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EDITORIAL

Vascular alterations upon activation of TGFβ signaling in fibroblasts - implications for systemic sclerosis

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Abstract

Tissue fibrosis and vascular disease are hallmarks of systemic sclerosis (SSc). Transforming growth factor β (TGFβ) is a key-player in fibroblast activation and tissue fibrosis in SSc. In contrast to fibrosis, evidence for a role of TGFβ in vascular disease of SSc is scarce. Using a transgenic mouse model with fibroblast-specific expression of a kinase-deficient TGFβ receptor type II, Derrett-Smith and colleagues demonstrate that aberrant TGFβ signaling in fibroblasts might result in activation of vascular smooth muscle cells and architectural changes of the vessel wall of the aorta.

Using the TβRIIΔk-fib transgenic mouse model, Derrett-Smith and colleagues [1] analyzed a potential role of transforming growth factor β (TGFβ) signaling in the vascular pathogenesis of systemic sclerosis (SSc).

SSc is a chronic autoimmune disease that affects the skin and various internal organs. The most obvious histopathological alteration of SSc is an extensive accumulation of extracellular matrix [2]. The resulting fibrosis disrupts the physiological tissue structure and frequently leads to dysfunction of the affected organs. The accumulation of extracellular matrix in SSc patients is caused by activated fibroblasts [3]. In addition to fibrosis, vascular changes are a major hallmark of SSc. These may be classified into a destructive- and a proliferative vasculopathy. The destructive vasculopathy affects small vessels and manifests early in the course of SSc as progressive loss of capillaries and insufficient angiogenesis. The clinical correlates of the destructive vasculopathy are Raynaud's phenomenon and fingertip ulcers. In contrast, the proliferative vasculopathy is characterized by proliferation of vascular cells with obstruction of the lumen, affects larger vessels like the pulmonary arteries and often manifests later in the course of the disease as pulmonary arterial hypertension [2].

The key-role of TGFβ in fibrosis is well established as TGFβ signaling is activated in SSc. Activated TGFβ signaling stimulates the release of collagen in cultured fibroblasts and overexpression of a constitutively active TGFβ receptor type I in fibroblasts results in progressive fibrosis [3]. Moreover, inhibition of TGFβ signaling exerted potent anti-fibrotic effects in different pre-clinical models of SSc [4].

In contrast to fibrosis, only few data suggest a role of TGFβ in the vascular pathogenesis of SSc. First data from mouse models suggest that aberrant TGFβ signaling might not result in only fibrosis, but also in vascular alterations. Vascular changes have been described in several models with activated TGFβ signaling, such as caveolin-1 knockout mice and fos-related antigen (Fra-2) transgenic mice [5-8]. However, apart from Fra-2 transgenic mice, the type of vessels involved and the histological changes differ from those observed in human SSc.

Derrett-Smith and colleagues describe macrovascular changes in the thoracic aorta with altered gene expression in vascular smooth-muscle cells (vSMCs) in TβRIIΔk-fib mice [1]. TβRIIΔk-fib mice selectively express a kinase-deficient TGFβ receptor type II (TβRIIΔk) in fibroblasts under a fibroblast-specific pro-α2(I) collagen promoter [9]. Although overexpression of the kinase-deficient TβRIIΔk construct interferes with TGFβ signaling in cultured fibroblasts *in vitro*, TβRIIΔk transgenic mice are characterized by activated TGFβ signaling and develop dermal and pulmonary fibrosis. The molecular mechanism underlying this paradoxical activation of TGFβ signaling in TβRIIΔk transgenic mice is incompletely characterized. Potential explanations include upregulation of wild-type TβRII and TGFβ1 [9]. The authors observed signs of activated TGFβ signaling in the aortas

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of TβRIIΔk-fib mice with increased expression of latency-associated peptide-TGFβ1 (LAP-TGFβ1) and TGFβ1 in the adventitia and accumulation of phosphorylated Smad 2/3. Of note, TGFβ signaling was not restricted to fibroblasts, but was also observed in other cell types, such as smooth muscle cells. Consistent with activated TGFβ signaling, the collagen content of the thoracic aorta was increased and the adventitial and the smooth muscle cell layers were thickened. These changes were functionally relevant and resulted in increased vascular stiffness. The contractility of isolated aortic rings upon incubation with KCl, α-adrenoreceptor agonists or thromboxane analogues was reduced in TβRIIΔk-fib mice. Surprisingly, a partial TGFβ gene signature and increased contractility was also observed *in vitro* in early passage cultured aortic vSMCs, even though the TβRIIΔk transgene was not detectable in vSMCs [1].

Although the authors elegantly demonstrate vascular alterations in TβRIIΔk-fib mice, additional studies are needed to establish increased TGFβ signaling in fibroblasts as a molecular mediator of the vascular disease in SSc. The molecular mechanisms by which the expression of the kinase-deficient TβRIIΔk construct in fibroblasts activates TGFβ signaling in other cell types such as vSMCs are poorly understood. Thus, confirmation of the altered phenotype of vSMCs in other models with fibroblast-specific activation of TGFβ signaling such as $T\beta RI^{CA}$ Cre-ER mice would be important and might provide further mechanistic insights [10]. Furthermore, localization and the kinds of vascular changes in TβRIIΔk-fib mice and also in most other animal models differ from those in SSc patients. Derrett-Smith and coauthors describe vascular changes in the aorta of TβRIIΔk-fib mice. However, the clinically relevant vascular manifestations in SSc affect the pulmonary arteries and the smaller vessels. Moreover, the histological changes described in TβRIIΔk-fib mice do not resemble the features of the destructive or proliferative vasculopathy in SSc. Does altered TGFβ signaling in fibroblasts also result in alterations of the pulmonary arteries, the small arteries and the capillaries and do the histological changes in these vessels resemble those observed in human SSc more closely? The demonstration of typical SSc-like changes in these vessels would further strengthen the importance of TGFβ signaling in the vascular pathology of SSc.

Abbreviations

SSc = systemic sclerosis; TβRII = TGFβ receptor type II; TβRIIΔk = kinase-deficient TGFβ receptor type II; TGF = transforming growth factor; vSMC = vascular smooth-muscle cell.

Competing interests

The authors declare that they have no competing interests.

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