Loss Of Growth And Differentiation Factor 15 Exacerbates Neonatal Hyperoxic Lung Injury

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BACKGROUND

• Bronchopulmonary dysplasia (BPD) is the most common chronic respiratory disease in preterm infants.
• Growth Differentiation Factor 15 (GDF15) is a divergent member of TGF-β superfamily.
• GDF15 expression increases under pathological conditions including inflammation and hyperoxia.
• Our prior studies showed that Gdf15 expression is increased in vitro and in vivo in neonatal mouse BPD models. Additionally, GDF15 loss exacerbates oxidative stress and decreases cellular viability in human pulmonary endothelial cells.

HYPOTHESIS

The loss of GDF15 will exacerbate neonatal hyperoxic lung injury with respect to alveologenesis, pulmonary vascular development and inflammation.

METHODS

• GDF15 knock out (Gdf15-/-) and wild type (WT) mice were used.
• Mouse pups were randomly allocated into room air or hyperoxia.
• Mice born at saccharal stage of lung development, which corresponds to 26-36 week of fetal period in human.
• Pups were exposed to hyperoxia (95% oxygen) between 12 hours to PND 5 to induce arrest in alveologarization, then transitioned to room air afterward during the alveolar stage of lung development, until time of euthanasia at PND 21.
• Survival data and mice body weights were collected. Lung morphology was assessed using mean linear intercept (MLI). Pulmonary vascular development was estimated by measuring the pulmonary vascular density. Inflammation was evaluated via measuring the pulmonary macrophage count.

RESULTS

• Upon exposure to hyperoxia, Gdf15-/- mice had lower survival, 26% survived compared to 57% of WT mice. (Fig 2)
• Hyperoxia-exposed Gdf15-/- mice had lower body weight than hyperoxia-exposed WT mice.
• Hyperoxia-exposed Gdf15-/- mice had higher MLI (higher alveolar simplification) than WT mice.
• In hyperoxia-exposed WT mice, female had lower MLI than male mice. This represent the sex-specific advantage of female in BPD. This advantage was lost in Gdf15-/- mice. (Fig 3)
• Gdf15-/- had significantly lower macrophage recruitment at both room air and under hyperoxic conditions. (Fig 4A)
• Hyperoxia caused a significant decrease in pulmonary vascular density in both genotypes, without difference between the two mice. (Fig 4B)
• At baseline, Gdf15-/- mice showed lower vascular density than WT mice (Fig 4B).

CONCLUSION

• GDF loss decreases the survival in hyperoxia
• Loss of GDF15 negatively effects the body weight in hyperoxia
• GDF15 loss exacerbates the arrest in alveolar development in neonatal hyperoxic lung injury, with evidence of sex-specific differences
• Loss of GDF15 leads to decreased macrophage population in the lung.

REFERENCES