Background: Fibroblast heterogeneity and homeostasis has long been recognized in patients with systemic sclerosis (SSc). However, there is no common consensus on fibroblast subtypes, lineages, biological properties, signaling, and plasticity, which severely hampers our understanding of SSc pathogenesis.

Objectives: This study aimed to comprehensively classify skin fibroblast populations from SSc patients.

Methods: We applied single-cell RNA sequencing on skin fibroblasts from two SSc patients and two health control (HC) with matched age and sex. Cell clustering were mainly determined by UMAP with batch effect correction. Differently expressed genes in each cell cluster was analyzed by Gene Set Enrichment Analysis (GSEA).

Results: With an unbiased approach, single-cell transcriptome analyses showed classified and defined eight fibroblast types in SSc skin and six in normal skin. The cell types seldom overlapped between the patients and HC. Extracellular interaction and collagen production were remarkably stronger in SSc fibroblasts. A subgroup of dramatic cell proliferation and activation was defined only in SSc fibroblast. Two subtypes responding inflammatory stimuli were only found in SSc patients. Furthermore, delineation of their differentiation trajectory was achieved by a machine learning method.

Conclusion: This collection of single-cell transcriptomes and the distinct classification of fibroblast subsets provide a new resource for understanding the fibroblast landscape and the roles of fibroblasts in SSc.

References: N/A

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