SMRT plays an important role for implantation and decidualization.

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Infertility is a major health issue that affects an estimated 10–15% of couples worldwide and has been growing at an alarming rate. Over 75% of failed pregnancies involve implantation defects. Epigenetic regulation has indeed gained significant attention for its role in implantation and decidualization during early pregnancy. However, little is known about the role of epigenetic regulation that contributes to early pregnancy establishment. Silencing Mediator of Retinoid and Thyroid hormone receptors (SMRT) is a transcriptional co-regulator of a variety of nuclear receptors and transcription factors. Our immunohistochemical analysis revealed that the expression of SMRT was significantly decreased in endometrial epithelial and stromal cells from infertile women with endometriosis compared to controls. Since mouse embryos with homozygous deletion of SMRT are embryonically lethal, we generated a mouse model with *Smrt* conditionally ablated in *Pgr*-positive cells ($Pgr^{cre/+}Smrt^{f/f;}$ $Smrt^{KO}$) to determine the effect of SMRT loss in the uterus. Ablation of *Smrt* in the uterus was confirmed by RT-qPCR, Western blot and IHC analyses. In fertility tests of female $Smrt^{f/f}$ and $Smrt^{KO}$ mice over 6 months, $Smrt^{f/f}$ mice were fertile, whereas $Smrt^{KO}$ mice were sterile. The number of implantation sites at GD4.5 revealed normal in both $Smrt^{f/f}$ and $Smrt^{KO}$ mice and histological analysis indicated normal embryo attachment to the uterine horn in $Smrt^{f/f}$ and $Smrt^{KO}$ mice. However, we did not detect implantation sites in the uterine horns of $Smrt^{KO}$ mice at GD5.5. Our histological analysis indicated that uterine luminal epithelial cells in $Smrt^{f/f}$ mice were disappeared, and embryos were attached to the uterine horn and surrounded by decidualized cells. However, in $Smrt^{KO}$ mice, uterine luminal epithelial cells were intact, and decidual cells were not evident. These results suggest that $Smrt^{KO}$ mice were infertile due to defective embryo implantation. We then used an artificial decidualization model to examine how *Smrt* ablation affects decidualization. $Smrt^{f/f}$ mice displayed a decidual uterine horn that responded well to this decidual induction. However, $Smrt^{KO}$ mice had a significant defect in the decidual response. We confirmed this decidual defect by histological analysis and reduced expression of the decidualization markers *Bmp2* and *Wnt4* in the $Smrt^{KO}$ mouse uterus. These results demonstrate that $Smrt^{KO}$ mice were infertile due to a decidualization defect. This work was supported by NIH P01HD106485 and R01HD102170.