Local TGF-beta sequestration by fibrillin-1 regulates vascular wall homeostasis in the thoracic aorta

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Background: Aortic dissection and rupture is the main cause of early cardiovascular mortality in patients with Marfan syndrome (MFS). MFS is caused by a fibrillin-1 deficiency, which binds transforming growth factor beta (TGF-beta) via interaction with latent TGF-beta binding proteins (LTBPs). The role of TGF-beta in MFS has been controversial, with earlier studies suggesting that excess release of TGF-beta due to decreased interaction with dysfunctional fibrillin-1 leads to aortic dilation and vascular damage, while other studies have shown an important protective effect for TGF-beta. To further elucidate the role of TGF-beta, we studied the *in vivo* effects of disrupted sequestration of TGF-beta to fibrillin-1 in mouse models of MFS.

Methods: Mice lacking the fibrillin-1 binding site for LTBPs (*Fbn1*$^{H1D/+}$), mice with a truncated fibrillin-1 (*Fbn1*$^{GT\text{-}8/+}$), and mice with a combination of both alleles (*Fbn1*$^{GT\text{-}8/H1D}$) were subjected to *in vivo* cardiac ultrasound analysis. *Ex vivo* phase-contrast synchrotron X-ray imaging of the entire excised thoracic aorta was performed at the Paul Scherrer Institute.

Results: While *Fbn1*$^{GT\text{-}8/+}$ and *Fbn1*$^{H1D/+}$ mice had a normal life span, *Fbn1*$^{GT\text{-}8/H1D}$ mice showed increased mortality due to aortic rupture starting at 4-5 months of age. The Sinuses of Valsalva was dilated both in *Fbn1*$^{GT\text{-}8/+}$ and *Fbn1*$^{GT\text{-}8/H1D}$ mice at 6 months of age, but not in *Fbn1*$^{H1D/+}$ mice. Significant elastic lamellae fragmentation was observed in the thoracic aortic wall of *Fbn1*$^{GT\text{-}8/+}$ mice, and to a larger extent in *Fbn1*$^{GT\text{-}8/H1D}$ mice. Surprisingly, localized elastin fragmentation was also found in the ascending thoracic aorta of *Fbn1*$^{H1D/+}$ mice despite a lack of aneurysm development.

Conclusions: Our data indicate that loss of LTBP binding to fibrillin-1 leads to the development of localized microdissections in the absence of aortic aneurysm, and exacerbates the aortic wall morphology in mice with truncated fibrillin-1. We therefore hypothesize that local TGF-beta sequestration is required to maintain aortic homeostasis.