Commentary: Of mice and Marfan

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Hereditary aortic pathology is typically characterized by destructive extracellular matrix remodeling. For Marfan syndrome (MFS), an autosomal dominant connective tissue disorder, the principal mutation in the fibrillin gene (*FBN1*) on chromosome 15 leads to dysregulated elastic fiber homeostasis with variable phenotypic expression but highly penetrant thoracic aortic disease. Murine models that have been developed to recapitulate the dominant negative effects of *FBN1* deletion have shown a complex interplay between angiotensin II (ANGII) and transforming growth factor- β (TGF- β) signaling. Although these murine models have identified promising targets, translation to clinical use has not materialized, suggesting that further studies are needed to elucidate the mechanisms behind MFS-induced aortic disease and cardiomyopathy. The FbnC1039G/+ mouse has been widely used to study MFS, but this model is hampered by the length of time (months) it takes for manifestations of cardiovascular disease. In this issue of *The Journal of Thoracic and Cardiovascular Surgery*, Gensicke and colleagues¹ have attempted to validate their accelerated (weeks) murine model of MFS by examining well-established signaling pathways in MFS.

Gensicke and colleagues¹ used FbnC1039G/+ heterozygous mice on a B6.129 background supplemented with ANGII infusion to study the downstream effects in canonical (Smad 2) and noncanonical (ERK and P38) pathways. They found that RNA and protein expressions of downstream signaling in both pathways were exaggerated relative to control in cardiac and aortic tissue of MFS-model mice infused with ANGII. Furthermore, with the same model in an earlier study, this group found accelerated thoracic aortic disease with aneurysm formation in the course of 14 days and an almost 40% mortality.² In contrast, other murine models without ANGII infusion can take months for disease development.³ Although this study does provide an accelerated murine MFS model, there are 3 main points that bear mentioning when considering this it. First, while the control mice were derived

Shuab Omer, MD (left), and Darrell Wu, MD (right)

Central Message

An accelerated murine Marfan model can lead to expeditious insight into the mechanism of Marfan syndrome aortopathy and cardiomyopathy.

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from the embryonic cell line 129/sv, the strain was backcrossed with C57BL/6 mice for more than 9 generations; however, the phenotypic expression of aortopathy for B6.129 is different than for C57BL/6 background mice with *FBN* mutation with B6.129 mice having aortopathy develop earlier than C57BL/6 mice.⁴ Second, the dose of ANGII is many times higher than in sporadic murine models of aortic disease.⁵ This raises the question of whether the cause of aortopathy from supratherapeutic doses of ANGII is indicative of MFS or is even clinically relevant. Third, although their results indicate that there is overexpression of TGF- β downstream signaling pathways, it remains unclear whether the phosphorylated or activated form in both canonical and noncanonical pathways truly drives this process, since there was no difference between ANGII-infused MFS mice and MFS mice. Furthermore, the differential role of TGF- β in murine MFS aortopathy⁶ and the crosstalk between ANGII and TGF- β are complex and unclear.⁷

Nonetheless, establishment of a consistent, time-sensitive murine model that reproduces the cardiovascular manifestations of MFS allows rapid investigation into the molecular mechanisms of MFS. This investigation can lead to development of new therapeutic targets.

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