Journal of the Formosan Medical Association (2015) 114, 1027–1028

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.jfma-online.com

PERSPECTIVES

Three-parent embryo: The therapeutic future for inherited mitochondrial diseases

Hui-Shan Liu [a], **Pei-Lun Chu** [b,*]

[a] *Department of Obstetrics & Gynecology, National Taiwan University Hospital Yunlin Branch, Yunlin, Taiwan*
[b] *Division of Nephrology, Department of Medicine, University of Virginia Health System, Charlottesville, VA, USA*

Received 25 March 2014; received in revised form 21 April 2014; accepted 30 April 2014

KEYWORDS
genetics;
inherited mitochondrial disease;
in vitro fertilization;
mitochondria;
three-parent embryo

Of approximately 25,000 genes in the entire human genome, the mitochondrial genome (mtDNA) accounts for a very small fraction of it and encodes only 37 genes. Currently, preimplantation genetic diagnosis (PGD) has emerged as a powerful tool to prenatally diagnose inherited genetic diseases, especially nuclear genetic diseases; however, it is not that useful for diagnosing inherited mitochondrial diseases. Recently, the US Food and Drug Administration advisory panel conducted a hearing to evaluate the feasibility of a novel *in vitro* fertilization (IVF) technique that might provide hope for women with mitochondrial diseases to allow them to have healthy children. This novel technique was approved in the United Kingdom in June 2013. The embryo generated using this technique is termed a "three-parent embryo" since its genome is derived from three sources.

The mitochondrion is a crucial eukaryotic organelle that regulates cell energy production through oxidative phosphorylation. Because of its role in energy metabolism, mitochondria are abundant in tissues with high energy demands, such as brain, heart, muscle, liver, kidney, and central nervous system tissues. This unique feature characterizes multiorgan involvement in mitochondrial genetic diseases. It has been estimated that the lifetime risk of developing a mitochondrial disease is approximately 1 in 5000 live births.[1] According to the Health Promotion Administration, Ministry of Health and Welfare, Taiwan, approximately 50 inherited mitochondrial diseases and up to 400 affected families in Taiwan were reported, which corresponds to an approximate mutation rate of 1/10,000 (http://gene.hpa.gov.tw/index.php?mo=DiseasePaper&ac=paper1_show&cate=Set1&csn=71&sn=144).

Conflicts of interest: The authors declare no conflicts of interest.

* Corresponding author. University of Virginia Health System, Division of Nephrology, Department of Medicine, University of Virginia, P.O. Box 800133, Charlottesville, VA 22908, USA.
E-mail address: pc4ed@virginia.edu (P.-L. Chu).

http://dx.doi.org/10.1016/j.jfma.2014.04.007

Mitochondrial genetic diseases can be caused by either mutations in the mtDNA or in the nuclear genes involved in mitochondrial function. In humans, the mtDNA is exclusively maternally inherited. Although sperm also carries mtDNA, its mtDNA is specifically removed by ubiquitination.[2] Moreover, compared with the oocyte which has almost 100,000 copies of mtDNA, sperm contains only 100 copies. After fertilization, the dilution effect and the bottleneck phenomenon might preferentially exclude the transmission of paternal mtDNA and lead to the maternal inheritance pattern of mtDNA.

Because of mitochondrial heteroplasmy and the bottleneck phenomenon,[3] it is challenging to utilize PGD for prenatal diagnosis of inherited mitochondrial diseases.[4] Heteroplasmy represents a mixture of mutant and normal mtDNA in a given cell, tissue, or an individual. A higher heteroplasmy of the mutant mtDNA predisposes to a greater chance of developing a mitochondrial disease. The bottleneck phenomenon would cause a marked variation of mutant mtDNA being transmitted to the embryo from a heteroplasmic mother. Thus, a woman carrying a low level of heteroplasmic mutant mtDNA may still transmit a substantial amount of mutant mtDNA to her offspring. There is also a concern about whether the biopsied blastomeres or the trophectoderm is able to precisely represent the entire embryo.[5] Hence, it is difficult to accurately predict the risk of transmission of a mitochondrial disease, particularly with regard to PGD, which has no useful role to play in diagnosing inherited mitochondrial diseases when a woman carries homoplasmic mutant mtDNA. These concerns plus recent advances in three-parent IVF have prompted the US Food and Drug Administration to step forward to evaluate the therapeutic potential of this technique.

In the three-parent embryo, the nuclear genome originates from both male and female biological parents just like every other embryo fertilized in the natural way, however, its mtDNA is derived from an oocyte of a healthy woman. Thus, it is hoped that the three-parent embryo will prevent the transmission of mutant mtDNA from the affected woman to the embryo. Currently, two major procedures are utilized to generate three-parent embryos: the pronuclear transfer and the spindle transfer. The pronuclear transfer is performed by removing both normal pronuclei from a zygote carrying mutant mtDNA to a donated enucleated zygote.[6] Alternatively, the spindle transfer is achieved by transferring the nuclear genome from an unfertilized oocyte of the affected woman to a mtDNA mutation-free oocyte from which the nuclear genetic material has been removed.[7] Because of the preferential elimination and dilution effect of paternal mtDNA after fertilization, paternal mtDNA is less likely to be used in place of the mtDNA from the donor woman.

Three-parent IVF provides a plausible therapeutic future for women with mitochondrial diseases, however, this technique also carries risks and ethical concerns. Both procedures of three-parent IVF still harbor the risk of carrying over a variable fraction of mutant mtDNA to the embryos,[7,8] that might potentially cause a detrimental effect in the fertilized embryo because of heteroplasmy and the bottleneck phenomenon. The possibility of generating abnormally fertilized embryos is also observed.[7,8] Moreover, the development of a three-parent embryo might also pose a challenge to the definition of biological parentage because of its three origins of genetic material. Lastly, subsequent emerging legal issues, profit-oriented behaviors, and the social impacts related to three-parent embryos might be different from gestational surrogacy issues we are now facing and should be well-assessed in advance.

References

1. Haas RH, Parikh S, Falk MJ, Saneto RP, Wolf NI, Darin N, et al. Mitochondrial disease: a practical approach for primary care physicians. *Pediatrics* 2007;**120**:1326—33.
2. Sutovsky P. Ubiquitin-dependent proteolysis in mammalian spermatogenesis, fertilization, and sperm quality control: killing three birds with one stone. *Microsc Res Tech* 2003;**61**: 88—102.
3. Taylor RW, Turnbull DM. Mitochondrial DNA mutations in human disease. *Nat Rev Genet* 2005;**6**:389—402.
4. Sallevelt SC, Dreesen JC, Drusedau M, Spierts S, Coonen E, van Tienen FH, et al. Preimplantation genetic diagnosis in mitochondrial DNA disorders: challenge and success. *J Med Genet* 2013;**50**:125—32.
5. Amato P, Tachibana M, Sparman M, Mitalipov S. Three-parent in vitro fertilization: gene replacement for the prevention of inherited mitochondrial diseases. *Fertil Steril* 2014;**101**:31—5.
6. McGrath J, Solter D. Nuclear transplantation in the mouse embryo by microsurgery and cell fusion. *Science* 1983;**220**: 1300—2.
7. Tachibana M, Sparman M, Sritanaudomchai H, Ma H, Clepper L, Woodward J, et al. Mitochondrial gene replacement in primate offspring and embryonic stem cells. *Nature* 2009;**461**:367—72.
8. Craven L, Tuppen HA, Greggains GD, Harbottle SJ, Murphy JL, Cree LM, et al. Pronuclear transfer in human embryos to prevent transmission of mitochondrial DNA disease. *Nature* 2010; **465**:82—5.