Transcription factor TBX4 regulates myofibroblast accumulation and lung fibrosis.

Journal: J Clin Invest

Publication Year: 2016

Authors: Ting Xie, Jiurong Liang, Ningshan Liu, Caijuan Huan, Yanli Zhang, Weijia Liu, Maya Kumar, Rui Xiao, Jeanine D'Armiento, Daniel Metzger, Pierre Chambon, Virginia E Papaioannou, Barry R Stripp, Dianhua Jiang, Paul W Noble

PubMed link: 27400124

Funding Grants: Innate Immune Regulation of Lung Alveolar Stem Cell Renewal in Mouse and Man

Public Summary:
Progressive tissue fibrosis is a major cause of the morbidity and mortality associated with repeated epithelial injuries and accumulation of myofibroblasts. Successful treatment options are limited by an incomplete understanding of the molecular mechanisms that regulate myofibroblast accumulation. Here, we employed in vivo lineage tracing and real-time gene expression transgenic reporting methods to analyze the early embryonic transcription factor T-box gene 4 (TBX4), and determined that TBX4-lineage mesenchymal progenitors are the predominant source of myofibroblasts in injured adult lung. In a murine model, ablation of TBX4-expressing cells or disruption of TBX4 signaling attenuated lung fibrosis after bleomycin-induced injury. Furthermore, TBX4 regulated hyaluronan synthase 2 production to enable fibroblast invasion of matrix both in murine models and in fibroblasts from patients with severe pulmonary fibrosis. These data identify TBX4 as a mesenchymal transcription factor that drives accumulation of myofibroblasts and the development of lung fibrosis. Targeting TBX4 and downstream factors that regulate fibroblast invasiveness could lead to therapeutic approaches in lung fibrosis.

Scientific Abstract:
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