Imparting Hormone Imprint on Estrogen Responsive Genes Leading to Increased Risk of Uterine Fibroids by Developmental Exposure to Endocrine Disrupting Chemicals

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Introduction

The period during which tissue and organ development occurs is a time of exquisite sensitivity to environmental exposure. However, the mechanism by which the epigenome is disrupted in response to developmental insults such as endocrine disrupting chemicals (EDCs) leading to increased risk of hormone-dependent diseases remains unclear. Therefore, this objective is to determine how EDC exposure alters the estrogen signaling in progenitor/myometrial stem cells (MMSCs) leading to increased risk of uterine fibroids (UFs) pathogenesis.

Materials and Methods

Female Eker rats were subcutaneously injected with diethylstilbesterol (DES) or sesame seed oil (VEH, n=5) on PND10-12, a critical period of uterine development. MMSCs were isolated from MM tissue using dual Stro-1 and CD44 surface markers at 5 months. RNA-sequencing and ChIP-sequencing with anti-H3K4me3 antibody were performed in DES- and VEH-MMSCs. Ad-estrogen response element (ERE)-luc adenovirus were used and luciferase activities were measured. Student T test was used for statistical analysis. $P \leq 0.05$ was considered significant

Results

Developmental exposure to EDC reprograms the estrogen responsive genes

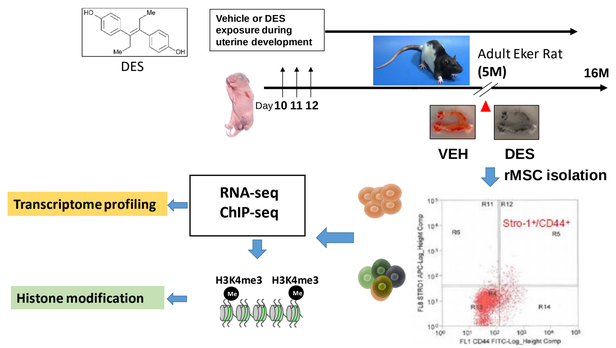


Fig. 1 Experimental paradigm

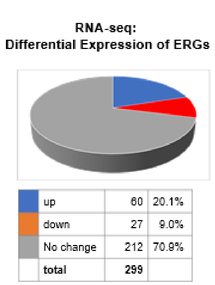


Fig. 2 Transcriptional profiling reveals reprogramming of estrogen responsive gene transcriptome

Epigenetic reprogramming of *Esr-1* and ERGs

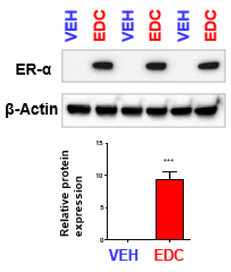


Fig. 3 ER-a is upregulated in EDC-MMSCs compared to VEH-MMSCs

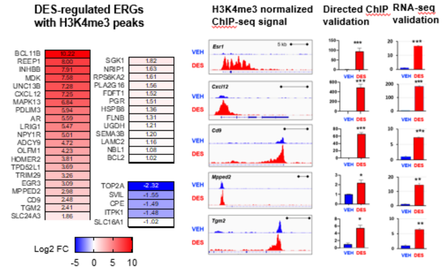


Fig. 4 EDC exposure disrupts the epigonome related ERGs in MMSCs

Developmental EDC exposure activates estrogen signaling in MMSCs

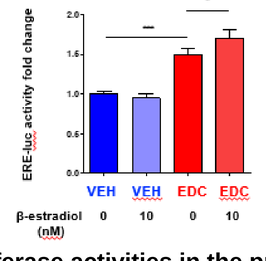


Fig. 5 Luciferase activities in the presence or absence β-estradiol (10 nM) are compared between EDC-MMSCs and VEH-MMSCs

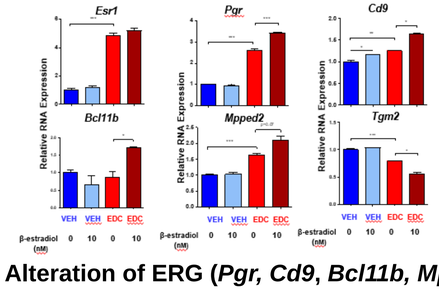
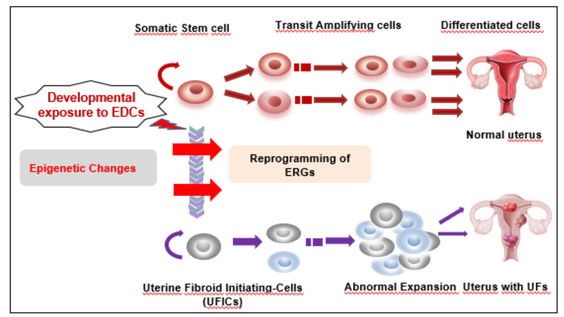


Fig. 6 Alteration of ERG (*Pgr, Cd9*, *Bcl11b, Mpped2*, and *Tgm2*) as well as *Esr1* expression in the presence or absence of estrogen in EDC-MMSCs and VEH-MMSCs

Summary

Working model



Conclusions

We provide compelling evidence that progenitor/MMSCs, the cell origin for UFs are the direct epigenetic targets of xenoestrogenic actions. These epigenetic changes impart hormone imprint on ERGs, resulting in a “hyper-estrogenized” phenotype that leads to increased risk of hormone dependent uterine related diseases such as UFs.

Acknowledgments

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