NEDDylation: An Essential Regulatory Pathway for Oocyte Quantity and Quality

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Reproductive decline and infertility in women are largely caused by diminished oocyte quality and quantity. The mechanisms underlying this decline are not yet fully understood but are attributed to various factors, including mitochondrial dysfunction, improper oocyte-granulosa cell communication, and changes to proteostasis. Neddylation, a ubiquitin-like post-translational modification that affects protein homeostasis and quality control, is implicated in various health conditions, but its role in oocyte biology remains unknown. Using CRISPR/Cas9 gene editing, we generated a novel conditional allele of *Uba3*, an essential enzyme in the NEDDylation pathway, and crossed it with the oocyte-specific cre driver line, *Gdf9-icre*. Continuous mating for 6-months of *Uba3* conditional knockout ("cKO") females failed to produce any pups, indicating that NEDDylation is required for female fertility. By histological and morphometric analysis,12 week old *Uba3* cKO ovaries are nearly devoid of follicles - severe premature aging phenotype. Prior to ovulation, GV oocytes of *Uba3* cKO mice have significantly higher levels of reactive oxygen species (ROS). Transmission electron microscopy showed that mitochondrial morphology was significantly altered in *Uba3* cKO oocytes. Additionally, *Uba3* cKO oocytes lack well-developed transzonal projections (TZPs), structures that span the zona pellucida to allow for bidirectional communication with the oocyte and surrounding somatic cells. By transcriptomic analysis of fully grown GV oocytes, we discovered changes in genes related to cell adhesion as well as cell projection. Thus, NEDDylation appears to be essential for maintaining oocyte organelle integrity and overall female fertility. Further studies will seek to elucidate NEDDylation targets as mediators of reproductive disease and oocyte aging. These studies were supported by NIH grants T32HD098068 and R21HD109807.