ABSTRACTS

The matricellular protein mindin induces a pro-inflammatory response in fibroblasts to manifest dermal fibrosis in scleroderma

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Scleroderma, or systemic sclerosis (SSc), is a rare autoimmune and genetic disease. It is characterized by chronic inflammation and fibrosis, primarily in the skin, and progresses to internal organs, including the heart, lungs, and kidneys. While the root cause of scleroderma remains elusive, a major driver of the pathology is chronically activated fibroblasts (myofibroblasts) that excessively secret extracellular matrix (ECM) proteins. The lack of an effective treatment for scleroderma underlies the need to elucidate the molecular mechanisms of scleroderma pathogenesis that will shed new insights into potential new routes of therapeutic intervention.

The team has engineered a novel mouse model that recapitulates the diagnostic features of scleroderma and utilized it to discover new pathways driving disease pathogenesis. One of the critical factors mediating the disease phenotype is the matricellular protein, mindin (SPON2), which is also overexpressed in human fibrotic conditions, including scleroderma. The study revealed that mindin is necessary and sufficient to induce dermal fibroblasts – migration, contraction, pro-inflammatory cytokine production, and ECM secretion – that collectively fuel fibrogenesis. The researchers found that these functional responses of fibroblasts to mindin are mediated by the NF-κB signaling pathway and the selective activation of specific members of the Src family of kinases. In order to more fully understand the signaling cascade initiated by mindin, the current focus is on the identification of the receptor of mindin on fibroblasts. The researchers demonstrated that the N-terminal F-spondin domain of the protein is sufficient to recapitulate the effects of full-length mindin on dermal fibroblasts. Using this minimal-functional domain of mindin, the team isolated protein interactors, which theoretically include the cognate receptor(s), and identified them through mass spectrometry. In summary, the study identified a novel target protein that can help in developing new therapies for the treatment of scleroderma.

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Reference

Rana I, Kataria S, Tan TL, Hajam EY, Kashyap DK, Saha D, et al. Mindin (SPON2) Is Essential for Cutaneous Fibrogenesis in a Mouse Model of Systemic Sclerosis.