Perinatal Acetaminophen Toxicity is Mediated by Cytochrome P450 2E1 (CYP2E1) In a Time and Cell-Type Specific Manner

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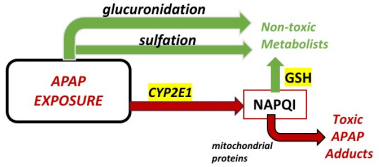
INTRODUCTION

Acetaminophen (APAP) exposures occur in 50-60% of pregnancies in the US[1] and is concerningly associated with childhood respiratory morbidity[2–23] . **The mechanism behind this remains unknown.**

Most of APAP can be metabolized through glucuronidation or sulfation pathways, producing non-toxic metabolites that can be excreted. These pathways can become overloaded. Cellular toxicity of APAP is dependent on its conversion by *Cyp2e1* into the mitochondrial toxin NAPQI, resulting in oxidative stress.



In adults, pericentral hepatocytes express highest levels of *Cyp2e1* making these liver cells highly susceptible to NAPQI injury. However, fetal hepatic *Cyp2e1* expression is low. Rather, Lung Map data show that in the developing murine lung, prenatal pulmonary *Cyp2e1* expression peaks during the saccular stage (E17.5-P4) and is limited to the myofibroblast.

This study sought to confirm preliminary data on *Cype2e1* expression and to interrogate the impact of APAP on the developing fetal lung.

HYPOTHESIS

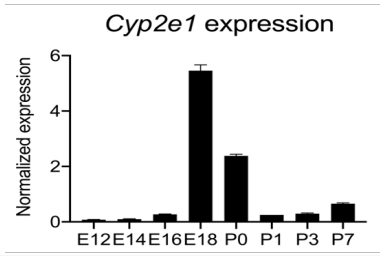
We hypothesize this peak in *Cyp2e1* expression predicts susceptibility to APAP-induced lung injury during this critical developmental period.

METHODS

Murine model: C57BL/6
Murine dam treatments:
-APAP dose: 250mg/kg IP; 6hr on E18
Outcome Measures:
-mRNA expression was evaluated by qPCR for *Il6, Mmp9, Gclc, Hmo1, Nqo1, Trp53, Puma, Noxa*
- RNA isolated from lungs of WT mice from E12-P7 and assessed for *Cyp2e1* expression by Western Blot
- *Cyp2e1* expression in Pdgfrα -GFP labeled pulmonary myofibroblasts was compared to *Cyp2e1* expression in all other lung cell types.
- Statistical analysis was preformed by t-test using GraphPad prism

RESULTS

Fig 1a: Cyp2e1 Expression from lungs of WT Mice



RESULTS

Fig 1b: Cyp2e1 Expression in Pdgfra -GFP Cells

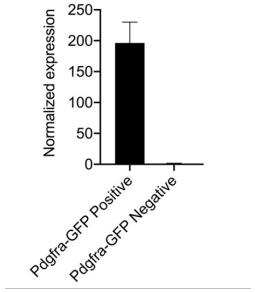


Fig 1c: APAP exposure induces Cyp2e1 on E18

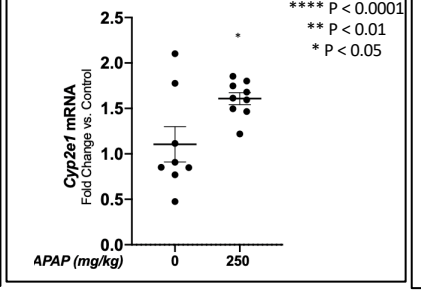


Fig 2a: APAP exposure induces inflammatory gene expression on E18

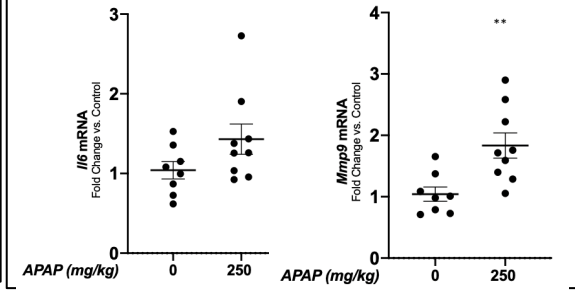


Fig 2c: APAP exposure induces oxidative stress element gene expression on E18

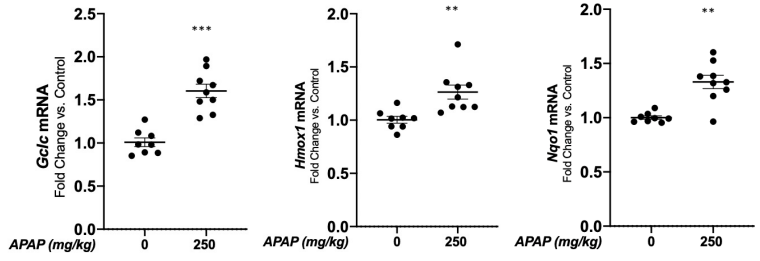
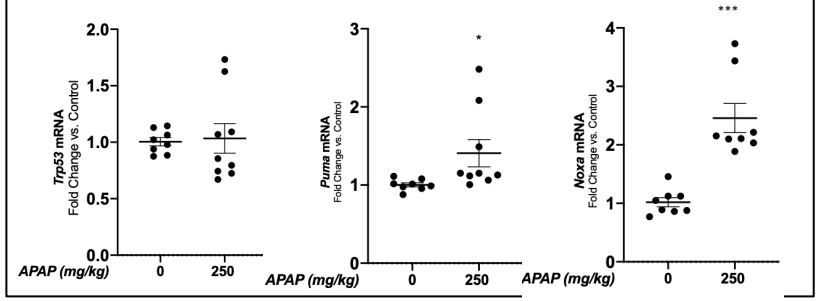


Fig 2b: APAP exposure induces apoptotic gene expression on E18



CONCLUSION

We demonstrated that pulmonary *Cyp2e1* expression is timing and cell-type specific, peaking at E18 and limited to the mesenchymal myofibroblast.

We also found that a non-lethal dose of APAP resulted in upregulation of expression of genes associated with antioxidant response elements, apoptosis, and inflammation.

Continued work is needed to determine whether perinatal APAP exposure has detrimental effects on the developing lung, its function, and the role of pulmonary *Cyp2e1* in this mechanism of lung injury.