TMEM100 Preserves Lung Growth and Prevents Pulmonary Hypertension in Chorioamnionitis-Induced Bronchopulmonary Dysplasia

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Background: Bronchopulmonary Dysplasia (BPD), the chronic lung disease of prematurity, is characterized by sustained abnormalities of distal lung alveolar and vascular growth after preterm birth. We have previously shown that disruption of angiogenesis during critical periods of lung growth impairs alveolarization. [1-4]

Objective: TMEM100 and BMP9 treatment will improve lung vascular and alveolar development and enhance PEC function in a rat model of BPD due to antenatal inflammation.

Design/Methods:
Time-dated pregnant rats underwent intra-amniotic injections with saline (Control; CTL) or Endotoxin (ETX) (10 ug/sac) at E20, and the pups were delivered at E22 by c-section. For in vivo studies, lung and endothelial-specific nanoparticles were used to deliver non-integrating TMEM100 plasmid by retroorbital injections in CTL and ETX rats at postnatal day 2 (P2) of life. At P14, rats were sacrificed, and lungs were inflated for histology and measurement of mean linear intercepts (MLI) to assess distal airspace structure. Hearts were dissected for measurement of Fulton's index (right ventricle/(left ventricle+septum) weight) to determine right ventricular hypertrophy (RVH). For in vivo studies, PECs were isolated from CTL or antenatally ETX-exposed rats shortly after birth using magnetic CD31 bead separation. PEC function was determined by standard proliferation and tube formation assays with the following treatments: CTL (no treatment), BMP9 (40ng/ml), TMEM100 plasmid (10ng/ml).

Results:
After antenatal exposure to ETX, lungs from infant rats at D14 had increased MLI ($p<0.05$) and increased RVH ($p<0.05$) compared to CTL rats. Postnatal TMEM100 treatment decreased MLI ($p<0.05$) and prevented RVH ($p<0.05$) after in infant rats that had been exposed to antenatal ETX. Compared to CTL PECs, PECs from antenatally ETX-exposed PECs had decreased proliferation in vitro ($p<0.05$). TMEM100 increased CTL PEC proliferation in comparison with untreated PEC ($p<0.05$). BMP9 also increased PEC proliferation ($p<0.05$), and tube formation ($p<0.05$) compared to untreated CTL PECs. Similarly, TMEM100 and BMP9 increased growth ($p<0.05$ for both treatments) and tube formation (TMEM100 $p<0.05$; BMP9 $p<0.01$) for PECs harvested from lungs after antenatal exposure to ETX.

Conclusion:
We found that nanoparticle delivery of TMEM100 plasmid treatment after birth improved alveolarization and reduced RVH in an experimental model of BPD induced by antenatal ETX exposure. In vivo studies demonstrated that TMEM100 and BMP9 treatment increased growth and tube formation in PECs from lungs of control and ETX-exposed newborns. We speculate that enhancement of the TMEM100 signaling pathway may preserve angiogenesis and alveolarization, and provide a novel therapy for the prevention of BPD and PH.