

## Abstract # 1857

### **Endometrial Epithelial ARID1A Loss Causes Defects of Uterine Receptivity and Endometrial Gland Function.** Ryan M. Marquardt, Michigan State University, USA

Endometrial receptivity is key to successful pregnancy establishment and is compromised in many women with endometriosis. ARID1A, a SWI/SNF chromatin remodeling complex subunit, is attenuated in the endometrium of women with endometriosis. Moreover, conditional uterine *Arid1a* knockout mice are infertile due to endometrial receptivity defects resulting from increased pre-implantation epithelial proliferation. We thus hypothesized that epithelial ARID1A loss compromises fertility by causing a non-receptive state in the endometrium. To examine the effects of endometrial epithelial-specific ARID1A loss, we established a conditional knockout mouse where *Arid1a* is ablated in the endometrial epithelium (*Ltficre/+Arid1af/f*). We observed severe subfertility in *Ltficre/+Arid1af/f* mice in a six-month breeding trial (n=6). Immunohistochemical analysis revealed a failure of embryo implantation and stromal cell decidualization at gestation day (GD) 4.5 (n=3-4), and an artificial decidualization test confirmed the compromised decidual response (n=6) caused by *Arid1a* loss in the endometrial epithelium. *Ltficre/+Arid1af/f* mice also exhibited a non-receptive endometrium at pre-implantation stage (GD 3.5) due to increased epithelial proliferation (n=3), and we found significant reduction in expression levels of endometrial gland-related genes including *Foxa2* (n=5; p<0.01) and *Lif* (n=4-5; p<0.05), critical factors for pregnancy establishment. Furthermore, ChIP analysis indicated that ARID1A directly binds the *Foxa2* promoter during early pregnancy in wild type mouse uterus (n=5), implying direct transcriptional regulation of *Foxa2* by ARID1A. Previous experiments revealed that implantation and decidualization can be rescued in uterine *Foxa2* knockout mice by LIF repletion at GD 3.5. However, LIF repletion did not rescue implantation in *Ltficre/+Arid1af/f* mice, assessed histologically at GD 5.5 (n=3). Despite the failure of LIF to rescue implantation, phospho-STAT3 and EGR1, downstream signaling targets of LIF important for implantation and decidualization, were significantly decreased around *Ltficre/+Arid1af/f* implantation sites at GD 4.5 based on IHC H-score (n=3; p<0.001). Taken together, these data indicate that loss of preimplantation LIF expression is disrupted by endometrial epithelial *Arid1a* ablation but is not the sole cause of implantation failure. Our results reveal the importance of epithelial ARID1A in promoting endometrial receptivity by allowing proper implantation and decidualization, regulating epithelial proliferation, and maintaining gland function. Research reported in this publication was supported in part by the Eunice Kennedy Shriver National Institute of Child Health & Human Development of the National Institutes of Health under Award Number R01HD084478 to J.W.J. and T32HD087166 to R.M.M., MSU AgBio Research, and Michigan State University. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.