

**EDITORIAL**

# Vascular alterations upon activation of TGF $\beta$ 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  $\beta$  (TGF $\beta$ ) is a key-player in fibroblast activation and tissue fibrosis in SSc. In contrast to fibrosis, evidence for a role of TGF $\beta$  in vascular disease of SSc is scarce. Using a transgenic mouse model with fibroblast-specific expression of a kinase-deficient TGF $\beta$  receptor type II, Derrett-Smith and colleagues demonstrate that aberrant TGF $\beta$  signaling in fibroblasts might result in activation of vascular smooth muscle cells and architectural changes of the vessel wall of the aorta.

Using the T $\beta$ RII $\Delta$ k-fib transgenic mouse model, Derrett-Smith and colleagues [1] analyzed a potential role of transforming growth factor  $\beta$  (TGF $\beta$ ) 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 TGF $\beta$  in fibrosis is well established as TGF $\beta$  signaling is activated in SSc. Activated TGF $\beta$  signaling stimulates the release of collagen in cultured fibroblasts and overexpression of a constitutively active TGF $\beta$  receptor type I in fibroblasts results in progressive fibrosis [3]. Moreover, inhibition of TGF $\beta$  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 TGF $\beta$  in the vascular pathogenesis of SSc. First data from mouse models suggest that aberrant TGF $\beta$  signaling might not result in only fibrosis, but also in vascular alterations. Vascular changes have been described in several models with activated TGF $\beta$  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 T $\beta$ RII $\Delta$ k-fib mice [1]. T $\beta$ RII $\Delta$ k-fib mice selectively express a kinase-deficient TGF $\beta$  receptor type II (T $\beta$ RII $\Delta$ k) in fibroblasts under a fibroblast-specific pro- $\alpha$ 2(I) collagen promoter [9]. Although overexpression of the kinase-deficient T $\beta$ RII $\Delta$ k construct interferes with TGF $\beta$  signaling in cultured fibroblasts *in vitro*, T $\beta$ RII $\Delta$ k transgenic mice are characterized by activated TGF $\beta$  signaling and develop dermal and pulmonary fibrosis. The molecular mechanism underlying this paradoxical activation of TGF $\beta$  signaling in T $\beta$ RII $\Delta$ k transgenic mice is incompletely characterized. Potential explanations include upregulation of wild-type T $\beta$ RII and TGF $\beta$ 1 [9]. The authors observed signs of activated TGF $\beta$  signaling in the aortas

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of T $\beta$ R11 $\Delta$ k-fib mice with increased expression of latency-associated peptide-TGF $\beta$ 1 (LAP-TGF $\beta$ 1) and TGF $\beta$ 1 in the adventitia and accumulation of phosphorylated Smad 2/3. Of note, TGF $\beta$  signaling was not restricted to fibroblasts, but was also observed in other cell types, such as smooth muscle cells. Consistent with activated TGF $\beta$  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,  $\alpha$ -adrenoreceptor agonists or thromboxane analogues was reduced in T $\beta$ R11 $\Delta$ k-fib mice. Surprisingly, a partial TGF $\beta$  gene signature and increased contractility was also observed *in vitro* in early passage cultured aortic vSMCs, even though the T $\beta$ R11 $\Delta$ k transgene was not detectable in vSMCs [1].

Although the authors elegantly demonstrate vascular alterations in T $\beta$ R11 $\Delta$ k-fib mice, additional studies are needed to establish increased TGF $\beta$  signaling in fibroblasts as a molecular mediator of the vascular disease in SSc. The molecular mechanisms by which the expression of the kinase-deficient T $\beta$ R11 $\Delta$ k construct in fibroblasts activates TGF $\beta$  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 TGF $\beta$  signaling such as T $\beta$ R1<sup>CA</sup> Cre-ER mice would be important and might provide further mechanistic insights [10]. Furthermore, localization and the kinds of vascular changes in T $\beta$ R11 $\Delta$ k-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 T $\beta$ R11 $\Delta$ k-fib mice. However, the clinically relevant vascular manifestations in SSc affect the pulmonary arteries and the smaller vessels. Moreover, the histological changes described in T $\beta$ R11 $\Delta$ k-fib mice do not resemble the features of the destructive or proliferative vasculopathy in SSc. Does altered TGF $\beta$  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 TGF $\beta$  signaling in the vascular pathology of SSc.

#### Abbreviations

SSc = systemic sclerosis; T $\beta$ R11 = TGF $\beta$  receptor type II; T $\beta$ R11 $\Delta$ k = kinase-deficient TGF $\beta$  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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