Session 7 - Reproductive Biology I

O-048 - Mitochondrial Stress Response Gene Clpp is Not Required for Granulosa Cell Function

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Keywords

Mitochondria,Oocyte,Fertility,,

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Abstract

Introduction: Mitochondrial unfolded protein response (mtUPR) is a highly conserved mechanism by which cells maintain homeostasis in the presence of cellular and metabolic stress. CLPP (caseinolytic peptidase P) plays a central role in this process by promoting degradation of unfolded mitochondrial proteins. We have previously shown that global deletion of *Clpp* in mice leads to female infertility and accelerated follicular depletion. However, it is not known whether the infertility phenotype observed in mice with global deletion of *Clpp* results from an impact on oocytes, granulosa cells, or both. In this study, we aimed to study whether CLPP is required for granulosa cell function. **Methods:** *Clpp*$^{flox/flox}$ mice were generated and crossbred with *Cyp19a1-Cre* mice in order to produce a mice with granulosa cell specific *Clpp* deletion (*Clpp*$^{-/-}$). Mature (8-week old) *Clpp*$^{-/-}$ female mice were compared to mature wild type (WT) mice. To evaluate fertility, *Clpp*$^{-/-}$ (n=8) and WT female mice (n=8) were mated with adult WT males with proven fertility for 12 weeks. Serial ovarian sections were obtained and stained with hematoxylin and eosin. Primordial, primary, secondary, early antral and antral stage follicles were counted to compare folliculogenesis. Germinal vesicle and MII stage oocyte generation was assessed after injection of PMSG (5IU) or PMSG and HCG (5IU) as indicated. ANOVA, student's t-test, and Chi Square analysis were used for statistical analysis as appropriate. **Results:** Mature *Clpp*$^{-/-}$ female mice demonstrated similar fertility compared to WT females, producing similar number of pups per litter (9.0±1.0 vs 7.32±0.58, p=0.067). The numbers of primordial (317.80±119.90 vs 278.20±13.08, p=0.69), primary (147.80±88.74 vs 135.30±31.47, p=0.87), secondary (71.0±26.16 vs 83.50±3.54, p=0.57), early antral (54.75±12.37 vs 46.25±13.08, p=0.57), and antral follicles (3.0±2.12 vs 1.75±0.35, p=0.5) were not changed significantly with loss of CLPP in granulosa cells. Number of GV (32.67±2.52 vs 40.67±6.11, p=0.10) and MII (19.0±8.19 vs 22±2.65, p=0.59) oocytes collected from *Clpp*$^{-/-}$ and WT female mice were also similar. **Conclusion:** Loss of mtUPR protein, CLPP, in granulosa cells does not alter fertility of female mice. In light of previous reports, our findings suggest that mtUPR and CLPP function is required for female fertility and oogenesis but not for granulosa cell function.