THE POTENTIAL ROLE OF AHR LIGANDS IN MALE INFERTILITY AND PROSTATE CANCER – STUDY USING PROSTATE CARCINOMA LNCAP CELLS

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Introduction: Exposure to dioxin analogues correlates with increased risk of unexplained infertility in men. These compounds are known to mediate their effect through a ligand-dependent transcription factor called aryl-hydrocarbon receptor (AHR). Besides direct transcriptional regulation, AHR interacts with estrogen receptor (ER) and alters the expression of ER responsive genes. The current study focuses on the processes affected by exposure to AHR ligands at physiological levels that can lead to male reproductive system dysfunction. In the study, ER and AHR positive human prostate cancer cell line LNCaP was used as a model to investigate global gene expression in male reproductive cells, exposed to two natural AHR ligands in presence and absence of oestradiol.
Methods:. RNA was extracted from cells, treated with oestradiol (10 nM), baicalein (1 uM), resveratrol (1 μM) and co-treated with baicalein/oestradiol at several time points, following cDNA synthesis. Chromatin was extracted and immunoprecipitated using ERα antibodies. HTP sequencing was applied for all samples.
Results: Analysis of the sequencing data revealed that the expression of thousands of genes was significantly regulated in LNCaP cells after treatment with baicalein and resveratrol. We also noticed remarkable influence of studied compounds on ER-responsive gene expression. Among the genes with the highest expression rate change (p0.05) were genes previously associated with carcinogenesis (*TGFB1, PRKCB*, etc.), endocrine disruption (*CYP1A1, CYP11A1,* etc.) and spermatogenesis (*CCNB1, CCNB2, CCND2*, etc.). RNA-seq and ChIP-seq results refer to the direct action of AHR ligands on ER signaling and suggest a set of ER-responsive genes directly regulated by baicalein and resveratrol.
Conclusions: A set of ER-responsive genes directly regulated by baicalein and resveratrol might serve as potential markers for AHR ligand action at physiological concentrations in male reproductive tissues and reveal their role in endocrine disruption, male infertility and prostate cancer. Further studies using patient samples as well as *in vivo* experiments will be performed to analyze the results of the current study.