Materials & Methods

1. All studies were approved by the Institutional Review Board (IRB) of the University of Colorado-Denver.
2. Endostatin mRNA expression was assayed in prenatal and postnatal samples of DS and non-DS human lung tissue using human Endostatin RT2 ProTmTM PCR-Array. Qagen PAHS-024Z.
3. Paraffin sections of human DS and normal (control) child lung tissue samples* were stained with hematoxylin and eosin (H&E) for assessment of lung architecture.
4. Cells cultured and maintained in fibronectin coated T-75 flasks.
5. Migration scratch assay performed in triplicates. Each well of cells was scratched with a 1 mL pipette tip and were treated with 10 ng/mL of VEGF and 50, 250, 500, 750, 1000, and 2000 ng/ml of endostatin in triplicates. Pictures taken before treatment (after scratch) and 24 hrs. after treatment.

Results

ES mRNA Expression is Markedly Increased in the Prenatal and Postnatal DS Lung

Graph 1. DS lung samples show significantly increased endostatin mRNA expression levels in the overall group of both prenatal and postnatal DS/control and also in just prenatal samples. Measured by relative fold change from age-matched controls (Ctrl).

Hypothesis

Increased endostatin (ES) expression in the developing lung impairs lung vasculature in children with DS.

Study Questions

1. Is lung vascular and alveolar growth abnormal in young infants with DS who die early?
2. Is lung-specific ES mRNA expression increased in prenatal and early postnatal human DS?
3. Does ES treatment impair cellular function in vitro?

ES Treatment Inhibits Migration of HMPEC in vitro

Figure 5a. Negative before ES treatment. At 1000 ng/mL, consistent migration inhibition results were seen.

References


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Conclusions

1. Lung Structure in DS is characterized by increased endostatin mRNA expression and impaired lung angiogenesis.
2. Early treatment with ES regulators or blockers may prevent the risk for postnatal disease.
3. Hypertensive remodeling of pulmonary arteries.
4. Increased lung ES expression in DS patients (Zorick et. al; 2001). This may benefit against the onset of tumor angiogenesis in DS patients, but it may also adversely affect lung structure growth based on mouse studies (see figures below).
5. Past studies from our lab showed that increased angiogenesis inhibits lung growth during development, but whether increased ES expression directly impairs lung angiogenesis in DS is unknown.

Study Questions

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