The Role of Secreted Frizzled-Related Protein 1 in Lung Development and Bronchopulmonary Dysplasia

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Rationale:Bronchopulmonary dysplasia (BPD), a pattern of chronic lung disease in premature infants, is associated with increased mortality and respiratory morbidity. Currently, treatment for BPD is largely supportive. To find targeted therapies that specifically promote lung growth and reduce respiratory illness, a deeper understanding of in utero lung development and postnatal repair is required. The Wnt/β-catenin signaling pathway is essential for normal lung development, and aberrant Wnt signaling is linked to BPD in humans and murine hyperoxia models of BPD. Our group identified a Wnt inhibitory modulator, secreted frizzled-related protein 1 (SFRP1), as an important factor in early distal airway morphology. Genetic ablation of Sfrp1 in mice leads to dilated alveolar ducts and increased mean linear intercept, compared to wild type mice. We hypothesize that SFRP1 is important in normal lung development and that it is aberrantly expressed in a hyperoxic lung injury model of BPD. Methods:Mouse lung tissue sections at 10.5, 12.5, 13.5, 14.5, 15.5, 16.5, 17.5, and 18.5 days post coitum (dpc) were collected and stained with immunofluorescent SFRP1 antibody in order to localize SFRP1 at various timepoints in development. Publicly available single cell RNA sequencing data from embryonic mouse lung (12 and 15 dpc) were analyzed using CLC Genomics Workbench to detect Sfrp1 expression. Adult mice were exposed to 85% O2 for 3 and 5 days in a chamber (Coy Laboratory) and Sfrp1 expression in the lung was assessed via northern blot. Results:Immunolocalization studies reveal presence of SFRP1 in the distal airway epithelium and surrounding mesenchyme from 13.5 to 15.5 dpc. Single cell RNA sequencing analysis revealed Sfrp1 expression is highest from 12-15 dpc, and almost entirely in mesenchymal cells. The majority of Sfrp1 expressing cells are Wnt2+ fibroblasts and adventitial fibroblasts. 3 and 5 days of exposure to 85% O2 led to upregulation of Sfrp1 compared to controls, and this was not seen in an acute inflammatory injury model or in a chronic smoke exposure model. Conclusions:Sfrp1 is expressed by mesenchymal cells, predominantly Wnt2+ fibroblasts and adventitial fibroblasts, between 13 and 15 dpc, corresponding to the pseudoglandular stage of lung development. Based on immunolocalization studies and sequencing data, SFRP1 may be involved in mesenchymal to epithelial signaling during development. In vivo studies reveal upregulation of Sfrp1 after hyperoxic injury in adult mice. Future studies will explore the expression pattern and function of Sfrp1 in a neonatal hyperoxic injury model of BPD.

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