Role of NCOR1 in implantation and decidualization.

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Epigenetic regulation plays an important role for steroid hormone responses in normal uterus. Nuclear receptor corepressor 1 (NCOR1) interacts with SMRT/HDAC3 complexes to repress target gene transcription. Furthermore, NCOR1 is a key regulator of both PGR and ESR1 transcriptional activity. Our previous work has elucidated that HDAC3 is downregulated in the endometrium of infertile women with endometriosis and that loss of HDAC3 results in non-receptive endometrium and female infertility due to dysregulation of PGR and ESR1 signaling. Our immunohistochemical analysis revealed that NCOR1 was significantly decreased in endometrial epithelial and stromal cells from infertile women with endometriosis compared to controls. It suggested that NCOR1 plays a critical role in normal endometrial functions during early pregnancy. To investigate the role of NCOR1 during early pregnancy, we generated a mouse model with *Ncor1* conditionally ablated in *Pgr*-positive cells ($Pgr^{cre/+}Ncor1^{f/f}$; $Ncor1^{d/d}$). Fertility test was performed by mating 8-weeks old control ($Ncor1^{f/f}$) and $Ncor1^{d/d}$ mice with wild-type male in 6-month period. $Ncor1^{f/f}$ mice were fertile with an average of 4.86 ± 0.34 litter per mouse and 33 ± 2.18 pups per mouse. However, 6 of 7 $Ncor1^{d/d}$ mice (85.7%) were infertile and one $Ncor1^{d/d}$ mice was severe subfebrile with one litter. $Ncor1^{d/d}$ mice showed normal histology of ovary, fertilization, and the serum levels of E2 and P4. To determine whether *Ncor1* loss impacts at early pregnancy, high frequency ultrasounds were performed to monitor pregnancy at GD5.5, GD7.5 and GD9.5 in uterus of $Ncor1^{f/f}$ and $Ncor1^{d/d}$ mice using Fujifilm Vevo 3100 Preclinical Imaging System. Although $Ncor1^{d/d}$ mice showed normal number of implantation sites at GD5.5, the sizes of implantation sites in $Ncor1^{d/d}$ mice were significantly smaller compared to $Ncor1^{f/f}$ mice. After that, we could not detect implantation site at GD7.5 and GD9.5 in $Ncor1^{d/d}$ mice. This result suggests that NCOR1 deficiency in the uterus causes early pregnancy loss. To address a defect of embryo implantation in $Ncor1^{d/d}$ mice, mice were dissected at GD4.5. $Ncor1^{f/f}$ mice showed visible implantation sites in uterine, but implantation sites in uterine of $Ncor1^{d/d}$ mice at GD4.5 could be divided into 2 groups: Group #1 with implantation sites were visible (4/10, 40%) and Group #2 with no implantation site (6/10, 60%) in the uterine. Next, we performed artificial decidualization to examine the effect of *Ncor1* ablation on decidualization. While $Ncor1^{f/f}$ mice displayed a decidual uterine horn that responded well to this decidual induction, $Ncor1^{d/d}$ mice exhibited a defect of decidualization. These results suggest that $Ncor1^{d/d}$ mice results in early pregnancy lost due to defects of implantation and decidualization. This work was supported by NIH P01HD106485, R01HD101243, and R01HD102170.