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Basic Science

Abstract Title
Maternal Diabetes Influences Sensitivity to Cigarette Smoke Induced Lung Inflammation and Gene Expression in Offspring

Background
COPD is primarily caused by smoking. However, <20% of smokers develop COPD, suggesting additional risk modifiers, such as early-life exposures. Previously, we found that males exposed to maternal diabetes (MD) had worse lung function and more inflammation when exposed to cigarette smoke (CS).

Objective
Here we build on that finding by investigating how offspring exposed to MD alters CS-induced changes in inflammatory biomarkers of COPD, DNA methylation (DNAm), and mRNA abundance for lung repair and detoxification genes.

Methods
Six-week-old C57BL/6NJ female mice were fed a high-fat-diet (45% kcal) to induce diabetes or low-fat-control-diet (10% kcal) for 6-weeks, and throughout pregnancy and weaning. Offspring were weaned onto standard diet until 8-weeks of age and then exposed to CS/Room air (RA) for four days. Lung tissue and lavage were analyzed for serum amyloid A (SAA) and myeloperoxidase abundance, DNAm (pyrosequencing), and mRNA (qPCR). Data analyzed by two-way ANOVA.

Results
CS exposure significantly increased cytochrome p450 1A1 (CYP1A1) abundance in both sexes, regardless of diet. Insulin-like growth factor binding protein-3 (IGFBP3) abundance in male offspring was reduced by MD, independent of CS, compared to control males (-1.4-fold). A similar decrease was seen in CS animals from non-MD mothers (-1.5-fold). Female MD-CS offspring had significant induction of epoxide hydrolase (EPHX1) abundance (1.4-fold). Changes in mRNA were not accompanied by specific DNA methylation changes at target CpGs. CS exposure in Male MD offspring had a higher lavage SAA (0.27±0.01μg/mL) compared to control-CS (0.19±0.02μg/mL). Lung tissue, but not lavage, myeloperoxidase was significantly elevated in CS exposed MD offspring compared to controls, regardless of sex (345.6±16.4 vs. 308.0±12.3pg/mg).

Conclusion
Exposure to MD alters the abundance of genes involved in lung growth and detoxification and promotes elevation of COPD biomarkers following CS. This suggests MD exposure may be a risk modifier determining susceptibility to CS in later life.

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