Female fertility: The role of mitochondrial protease LONP1 in oocyte development and survival

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Mitochondria, as one of the most important organelles in oogenesis, not only provide ATP to support oocyte maturation, but also play as the key element to regulate calcium homeostasis, apoptosis and autophagy during oogenesis.[1] In human, the number of mitochondria increases from dozens to more than 100,000 during the oocyte maturation, which determines the quality of ovulated oocytes directly.[2] Although the crucial role of mitochondria in controlling oogenesis has been well recognized, the detailed molecular regulation of this process remains unclear. A study by Sheng et al. in recent issue of *EBioMedicine* reveals the essential roles of mitochondrial protease LONP1 in the regulation of the oocyte development and survival during the folliculogenesis and female fertility.[3]

Lon proteases (LONP) are ATP-dependent mitochondrial protease that responsible for the degradation of the imported mitochondrial matrix proteins, helping to maintain efficient cellular hemostasis.[4] Two LONPs, known as mitochondrial LON (LONP1) and peroxisome LON (LONP2), have been reported in human cells. LONP1 was reported ubiquitously expressed in organs including liver, brain, heart, skeletal muscle and placenta. Mutations in the gene encoding LONP1 are associated with various diseases such as cerebral, ocular, dental, auricular and skeletal anomalies (CODAS) syndrome, suggesting LONP1's essential role in mitochondrial and cellular homeostasis.[5,6] In their *EBioMedicine* paper, Sheng and colleagues used genetically modified mouse models to provide a comprehensive picture of how LONP1 participates in the regulation of oocyte quality.

The authors demonstrated that *Lonp1* deletion in oocytes at different developing stages of follicles (primordial and primary stages) dramaticly decreases the quality of oocytes and leads to female infertility. With multiple molecular approaches, the authors clarified that LONP1 controls the oocyte development by interacting with apoptosis-inducing factor mitochondria-associated 1 (AIFM1), a mitochondrial inner-membrane-anchored protein.[7] AIFM1 was found expressed in both oocytes and granulosa cells in ovaries,[8] functioning as an apoptosis related factor to eliminate the cells through a process of nuclear translocation. In Sheng's paper, authors found the ablation of LONP1 resulted in a translocation of AIFM1 from cytoplasm to the nucleus and subsequently induced apoptosis of oocytes. In consistent with these observations, the AIFM1-induced apoptosis inhibitor, 3-aminobenzamide, efficiently rescued the development of $Lonp1^{Gdf9Cre}$ *cKO* oocytes. The novel finding in this work may extend our understanding of LONP1's involvement in oogenesis and provide a potential therapeutic target to improve oocyte quality in clinical practice. Interestingly, the authors also observed a decreased LONP1 expression in oocytes of aged animals, which indicate that LONP1 might also be an essential molecule to determine the oocyte aging. Thus, whether 3-aminobenzamide could improve the quality of aged oocytes becomes an interesting question to address in the future.

The authors also extended their finding in basic science by identifying the human mutations of *LONP1* in patients with premature ovarian insufficiency (POI). The pathogenic variants of *LONP1* associated with developmental abnormalities of follicles were found in the POI women. All patients with *LONP1* mutations represent secondary POI symptoms since they all had the menstrual cycle in the early life, which mimic the symptom observed in the $Lonp1^{Gdf9Cre}$ *cKO* mice, in which the ovarian development was generally normal before the puberty onset at 3 weeks of age, and the size of the ovaries was reduced significantly and no longer produced metaphase II (MII) oocytes in adult life at 6 weeks of age. The consistent clinical phenotypes observed in the $Lonp1^{Gdf9Cre}$ *cKO* female mice and in POI patients with *LONP1* mutations suggests that LONP1 may serve as a novel biomarker for clinical POI detection.[9]

Despite the observed role of LONP1 in the development of growing follicles in adult females, the specific ablation of LONP1 from oocytes in primordial follicles did not lead to significant morphological abnormalities and follicle atresia until adulthood. Moreover, an increased number of primordial follicles was found in $Lonp1^{Gdf9Cre}$ ovaries compared to $Lonp1^{flox/flox}$ ovaries at 3 weeks, the time of puberty onset. These paradoxical

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phenotypes are interesting as it is known that mammalian ovaries have two waves of follicles,[10] which might indicate the involvement of mitochondria in the formation of ovarian follicular waves. Further research is required to clarify this issue.

Declaration of interests

The authors declare no conflicts of interest.

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