OPEN ACCESS Freely available online

PLOS | GENETICS

Viewpoints

The Challenges of Mitochondrial Replacement

Patrick F. Chinnery[1,2], Lyndsey Craven[1], Shoukhrat Mitalipov[3], James B. Stewart[4], Mary Herbert[1,5], Douglass M. Turnbull[1]*

1 Wellcome Trust Centre for Mitochondrial Research, Institute for Ageing and Health, Newcastle University, Newcastle upon Tyne, United Kingdom, **2** Institute of Genetic Medicine, Newcastle University, Central Parkway, Newcastle upon Tyne, United Kingdom, **3** Division of Reproductive & Developmental Sciences, Oregon National Primate Research Center, Oregon Health & Science University, Beaverton, Oregon, United States of America, **4** Max Planck Institute for Biology of Ageing, Cologne, Germany, **5** Newcastle Fertility Centre, International Centre for Life, Newcastle University, Newcastle upon Tyne, United Kingdom

New advances in medicine often raise challenges, and none more so than those involving the manipulation of human oocytes and embryos. Issues around clinical need and ethical considerations must be taken into account, as well as the safety of the proposed technique. The discussion around the proposed mitochondrial replacement techniques to prevent the transmission of mitochondrial DNA disease has perhaps raised more challenges than most [1].

Mitochondrial DNA diseases are both common and, in their severest forms, devastating [2]. There are limited treatments available for these patients, and those that are successful are focused on treating complications such as epilepsy and cardiac disease [3]. Mitochondrial DNA diseases are transmitted maternally, and for families carrying these mutations, a major, and justifiable, desire is to have unaffected children. For some women, preimplantation or prenatal diagnosis may be helpful [4,5], but for other women, these techniques will not result in disease-free offspring and the only options available are either oocyte donation or mitochondrial replacement at the oocyte or zygote stage. The need for this technique for these families is well established, as are the experimental methods that are required for mitochondrial replacement [6–8]. The major scientific concerns for those of us working in the field revolve around safety and efficacy.

In the United Kingdom, the Human Fertilisation and Embryology Authority (HFEA) recently considered the safety issues after extensive expert and public consultation [9]. This independent group of scientists reviewed all the evidence and concluded that mitochondrial replacement techniques have the potential to be used for patients with mitochondrial DNA disease, although further experiments are required before introduction into clinical practice, to provide further reassurance with respect to efficiency and safety. Recently [10], it has been suggested that the possibility of a harmful interaction between the mitochondrial and nuclear genomes has not been given due weight. Should we therefore stop further clinical developments in this area with immediate effect?

The authors raise an interesting evolutionary argument that the human mitochondrial genome co-evolves with the nuclear genome in females, raising the possibility of a conflict with the paternal nuclear genome. They suggest Leber's hereditary optic neuropathy (LHON) and male infertility could be potential examples of this in humans [10]. Firstly, LHON is not a male-limited disease as they suggest [11]. The disorder affects ~10% of women carrying specific mtDNA mutations, and although there is increased penetrance in males, strenuous efforts have failed to identify a nuclear modifier gene to date, and the increased penetrance in men could simply reflect the absence of oestrogens [12]. As regards male infertility, there is no convincing evidence in man that inherited variants of mtDNA are at all relevant in the general population [13,14]. Indeed it is interesting that even in male patients with pathogenic mitochondrial DNA mutations, such as LHON, reduced fertility has not been reported to be a major clinical feature.

The studies in macaques are also highly relevant to the risks proposed in humans associated with mitochondrial replacement. There are now multiple reports of the health status of the offspring born after mitochondrial replacement, and all have shown no difference between these offspring and controls [6,7,15]. As highlighted in the reports, the macaques used for these experiments were not, as suggested by the authors of the recent commentary [10], highly genetically related, but some were from divergent subspecies with extensive differences in the rhesus macaque genome [6]. Thus, the experiments using the animal model closest to man have not shown any adverse effects from mitochondrial transfer.

Some studies in laboratory mice have proposed a nuclear DNA–mitochondrial DNA interaction, but there are others that have reported no defect despite the use of very divergent genomes [16–18]. It is important to recognise that these studies, and those in invertebrates, have been performed on highly inbred species (often inbred over thousands of generations) and the relevance to human populations must be questioned. Most human populations are outbred with

Citation: Chinnery PF, Craven L, Mitalipov S, Stewart JB, Herbert M, et al. (2014) The Challenges of Mitochondrial Replacement. PLoS Genet 10(4): e1004315. doi:10.1371/journal.pgen.1004315

Editor: David R. Thorburn, Royal Children's Hospital, Australia

Published April 24, 2014

Funding: PFC, MH and DMT are all supported by The Wellcome Trust Centre for Mitochondrial Research [G906919]. PFC is a Wellcome Trust Senior Fellow in Clinical Science (084980/Z/08/Z), and a UK NIHR Senior Investigator and receives additional support from the Medical Research Council (UK) Centre for Translational Muscle Disease research, the Association Française contre les Myopathies, and EU FP7 TIRCON, and the National Institute for Health Research (NIHR) Newcastle Biomedical Research Centre based at Newcastle upon Tyne Hospitals NHS Foundation Trust and Newcastle University. SM is supported by grants from the National Institutes of Health R01HD057121, R01HD059946, R01HD063276, R01EY021214 and 8P51OD01109. SM also receives support from the Leducq Foundation and other OHSU institutional funds. DMT is also supported by Newcastle University Centre for Brain Ageing and Vitality (supported by the BBSRC, EPSRC, ESRC and MRC) [G0700718]), MRC Centre for Neuromuscular Disease [G000608-1], The MRC Centre for Translational Research in Neuromuscular Disease Mitochondrial Disease Patient Cohort (UK) [G0800674], Lily Foundation, the UK NIHR Newcastle Biomedical Research Centre in Age and Age Related Diseases. The funders had no role in the preparation of the article.

Competing Interests: The authors have declared that no competing interests exist.

* E-mail: doug.turnbull@newcastle.ac.uk

considerable mixing of the genome over recent generations. In these populations the mixing of alleles will inevitably dilute the effect of potentially harmful nuclear DNA-mitochondrial DNA interactions. There has never been any direct evidence of a ''mismatch'' between the two in humans—either on an evolutionary scale or in the context of disease. This is even the case for couples from divergent haplogroups, where potential nuclear-mitochondrial mismatches are at their most extreme. Thus, from the mitochondrial DNA perspective, any mitochondrial transfer experiment is just recapitulating what is happening every day all around the world—and without any known adverse effects.

Whilst we accept that any new technique is associated with risk, we think the lack of any reliable evidence of mitochondrial-nuclear interaction as a cause of disease in human outbred populations provides the necessary reassurance to proceed. The recent studies in macaques after mitochondrial replacement are also supportive that the possible harmful interactions are unlikely to occur in man [6,7]. Human preimplantation embryos and embryonic stem cells generated with ''unmatched'' mtDNA replacement demonstrated normal development and differentiation potential [7,8]. As suggested by the HFEA [9], it is possible to match mitochondrial haplotype between the mother and the mitochondrial donor to avoid any concern, even though the evidence says it should not be needed. We do not believe this important development should be delayed—for families carrying mtDNA mutations, the clock is ticking, and the desire to have children free of mitochondrial DNA disease is entirely justified. Ultimately, we believe those that carry mitochondrial DNA mutations must be fully informed of the potential risks, and that they will decide which option to take.

References

1. HFEA, Mitochondria public consultation (2012) Available: http://www.hfea.gov.uk/6896.html. Accessed 29 March 2014.
2. Koopman WJ, Willems PH, Smeitink JA (2012) Monogenic mitochondrial disorders. N Engl J Med 366: 1132–1141.
3. Wellcome Trust Centre for Mitochondrial Research (2014) Patient Care Guidelines. Available: http://www.newcastle-mitochondria.com/service/patient-care-guidelines/. Accessed 29 March 2014.
4. Steffann J, Frydman N, Gigarel N, Burlet P, Ray PF, et al. (2006) Analysis of mtDNA variant segregation during early human embryonic development: a tool for successful NARP preimplantation diagnosis. J Med Genet 43: 244–247.
5. Steffann J, Gigarel N, Corcos J, Bonnière M, Encha-Razavi F, et al. (2007) Stability of the m.8993T→G mtDNA mutation load during human embryofetal development has implications for the feasibility of prenatal diagnosis in NARP syndrome. J Med Genet 44: 664–669.
6. Tachibana M, Sparman M, Sritanaudomchai H, Ma H, Clepper L, et al. (2009) Mitochondrial gene replacement in primate offspring and embryonic stem cells. Nature 461: 367–372.
7. Tachibana M, Amato P, Sparman M, Woodward J, Sanchis DM, et al. (2013) Towards germline gene therapy of inherited mitochondrial diseases. Nature 493: 627–631.
8. Craven L, Tuppen HA, Greggains GD, Harbottle SJ, Murphy JL, et al. (2010) Pronuclear transfer in human embryos to prevent transmission of mitochondrial DNA disease. Nature 465: 82–85.
9. HFEA (2011) Review of scientific methods to avoid mitochondrial disease 2011 (including 2013 update). Available: http://www.hfea.gov.uk/6372.html. Accessed 29 March 2014.
10. Reinhardt K, Dowling DK, Morrow EH (2013) Mitochondrial replacement, evolution, and the clinic. Science 341: 1345–1346.
11. Yu-Wai-Man P, Griffiths PG, Hudson G, Chinnery PF (2009) Inherited mitochondrial optic neuropathies. J Med Genet 46: 145–158.
12. Giordano C, Montopoli M, Perli E, Orlandi M, Fantin M, et al. (2011) Oestrogens ameliorate mitochondrial dysfunction in Leber's hereditary optic neuropathy. Brain 134: 220–234.
13. Pereira L, Gonçalves J, Franco-Duarte R, Silva J, Rocha T, et al. (2007) No evidence for an mtDNA role in sperm motility: data from complete sequencing of asthenozoospermic males. Mol Biol Evol 24: 868–874.
14. Mossman JA, Slate J, Birkhead TR, Moore HD, Pacey AA (2012) Mitochondrial haplotype does not influence sperm motility in a UK population of men. Hum Reprod 27: 641–651.
15. Lee HS, Ma H, Juanes RC, Tachibana M, Sparman M, et al. (2012) Rapid mitochondrial DNA segregation in primate preimplantation embryos precedes somatic and germline bottleneck. Cell Rep 1: 506–515.
16. Battersby BJ, Shoubridge EA (2001) Selection of a mtDNA sequence variant in hepatocytes of heteroplasmic mice is not due to differences in respiratory chain function or efficiency of replication. Hum Mol Genet 10: 2469–2479.
17. Cannon MV, Dunn DA, Irwin MH, Brooks AI, Bartol FF, et al. (2011) Xenomitochondrial mice: investigation into mitochondrial compensatory mechanisms. Mitochondrion 11: 33–39.
18. Gregorová S, Divina P, Storchova R, Trachtulec Z, Fotopulosova V, et al. (2008) Mouse consomic strains: exploiting genetic divergence between Mus m. musculus and Mus m. domesticus subspecies. Genome Res 18: 509–515.