CXCL4 DRIVES FIBROSIS BY PROMOTING SEVERAL KEY CELLULAR AND MOLECULAR PROCESSES

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Background: Fibrosis, characterised by excessive accumulation of extracellular matrix (ECM) through myofibroblasts, is a leading cause of mortality worldwide1,2. Understanding the pathways involved in myofibroblasts activation is crucial to develop novel treatment strategies. Systemic sclerosis (SSc) is a prototypic fibrotic disease in which we previously identified CXCL4 to be strongly correlated with skin and lung fibrosis3.

Objectives: We aimed to elucidate the role of CXCL4 in fibrosis development using in vitro and in vivo assays.

Methods: Human primary dermal fibroblasts, endothelial cells, and pericytes, were (co-) cultured in the presence or absence of recombinant human CXCL4. CXCL4−/− mice were used in bleomycin-induced skin and lung fibrosis models, and pressure-overload cardiac fibrosis model. Gene expression was assessed by qPCR, protein expression was determined by western blot or immunofluorescence, and collagen content was measured by trichrome staining or hydroxyproline assay.

Results: We found that CXCL4 induced the expression of myofibroblast markers αSMA and SM22α, and collagen synthesis in human dermal fibroblasts, endothelial cells, and pericytes. CXCL4 also suppressed endothelial cell tubular formation in a co-culture with pericytes. In mice, CXCL4 expression was increased in a variety of mouse inflammatory and fibrotic models. Using CXCL4−/− mice, we confirmed the essential role of CXCL4 in promoting fibrotic events in the skin, lung, and heart using two independent fibrosis models.

Conclusions: CXCL4 drives myofibroblast transformation from different precursors and it is required for fibrosis development across organs. Our findings implicate a pivotal role of CXCL4 in fibrosis further substantiating the potential role for neutralising CXCL4 as a novel therapeutic strategy.

REFERENCES:

Disclosure of Interest: None declared