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Short Communication
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Mitochondria and Aged Women Egg

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Short Communication

Since the first "test-tube baby" named Louise Joy Brown was born in 1978 [1,2], human *in vitro* fertilization (IVF) has become widely accepted by infertile couples for fertility treatments. There are more than 0.2 million babies born every year and a cumulative total of 6.5 million IVF babies have been born worldwide [3,4]. Moreover, the average pregnancy rate (PR) in overall cycles has significantly increased from 11.1% in 1984 to a current rate of 30% or more [4,5]. Unfortunately, female age may have a significant effect on PR [6]. It is foreseeable that the population of women aged 40 years or older will increasingly use ART due to high social pressure or a cultural shift, with other potential reasons such as: endometrial receptivity, the quality of oocyte or sperm, and the number of embryo transfers. The world report shows that the PR decreased from more than 30% in women <35 years to around 10% for those ≥ 40 years [4]. Obviously, the clinical pregnancy rate is significantly associated with reproductive age. However, many studies have validated that the human aging process is closely related to mitochondrial dysfunction (MiDAS) [7,8], which is not conducive to cell survival and functional exertion.

Mitochondrion, also known as the semi-autonomous organelle coated with dual cell membranes, has its own circular mitochondrial DNA (mtDNA) as the genetic code and the autocephalous system for RNA transcription and protein translation. As the power plant of energy in eukaryotic cells, mitochondria play a key role in cell respiration, substrate oxidation, ATP synthesis, cell apoptosis, mitosis, meiosis and other unexplored fields, any mitochondrial malfunctions, Mt DNA mutation, defects in maternal mRNA storage, insufficient synthesis of proteins or untimely destruction of proteins, improper protein phosphorylation and signal transduction, accumulation of irreparable damage to bio-molecules, and oocyte plasma membrane age, which will decrease the oocyte's competence and lead to either fertilization failure or an incorrect switch from maternal to embryonic control during embryogenesis. Here we mainly introduce mitochondria malfunctions in oocytes with advanced maternal age because mitochondria are the most prominent cell organelles in oocyte's cytoplasm, which corresponds to an important maternal contribution to embryogenesis, ATP generation and apoptosis. Mitochondrial swelling, cristae disruption, mtDNA mutation, deletion, CoQ10 deficiency, reduced ATP and mtDNA copies are the common structural and functional features of the oocytes from aged women, which may be responsible for aberrations in the assembly of the meiotic spindle, cell cycle progression, and timely chromosome segregation in oocytes from aged women, which consequently may increase the risk of chromosomal abnormalities and a range of metabolic disorders, and a reduced outcome of pregnancy [9]. Also, it has been gradually realized to be germane to the aberrant cell function in some disease progressions including, but not limited to: Alzheimer's disease, Parkinson's disease, diabetes, tumours and so on [10-13].

With the deepening of mitochondria-related studies, we gradually understand that there is a highly interdependent existence between the normal mitochondrial morphological structure and regular energy metabolism. Additionally, it can maintain high stability of the interconnected tubular network ultra structure in the cytoplasm via cyclic fusion and fission relying on the mitochondrial trans-membrane potential ($\Delta\Psi m$) and the change of GTP, which have been recognized as the critical process to ensure normal mitochondrial function and cell survival.

As is commonly known, it is a complicated and reciprocal process for mitochondrial fusion and fission, among which three kinds of related dynamin (Mfn1, Mfn2, Opa1) have been reported to possess membrane-fusion properties [14]. These mitofusins, located in the mitochondrial membrane, have a completely different meaning and play a respective role in the remodelling of mitochondrial morphology, but collectively maintain the integrity of mitochondrial function. Many studies have shown that it was enough to block the process of mitochondrial fusion and

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cause detrimental effects on mitochondrial and cellular function by interfering in the signal pathways of Mfns or Opa1 [15-17]. Moreover, in *Mfn*-deficient embryonic fibroblasts (MEFs), more than 80% of mitochondria displayed dramatically fragmented mitochondria and scarce tubular mitochondria, while the long extended-tubule mitochondria were mainly distributed in wild-type MEFs [18]. This suggests that mitofusins play a crucial role in sustaining mitochondrial morphology and function.

The *Mfn2* encodes mitofusin2 related to mitochondrial outer membrane structural dynamics, which is a conserved dynamin-like GTPase required for mitochondrial fusion and the maintenance of normal mitochondrial structure. This gene was derived and screened from Wistar rats and spontaneously hypertensive rat (SHR) genes via differential display technology in 1997 and it was widely expressed in various tissues of the body, especially in cardiac muscles and skeletal muscles with high-energy demand. In mammalian cells, over-expression and deletion studies revealed that Mfn2 also contributes to the other processes, except for mitochondrial fusion such as cell metabolism, signal transduction, cell proliferation, Ca^{2+} signalling, endoplasmic reticulum (ER)–mitochondrial tethering and cell apoptosis [19-21]. In all, the *Mfn2* expression is closely associated with cellular function and survival via affecting mitochondrial biogenesis. In addition to cardiovascular disease, insulin resistance-related disease, genetic kinaesthetic neurosis, tumours, etc. [16,22,23], the gene may also be involved in the process of embryonic development and oogenesis, as well as oocyte maturation with the research field expanded.

In mammals, mitochondria are extremely enriched in mature oocytes with a content of approximately 0.15 million copies of mtDNA for the reason of increasing demand for ATP, the copies of which are more than that in most somatic cells [24]. Furthermore, high ATP production proved to contribute to the oocytes maturation. Many studies showed that mitochondrial biogenesis was closely associated with the maturation and quality of oocytes. It was also suggested that *Mfn2* regulates the oocytes quality and fertilization by modulating meiosis and mitochondrial function, including the morphogenesis of spindle, chromosome separation, and so forth [25,26]. Additionally, *Mfn2* also indicated to be indispensable during the process of embryonic development in mice and low-level expression of *Mfn2* in placental villous cells has been revealed to result in spontaneous abortions in reproductive females [27,28].

During aging, a general metabolism deregulation or mitochondrial dysfunction occurs and affects cell homeostasis in the organism [29,30]. It gradually becomes the focus of attention for mitochondrial dysfunction in the process of oocytes aging. According to the investigation, mutations of mtDNA, loss of respiratory Complex subunits, and alterations of mitochondrial morphology was detected to confirm the correlation with maternal age, and it suggested that the dysfunction of mitochondria in oocytes derived from aging females may contribute to lower embryo formation rates and PRs [31,32]. Therefore, we posit that the level of *Mfn2* expression may have a significant effect on PRs by interfering with the balance of mitochondrial fusion and fission, as well as cellular energy metabolism. Additionally, our research team further verified the inference via granular cells, the key cells for follicular development and maturation. This showed an obvious attenuation of mitochondrial function and *Mfn2* expression with gradually increasing age and that the low *Mfn2* expression in granular cells obtaining from follicular fluid of aging female may result in lower PRs. Moreover, the result resembles the World Report published by ICMART (International Committee for Monitoring Assisted Reproductive Technology) in 2002 [4].

For future perspectives, with the development of new knowledge and techniques, novel measures for aged women's infertility rescue may be possible, such as mitochondria transfer (MIT) into oocyte from autologous cumulus granulose cells (cGCs), spindle transfer, pronuclear transfer, or directly injecting ATP into oocytes. Supplementation with mitochondrial nutrients such as CoQ10 and r-alpha lipoic acid (ALA) may lessen the risks of oocyte aging-related chromosomal aneuploidy. These techniques are proved to be feasible, however, major concerns exist about the ethnic problems of these manipulations, as they are prohibited in many countries. Transplantation of oogonial stem cells (OSCs) or germline stem cells (GSCs), embryonic stem (ES) cells, and bone marrow stem cells may provide more help with infertility treatments in aged women. Although oocytes derived from ES cells and iPS cells will be a long match to achieve functional oocytes for aged women undergoing assisted reproductive technology (ART) treatment, even if a dysfunctional oocyte is differentiated, it may still possibly transfer its GV into a donated oocyte cytoplasm to construct a functional oocyte. The new technologies mentioned, even though they are currently being debated, may soon bring new hope for aged-women lacking oocytes.

References

1. Zegers-Hochschild F, et al. International Committee for Monitoring Assisted Reproductive Technology; World Health Organization. International Committee for Monitoring Assisted Reproductive Technology (ICMART) and the World Health Organization (WHO) revised glossary of ART terminology, 2009. Fertil Steril. 2009; 92: 1520-1524.
2. Steptoe PC, et al. Birth after the implantation of a human embryo. Lancet. 1978; 2: 366.
3. International Committee for Monitoring Assisted Reproductive Technology, et al. World collaborative reports on *in vitro* fertilization, 2000. Fertil Steril. 2006; 85: 1586-1622.
4. International Committee for Monitoring Assisted Reproductive Technology., et al. World collaborative report on Assisted Reproductive Technology, 2002. Hum Reprod. 2009; 24: 2310-2320.
5. Seppälä M. The world collaborative reports on *in vitro* fertilization and embryo replacement: current state of the art in January 1984. Ann N Y AcadSci. 1985; 442: 558-563.
6. Shea LO, et al. Advanced Maternal Age and Assisted Reproductive Technologies in an Irish Population. Ir Med J. 2015; 108: 243-246.
7. Melov S, et al. Marked increases in the number and variety of mitochondrial DNA rearrangements in aging human skeletal muscle. Nucleic Acids Res. 1995; 23: 4122-4126.
8. Van Blerkom J. Mitochondrial function in the human oocyte and embryo and their role in developmental competence. Mitochondrion. 2011; 11: 797-813.
9. He YH, et al. Mitochondrial DNA content contributes to healthy aging in Chinese: a study from nonagenarians and centenarians. Neurobiol Aging. 2014; 35: 1779. e1-4.
10. Manczak M, et al. Mitochondria area direct site of A beta accumulation in Alzheimer's disease neurons: implications for free radical generation and oxidative damage in disease progression. Hum Mol Genet. 2006; 15: 1437-1449.

11. Morais VA, et al. PINK1 loss-of-function mutations affect mitochondrial complex activity via NdufA10 ubiquinone uncoupling. Science. 2014; 344: 203-207.

12. Petersen KF, et al. Effect of aging on muscle mitochondrial substrate utilization in humans. PNAS. 2015; 112: 11330-11334.

13. Liu L, et al. Mitochondrial outer-membrane protein FUNDC1 mediates hypoxia-induced mitophagy in mammalian cells. Nat Cell Biol. 2012; 14: 177-185.

14. Lee H, et al. Mitochondrial fission and fusion. Biochem Soc Trans. 2016; 44: 1725-1735.

15. Kushnareva Y, et al. Mitochondrial dysfunction in an Opa1 (Q285STOP) mouse model of dominant optic atrophy results from Opa1 haploinsufficiency. Cell Death Dis. 2016; 7: e2309.

16. Burté F, et al. Disturbed mitochondrial dynamics and neurodegenerative disorders. Nat Rev Neurol. 2015; 11: 11-24.

17. Wakai, T., et al. Mitochondrial dynamics controlled by mitofusins defines organelle positioning and movement during mouse oocyte maturation. Mol. Hum. Reprod. 2014; 20: 1090–1100.

18. Chen H, et al. Mitofusins Mfn1and Mfn2 co-ordinately regulates mitochondrial fusion and are essential for embryonic development. J Cell Biol. 2003; 160: 189-200.

19. De Brito OM, et al. Mitofusin 2 tethers endoplasmic reticulum to mitochondria. Nature. 2008; 456: 605-610.

20. Schrepfer, Emilie; et al. Mitofusins, from Mitochondria to Metabolism. MOLECULAR CELL. 2016; 61: 683-694.

21. Karbowski M, et al. Role of Bax and Bakin mitochondrial morphogenesis. Nature. 2006; 443: 658-662.

22. Hall AR, et al. Hearts deficient in both Mfn1 and Mfn2 are protected against acute myocardial infarction. Cell Death Dis. 2016; 7: e2238.

23. Zhao J, et al. Mitochondrial dynamics regulates migration and invasion of breast cancer cells. Oncogene. 2013; 32: 4814-4824.

24. Wai T, et al. The role of mitochondrial DNA copy number in mammalian fertility. Biol Reprod. 2010; 83: 52-62.

25. Zhang JH, et al. Mitofusin-2 is required for mouse oocyte meiotic maturation. Sci Rep. 2016; 6: 30970.

26. Liu Q, et al. Mitofusin 2 regulates the oocytes development and quality by modulating meiosis and mitochondrial function. Sci Rep. 2016; 6: 30561.

27. Zhao N, et al. Mfn2 Affects embryo development via mitochondrial dysfunction and apoptosis. PLoS.One. 2015; 10: e0125680.

28. Pang, W. et al. Low expression of Mfn2 is associated with mitochondrial damage and apoptosis in the placental villi of early unexplained miscarriage. Placenta. 2013; 34: 613–618.

29. López-Lluch G. Mitochondrial activity and dynamics changes regarding metabolism in ageing and obesity. Mech Ageing Dev. 2016. 162: 108-121.

30. Cree LM, et al. Maternal age and ovarian stimulation independently affect oocyte mtDNA copy number and cumulus cell gene expression in bovine clones. Hum Reprod. 2015; 30: 1410-1420.

31. Müller-Höcker J, et al. Morphological-cytochemical and molecular genetic analyses of mitochondria in isolated human oocytes in the reproductive age. Mol Hum Reprod. 1996; 2: 951-958.

32. Wilding M, et al. Mitochondrial aggregation patterns and activity in human oocytes and preimplantation embryos. Hum Reprod. 2001; 16: 909-917.