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Pulmonary fibrosis and alveolar lipid levels in Bleomycin challenged Type 2 cell LRP1 KO mice.

Pulmonary fibrosis (PF) is an interstitial lung disease with poor prognosis and limited treatment options. Recurrent damage to the alveolar type 2 cells (T2C) is a proposed cause of PF. Our prior research showed that mice with T2C-loss of LDL-related protein 1 (LRP1 (SPC-LRP1-/-) have decline in pulmonary compliance, a hallmark of PF, and decreased surfactant lipids. We hypothesized that LRP1 loss in T2C primes the alveoli for fibrosis and used bleomycin (BLM) as a profibrotic agent in 6-months old WT and SPC-LRP1-/- mice.

Inducible SPC-LRP1-/- mice were bred by crossing LRP1-floxed mice with mice expressing Cre recombinase under the control of the promoter of T2C-specific surfactant protein C (SP-C). The knockout was induced at 7 weeks of age, and at 6 months of age mice were challenged with repeated low dose of BLM (0.035 U/g) twice weekly for 4 weeks. At 33 days after initiation of the challenge, mice were euthanized. Inflammation was assessed by body weight tracking, and after euthanasia by bronchoalveolar lavage (BAL) protein concentration. Pulmonary function was measured, fibrosis was assessed by Ashcroft grading of histological sections, and BAL lipids were analyzed by mass spectrometry.

SPC-LRP1-/- mice showed exacerbated body weight loss and higher protein concentration in BAL than WT mice, suggesting increased inflammation. BAL lipid profiling showed lower concentration of surfactant total phosphatidylcholine (PC) and of other lipid species in SPC-LRP1-/- than in WT mice after BLM challenge. Higher fibrotic scores were observed in the lung sections of SPC-LRP1 -/- mice. However, pulmonary function showed a similar decline in static compliance, inspiratory capacity and forced vital capacity for WT and SPC-LRP1-/- mice.

We conclude that LRP1 loss in T2C exacerbates BLM-triggered inflammation, lung function defects, and fibrosis development.