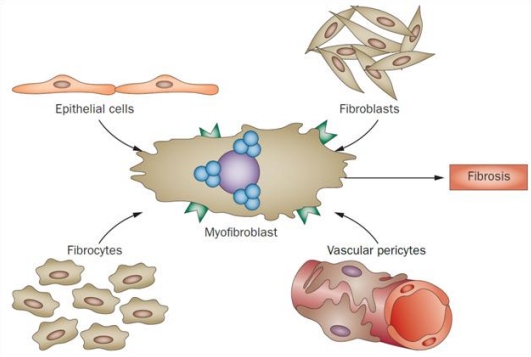
EXPERIMENTAL RHEUMATOLOGY

Title
Transforming the future of SSc patients by targeting excessive TGFβ signaling

Clinical Relevance
Systemic sclerosis or scleroderma (SSc) is a rare but severe systemic autoimmune disease. Scleroderma, literally "hard skin" is characterized by vasculopathy and excessive fibrosis of skin, hardening it to the point that any flexibility is lost and movement of affected areas becomes difficult. Many patients also develop progressive fibrosis in their visceral organs, leading to *e.g.* kidney and respiratory failure. In severe cases, SSc can rapidly (< 3 years) lead to organ failure and death. Unfortunately, the etiology of SSc is only poorly understood, greatly hampering the development of a treatment. Therefore, there is great need for a better understanding of what drives the excessive fibrosis in this devastating disease.

Background


Fibrosis in SSc is characterized by excessive deposition of collagen type I by myofibroblasts. In healthy tissue, myofibroblasts are extremely rare, but in SSc, these cells originate by differentiation of cell types like fibroblasts, epithelial cells (Epithelial to mesenchymal transition) or endothelial cells (Endothelial to mesenchymal transition). Signaling by transforming growth factor β (TGFβ) has been implicated as an important driver in the formation of myofibroblasts. TGFβ signaling can be potentiated by inflammatory conditions and hypoxia, both of which are observed in SSc patients due to their vasculopathy. However, how inflammation and hypoxia potentiate TGFβ signaling is poorly understood.

Goals
Our aim is to elucidate how inflammatory conditions and hypoxia mediate excessive TGFβ signaling to induce EMT and EndoMT in cells of SSc patients. We will focus on how inflammatory signaling and hypoxia affects intracellular TGFβ signaling and TGFβ-induced gene and protein expression. Furthermore, we will screen small molecule inhibitors of inflammation for their ability to prevent the excessive activation of TGFβ.

We Offer
We are working in a state of the art laboratory that is internationally renowned for its research that combines therapeutic strategies with diagnostics in rheumatic diseases. You will participate in a project that includes a broad spectrum of techniques including, amongst others, work with patient material, histology, immunohistochemistry, cell culture, Western blot, FACS and qPCR. You will be able to improve your laboratory skills, develop your scientific thinking and expand your knowledge on molecular processes and immunology.

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