LOSS OF GROWTH AND DIFFERENTIATION FACTOR 15 EXACERBATES NEONATAL HYPEROXIC LUNG INJURY

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Background: Bronchopulmonary dysplasia (BPD) is one of the most common morbidities among surviving premature infants. BPD is characterized by abnormal alveolar septation and aberrant vascular development. Growth Differentiation Factor 15 (GDF15) is a divergent member of the Transforming growth factor-beta (TGF-β) superfamily and its expression increases under various stress conditions including inflammation, hyperoxia, and senescence. Our prior studies showed that GDF15 expression is increased in neonatal mouse BPD models and that GDF15 loss exacerbates oxidative stress and decreases viability in human pulmonary endothelial and epithelial cells. Our overall hypothesis that loss of GDF15 will exacerbate hyperoxic lung injury in the neonatal lung in vivo.

Materials/Methods: We exposed neonatal Gdf15⁻/⁻ mice, and wild type (WT) controls on a similar background to room air or hyperoxia (95% O2) for 5 days after birth (saccular stage of lung development). The mice were euthanized on PND 21 (alveolar stage of lung development). Lung morphometry was evaluated by the mean linear intercept (MLI). Pulmonary vessel density and macrophage count were quantified using immunohistochemistry. Statistical analyses were performed using the Prism 8 software.

Results: Upon exposure to hyperoxia, the survival in Gdf15⁻/⁻ mice was significantly decreased compared to WT mice (26% vs 57% respectively, p <0.01) (n=32-54/group). MLI was increased by hyperoxia exposure in both genotypes. Interestingly, alveolar simplification was higher in the Gdf15⁻/⁻ females than WT females when exposed to hyperoxia (MLI = 30.0µm vs 26.2µm; n=5 vs n=3, respectively, p <0.001), with no significant difference among WT and Gdf15⁻/⁻ males. Interestingly, Gdf15⁻/⁻ mice had lower macrophage count in the lung compared to WT mice (macrophage counts/HPF = 4.9 vs 12.4 respectively, n=8/group, p <0.001), with no sex-specific differences. The pulmonary vascular density was decreased in hyperoxia with no significant differences between both genotypes.

Conclusions: Our results suggest that in the neonatal mouse BPD models, loss of GDF15 exacerbates neonatal hyperoxic lung injury with respect to alveolar development. We are currently measuring the cell-specific expression of GDF15 in the neonatal lung at different developmental time points. GDF15 is a stress-responsive cytokine that may modulate alveolarization in the developing lung.

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