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Sfrp1 inhibits lung fibroblast invasion during transition to injury-induced myofibroblasts

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This single-cell study discovered a transitional cell state that appears early after injury and precedes the generation of myofibroblasts. This cell state is characterised by expression of SFRP1, which inhibits fibroblast invasion in fibrogenesis. <https://bit.ly/3uifxmJ>

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Abstract

Background Fibroblast-to-myofibroblast conversion is a major driver of tissue remodelling in organ fibrosis. Distinct lineages of fibroblasts support homeostatic tissue niche functions, yet their specific activation states and phenotypic trajectories during injury and repair have remained unclear.

Methods We combined spatial transcriptomics, multiplexed immunostainings, longitudinal single-cell RNA-sequencing and genetic lineage tracing to study fibroblast fates during mouse lung regeneration. Our findings were validated in idiopathic pulmonary fibrosis patient tissues *in situ* as well as in cell differentiation and invasion assays using patient lung fibroblasts. Cell differentiation and invasion assays established a function of SFRP1 in regulating human lung fibroblast invasion in response to transforming growth factor (TGF)β1.

Measurements and main results We discovered a transitional fibroblast state characterised by high *Sfrp1* expression, derived from both *Tcf21*-Cre lineage positive and negative cells. *Sfrp1*⁺ cells appeared early after injury in peribronchiolar, adventitial and alveolar locations and preceded the emergence of myofibroblasts. We identified lineage-specific paracrine signals and inferred converging transcriptional

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trajectories towards *Sfrp1*⁺ transitional fibroblasts and *Cthrc1*⁺ myofibroblasts. TGFβ1 downregulated SFRP1 in noninvasive transitional cells and induced their switch to an invasive CTHRC1⁺ myofibroblast identity. Finally, using loss-of-function studies we showed that SFRP1 modulates TGFβ1-induced fibroblast invasion and RHOA pathway activity.

Conclusions Our study reveals the convergence of spatially and transcriptionally distinct fibroblast lineages into transcriptionally uniform myofibroblasts and identifies SFRP1 as a modulator of TGFβ1-driven fibroblast phenotypes in fibrogenesis. These findings are relevant in the context of therapeutic interventions that aim at limiting or reversing fibroblast foci formation.