Antenatal Mesenchymal Stromal Cell Extracellular Vesicle Treatment Preserves Lung Development in a Model of Bronchopulmonary Dysplasia due to Chorioamnionitis

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Background

Bronchopulmonary Dysplasia (BPD):  
- BPD is the chronic lung disease of prematurity characterized by early disruption of lung growth and contributes to late morbidity and mortality.  
- Although the etiology of BPD is multifactorial, strong evidence has shown that antenatal factors, such as chorioamnionitis (CA), are associated with an increased risk for BPD.  
- Antenatal endotoxin (ETX) exposure as an experimental model of CA causes sustained disruption of lung alveolar and vascular growth hallmark findings in BPD.

Mesenchymal Stromal Cell (MSC) Extracellular Vesicles (MEx):

- MEx are secreted membrane vesicles from MSC that modulate many cellular functions, including growth, differentiation and function in health and disease.  
- Experimentally, MEx has shown promising effects in preventing or restoring lung function in models of lung disease.  
- Postnatal treatment with MEx can improve lung structure in experimental BPD due to postnatal hyperoxia, however, the potential efficacy of MEx for the prevention of BPD due to antenatal stress is unknown.

Hypothesis

Antenatal MEx treatment will prevent the development of BPD in an experimental rat model of CA.

Methods

**Whole Animal Model:**  
- Lungs were inflated at 20cm H2O for an hour and fixed in 4% paraformaldehyde  
- H&E staining used to determine distal lung structure with Mean Linear Intercepts (MLI) and Radial Alveolar Counts (RAC)  
- vWF immunostaining used to identify pulmonary vessels for determination of vessel density (VD) and medial wall thickness (MWT).  
- Right ventricular hypertrophy (RVH) calculated Lung Mechanics Studies.  
- Flexivent® single compartment analysis used to measure resistance and compliance

**In Vitro Model:**  
- Fetal Lung Explants  
- Lung explants at E15 gestation; distal branching was assessed day 0-3

**Study Questions**

- Will intra-amniotic injection of MEx:  
  - Preserve vessel and alveolar growth and improve lung structure in infant rats exposed to antenatal ETX?  
  - Improve lung mechanics in infant rats exposed to ETX?

**Results**

- **Antenatal MEx Treatment Preserves Lung Alveolar Growth in BPD:**  
  - Amniotic MEx preserves lung alveolar and vascular growth and restores alveolar and vascular growth and mechanics in infant rats.  
  - Intraamniotic ETX impairs alveolar and vascular growth and restores lung mechanics after ETX-exposure.  
  - Antenatal MEx significantly increases SPC and VEGF gene expression in comparison to ETX-exposed samples.

**Conclusion**

Early antenatal MEx treatment may prevent the development of BPD in premature infants, especially in the clinical setting of antenatal inflammation.

**Disclosure:** Exosomes used in these studies are provided in collaboration with the Kourembanas lab at the Department of Neonatology at Boston Children’s Hospital, Harvard Medical School, in conjunction with United Therapeutics.

Summary

- Intra-amniotic ETX impairs alveolar and vascular growth and restores lung mechanics in infant rats.
- Antenatal MEx injections preserve lung alveolar and vascular growth and restores lung mechanics after ETX-exposure.
- Antenatal MEx significantly increases SPC and VEGF gene expression in comparison to ETX-exposed samples.

Speculation

- Early antenatal MEx treatment may prevent the development of BPD in premature infants, especially in the clinical setting of antenatal inflammation.