MATERNAL EXPOSURE TO POLYCYCLIC AROMATIC HYDROCARBONS (PAHS) AUGMENTS NEONATAL HYPEROXIC LUNG INJURY AND ALTERS THE GUT MICROBIOME IN MICE: MECHANISTIC ROLE OF CYTOCHROME P450 (CYP)1A1, 1A2, AND 1B1

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Background: Pregnant women exposed to high levels of polycyclic aromatic hydrocarbons (PAHs) are at increased risk for premature delivery. Preterm infants often require supplemental oxygen that could lead to chronic lung disease. Early studies from our lab suggest that PAH exposure in utero may modify the newborn mouse's risk of developing lung disease in response to oxygen. The molecular mechanisms by which hyperoxia causes lung injury are not understood, but cytochrome P450 (CYP) enzymes have been implicated. Gut-lung crosstalk has also been suggested, as alterations in the gut microbiome have been shown to influence certain lung diseases. We hypothesize that prenatal administration of PAHs [i.e. benzo[a]pyrene (BP), or a mixture of BP and benzo(b)fluoranthene (BbF)] differentially exacerbates lung injury and alters the gut microbiome in neonatal mice following postnatal hyperoxia, and that this effect is altered in mice lacking the gene for cytochrome P450 (Cyp)1a1, 1a2, or 1b1.

Materials/Methods: Dose response of prenatal PAH administration on postnatal hyperoxic lung injury was tested using BP doses of 7.5, 15, and 30 mg/kg. Timed pregnant WT (C57BL/6J), Cyp1a1-null, Cyp1a2-null, and Cyp1b1-null mice were treated orally with the vehicle corn oil (CO) or mixture of PAHs BP and BbF (7.5 mg/kg each) on gestational days 16-19. Offspring were exposed to hyperoxia or room air for 14 days. Mice were sacrificed on PND14, and lung injury was assessed by radial alveolar count (RAC). 16S rRNA gene sequencing was performed on intestinal samples to analyze the effect of PAH exposure on the gut microbiome.

Results: Hyperoxic lung injury is augmented by prenatal PAH exposure in a dose-dependent manner. This effect is differentially altered in Cyp1a1-null, Cyp1a2-null and Cyp1b1-null mice. Gut microbiome analysis revealed differences in Bray-Curtis beta diversity observed between PAH and CO groups in WT mice.

Conclusions: Results suggest that the metabolism of PAH by Cytochrome P450 (CYP)1A1, 1A2, and 1B1 enzymes may play a mechanistic role in the augmentation of hyperoxic lung injury by PAH. In addition, PAH-induced alterations in the gut microbiome may play a role in augmentation of hyperoxic lung injury. Future studies could lead to the development of novel strategies against BPD in premature infants exposed prenatally to PAHs.