

## **Abstract**

Systemic sclerosis (SSc) is immune-mediated fibrotic disease of unknown aetiology. Among the dominant pathogenic manifestations of SSc belong vascular changes, production of autoantibodies, activation of innate and adaptive immune responses and fibrotic processes. Transforming growth factor beta (TGF- $\beta$ ) has been identified as a central profibrotic factor stimulating fibroblasts to produce collagen. There are, however, a number of other mediators involved in the pathogenesis of SSc. Mutual activation and amplification of these molecules and their cascades may be a central mechanism of the SSc pathogenesis. Hedgehog (Hh) canonical signalling pathway plays an important role in the development and progression of fibrotic diseases. Expression of Hh target genes can be regulated through a canonical or non-canonical signalling cascade. The non-canonical activation of GLI transcription factors by TGF- $\beta$  has not yet been investigated in SSc. The substantial part of this thesis is focused on the study of the mutual interaction of TGF- $\beta$  and Hh signalling pathway. *In vitro* analysis confirmed TGF- $\beta$ /SMAD3 dependent activation of GLI2 in dermal fibroblasts. Fibroblasts specific knockout of *GLI2* prevented the development of experimental fibrosis *in vivo*. Combined targeting of canonical and non-canonical Hh signalling with GLI2 inhibitors exerted more potent antifibrotic effects than individual inhibition of the canonical signalling pathway in experimental dermal and pulmonary fibrosis. These data may have translational implications as selective inhibitors are currently in development. The rest of the thesis is focused on the role of new profibrotic molecules (TRB3, Twist1, S100A4 and Sirt1) in the pathogenesis of SSc. The results of this thesis contribute to better understanding of the pathogenesis of SSc and characterize novel potential therapeutic targets.

**Key words:** systemic sclerosis, TGF- $\beta$  signalling pathway, Hedgehog signalling pathway, fibroblast, targeted therapy, TRB3, Twist1, S100A4, Sirt1