Background: Systemic sclerosis (SSc) is a chronic autoimmune disease characterized by microangiopathy and fibrosis. In physiological wound healing, fibroblasts are transiently activated for tissue repair. In contrast, fibroblasts are persistently activated during fibrosis and thus resulted in progressive matrix deposition and tissue remodeling. However, the pathogenesis of the fibrotic process is not fully understood.

Objectives: We aimed to identify molecules that play a role in chronically activated fibroblasts.

Methods: To identify molecules specifically upregulated in human fibroblast cells, RNA-seq was performed. Identified adaptors were further validated in skin biopsy samples from patients with limited cutaneous SSC (lcSSc) and diffuse cutaneous SSc (dcSSc), and evaluated correlation between expression levels and clinical parameters. Resulting overexpression and siRNA knockdown were further addressed in vitro. Functional effects were assessed by qPCR, hydroxyproline, and migration assays. Mouse models of systemic sclerosis were used to functionally validate adaptor proteins in vivo.

Results: We identified adaptors as significantly upregulated molecules in chronically active fibroblasts of skin biopsy samples from SSc patients compared to fibroblasts from healthy controls. Expression levels were correlated with the modified Rodnan skin score in the skin of SSc patients. We observed higher expression levels also in the mouse model of topoisomerase I induced skin fibrosis. This result was also observed in bleomycin induced lung fibrosis model suggesting important functions of adaptor proteins during fibrotic tissue remodeling across different organs. Fibroblast-specific knockout resulted into significantly attenuated bleomycin-induced fibrosis. Upon bleomycin challenge, hydroxyproline content was diminished in mice with genetic deficiency of adaptor proteins. In addition, COL1A1, COL1A2 and Lum mRNAs and also the number of extracellular matrix proteins are reduced, which might indicate an altered extracellular matrix composition.

Conclusion: Our results demonstrate that adaptor proteins play an essential role in the pathogenesis of systemic sclerosis. Understanding the molecular mechanism of adaptor proteins may lead to a novel therapeutic intervention in human SSC and related disorders.

Disclosure of Interests: None declared.