STRONG CHILDREN'S RESEARCH CENTER

Summer 2014 Research Scholar

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ABSTRACT

Title: ***Exploring the Effect of Ectopic Activation of Hh Signaling on the Differentiation of the Alveolar Epithelium***

Background: Joubert Syndrome (JBS) occurs in approximately 1 in 100,000 newborns and affects multiple organ systems. JBS patients have a unique respiratory pattern during the neonatal period characterized by episodes of tachypnea (as high as 200 breaths/min) followed by apnea. The JBS respiratory pattern has been attributed to a congenital malformation of the brainstem; however JBS patients do not have issues at any of the other medullary control centers. The unusual respiratory pattern is transient, and the reason for its spontaneous resolution during the first year of life is unknown.

Over half of the recognized JBS genes encode components of the primary cilium, an organelle required for hedgehog signaling. Hedgehog (*Hh*) signaling is necessary for the development of numerous organs including the lung. Mutations in genes associated with the primary cilium have been associated with both activation and inhibition of Hh signaling. We have hypothesized that JBS patients may have delayed or abnormal saccular and alveolar lung development, and that these abnormalities may contribute to the respiratory phenotype.

Objective: Mouse genetic models were used to determine whether aberrant activation of *Hh* signaling during the canalicular and saccular stages of lung development alters the morphology or maturation of the distal newborn lung.

Results: Immunofluorescent analysis of cell type specific markers for the type I and type II pneumocytes showed that activation of *Hh* during the canalicular stage of lung development is not sufficient to inhibit the differentiation of the Type I and II pneumocytes at E18.5. Real-time quantitative polymerase chain reaction (RT-PCR) was performed to confirm that *Smo* was upregulated in the perinatal lung. Immunofluorescent staining was also performed to examine the effect that *Hh* activation had on epithelial cell proliferation during the saccular stage of development. Preliminary results suggest that epithelial cell proliferation may be upregulated following the activation of this pathway. These findings are interesting as activation of the pathway did affect the differentiation of the alveolar epithelium.

Conclusion: Mutations in genes associated with the primary cilium have been associated with both activation and inhibition of Hh signaling. Our results suggest that mis-activation of Hh signaling after E14.5 is not sufficient to disrupt lung development. Further work will be needed to determine how mutations which perturb the primary cilium affect lung development and neonatal lung function.