# Lung Biology Research & Trainee Day
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Title: Low Dose Hyperoxia Primes Airways for Fibrosis in Mice after Influenza A Infection
Abstract: Background: Despite improved ventilation strategies, preterm infants exposed to oxygen (O2) remain at risk for developing airway hyperreactivity (AHR) through poorly understood mechanisms. We previously described a mouse model wherein low dose O2 (40% for 8 days at birth, 40x8) causes transient AHR that resolves. Pilot studies revealed the unexpected finding of peribronchial fibrosis and AHR when 40x8 mice were challenged with Influenza A Virus (IAV). Objective: To determine whether low dose hyperoxia primes the lung for profibrotic TGFβ signaling following IAV infection and identify predisposing factors driving morbidity. Design/Methods: Naïve and infected adult (8-10 week old) mice exposed to room air (RA) and 40x8 hyperoxia were evaluated for airway function, fibrosis, TGFβ signaling receptors/mediators, and activators of TGFβ signaling such as Thrombospondin 1 (TSP-1). Mice from both groups were intranasally infected with 10^5 PFU of H3N2 (HKx31) Influenza A virus or sham control. Viral titers, bronchoalveolar lavage (BAL) cell counts, TSP-1 levels, TGFβ levels, collagen deposition, and respiratory function were analyzed after infection. Expression of candidate TGFβ genes (including TSP-1) were also assessed in early-childhood autopsy lung sections from infants with BPD and compared to age-matched controls. Results: Naïve adult mice had similar baseline respiratory function and lung morphology. After IAV infection, 40x8 mice had decreased compliance, increased resistance, and increased peribronchial/perivascular fibrosis compared to RA controls at post-infection day (PID) 14. Increased Fibroblast Specific Protein 1 (FSP-1) positive inflammatory cells were present around the fibrotic airways of 40x8 IAV infected mice at PID14. Active TGFβ was increased in lavage of 40x8 mouse lungs at PID 3, which correlated with a peak in TSP-1 levels, likely in activated platelets. While higher TGFβ activation was not associated with higher levels TSP-1 during infection, baseline levels of TSP-1 were significantly higher in uninfected 40x8 mice. Increased TSP-1 was also evident in human BPD samples compared to non-BPD controls. Conclusions: Neonatal hyperoxia causes increased TSP-1 levels in both mice and children with a history of BPD, thus potentially priming the lung for AHR and increased morbidity via hyperactivated TGFβ signaling and extracellular matrix remodeling. These findings may help explain why former preterm infants are predisposed to airway obstruction and increased morbidity after viral infection.