Abstract # 2064

Spatial and temporal dynamics of FGL2 expression reveal immunoregulatory function essential to the establishment and outcome of pregnancy. Pascale Robineau-Charette, Ottawa Hospital Research Institute

Fibrinogen-like protein 2 (FGL2) is a known immunomodulator and prothrombinase, previously suggested to be involved in the immune balance of the maternal-fetal interface that is crucial to reproductive success. The female reproductive tract is the site of several key events that require careful endocrine and immunological regulation, from ovulation to pre-implantation embryo transport and placentation. We mapped spatial and temporal dynamics of FGL2 expression through murine reproductive tissues, which revealed remarkable cell type specificity hinting at precise function. We carefully examined several parameters of reproductive performance in our Fgl2 knockout (ko) and overexpressing (tg) mouse colonies. Fgl2 ko females produced only half as many pups as their wild-type (wt) counterparts, due to smaller and less frequent litters. Interestingly, this phenotype was rescued in Fgl2 tg X Fgl2 ko mating pairs, despite the presence of only one overexpressing allele. We observed equal rates of embryo resorption in all three genotypes, suggesting a defect in Fgl2 ko ovarian or oviductal (pre-implantation) function. In the ovary, FGL2 is expressed in the stroma and theca cell layer of follicles, and intensity of expression peaks 8 hours after hCG injection in a superovulation cycle. Strong expression is acquired by some cumulus granulosa cells shortly before ovulation and persisting in cumulus-oocyte complexes (COCs) found in the oviduct, suggesting a role in ovulation and in luteinization. Fgl2 ko and Fgl2 tg animals however had a normal ovulation efficiency, as measured by the number of COCs retrieved after superovulation. Fgl2 ko and wt ovaries showed equivalent numbers of functional corpora lutea, demonstrating normal luteinization. In the oviduct, FGL2 expression is restricted to secretory cells of the epithelium, whose frequency increase from the fimbrial to the isthmal end. We detected FGL2 in the culture medium of OVE4, primary oviductal epithelial cells, confirming its secretion into oviductal fluid, where it likely contributes to the immunosuppressive environment conducive to fertilization and to tolerance of paternal/fetal antigens. Single-nuclei RNA sequencing of the ovary, ampulla and isthmus at different timepoints after superovulation will reveal differential immune dynamics between Fgl2 wt and ko animals, to identify mechanistic actions of FGL2 in these tissues. Despite being born at rates comparable to wt mice, Fgl2 tg pups are significantly smaller than their wt and ko counterparts, at birth and at weaning, indicating a probable deficient placental function.

Interestingly, we found that women with high placental FGL2 expression tend to be affected by an immunological subtype of preeclampsia, characterized by chronic inflammatory placental lesions and small for gestational age infants. Our histological examination of term placentas from Fgl2 tg animals will confirm correlative evidence, in the human placenta, of FGL2's role as an immunoregulator at the maternal-fetal interface. Overall, this work supports the hypothesis that FGL2 is secreted throughout the female reproductive tract at precise stages of the estrous cycle, and in the developing placenta, as a physiological attempt to maintain the careful immune equilibrium required for the successful establishment and maintenance of pregnancy.