Investigating the Effects of PFAS Treated Cells on Key CYP450 Gene Regulation

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Per- and polyfluoroalkyl substances (PFAS) are environmentally persistent synthetic chemicals with documented hepatotoxicity; however, their effect on the hepatic drug-metabolizing enzymes and transporters remain incompletely characterized. Previous studies suggest that individuals with elevated PFAS plasma concentrations have worse cancer treatment outcomes. Whether altered expression of drug metabolizing enzymes contributes to these outcomes remains unknown. This study investigated whether PFAS exposure alters the expression of key CYP450 drug metabolizing genes and whether these effects are dose dependent. We performed a focused transcriptomic reanalysis of publicly available TempO-Seq data (GEO: GSE244107) from human induced pluripotent stem cell-derived (hiPSC) hepatocytes exposed to 3 PFAS (PFOA, PFUnDA, 8:2 FTS) representing 2 structural classes at 0.1, 1, 10 µM. Differential expressions of 5 key hepatic CYP450 drug metabolizing genes were assessed using the limma package in R, and expression patterns were visualized using heatmaps. For each CYP450 gene and PFAS, differences among vehicle control and the three exposure concentrations were evaluated in GraphPad Prism using one-way ANOVA and Dunnett's multiple comparison test. Statistical significance was defined as $p<0.05$. PFAS exposure produced gene and concentration specific changes in CYP450 expression both within and across PFAS structural classes. CYP3A4 and CYP2C9 were significantly induced by all 3 PFAS, while CYP3A5 has shown significant induction under selected exposure conditions. These findings suggest that PFAS exposure may alter hepatic drug metabolism through changes in the expression of CYP450 enzymes. Functional assays are needed to determine whether these transcriptional changes alter CYP450 activity and drug disposition. Supported by NJ ACTS CREST Program funded by NIH R25TR004777.