Loss of Uterine Histone Deacetylase Activity in Neonatal DES Exposed Mice Contributes to Persistent Changes in Gene Expression and the Epigenome

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Estrogen exposure during development results in abnormal uterine differentiation that leads to infertility and cancer. Mice exposed to diethylstilbestrol (DES) exhibit extensive uterine gene expression changes that are accompanied by excessive histone H3K27ac occupancy at nearby enhancers. Histone deacetylase proteins are reduced following neonatal DES exposure and could contribute to this phenotype. To test this idea, we generated a mouse line in which HDAC2 was conditionally overexpressed in the uterus (HDAC2cOE) to prevent the DES-induced reduction in HDAC activity. HDAC2cOE mice exposed neonatally (postnatal day 1 [PND1] to PND5) to DES (1 mg/kg/day) had 529 differentially expressed uterine genes (DEGs) when compared to wild type (WT) DES-exposed mice on PND5. This number represents ~10% of the 6,328 DEGs between WT DES-exposed and WT control (CON) uteri. In adults, there were 1,495 DEGs when comparing DES-exposed HDAC2cOE and WT; 1,009 (~11%) of these overlapped the 9,174 DES induced DEGs when comparing WT DES versus WT CON. HDAC2 overexpression resulted in extensive removal of acetylated H3K27 but only minor changes in H3K9ac for both CON and DES as determined by CUT&RUN sequencing. Robust epigenetic changes were observed in WT DES compared to WT CON with 4,155 regions of H3K27ac gain; of these, 1,866 (45%) were reduced toward WT CON levels in the HDAC2cOE DES group. These 1,866 locations were near 752 DES-induced DEGs including *Wnt5a*, a gene important for uterine differentiation. An overlap of PND5 and adult DES-induced H3K27ac revealed ~400 locations that persisted over time. We conclude that reduced HDAC activity accounts for a small but significant percentage of the persistent DES induced epigenome and gene expression changes observed following neonatal DES exposure. These findings suggest that alterations in the levels of chromatin remodeling proteins induced by developmental chemical exposures is one mechanism to explain the developmental origins of adult health and disease.