Marfan syndrome (MFS) is characterized by mutations in the fibrillin-1 gene and dysregulation of transforming growth factor-β (TGFβ) signaling, which is phenotypically associated with gradual weakening of connective tissue throughout the body, including the lungs, bones and cardiovascular system. A primary cause of mortality in MFS patients reaching adolescence or adulthood is aortic rupture or dissection. Surgery is generally performed to remove the affected portion of the aorta, but more than half of patients who have had their aortas repaired require additional surgery or manifest aortic rupture because of expansion of the unrepaired regions of the aorta over time. At present, measures to identify patients exhibiting progressive expansion or re-expansion of the aorta after surgery is a topic of importance. On medical therapy, β-blockers have been historically used as the anchoring agent. The renin-angiotensin system (RAS) has also recently been implicated in the pathogenesis of Marfan aortopathy, with initial experiments showing prevention of aortic root expansion in a mouse model of MFS using RAS blockade, which was followed by studies in human patients that showed similar results. These findings were welcomed with enthusiasm as a pharmacological solution for MFS, and have prompted several human clinical trials, which are presently ongoing to determine the possible benefit of RAS blockade in aortopathy in MFS patients. TGFβ signaling has also received attention as a key factor in the aortopathy of MFS patients, as not only the canonical regulatory pathway involving downstream Smad proteins but also a non-canonical pathway involving ERK and JNK kinases has been recently described as implicated in MFS pathology upon activation of the TGFβ pathway. Moreover, circulating levels of TGFβ have received attention because they are not only elevated in patients with MFS aortopathy but are also responsive to pharmacological treatment, thus suggesting their possible use as a sur-

**Figure.** Proposed mechanism whereby transforming growth factor β (TGFβ) affects Marfan aortopathy. Fibrillin-1 (FBN1) gene mutation triggers TGFβ signaling activation, which in turn mediates cystic medial necrosis by smooth muscle cell apoptosis and extracellular matrix degradation. Circulating TGFβ levels may reflect TGFβ signaling activation in the aortic wall.
which is of clinical importance. The present study showed a
levels are truly associated with dilation of the aorta,
\[\text{TGF}\beta\]
sampling). One is that it is still unclear is whether circulating

Another feature of the present study is the patient cohort.
more severe cystic medial degradation, and increased circulating or aortic
\[\text{TGF}\beta\]
levels had been reported.\(^9\) MFS patients with aortic dissection were also shown to exhibit more severe
cystic medial degradation, and increased circulating or aortic
\[\text{TGF}\beta\]
levels. Although this finding is descriptive and not necessarily causal, it describes an association between the severity of aortic remodeling and circulating \[\text{TGF}\beta\] levels.

Several issues remain unanswered in the application, in the real world, of circulating \[\text{TGF}\beta\] levels as a surrogate biomarker to monitor disease activity or therapeutic efficacy in MFS or other aortopathic patients, in addition to the technical difficulties that lead to false-positive results (eg, method of blood sampling). One is that it is still unclear is whether circulating \[\text{TGF}\beta\] levels are truly associated with dilatation of the aorta, which is of clinical importance. The present study showed a
dilated aorta with an average width of 59 mm at the sinus of Valsalva regardless of circulating \[\text{TGF}\beta\] levels. Lack of correlation between the z value (an indicator of aortic root expansion) and circulating \[\text{TGF}\beta\] level, despite reduction in the level by pharmacological intervention, has also been reported.\(^8\) Another issue is the need to better understand the relative contribution of \[\text{TGF}\beta\] and its downstream signaling molecules in aneurysmal formation in the Marfan aorta.

Collectively, circulating \[\text{TGF}\beta\] levels may be associated with progression of aortic remodeling as reflected by activated Smad (phosphorylation) protein on histopathologic analysis. Importantly, however, other mechanisms, including Smad-independent pathways and/or inflammatory processes, might also contribute to clinical aneurysmal dilatation, rupture or dissection.\(^3\)

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References