The role of PARP1 in female gametogenesis

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Premature Ovarian Insufficiency (POI), affecting 1% of women, is marked by early onset of menopause, impacting fertility, and increasing vulnerability to cardiovascular issues, osteoporosis, and premature mortality. While the causes remain undefined, in most cases, it is attributed to a small primordial follicle pool, rapid follicle exhaustion, or dysfunction of the ovarian follicles. The follicle pool, comprised of germ cells (oocytes) and surrounding supporting cells, defines a women´s reproductive lifespan. Female gametogenesis, the process involving the generation of germ cells, is crucial for forming the follicle pool (Rudnicka, Kruszewska et al. 2018).

In a Genome-Wide Association Study (GWAS), we identified a PARP1 variant (V762A) linked to an earlier onset of menopause (Stankovic, Shekari et al. 2022) and a 40% reduction in PARP1 activity (Wang, Wang et al. 2007). In this project, we aim to unravel the role of PARP1 and its activity in female gamatogenesis. Using the CRISPR/Cas9 gene editing system, we generated mouse embryonic stem cells carrying the PARP1 V762A variant. Employing an *in-vitro* protocol (Hayashi, Ohta et al. 2011), we are able to replicate the differentiation of embryonic stem cells into primordial germ cells, enabling us to examine the specific involvement of PARP1 in early gametogenesis. We found that mouse embryonic stem cells carrying the PARP1 variant display a reduced ability to differentiate into primordial germ cells-like cells when compared to wildtype PARP1. Further, we aim to elucidate the molecular mechanisms underlying PARP1 activity during early gametogenesis.

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