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Treatment of pulmonary hypertension in miR-200b knockout mice with the non-specific endothelin receptor antagonist bosentan

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Background:

Pulmonary hypertension is one of the leading causes of morbidity and mortality in patients with congenital diaphragmatic hernia. We have previously shown that decreased expression of microRNA-200b (miR-200b) is associated with poor outcomes in CDH patients and that miR-200b knockout (KO) mice also have pulmonary hypertension. MiR-200b KO mice have increased levels of endothelin receptor-A (ETA), which contributes to pulmonary hypertension.

Objective:

The goal of this study is to determine the effects of bosentan, an endothelin antagonist, in miR-200b KO mice lungs.

Methods:

Male and female miR-200b KO (n=7 male; n=7 female) and WT (n=7 male; n=7 female) mice will be used. Daily gavage of bosentan will be administered for three weeks to knockout and WT mice. Vehicle-treated knockout mice serve as controls. Echocardiography and graded maximal exercise tests will be performed before start of bosentan and once weekly after treatment to track changes in pulmonary hypertension. At the end of three weeks, all mice will be euthanized and lungs will be used to determine histological differences.

Results:

We predict that bosentan will competitively bind to ETA against endothelin 1, its natural ligand, in the pulmonary vessels and decrease vasoconstriction. Decreased vasoconstriction will lead to a decrease in pulmonary hypertension in miR-200b KO mice. We predict that a decrease in pulmonary hypertension will lead to an increase in VO_2 maximum and stamina in these mice. Comparison of treated and untreated male and female mice will be conducted.

Conclusion:

Current treatment options for pulmonary hypertension in CDH include the use of sildenafil, nitric oxide, and other vasodilators, but reports on their effectiveness are inconclusive. Understanding the effect of bosentan in miR-200b deficient lungs may provide insight into how this drug could affect CDH patients

with a similar lung phenotype and lead to better treatment options.