

Exploring Metabolic Enzymes and Transporters in Human Placentas: Expression Profiling by RNA-Sequencing

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The placenta protects the fetus and transports nutrients while allowing for waste excretion. As a metabolically active tissue, the placenta is comprised of enzymes and transporters that can impact xenobiotic disposition and in turn, development of the fetus. The processing of drugs and chemicals by the placenta is regulated by uptake and efflux transporters and drug metabolizing enzymes. For this study, we sought to evaluate expression of 250 xenobiotic metabolizing enzyme and transport genes and their transcriptional regulators in healthy human placentas from mid-term to term pregnancy. Using existing RNA-sequencing data (GSE124282), differences in mRNA levels in human primary cytotrophoblasts were evaluated at mid-term (18-22 weeks, N=4) and term (38-40 weeks, N=4). Mean FPKM values were calculated for each gene and used to assess overall abundance (FPKM > 1) at mid-term and term gestation. The edgeR package for R software was used to ensure quality control and to identify differentially expressed genes (false discovery threshold <0.05). Of the 250 genes evaluated, 59% and 93% were expressed in trophoblasts at mid-term and term, respectively. The most highly expressed gene families included HSD (hormone pathways), ALDH (phase I metabolism), GST (phase II metabolism), SLC (uptake transporters), and select ABC (efflux transporters). As expected, time-dependent expression was observed for hormone-related genes including those enriched at midterm (CGA, HSD3B2, HSD17B1, CYP11A1 and 19A1) and term (CRH). Select xenobiotic processing genes enriched at mid-term included the phase I enzyme EPHX1 (3-fold) and the uptake carrier SLCO2B1 (18-fold). By late in pregnancy, higher mRNA levels of phase I enzymes CES1 (29-fold), ALDH1A2 (3-fold), and ALDH2 (3-fold), as well as uptake transporters SLC22A1 (13-fold), SLCO3A1 (2-fold), SLCO4A1 (7-fold), and SLC11A1 (4-fold) were observed. These data suggest dynamic changes in the processing of drugs and toxicants across gestation which may impact placental functions and fetal exposure to xenobiotics. Funded by NIH ES020721, ES001748, ES005022, TR003017, ES029275, and ORED.

