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Commentary

Increased TGF-β Signaling Precedes Aneurysm Formation in SMAD3 Deficient Mice

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Aortic aneurysm describes a pathological enlargement of the main vessel in the body, the aorta, which ultimately leads to dissection or rupture. Aortic dissection is a life-threatening event associated with a mortality of 1–2% per hour.

Over the past decade, the medical community has slowly accepted the idea that patients presenting with aortic aneurysms and dissections are part of a wide spectrum of genetically mediated diseases that present in syndromic as well a non-syndromic forms. Marfan syndrome (MFS) has long been the only seriously considered differential diagnosis in terms of a heritable disorder of connective tissue in patients with aortic aneurysm. MFS is an autosomal dominant disorder affecting about 1 in 5000 individuals. The phenotypic changes of MFS are imposed by mutations in the gene encoding for the extracellular matrix protein fibrillin-1 (Dietz et al., 1991). It has been shown that aneurysm formation in MFS is driven by excessive transforming growth factor-β (TGF-β) signaling through the "non-canonical" pathway via extracellular signal-regulated kinase (pERK) (Habashi et al., 2011; Holm et al., 2011). TGF-β is a ubiquitous cytokine in most mammalian cells and involved in cellular proliferation and differentiation.

Ten years ago Loeys and Dietz identified a subset of patients sharing certain features such as a bifid uvula, hypertelorism and marked tortuosity of the vessels that had not been typically associated with MFS. The group identified mutations in the gene encoding for the TGF-β receptors 1 and 2 as the causative mutation (Loeys et al., 2006; Loeys et al., 2005). Identifying Loeys-Dietz syndrome (LDS) as a separate entity was important as patients with LDS suffered from acute aortic dissection at aortic diameters that had not been considered a cut-off to proceed to surgery in MFS patients. Therefore, the diagnosis LDS carries immediate therapeutic consequences and has made genetic testing an important step in evaluating patients with aortic aneurysms for surgery. The initial patients were mostly children with a strong phenotype that had been referred to Loeys and Dietz since they clearly exhibited a syndromatic phenotype but did not fit other known aneurysm syndromes. Meanwhile the phenotype has broadened and it has been realized that e.g. a bifid uvula is not an essential feature in diagnosing LDS (Loeys et al., 2005).

In 2011, van de Laar and colleagues described a group of patients presenting with aortic aneurysms and early onset osteoarthritis (AOS) and identified a mutation in the gene encoding for SMAD3, a downstream regulatory protein of the TGF-β pathway as the causative mutation (van de Laar et al., 2011). Patients presenting with SMAD3 mutations have meanwhile been classified as being part of the LDS spectrum.

While it has been shown that TGF-β signaling in LDS patients is altered and results in an increased tissue signature for downstream molecular events, the mechanism that leads to aneurysm formation is less well established than in MFS. In their current study in *EBioMedicine*, van der Pluijm and colleagues present an important contribution to establish altered TGF-β signaling as the culprit of aneurysm formation in LDS using $Smad3^{-/-}$ mice that serves as a model for the recently described aneurysm-osteoarthritis syndrome, now referred to as type 3 Loeys-Dietz syndrome (van der Pluijm et al., 2016).

The authors saw a marked dilatation of the aorta in $Smad3^{-/-}$ mice at 6 weeks of age and report 65% mortality in male $Smad3^{-/-}$ mice at 3 months. The authors chose the $Smad3^{-/-}$ mouse model, as the functional consequences of heterozygous mutations seen in people with LDS are unclear. Nevertheless, data derived from mouse models for MFS, clearly show phenotypic and functional differences in animals carrying a heterozygous FBN1 mutation compared to hypomorphic (e.g. $Fbn1^{mgR/mgR}$) or $Fbn1^{-/-}$ mice. Although similarities are seen between the $Smad3^{-/-}$ mouse model and AOS/LDS3 this might raise the question to what extent a $Smad3^{-/-}$ mouse model will be able to recapitulate events seen in people with LDS type 3.

The authors show that pSMAD2 and pERK, markers of canonical and non-canonical TGF-β signaling are increased in tissue of $SMAD3^{-/-}$ mice before aneurysms develop. Although this is only observational data, it is further evidence for increased TGF-β signaling being the cause rather than the effect of aneurysm formation in LDS. The authors then examined the transcriptional response of vascular smooth muscle cells (VSMC) in $Smad3^{-/-}$ mice and saw a significantly impaired response compared to $Smad3^{+/+}$ mice. Furthermore, the authors observed markedly less accumulation of collagen and extracellular matrix (ECM) proteins than in other mouse models for aortic aneurysms.

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The authors speculate that this diminished ECM accumulation together with the altered transcriptional response of the VSMC triggers an immune response that leads to the structural failure they observed in aortas from Smad3$^{-/-}$ mice. Unfortunately, so far there is no experimental data that challenges parts of this proposed mechanism.

The authors compare their results with data derived from Fibulin-4$^{R/R}$ animals. While this is certainly interesting from a disease model point of view, there is very little known about the human phenotype. Since SMAD3 mutations are discussed in the context of LDS and given the phenotypic overlap with MFS, it might be interesting to extend the discussion including the well-characterized mouse models for MFS.

Disclosures

None.

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