Mesenchymal Stem Cell Biomarkers Prevent Bronchopulmonary Dysplasia Via Suppression of Lung Inflammation

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BACKGROUND

- Bronchopulmonary dysplasia (BPD) – a chronic debilitating disease of prematurely born infants resulting from:
  - Oxygen toxicity
  - Inflammation
  - Ventilator use
- Antenatal and postnatal factors contribute to increased cytokine signaling and inflammatory reactions that lead to arrested alveolar development and vascular remodeling
  - Perturbations exist in the protein levels of tracheal aspirate fluid samples of infants at risk to develop BPD
- Clinically defined as supplemental oxygen requirement at 36 weeks post-menstrual age
- Current therapies lack effectiveness and lead to undesirable side effects
  - No targeted therapies for repair or reversal exist
- Mesenchymal stem cell conditioned media (MSC-CM) has been shown to have protective effects against the development of BPD in mouse models
  - Acts in a paracrine manner via the release of immunomodulatory and vasoprotective factors
  - Analysis of MSC-CM identified Osteopontin (Opn) and Macrophage colony stimulating factor 1 (Csf1) as key mediators related to BPD

STUDY POPULATION

Inclusion Criteria

- <32 weeks gestation and/or BW <1500 grams
- Intubation within the first 24 hours from birth

Exclusion Criteria

- Major congenital anomalies
- Neuromuscular disorders
- Pulmonary hemorrhage

RESULTS – HYPOTHESIS TESTING

• Bronchopulmonary dysplasia (BPD) – a chronic debilitating disease of prematurely born infants resulting from:

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HYPOTHESIS

Reduced pulmonary effluent Opn and Csf1 levels are associated with BPD in prematurely born infants

SPECIFIC AIMS

To determine the association between Opn and Csf1 and BPD by quantifying Opn and Csf1 levels in the tracheal aspirate fluid (TAF) of prematurely born infants

MATERIALS & METHODS

- Eligible preterm infants were enrolled into the UCI IRB-approved study
  - Samples collected by RT/RN during routine ETT care using a Leukens trap and standard suctioning techniques
  - Samples placed on ice and stored in a -20°C freezer prior to transport to the research lab for processing
  - ELISA kits used on tracheal aspirate samples to detect:
    - Opn
    - Csf1
    - TGF-β
    - IgA
- IgA control to correct for TAF volume and sampling efficiency
  - IgA is a secretory protein
  - Levels do not change with gestational age or respiratory distress
- Samples hemolyzed after processing were excluded
- Infants followed prospectively for maternal and neonatal characteristics and clinical outcomes, including the development of BPD

BIOMARKER ANALYSIS

Table 2. Power for logistic regression model of BPD.

<table>
<thead>
<tr>
<th>R²</th>
<th>Sample Size</th>
<th>Power (Percent)</th>
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<tbody>
<tr>
<td>0.2</td>
<td>20, 60, 100</td>
<td>60, 20, 60</td>
</tr>
<tr>
<td>0.5</td>
<td>20, 60, 100</td>
<td>36, 46, 55</td>
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R²: R-squared of the predictor of interest with other covariates.
P: Proportion of BPD at baseline.
P: Proportion of BPD at one unit different from the baseline level.

CONCLUSIONS

- Our pilot study showed that quantification of Opn, Csf1, and TGF-β in the TAF of preterm infants at risk to develop BPD is feasible
- Early trends
  - BPD – low baseline Opn/Csf1, rising post-ventilation TGF-β
  - No BPD – high baseline Opn/Csf1, stable post-ventilation TGF-β
  - Opn and Csf1 levels appear to be associated with developing BPD
  - Subjects with lower baseline levels appear unable to suppress the TGF-β surge
- Further data collection is underway to reach study power
- Completion of analysis and statistics needed to confirm this association
- May guide the development of targeted therapy against BPD

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