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Pulmonary Vascular Disease

APELINERGIC SIGNALING: A NEW TARGET FOR PULMONARY HYPERTENSION ASSOCIATED WITH BRONCHOPULMONARY DYSPLASIA

Oral Contributions
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Abstract Category: 43. Pulmonary Vascular Disease: Basic and Translational Science
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Background: Bronchopulmonary dysplasia (BPD) is the leading morbidity in survivors of preterm birth, with resulting impaired alveolarization and fibrosis. Infants with severe BPD have associated vascular changes and pulmonary hypertension (PH). The molecular mechanisms resulting in BPD and PH are poorly understood, and there are no curative therapies. Apelin is a peptide made by endothelial cells of the heart and lung that has been previously shown to be associated with endothelial repair, though its role in lung vascular development and injury is unclear.

Methods: To characterize expression of apelin and its receptor in lung development, we performed single cell RNA sequencing (scRNAseq) across 7 time points from embryonic day 15 to postnatal (P) day 14. To study apelin expression during lung injury, we used a murine model combining hyperoxia (70% from P1-5) and inflammation (intratracheal lipopolysaccharide). For validation, we examined human lung tissue from preterm infants with and without lung injury. Apelin and apelin receptor expression were localized in lung tissue using RNA in situ hybridization (ISH), with quantification using Halo software.

Results: By scRNAseq, apelin and its receptor are expressed by distinct subpopulations of endothelial cells in the lung. Apelin expression increases before birth at embryonic day 18 and is relatively constant across the lifespan. In acute lung injury, we found decreased expression of apelin by RNA ISH in endothelial cells when compared with normoxia-exposed controls at P5 ($p<0.001$). This decrease in apelin expression persisted during recovery at P14 ($p<0.01$). There were no significant changes in apelin receptor expression with injury. Examination of human infant lungs in the saccular stage showed decreased apelin expression after 4 days of mechanical ventilation when compared with infants who were never mechanically ventilated ($p<0.001$).

Conclusion: Apelinergic signaling is a conserved pathway that emerges in the saccular stage of lung development. During acute neonatal injury and recovery, there is a significant decrease in apelin expression. Future work to target this pathway may identify novel therapies in infants with BPD and PH.