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Succinate aggravates pulmonary fibrosis through the Succinate-GPR91 axis.

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Pulmonary fibrosis (PF) is a chronic, progressive, and restrictive pulmonary disorder estimated to affect 3 million people. It progresses with an increase in fibrotic tissue presenting as scarring of lung tissue, and deposition of extracellular matrix (ECM), obliterating the alveolar architecture. Consequently, there is loss of compliance, compromising the alveolar gas exchange capacity. Substantial findings from transcriptomic and metabolic profiling of fibrotic lungs point towards a dysregulation of metabolic pathways in the diseased state. The tricarboxylic acid (TCA) cycle, which is at the center of several metabolic pathways, has gained traction in fibrosis research. Intermediate members including succinate, acetyl CoA, and alpha ketoglutarate, have now been associated with non-metabolic functions such as cellular signaling, chromatin modification, and post-translational modification of proteins. In this study, we aim to understand the role of succinate, and its receptor GPR91 in regulating the outcomes of PF. METHODS Western blotting, qPCR, and FISH were employed to investigate the expression of GPR91 in human and mouse lung and in fibroblasts. In vitro assays were performed with IPF patient derived fibroblasts to evaluate the effect of succinate treatment on the expression of fibrotic markers. In vivo studies with the bleomycin mouse model of PF were used to evaluate the role of succinate in governing the outcomes of PF. RESULTS Several cell types in the lung express GPR91 including ATII cells, fibroblasts, and macrophages. In IPF patient derived fibroblasts, succinate treatment increased expression of markers associated with fibrosis such as alpha smooth muscle actin and collagen. In vivo, succinate significantly increased collagen accumulation and exaggerated weight loss in a model of pulmonary fibrosis. CONCLUSION The succinate-GPR91 axis appears to worsen PF. Deciphering the mechanisms involved will be key to investigating GPR91 as a therapeutic target.