

BACKGROUND

Pregnant women who are environmentally exposed to polycyclic aromatic hydrocarbons (PAHs) are at increased risk for preterm delivery. Preterm infants often require supplemental oxygen (hyperoxia) that can lead to a chronic lung disease called bronchopulmonary dysplasia (BPD). Studies from our lab show that cytochrome P450 genes (*Cyp1a1*, *1a2*, and *1b1*) are mechanistically involved in hyperoxic lung injury with CYP1A expression being protective and CYP1B1 acting as a pro-oxidant. Both prenatal BP and postnatal hyperoxia exposure alter the neonatal gut microbiome, which may modulate neonatal hyperoxic lung injury via the gut-lung axis.

HYPOTHESIS

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 alveolar simplification in neonatal mice following postnatal hyperoxia., and this effect is altered in mice lacking the gene for cytochrome P450 (*Cyp1a1*, *1a2*, or *1b1*).

METHODS

- Timed pregnant WT (C57BL/6J), *Cyp1a1*-null, *Cyp1a2*-null, and *Cyp1b1*-null mice (n=4) treated orally with vehicle corn oil (CO) or a mixture of PAHs BP and BbF (7.5 mg/kg each) on gestational days 16-19.
- Newborn mice (term, day 21) were exposed to hyperoxia or room air for 14 days.
- On PND14, mice were euthanized and lung tissue analyzed for alveolar simplification by radial alveolar count (RAC)
- Lung inflammation was analyzed using qPCR to measure TNF and IL-6 mRNA expression
- qPCR also used to analyze CYP1A1 and CYP1B1 mRNA expression
- Intestinal tissue samples obtained on PND 14 sent for 16S rRNA gene sequencing for microbiome analysis.

RESULTS

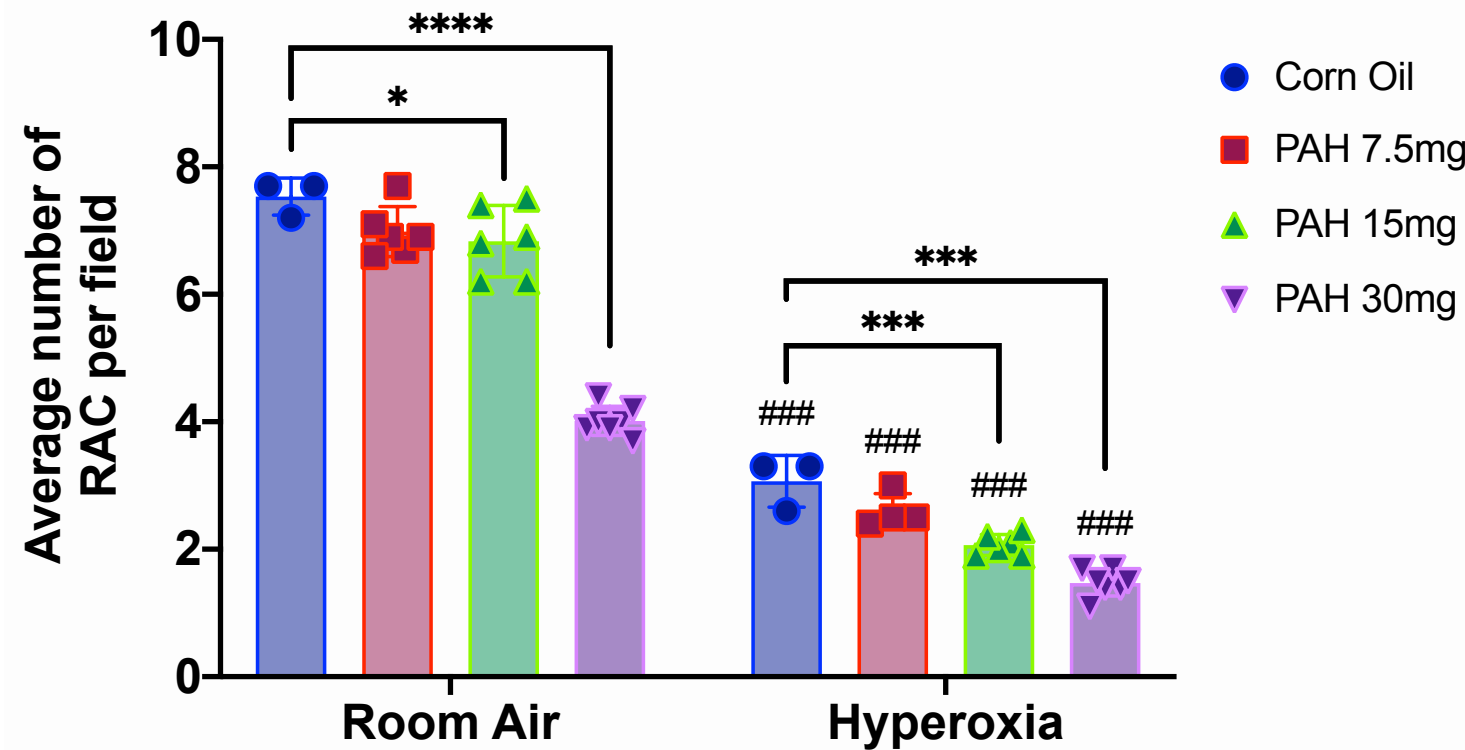


Fig 1: Dose Response of prenatal polycyclic aromatic hydrocarbon (PAH) exposure on hyperoxic lung injury in WT mice by comparison of radial alveolar count (RAC).

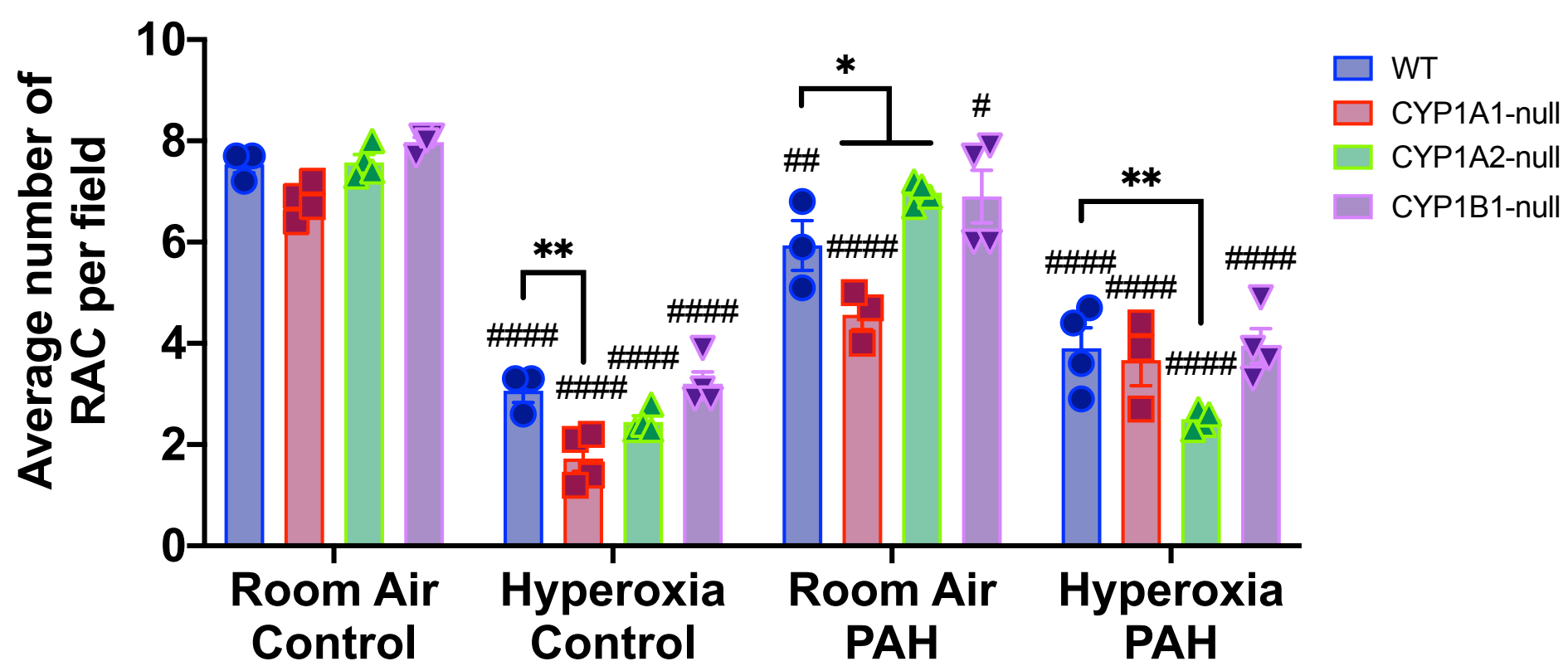


Fig 2: Effect of prenatal PAH exposure on hyperoxic lung injury in WT, *Cyp1a1*-null, *Cyp1a2*-null, *Cyp1b1*-null mice by measurement of radial alveolar count (RAC)

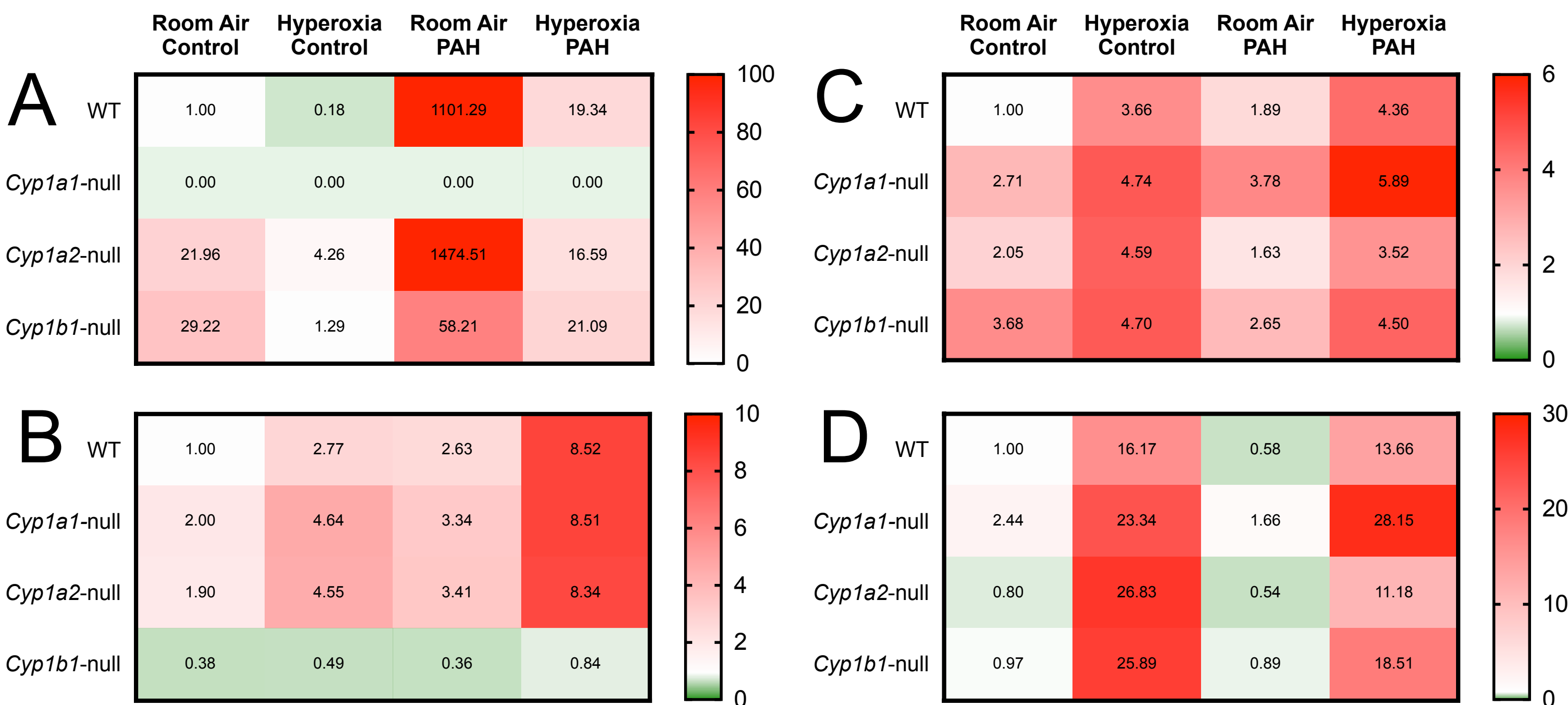
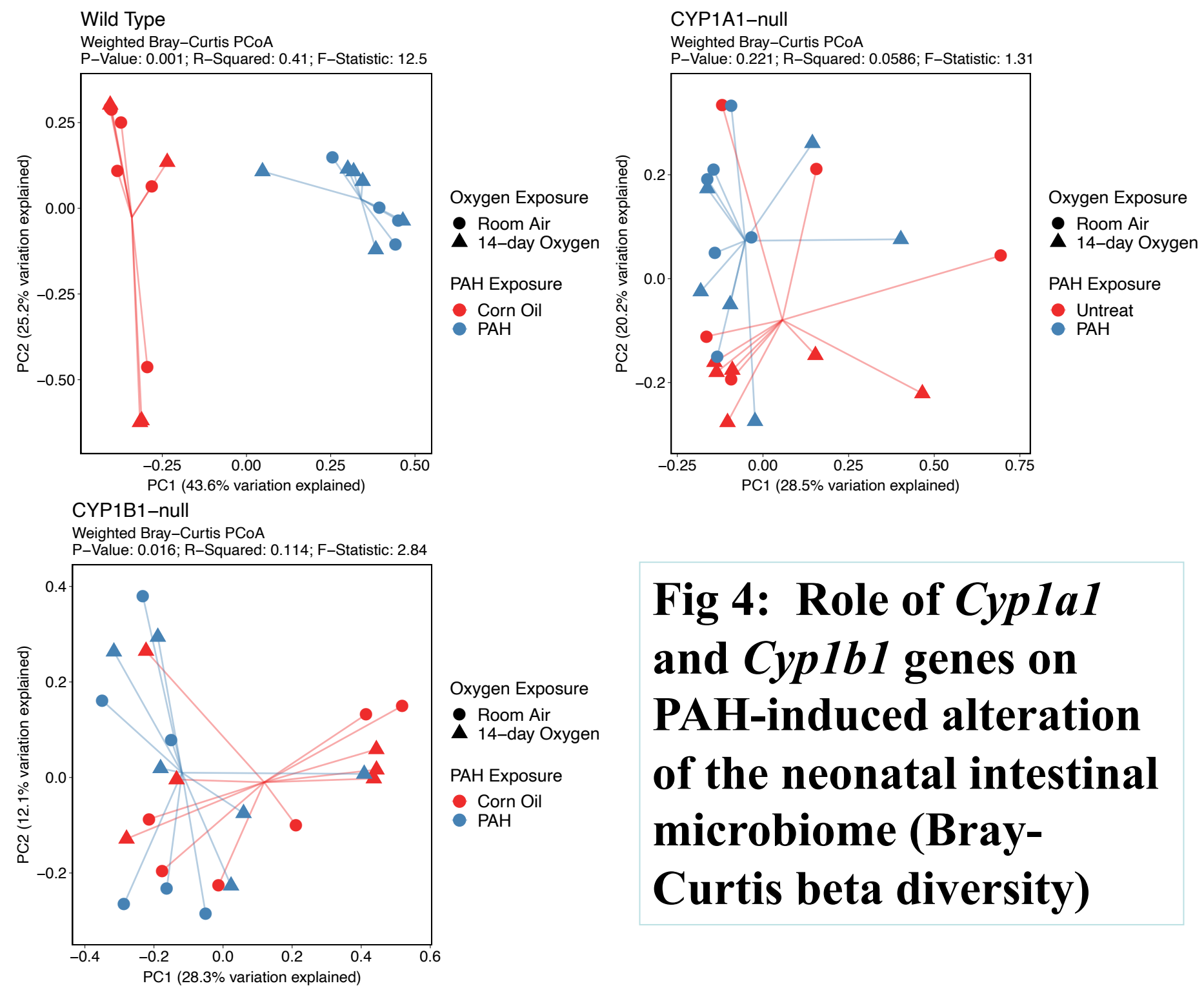


Fig 3: Effect of prenatal PAHs and postnatal hyperoxia exposure on lung mRNA expression in newborn mice. A. CYP1A1 mRNA expression B. CYP1B1 mRNA expression C. TNF expression D. IL-6 expression.

CONCLUSIONS

- Hyperoxic lung injury is augmented in a dose-dependent manner following prenatal PAH exposure.
- PAH exposure differentially alters lung injury in WT, *Cyp1a1*-null and *Cyp1a2*-null, but not *Cyp1b1*-null mice.
- There was significant induction of CYP1A1 expression in neonatal mice exposed prenatally to PAH in room air and suppression of CYP1A1 expression following hyperoxia, suggesting that CYP1A1 expression is protective against hyperoxic lung injury and at low doses, PAH administration results in induction of CYP1A1 expression.
- Hyperoxia and PAH alone caused modest increase in CYP1B1 expression but together caused significant induction, suggesting that CYP1B1 may contribute to the potentiation of lung injury by PAH.
- Prenatal PAH exposure causes significant alterations in neonatal intestinal microbiome compared with corn oil (CO).
- The microbiome difference observed between PAH and control groups in WT mice was no longer significant in *Cyp1a1*-null mice, suggesting that CYP1A1 metabolism of PAH plays a role in altering the microbiome.