

A32

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Repeated low dose of bleomycin impacts lung function in alveolar type 2 cell-specific LRP1 knockout male mice

Pulmonary fibrosis is a chronic interstitial lung disease characterized by excessive collagen deposition and progressive loss of compliance, with poor prognosis and often terminating in lung transplantation or death from respiratory failure. The current hypothesis is that repetitive damage to the alveolar type 2 cells (T2C) is the origin of later pulmonary fibrosis development. Studies in our lab have shown that loss of the LDL-related protein 1 (LRP1) in T2C (SPC-LRP1^{-/-}) results in decreased pulmonary compliance at baseline in female mice, and after smoke exposure in male mice. We hypothesized that LRP1 loss in T2C primes the alveoli for fibrosis. Using repeated low dose of bleomycin (BLM) as a profibrotic challenge, we studied pulmonary function by invasive and non-invasive methods in one year old male WT and SPC-LRP1^{-/-} mice.

Inducible SPC-LRP1^{-/-} mice were generated and the knockout induced after completion of post-natal mouse lung development, at 7 weeks of age, by tamoxifen injection. One-year aged mice were challenged with repeated doses of BLM (0.035 U/g) and pulmonary function was measured at 7 and 33 days after initiation of the challenge. Pulmonary mechanics was measured using invasive SCIREQ-FlexiVent and noninvasive whole body plethysmography (WBP). Inflammation was assessed by body weight tracking, bronchoalveolar lavage (BAL) cellularity and protein concentration.

At 33 days of BLM challenge, WBP in WT mice showed significantly decreased peak inspiratory flow, whereas SPC-LRP1^{-/-} mice showed decreased rate of ventilation. Invasive PFT in WT mice showed no apparent differences in compliance, inspiratory capacity and forced vital capacity, despite it did in 6 month old mice. At 7 days of BLM challenge, in SPC-LRP1^{-/-} mice showed significantly decreased breathing frequency and time to peak expiratory flow, and increased time of expiration and pause at end of expiration than prior to starting the challenge. Inflammation changes between WT and SPC-LRP1.