Abstract

The extracellular matrix (ECM) provides a tissue specific microenvironment for resident cells that not only constitutes structural support, but also impacts cellular proliferation and differentiation by controlling growth factor bioavailability. The ECM glycoprotein fibrillin-1 assembles into fibrillin microfibrils, which play essential roles in elastogenesis and sequestration of TGF-β and BMP family members. Fibrillin-1 deficiency is causative for the Marfan syndrome, a multi-system connective tissue disorder with aortic root aneurysm formation and dissection as the most life-threatening clinical manifestations. Studies of aneurysm development in the *Fbn1GT8* Marfan mouse model revealed elevated BMP signalling and upregulated expression of sclerostin (SOST), a BMP and Wnt signalling inhibitor that was originally described to be involved in the regulation of bone formation.

To investigate the role of SOST in the aortic aneurysm formation caused by fibrillin-1 deficiency, the molecular interactions and functions of SOST, as well as the consequence of *Sost* ablation in *Fbn1GT8* Marfan mice, were assessed. The binding site of SOST was mapped to the N-terminal FUN-domain of fibrillin-1. Direct interactions of SOST with BMP growth factors (GFs), their prodomains (PDs), assembled complexes, and to itself were demonstrated. To exert its inhibitory function, it was shown that SOST competes with the BMP type II receptor for GF binding, facilitates PD displacement and reduces cellular uptake of the GF. Moreover, it was shown that the ECM component heparin interferes with SOST binding and thereby preserves active BMP PD-GF complexes in the extracellular space for subsequent signalling events.

Increased SOST levels were detected in male human patient samples and persistent upregulation of SOST was found in *Fbn1GT8* mouse aortas during postnatal life. Cell stimulation experiments revealed induced *SOST* expression upon BMP stimulation as well as induced *MMP9* and *MMP13* expression by SOST administration. Interestingly, echocardiography measurements and functional testing of the aorta revealed a complex role of SOST since a detrimental effect of *Sost* ablation on aortic dilatation, tension and passive stretching was already observed in $Sost^{-/-}$ mice, but no additive effects were found in $Fbn1^{+/GT8};Sost^{-/-}$ mice. Remarkably, immunofluorescence analysis demonstrated a pronounced positive effect of *Sost* ablation on the impaired endothelial integrity and decorin deposition in *Fbn1GT8* mice.

This study contributes to a better understanding of the aortic pathogenesis caused by fibrillin-1 deficiency. Moreover, the BMP inhibitor function of SOST and its potential role in thoracic aortic aneurysm formation was further investigated. A detailed understanding of the pathomechanisms in the course of aneurysm formation in Marfan syndrome is essential for future development of therapeutic interventions.