Low-Dose PFOS Exposure Alters the Placental Transcriptome in C57BL/6 Mice

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The placenta plays a vital role in fetal development and health. As the primary conduit for fetal development, the placenta mediates nutrient transfer, waste elimination, gas exchange, hormone production, and development of the fetal immune system. Per- and polyfluoroalkyl substances (PFAS) are a class of man-made, ubiquitous environmental toxicants known to cause adverse health effects. Perfluorooctanesulfonic acid (PFOS), the most prevalent PFAS member, consists of a synthetic perfluorinated eight-carbon backbone with a sulfonic acid head group. Evidence suggests that PFOS can induce developmental toxicity in humans and rodents following placental transfer and has been associated with low birth weight in humans. Furthermore, PFOS is detected in both human and rodent umbilical cord blood and in breast milk. The overarching hypothesis of the work is that PFOS exposure impacts placental health and function through modulation of the placental transcriptome. The aim of this study was to elucidate the effects of developmental PFOS exposure at 3 ppm (~0.3 mg/kg/day) or 30 ppm (~3 mg/kg/day) per day in feed on the placental response *in vivo* using 10-week old C57BL/6 timed-pregnant dams. On gestational day 1 (GD1), dams were assigned to one of the following blinded experimental diets and fed *ad libitum*: 1) Standard chow diet, 2) 3 ppm PFOS (w/w) or 3) 30 ppm PFOS (w/w). Dams were euthanized at GD17 and placentae collected. Fetal weight collection confirmed statistical significance in low birth weight association to PFOS exposure with a more robust weight reduction in the 3 ppm PFOS-treated. RNA integrity was confirmed, libraries were prepared, and next-generation sequencing (RNA-Seq) was performed to investigate the impact of PFOS exposure on the placental transcriptome. Our studies indicate upregulation of Phospholipase C signaling, Actin Cytoskeleton Signaling, Rho Family GTPase, EIF2 Signaling, Oxidative Phosphorylation signaling pathways, with 3 ppm PFOS inducing a more robust transcriptional response. In addition, at 3 ppm PFOS elicited a fold change of ~2.0 in the Gzmf, Emilin1, Gzmg, Slit1, and Lrp1 genes. Interestingly, gene Hsd3b1 resulted in a fold change of ~2.0 within the PFOS-treated. Hsd3b1 is responsible for the conversion of pregnenolone to progesterone in the placenta. In summary, our data suggest that PFOS, at relatively low concentrations in diet, can induce a significant placental response.