[A-16] Soluble guanylate cyclase (sGC) modulates alveolarization in a mouse model of bronchopulmonary dysplasia (BPD)

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Background: BPD, a chronic lung disease of prematurely born infants, leads to reduced and abnormal alveolarization, impaired gas exchange, and diminished lung function that often persists into adolescence. Many BPD patients require anesthesia care for procedures related to prematurity and associated medical support (e.g. inguinal hernia repair, central lines). BPD is associated with oxygen- and ventilator-induced injury to the developing lung. Decreased nitric oxide (NO) signaling is likely a component of BPD because NO signaling is reduced in newborn lung injury models and impaired NO production inhibits lung development (1). NO activates sGC to produce cGMP, which promotes vasodilation. sGC is a heterodimer; the sGCα1β1 dimer is the most abundant in lung. Although we previously reported that sGC protein expression is decreased in the hyperoxic newborn mouse lung (2), the role of sGC in lung development is unknown.
Objective: To examine the role of sGC in lung development, we tested whether mouse pups with decreased sGC enzyme activity, with and without lung injury, have reduced pulmonary alveolarization and myofibroblast differentiation.
Methods: C57BL6 sGCα1-null (KO) mouse pups were generated and decreased pulmonary sGC activity was confirmed, as described (3, 4). Inflation-fixed lungs from KO and wild-type (WT) pups exposed to air or 70% O2 for postnatal days 3-13 (P3-P13) were analyzed to determine volume, mean linear intercept (Lm), numbers of alveolar openings, and terminal airway units quantified by log area-circularity (LArC; (4)). Smooth muscle myosin heavy chain (SMMHC) and α-smooth muscle actin (αSMA) immunoreactivity were detected in P13 mouse lung sections. Myofibroblasts were isolated from pup lung periphery and αSMA expression was quantified with flow cytometry and objective gating methods. The results presented are significant at $P<0.05$.
Results: Air-exposed KO pup lungs had fewer terminal airway structures and decreased volume compared with air-exposed WT pup lungs. Compared with the air-exposed KO and the WT pups, 70% O2-exposed KO pups exhibited marked inhibition of alveolarization, evidenced by a decrease in alveolar openings, an increase in Lm, and a further reduction in terminal airway units (LArC), and had decreased body weights. Immunoreactivity to SMMHC and αSMA, which denote smooth muscle cell and myofibroblast differentiation, was decreased in alveolar septae and pulmonary microvascular cells in 70% O2-exposed KO pups compared with the other groups. Moreover, we observed that interstitial fibroblasts isolated from KO pup lung periphery had decreased expression of αSMA and that this reduction persisted with 70% O2-induced lung injury.
Conclusion: These data indicate that lung development, particularly during hyperoxia, is impaired in mouse pups with diminished sGC activity, and these results support the importance of sGC during development of the normal and oxygen-injured newborn lung.
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