Spred2-Deficiency Enhances the Proliferation of Lung Epithelial Cells and Alleviates Pulmonary Fibrosis Induced by Bleomycin

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Abstract

The mitogen-activated protein kinase (MAPK) pathways are involved in many cellular processes, including the development of fibrosis. Here, we examined the role of Sprouty-related EVH-1-domain-containing protein (Spred) 2, a negative regulator of the MAPK-ERK pathway, in the development of bleomycin (BLM)-induced pulmonary fibrosis (PF). Compared to WT mice, Spred2$^{-/-}$ mice developed milder PF with increased proliferation of bronchial epithelial cells. Spred2$^{-/-}$ lung epithelial cells or MLE-12 cells treated with spred2 siRNA proliferated faster than control cells in vitro. Spred2$^{-/-}$ and WT macrophages produced similar levels of TNFα and MCP-1 in response to BLM or lipopolysaccharide and myeloid cell-specific deletion of Spred2 in mice had no effect. Spred2$^{-/-}$ fibroblasts proliferated faster and produced similar levels of MCP-1 compared to WT fibroblasts. Spred2 mRNA was almost exclusively detected in bronchial epithelial cells of naïve WT mice and it accumulated in approximately 50% of cells with a characteristic of Clara cells, 14 days after BLM treatment. These results suggest that Spred2 is involved in the regulation of tissue repair after BLM-induced lung injury and increased proliferation of lung bronchial cells in Spred2$^{-/-}$ mice may contribute to faster tissue repair. Thus, Spred2 may present a new therapeutic target for the treatment of PF.

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