Review Article

Mitochondria: the panacea to improve oocyte quality?

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Abstract: Oocyte quality is one of the most important factors involving in female reproduction. The number of compromised oocytes will increase with maternal age, while mitochondrial dysfunction has implicated in age-related poor oocyte. Together with the successful application of ooplasmic transfer (OT) and the critical role of mitochondria in the oocyte, functional mitochondria transfer may be a feasible strategy to improve oocyte quality. However, limitation on ethics and laws are strictly and optimal condition or methods to exert transferring need to be further explored. Therefore, the role of oocyte mitochondria and the effective molecular involving in oocyte quality will be hot topics in next few years. In this review, we summarize the potential mechanism of mitochondria in oocyte and embryo development and discuss the next step for mitochondrial transfer therapy.

Keywords: Mitochondria; mitochondrial replacement therapy; mitochondrial transfer therapy; infertility; oocyte quality

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Introduction

Infertility has become a growing problem worldwide, and decreased oocyte quality mainly culminates in the age-related deterioration of reproductive capacity (1). Network of regulating oocyte quality is greatly complicated and mechanism is still unclear, but it's certain clear that energy metabolism and competing endogenous RNA (ceRNA) regulating network are hugely essential (2).

Attributed to the key role in regulation of cellular metabolism and epigenetics, mitochondria have been paid more attentions in recent years (3-6). Several hypotheses implicate that mitochondria are one of the critical indicators in oocyte quality (7). Mitochondrial functions are important for the early embryo development and implantation, including the formation of meiotic spindles and the maintenance of the metaphase II (MII) spindle before fertilization (8). All of the complex processes oocyte goes through prior to ovulation and fertilization require energy, especially those adenosine triphosphate (ATP) derived from mitochondrial oxidative phosphorylation (OXPHOS) (9). It has been shown that insufficient ATP production during the oogenesis and embryogenesis will result in aneuploidy, a condition in which chromosomal segregation errors are frequently encountered (10). Furthermore, mitochondria as the center of cellular metabolism will have an impact on

gene expression by cross-talk with nucleus (11). Interaction between mitochondria and nucleus can involve in many biological progresses which are important for both oocyte maturation and embryonic development (11-13). Autologous mitochondrial transfer technologies (AUGMENT, one of strategy in assisted reproduction technology) which transfer mitochondria from oocyte precursor cells to MII oocyte have succeeded in promoting outcome (14). Subsequently, clinical research also indicates that mitochondrial transfer actually can rejuvenate ageing oocyte (15).

However, a recent randomized pilot trial finds AUGMENT had no significant curative effect on ameliorating oocyte quality (16). This result strong strikes the previous study and give us more consideration about the credibility of mitochondrial transfer therapy. Therefore, what bioprocesses happen after transferring and why reverse results can be received by the similar operations will be highly concerned in the next few years. Here, we will describe the potential mechanism for mitochondria involving in oocyte quality and the future of mitochondria-related therapy.

Mitochondrial dynamics: power to maintain normal oocyte and embryonic development

In human, quantity of mitochondria suffer from a great variation during oocyte maturation. Mitochondria in mature oocyte have been increased 1,000 times from only few dozens to more than 100 thousand ones comparing to primary follicles (17,18). Then, mitochondria are averagely distributed to each blastomere during embryonic development, but the total number is relatively stable before the blastocyst stage (19). Likewise, mitochondrial activity is also relatively stable before the blastocyst stage. Although reasons of this appearance are still obscure, disorder of mitochondria activation can certainly cause serious oocyte dysplasia (20,21). Mitochondria in mammalian oocytes are transcriptionally and bioenergetically silent (22), especially in immature eggs (23). This quiescent state is believed to be important to keep minimal mitochondrial DNA (mtDNA) mutations, because these mutations will then be passed down to the embryo (24). The energy required for oocyte maturation is mainly provided by surrounding granulosa cells and cumulus cells (25,26). Along with the accomplishment of fertilization and the ensuring embryonic development, mitochondria-derived energy gradually come to dominate (9,27,28). When the embryo develops to the blastocyst stage, mitochondria in the embryo have become slender, the structure of ridges is intact, and the mtDNA is largely replicated, indicating that mitochondria have completed the transition from quiescence to activation (29,30). Thus, mitochondrial dynamics are involved in protecting oocyte from oxidative damage and support early embryonic development. Decline in oocyte mitochondrial reserve will trigger the energic shortage during pre-implantation which may induce embryo arrested. For the purpose of rescuing poor oocyte, injection of function mitochondria during intracytoplasmic sperm injection may be effective to compensate maternal mitochondria deficient, then reconstructing mitochondrial activation.

Mitochondrial metabolites: affect oocyte quality on epigenetic modification

Increasing evidences have demonstrated that age-related decline in oocyte quality partly ascribes to alter epigenetic modification (11,31-33) (*Figure 1*). The inducements of epigenetic alteration are intricate, but the role of mitochondria in these progresses is worth being focused on. Actually, previous data has revealed that metabolites produced by mitochondria could remodel chromatin then regulating genetic expression (11). For instance, citrate could be cracked into acetyl-CoA which would donate the acetyl groups for histone acetyltransferases (HATs) (34). Certainly, content of acetyl-CoA is mitochondria-dependent in most parts. When mitochondrial metabolism is high, acetyl-CoA levels will increase, then advancing histone acetylation to drive gene expression by chromatin loose or vice versa (35). Mitochondrial generated α-Ketoglutarate (α-KG) is also a crucial accessory factor of histone methylation. It could be a key co-factor to initiate the function of histone demethylases (HDMs) to identify special substrates and undock methyl groups from histones (36). Simultaneously, S-adenosyl methionine (SAM) engages most parts of histone methyltransferases (HMTs) to activate methyl group transfer (37). And synthesis of SAM relies on folate cycle and ATP which are both controlled by mitochondria. Importantly, ATP-dependent chromatin remodeling complexes require mitochondrial ATP to support necessary energy for chromatin modulating, then binding to genes specially (38). Previous research found levels of SAM is a key regulator for naïve-primed transition of human embryonic stem cells (hESCs) (39). This data imply that mitochondria are critical in modifying epigenetics on human early embryos and even oocytes.

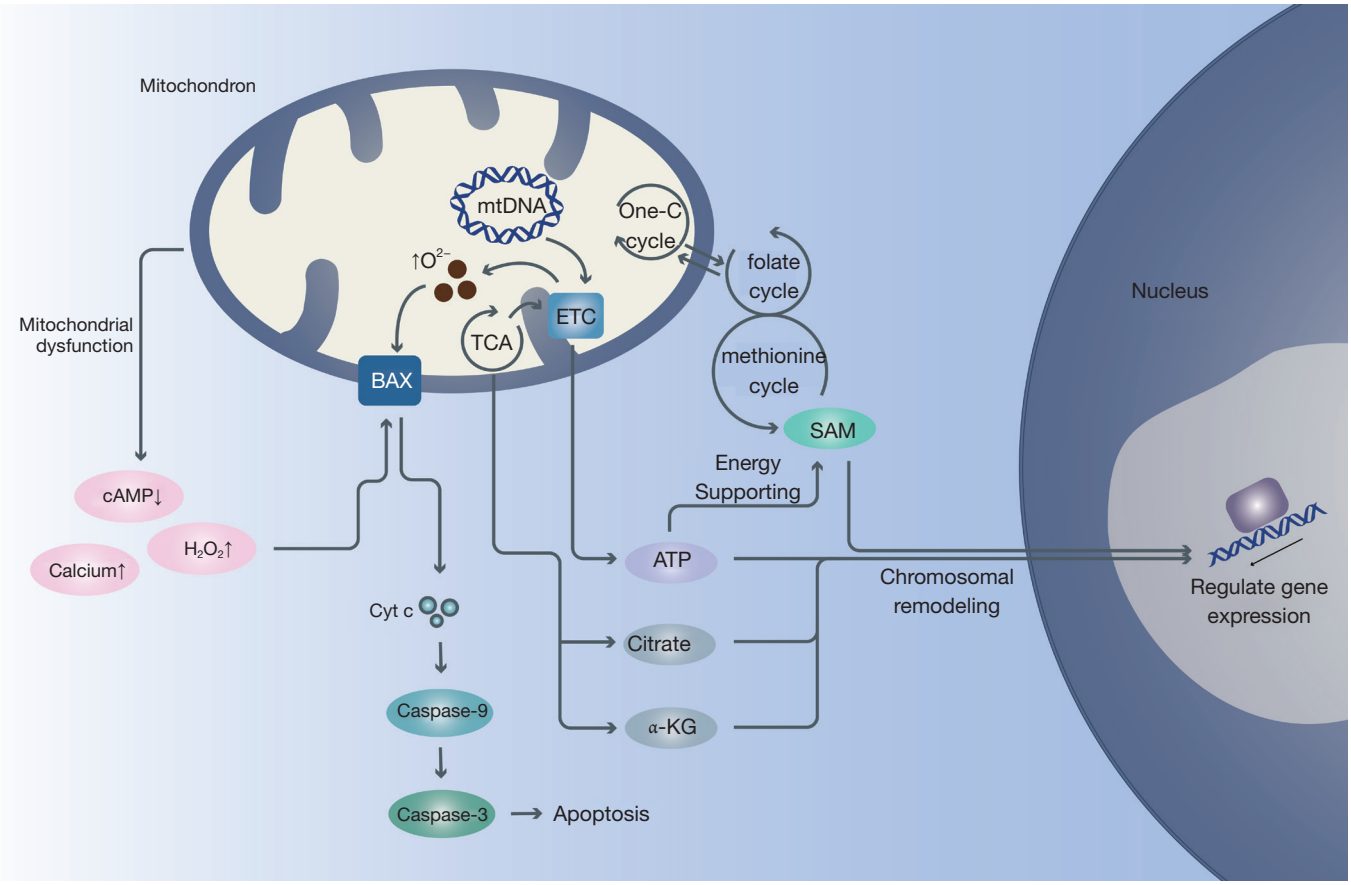

Figure 1 The role of mitochondria in metabolism, apoptosis and gene expression. For caspase activation by mitochondria, multiple signal factors (such as Ca^{2+}, cAMP and ROS) can modify permeability of mitochondrial membrane by activating Bax then releasing cyt c from mitochondria into the cytosol. Thereby, cyt c triggers caspase-9 and initiates the proteolytic cascade that culminates in apoptosis. Simultaneously, caspase-8 can also activate Bax by slicing Bid, which results in the similar apoptosis pathway. Additionally, mitochondria could provide enough energy for cell by synthesize ATP via ETC. Mitochondrial metabolites of TCA cycle (such as ATP, -KG and citrate) could also regulate gene expression via remodeling chromatin. ATP synthesis is dependent on mitochondria oxidative phosphorylation driven by the ETC and ATP synthase. SAM is one of metabolites of methionine and folate cycles that supported by mitochondrial one-carbon cycle. While SAM synthesis requires ATP to support necessary energy for chromatin modulating and then binding to genes specially. mtDNA, mitochondrial DNA; ETC, electron transport chain; TCA, tricarboxylic acid cycle; SAM, S-adenosyl methionine; cAMP, cyclic adenosine monophosphate; ATP, adenosine triphosphate; cyt c, cytochrome c; α-KG, α-ketoglutaric acid.

Experience on mouse reveals that lysine acetyltransferase 8 (KAT8, one kind of HATs and depend on acetyl-CoA) is essential for oocyte maturation and follicular reserved (40). What's more, mitochondrial heteroplasmy might increase the risk of preterm birth by interaction with nucleus (41). These evidences clue us that mitochondrial dysfunction and mtNDA mutation are likely to affect the expression of nuclear genes by modifying the whole epigenetic landscape then inducing many extremely serious consequences in oocyte and pre-plantation development.

Mitochondria-related signaling pathway: threshold of oocyte survivals

The amounts of matured oocyte in each menstrual cycle is controlled by apoptosis strictly, where only less than one percent germ cells can strive into survival at last (42). Mitochondria play a critical role in apoptosis via regulating many signal factors involving in apoptosis such as Ca^{2+}, cyclic adenosine monophosphate (cAMP), reactive oxygen species (ROS), etc. (43) (*Figure 1*). There are two major

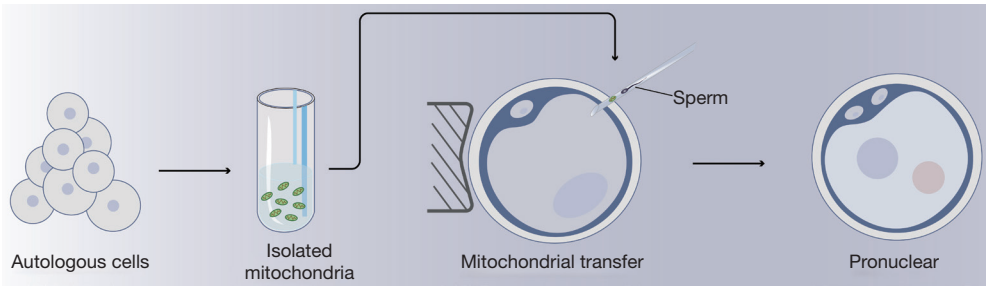

Figure 2 Technological process of mitochondrial transfer therapy (AUGMENT). Mitochondria were isolated from autologous cells germlines such as granular and cumulus cells, oogonial stem cells or mesenchymal stem cells from diverse tissues, and injected into oocyte with a sperm by ICSI to form a reconstructed zygote. ICSI, intracytoplasmic sperm injection.

mechanisms in apoptosis, the intrinsic and the extrinsic pathways (44). For the intrinsic pathway, mitochondrial membrane permeabilization (MMP) can be altered by apoptosis signals then releasing pro-apoptotic factors such as cytochrome c (cyt c) from mitochondria (45,46). As a result, apoptosis-dependent effectors such as caspase-3 will be activated and fragment nucleus DNA then resulting in apoptosis. Calcium is one of the most important factors in cellular homeostasis, which can be regulated by mitochondria. Mitochondria can absorb calcium by anion-selective channels or transporters to maintain calcium homeostasis (47). When mitochondria dysfunction happen, balance of calcium will be broken out and high concentration of Ca^{2+} in cytoplasm will disturb MMP then inducing apoptosis (48). And relationship between oocyte ageing and calcium homeostasis mess has been identified in mice (49). Additionally, mitochondrial dysfunction will increase the production of ROS. Increasing ROS level have been identified strong relationship with oocyte ageing, which can intensify apoptosis in oocyte (50) and lower fertilization rates (51). What's more, mitochondria remain relatively low activity until developing to the blastocyst stage proposal for reducing superfluous ROS (52). It has been identified that healthy cells can rescue apoptotic cells via transferring mitochondria (53). Coincidentally, mitochondrial transfer has capacity to provide against oxidative stress-mediated mitochondrial dysfunction (54). Looking ahead, it's possible to presume that replenishing mitochondria in a suitable degree might be a selective method to cope with mitochondrial decline in ageing oocyte.

Practice of the "mitochondrial therapy": overhastiness

Based on the well therapeutic use by ooplasmic transfer (OT) (55), we know that compromised oocyte may have deficiency in ooplasmics (56). Additionally, preciousness of benign MII oocyte and problem of "3 parents babies" both press people to find out the effective ingredient in ooplasmics. According to the context, mitochondria are the most expected targets. If assumed, transferring autogenous mitochondria (AUGMENGT) is suitable to improve oocyte quality for avoiding above problem caused by OT (57). The general processes of AUGMENGT are that: (I) prepare autologous cell germlines such as oogonial stem cells, granulosa cells or mesenchymal stem cells from diverse tissue; (II) isolate mitochondria from them; (III) inject isolated mitochondria to MII oocyte by microinjection (*Figure 2*). This technology is led by OvaScience Inc., who annotated they had rescued poor oocyte by AUGMENT in 2014 (58). Since emergence of AUGMENT, trends of following were raised overwhelming the world rapidly. Observations from some international fertility clinics show that the successful rates of AUGMENT range from 25% to 53% and pregnancy rates are increased greatly (between 3- and 18-fold increase compared to control group) (59). There is no doubt that it's a bold attempt and may be good news for those people with poor oocyte quality. But in some ways, this strategy seems too much radical. It's unadvisable to experience this technology on patients in the absence of firm support from completed basic and clinical trials. A recent prospective

study demonstrated that AUGMENT technique does not seem to improve embryo quality in infertile patients with premature ovarian ageing and a background of poor embryo quality in previous *in vitro* fertilization (IVF) cycles. Moreover, there were no significantly difference in the ratio of euploid embryos obtained per injected MII and per fertilized oocyte between experimental and control groups (16). So far, Food and Drug Administration of American has forbidden this technology to perform on clinic, and the pioneer, OvaScience, have turn to join other researches (59).

Generally speaking, AUGMENT has some advantages. Firstly, compared with nucleus transfer, AUGMENT can overcome the inherited bottleneck which is in case of making so-called "three parents" baby. Secondly, transferring functional mitochondria to sluggish oocyte could provide enough energy for them to develop as normal. And diverse mitochondrial-related metabolites can be adjusted to the regular levels. What's more, cell survival pathway is proposed to be activated after transferring, then initiating the quiescence mitochondria and prevent oocyte from apoptosis. However, this technology now is still immature. On one hand, autologous stem cells are uneasy to acquire. More importantly, technologies for isolating and authenticating functional mitochondria from cell cultures are puerile. It's difficult for us to analyze the number and completed function of isolated mitochondria, while the dosage and quality of transferring mitochondria are definitive to the success. Previous studies demonstrated that overfull replication of mtDNA could reduce early embryo activity and implantation potential (60). On another hand, the detailed internal mechanism of this therapy is now yet not clear. It's unclear about how the complementary mitochondria work in low-quality oocyte and how mitochondria cooperate with nucleus to regulate cellular proliferation and to refresh oocyte. Thus, it is recommended that mitochondrial transfer therapy is unsuitable to use for curing infertility in current conditions, and the efficacy and safety of this technology are need to be investigated further.

Perspectives and conclusion

Beyond mitochondrial replacement therapy (i.e., nucleus transfer), much interest in this field has concerned on AUGMNET as a potential therapeutic option for rescuing compromised oocyte. The development of this technology seems rough, but it's only limited on clinical application. Basic research of discovering the relationship between mitochondria and oocyte quality and potential effective factors involving in OT are much more intriguing. What's more, sufficient evidences on basic researches is fundamental to advance AUGMENT in stability and efficiency. Emerging data suggest that mitochondrial metabolism is significantly important to prevent oocyte from death (61), but directly injecting purified mitochondria doesn't work well. The reasons for failure may be attributed to the following points: (I) exfoliate mitochondria from endoplasmic reticulum (ER) which is essential to keep mitochondrial function (62); (II) too much cell debris containing in isolated mitochondria may cause overload metabolism in poor oocyte; (III) discard multiple other functional small molecular that is potential to benefit oocyte quality. Therefore, advancing in the technologies of isolating and optimizing scheme of transferring may make revolution in this scope. Once its effectiveness and safety are appropriately confirmed, mitochondrial transfer therapies will have great potential to be used as a novel treatment in assisted reproduction. Although alternative and innovative approaches are being proposed, it still remains in a very early stage. Nevertheless, search for an effective solution to improve oocyte quality will be continuous.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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