Background

- Congenital diaphragmatic hernia (CDH) is a common and severe congenital malformation affecting 1 in 3,500 live births.
- The morbidity and mortality in patients with CDH is due to lung hypoplasia and pulmonary hypertension.
- PBX1: Pre-B-cell leukemia transcription factor
- Pbx deletion in fibroblasts causes CDH in mice

Hypothesis/ Objective

- Our hypothesis is that a core group of genes is required for alveologenesis.
- Defects in alveologenesis are common in patients with CDH
- Mutation of the PBX1 gene has been identified in patients with CDH
- Does deletion of Pbx in mice cause defects in alveologenesis?

Alveologenesis in CDH

- Alveologenesis starts at 38 weeks in human fetuses (5-day-old mice) and ends during school age (36-day-old mice).
- Lung hypoplasia is a leading cause of mortality and morbidity in patients with CDH

Methods: Tissue specific deletion of Pbx in the developing lung

Lung mesenchyme specific deletion

Figure 4: Tbx4-rtta; Tet-O-Cre directs inducible recombination throughout the lung mesenchyme

Figure 5: To induce Pbx deletion in the last stages of development, doxycycline was administered via food given to the mothers at E18, and then injected into the pups at P1 and P3

Results: Late embryonic Pbx deletion causes failure of alveologenesis

Figure 6: Compared to controls (A,C), early postnatal deletion of Pbx causes failure of alveologenesis (B) that is first detected at P5 (D) quantified by mean linear intercept (MLI, E).

Results: Late embryonic Pbx deletion increases α-SMA myofibroblasts

Figure 7: Compared to the controls (A), the mutants have increased α-SMA myofibroblasts in a more diffuse organization (B).

Results: Late embryonic Pbx deletion does not affect Pdgfra+ myofibroblasts

Figure 8: Compared to the controls (A), there is no difference in the mutant Pdgfra+ cell population (B) as quantified by a ratio over total live cells (C).

Results: Late embryonic Pbx deletion affects extra cellular matrix production

Figure 9: Compared to the controls (A), the mutants have increased extra cellular matrix that is more diffusely organized (B).

Conclusions

- Postnatal deletion of Pbx in lung mesenchyme results in failure of alveologenesis
- Pbx deletion results in increased and more disorganized α-SMA myofibroblasts and extra cellular matrix production

Future Directions

- Determine the cellular and molecular mechanisms responsible for failure of alveologenesis caused by the deletion of Pbx
- Conduct lung mesenchyme specific gene expression analysis to identify the genetic defects responsible for failure of alveologenesis following loss of PBX function

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CDH Gene PBX1 is Required in the Mesenchyme for Postnatal Alveologenesis

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