

Chronic Low-Dose PFOS Exposure Alters the Transcriptome and DNA Methylome of Human Fallopian Tube Epithelial Cells

ABSTRACT

Per- and polyfluoroalkyl substances (PFAS) such as perfluorooctane sulfonate (PFOS) are persistent environmental contaminants of increasing concern for human health, yet their molecular effects on fallopian-tube-derived epithelial cells remain poorly characterized. Here we integrated cell proliferation rates with transcriptomic and methylation datasets generated from fallopian non-ciliated epithelial (FNE) cells expressing human telomerase and exposed to 20 nM PFOS vs vehicle control over the time of 8-week tissue culture experiments. FNE cells exposed to 20nM PFOS concentrations significantly increased proliferation as assessed by live cell imaging, BrdU incorporation, metabolic experiments. The RNA sequencing experiment identified 1,412 significant differentially expressed genes with 1,002 down-regulated, 410 up-regulated. All top ten differentially expressed genes that were upregulated, belonged to DNA replication and proliferation control. Methylation profiling detected 8,751 differentially methylated regions (DMRs), with 5,513 hypermethylated and 3,238 hypomethylated regions spanning 4,034 genes. Intersecting transcriptomic signature with the methylome revealed strongest downregulation of DEPTOR transcript and hypermethylation of three intronic DMRs within the DEPTOR locus, one of which directly overlaps an annotated enhancer element (ENCODE cCRE EH38E2660818). Biochemistry experiments validated DEPTOR inhibition by PFOS, and demonstrated that PFOS activates mTOR pathway. Inhibition of DEPTOR mimicked PFOS effects on FNE cell proliferation, while inhibition of mTOR rescued FNE cell proliferation in the presence of PFOS. These results indicate that long-term non-toxic exposure to nM PFOS concentrations can modify epigenetic and transcriptomic programs leading to dysregulation of DEPTOR/mTOR signals and increase FNE cell proliferation. Because telomerase is detectable in normal female reproductive tissue and further elevated in neoplasms in the distal fallopian tube, our data might support the idea that PFOS exposures through mTOR signaling aid oncogene-driven proliferation.