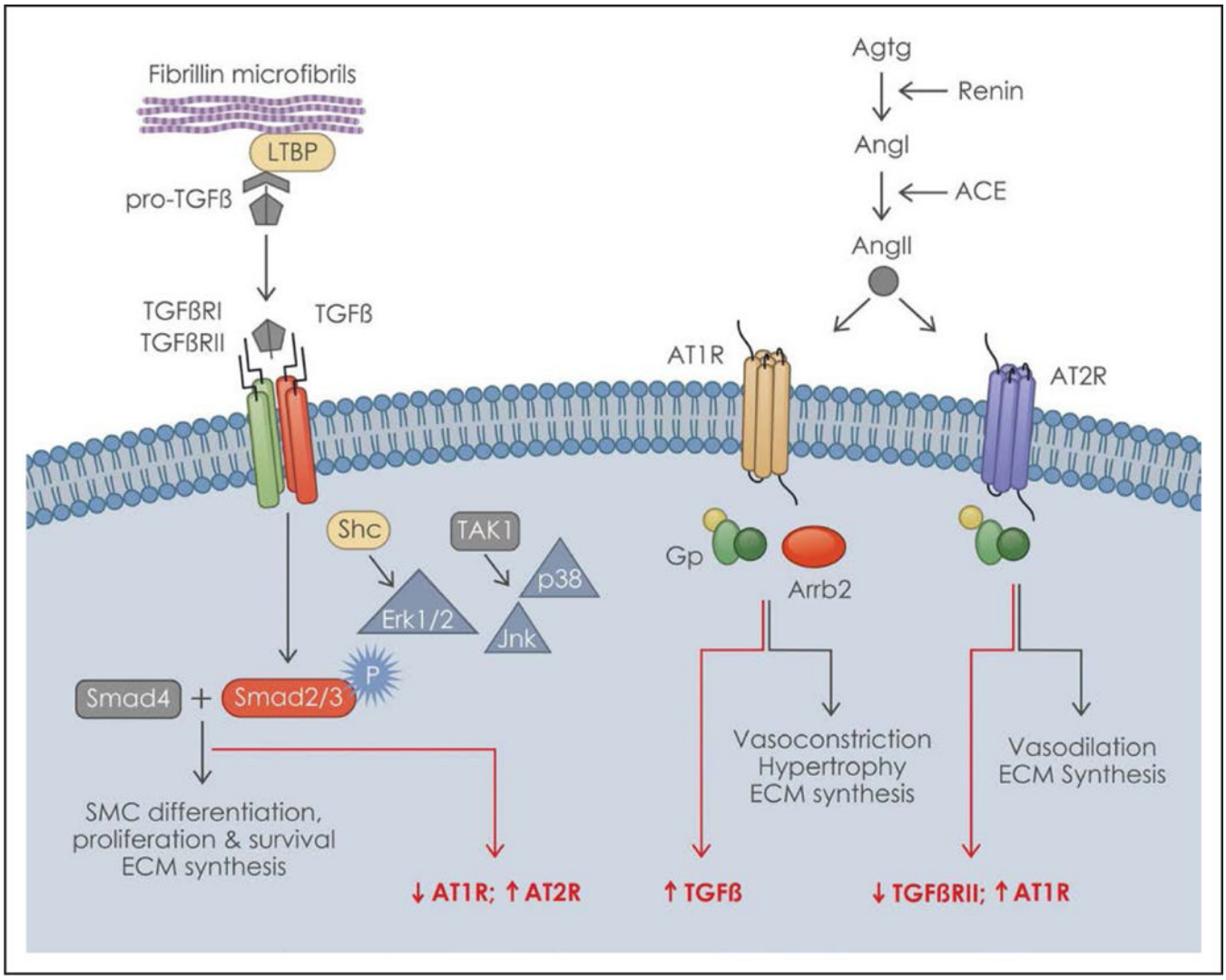

Figure 2.

TGFβ (transformation growth factor-β) and angiotensin signaling pathways. Depicted on the (**left**) and (**right**) are the TGFβ- and Ang II (angiotensin II)-signaling pathways, respectively, and their effects on aortic homeostasis. The interaction of the latent TGFβ complex with the extracellular fibrillin-containing microfibrils is shown outside the cell, whereas the interaction between TGFβ canonical (Smad) and noncanonical (MAPKs [mitogen-activated protein kinases]) signaling pathways is shown within the cell. Some of the regulatory interactions between the TGFβ and Ang II pathways are indicated in red. Ang I indicates angiotensin I; Arrb2, beta-arrestin-2; AT1R, angiotensin II type I receptor; AT2R, angiotensin II type II receptor; ECM, extracellular matrix; Erk1/2, extracellular signal–regulated kinase; Jnk, Jun N-terminal kinase; LTBP, latent TGFβ-binding protein; Shc, Src homology and collagen family of docking proteins; SMC, smooth muscle cell TAK1, TGFβ-activated kinase; TGFβRI, TGFβ receptor type I; and TGFβRII, TGFβ receptor type II. Modified from Yu and Jeremy with permission.[4] Copyright ©2018, the Authors.

Table 1.

Randomized Clinical Trials of Losartan in Marfan Syndrome*

Trial Name	Trial Type	Drugs Tested	Dose Range	No. Enrolled	Enroll Age, y	Follow-Up, y	Primary Outcome	Results	Notes
Pediatric Heart Network[28,29]	Double blind, stratified	Atenolol	0.5–4.0 mg/kg per d	608	0.5–25	3.0±0.1	Rate of change in root *Z* score per year	Not significant (*P*=0.08)	*FBN1* sequencing and pharmacogenomics studies pending
		Losartan	0.4–1.4 mg/kg per d						
COMPARE[33]	Open label	Losartan	50 or 100 mg/d	233	>18	3.1±0.4	Change in absolute root diameter	*P*=0.014	Significant only in individuals with *FBN1* haploinsufficiency mutations
		No additional drug							
Spanish[31]	Double blind	Atenolol	25–100 mg/d	140	5–60	3.0	Change in absolute diameter or *Z* score of root and ascending aorta	Not significant (*P*=0.193)	Ambulatory blood pressures were not different between groups
		Losartan	25–100 mg/d						
Marfan Sartan[30]	Double blind	Losartan	50 or 100 mg/d	299	>10	3.5	Rate of change in root *Z* score per year	Not significant (*P*=0.36)	100% sequenced and 78% had *FBN1* mutations
		Placebo							
Taiwanese[34]	Open label	Losartan+BB	Losartan: 25–100 mg/d or 0.7 mg/kg per d to 50 mg/d	29				*P*=0.02	
			BB: 50 mg atenolol/20 mg propranolol or 1 mg/kg per d						
		BB	Any dose <150 mg/d or <2 mg/kg/d						
		Placebo							
Ghent Marfan Trial[35]	Double blind, stratified	Losartan+BB	Losartan: 50 or 100 mg/d	22	>10	3	Rate of change in absolute root diameter or *Z* score per year	Not significant	
		Placebo+BB	mg/d BB: NA						

BB indicates β-blocker; COMPARE, Cozaar in Marfan Patients Reduces Aortic Enlargement; and NA, not available.

*All studies included the modified Ghent criteria as an inclusion criterion.

Table 2.

Treatment Trials in Mouse Models of Marfan Syndrome

MFS Model	Treatment	Dilation	Histopathology	Dissection	Study
Fbn1$^{C1039G/+}$	TGFβ blockade	+	+		Habashi et al, 2006[27]
	At1r antagonism	+	+		
	β-blockers	0	0		
	ErK inhibition	+	ND		Holm et al, 2011[48]
	At2r agonism	0	0		Verbrugghe et al, 2018[69]
	NO inhibition	+	+		Oller et al, 2017[66]
	EZH2 inhibition	+	+		Lino Cardenas et al, 2018[75]
	EZH2 inhibition+AT1r antagonism	+	0		
	miR29 blockade	+	+		Merk et al, 2012[76]
	Ca^{+2} channel blockade	−	−	−	Doyle et al, 2015[77]
	Statins	+	+		McLoughlin et al, 2011[85]
	Resveratrol	+	+		Hibender et al, 2016[86]
	MMP inhibition	+	+		Chung et al, 2008[87]
	Moderate exercise	+	0		Mas-Stachurska et al, 2017[88]
	Caspase inhibition	+	+		Enrich et al, 2015[89]
Fbn1$^{MgR/MgR}$	At1r antagonism	+	+	Delayed	Cook et al, 2015[49]
	Early TGFβ blockade	−	−	Accelerated	
	Late TGFβ blockade	+	+	Delayed	
	AT1r+late TGFβ blockade	+	+	Prevented	
	MMP inhibition	+	+	Delayed	Xiong et al, 2008[90]
	Indomethacin	ND	+	ND	Guo et al, 2013[91]

Symbols indicate that thoracic aortic disease was mitigated (+), exacerbated (−), or unchanged (0) with the treatment. At1r indicates angiotensin II type I receptor; At2r, angiotensin II type II receptor; ERK, extracellular signal–regulated kinase; EZH2, enhancer of zeste homolog 2; MFS, Marfan syndrome; MMP, matrix metalloproteinase; ND, not determined; and TGFβ, transformation growth factor-β.