Identification of Novel Mediators of Fibrosis in Scleroderma

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Background: Fibrosis is a major pathological feature of many chronic diseases such as SSc, an autoimmune rheumatic disease characterized by activation of fibroblasts, accumulation of extracellular matrix (ECM) and persistent inflammation that can lead to impaired organ function. Fibrotic disorders share common features, although it is unclear which of these occur as a result of shared mechanisms and pathways and which are mediated by unique organ-specific mechanisms. The aims of this project were to identify common and unique genes involved in fibrosis of diverse aetiologies. In addition, a thorough in silico data-mining exercise was conducted using all published microarray data (GEO database). A short list of genes was compiled based on several criteria, including common/specific targets for lung, skin and kidney fibrosis, druggability and availability of reagents. Validation of expression levels of the short-listed genes was performed in human primary fibroblasts (n = 3) by quantitative PCR (mRNA), western blotting (protein) and immunohistochemistry (IHC). Fibroblasts were derived from normal, SSc lung and skin tissue and normal kidney. TGF-β was used to induce fibrotic genes in fibroblasts from healthy controls as a model of generic fibrosis since TGF-β is regarded a major profibrotic cytokine.

Results: A list of the 100 most altered (up- or downregulated) genes was compiled, from which 12 genes were short-listed. Pathway analysis of all 100 altered genes highlighted the hyaluronic acid (HA) pathway, a major component of ECM, from which 2 genes were in the 12-gene short list, hyaluronan synthase 2 (HAS2) and cell migration-inducing protein (CEMIP). HAS2, responsible for hyaluronan polymerization, was the most significantly upregulated gene. Significantly elevated mRNA and protein levels of HAS2 were observed in skin and lung SSc fibroblasts and in TGF-β-treated fibroblasts from all 3 organs. The IHC data showed that HAS2 was higher in skin and lung tissues from SSc patients compared with controls. CEMIP, an HA binding protein, was significantly downregulated in fibroblasts from SSc lung and skin and in TGF-β-treated fibroblasts from all three organs.

Conclusion: Taken together, these data reveal that HAS2 is significantly upregulated and CEMIP is significantly downregulated in lung and skin fibroblasts from SSc patients compared with controls and in fibrotic conditions in all three organs. These data suggest an important role of the HA pathway for HAS2 and CEMIP in SSc. These potential mediators of fibrosis could be novel targets for antifibrotic therapies.

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