STRONG CHILDREN'S RESEARCH CENTER

Summer 2015 Research Scholar

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ABSTRACT

Title: Analysis of FOXF1 Gene Expression in an Alveolar Capillary Dysplasia Patient

Background:

Alveolar Capillary Dysplasia with Misalignment of Pulmonary Veins (ACD/MPV or ACD) is a genetic disease affecting infants. Despite normal Apgar scores and a healthy appearance at birth, patients rapidly decline, experiencing severe respiratory distress and persistent pulmonary hypertension. Current treatments (mechanical ventilation and extracorporeal membrane oxygenation) are life-sustaining but do not treat the disease. ACD is thought to be associated with a large deletion including the lung-specific FOXF1 (forkhead box F1) gene on human chromosome 16, and is subject to paternal imprinting. The patient of interest in this project was a healthy male baby born full-term plus one day who developed respiratory distress about 12 hours after birth, and died at 15 days of life. The patient has a de novo 340kb deletion upstream of FOXF1, not including the FOXF1 gene. This region of deletion does include the IRF8 gene (transcription factor regulating the immune response) and several important regulatory elements of the FOXF1 gene. FOXF1 is highly expressed primarily in lung tissue, while IRF8 is expressed in several other tissues; as a result, IRF8 was excluded from the analysis. As a result, analysis focused on identifying regulatory elements in the deleted region that drive FOXF1 expression.

Objective:

The objective of the project was to determine the function of several FOXF1 regulatory elements in the Alveolar Capillary Dysplasia phenotype.

[c 0 5.003(e) >>BDC 0.003 Tc -0.00TrFOXF1 expression was found to be lower in ACD patient tissues than in HIE (hypoxic ischemic encephalopathy), CPD (congenital diaphragmatic hernia), and meconium aspiration tissues. These age-matched tissues (14-15 days old) were used as controls for infection, injury to tissuhy tn1 Td ( )10.8(th)19.9(a76(n)7(t))4(n)1a

The ACD phenotype is typically driven by a large deletion in chromosome 16 that encompasses the FOXF1 gene. In the patient of interest, the FOXF1 gene was not deleted, leading us to determine which factors in the overlapping deleted region could contribute to the loss of FOXF1 expression and the ACD phenotype. Thus, our goal was to identify lung-specific enhancers involved in driving lung-specific FOXF1 expression, while future work will test enhancer function with a luciferase assay. In addition, the identified enhancers will be further characterized with the CRISPR/Cas9 knockdown system in IMR-90 cells (human lung fibroblasts).