Lung Biology Research & Trainee Day
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Category: Staff/Tech/Other
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Title: Neonatal hyperoxia stimulates ATF4-dependent folate metabolism in proliferating alveolar epithelial type 2 cells
Abstract: Neonatal hyperoxia stimulates ATF4-dependent folate metabolism in proliferating alveolar epithelial type 2 cells Min Yee1, Andrew N. McDavid2, Ethan David Cohen1, Heidie Huyck1, Corry Poole1, Brian J. Altman3 ,William M. Maniscalco1, Gail H. Deutsch4, Gloria S. Pryhuber1, and Michael A. O'Reilly1 Departments of 1Pediatrics, 2Biostatistics and Computational Biology, and 3Biomedical Genetics School of Medicine and Dentistry, The University of Rochester Rochester, New York, 14642 USA and Department of 4Pathology Seattle Children's Hospital University of Washington, Seattle, Washington Background: Supplemental oxygen in preterm infants alters postnatal lung development and the host response to respiratory viral infections through poorly understood mechanisms. We previously showed how neonatal hyperoxia enhances the pathogenesis of influenza A virus infection in mice by inappropriately stimulating the proliferation of alveolar epithelial type 2 (AT2) cells that normally takes place on postnatal day (PND) 7. Understanding how hyperoxia stimulates proliferation of AT2 cells in mice may help explain how it disrupts lung development in preterm infants. Objective: To understand how neonatal hyperoxia stimulates proliferation of AT2 cells. Design/Methods: RNA-seq was performed on AT2 cells isolated from PND4 mice exposed to room air or 100% oxygen. Candidate genes were studied during postnatal lung development, in adult mice undergoing alveolar regeneration, in response to fibroblast growth factor (FGF) 7, and in human and baboons with bronchopulmonary dysplasia (BPD). Results: RNA-seq analysis of AT2 cells isolated on PND4 revealed neonatal hyperoxia stimulated expression of genes involved in one carbon-coupled folate metabolism, including the mitochondrial-specific methylenetetrahydrofolate dehydrogenase (Mthfd) 2, the mitochondrial serine mitochondrial methyltransferase (Shmt) 2 used to produce folate from serine, and the phosphoglycerate dehydrogenase (Phgdh). Consistent with their role in promoting proliferation, expression of these genes was also increased when AT2 cells normally proliferate on PND7, when they proliferate following tissue injury, and when they proliferate in response to FGF7. However, unlike these conditions, hyperoxia uniquely stimulated expression of activating transcription factor 4 (ATF4), which mediates the response to mitochondrial stress. Scavenging mitochondrial superoxide or depleting ATF4 using siRNA revealed hyperoxia stimulated ATF4-dependent folate expression via mitochondrial oxidation. These findings were not restricted to mice because increased expression of MTHFD2 and ATF4 was seen in hyperplastic AT2 cells of human and baboon lungs with bronchopulmonary dysplasia. Conclusion: Our findings reveal hyperoxia inappropriate stimulates folate metabolism and proliferation of AT2 cells via mitochondrial oxidative stress and ATF4. Modulating this pathway may provide new opportunities for improving health of preterm infants exposed to oxygen. Funding Sources: NHLBI R01HL091968 (MOR), NCI R00CA204593 (BJA), NHLBI U01HL122700 (GSP) Key Words: Neonatology, hyperoxia, lung