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COMMENTARY

Easing US restrictions on mitochondrial replacement therapy would protect research interests but grease the slippery slope

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Introduction

Mitochondria are essential organelles found in most eukaryotic cells [1, 2]. They play important roles not only in the production of cellular energy but also in metabolic [3], immune [4], neural [5], and psychiatric function [6, 7], as well as aging [2, 8]. Mitochondria originated billions of years ago as separate bacteria-like organisms, and over the intervening millennia developed symbiotic relationships with our eukaryotic ancestors. The relationship between mitochondria and eukaryotic cells has proven mutually beneficial, though at times precarious [9, 10]. Concordant with their origin as separate organisms, mitochondria contain their own DNA, called mitochondrial DNA [11] (mtDNA). mtDNA retains many features of bacterial DNA, including exquisite susceptibility to damage, rapid mutagenesis, and limited repair capacity.

mtDNA transmits exclusively via the maternal germ line. Oogenesis provides critical quality control to ensure the fittest mtDNA cross into the next generation, and that these mtDNA interact optimally with the nuclear genome [1, 2, 12]. Primordial germ cells and oogonia contain only few mitochondria in their scant cytoplasm. During later oogenesis, mitochondria proliferate within the oocyte's expanding cytoplasm. Germ cells that start with a few mutant mtDNA end up with a large number of abnormal mitochondria and fail to pass muster. Oocytes that inherit healthy mitochondria survive this developmental gauntlet. As a result, mature oocytes have large numbers (200,000 +) of mitochondria, which mainly are normal. Sperms contain mitochondria, which provide ATP to propel the sperm through the reproductive track, but sperm mtDNA are excluded from the embryo at the time of fertilization [13].

Intriguingly, mitochondria are extraordinarily quiescent during early development, from the mature oocyte until early blastocyst stages of development. During this time, oxygen uptake is exceptionally low [14, 15] and mitochondria are devoid of cristae, the folded inner membranes which accommodate proteins involved in oxidative phosphorylation (oxphos). Presumably the quiescent state of mitochondria during early development provides a sanctuary to safely usher mtDNA through to the next generation. Mitochondria, then, are passengers rather than power plants during early development.

Rarely, mutant mitochondria slip past the quality control checkpoints provided during oogenesis. Each year in the USA, about 700 to 1000 babies are born with mitochondrial diseases [2, 12, 16]. Why, from the billions of embryos created naturally each year, only a tiny percentage of infants inherit mitochondrial disease remains poorly understood. Perhaps some mtDNA mutants gain a replicative advantage vis a vis wild type mtDNA, the natural bottleneck provided by oogenesis fails to exclude all abnormal mtDNA, and/or variation in some nuclear-encoded DNA promotes survival of mutant mtDNA [16]. Babies born with a high proportion of sub-par mitochondria develop deadly and debilitating diseases, typically characterized by dysfunction of tissues with the highest energetic demands, e.g., brain, muscle, and retina, i.e., myopathy, encephalopathy, and blindness.

Mitochondrial transfer

Mitochondrial transfer (MT) is an experimental procedure, which attempts to prevent maternal transmission of mutant

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mitochondria by replacing them with wild type mitochondria, via various micromanipulation techniques. MT can be performed at the germinal vesicle (GV) (immature oocyte) [17], metaphase II [18], or zygote stages [19] of development, via GV, cytoplasmic, spindle, or pronuclear transfer, respectively. Experimental MT for prevention of mitochondrial disease has triggered active debate throughout the world and currently is proscribed in the USA [20–22]. Arguments against experimental MT to prevent mitochondrial diseases include that it contravenes the long-held, widely accepted ban on germ-line gene therapy [23] may not be safe nor effective and diverts patients from existing treatments, such as egg donation or preimplantation genetic testing for monogenic disease (PGT-M) [24].

Arguments in favor of experimental MT [20–22] include that egg donation is not acceptable and/or available to some couples, mtDNA genes somehow do not contribute to our genetic identify, and that limited data from experiments conducted on model systems, including non-human primates, human embryos, and embryonic stem cells, suggest no clear and present danger of the procedure to potential offspring [25–27]. Some argue that all current assisted reproductive technology (ART) procedures (e.g., IVF, ICSI, PGT-M) entered clinical practice before any data was available on their safety or efficacy, despite resistance from naysayers [28]. Finally, banning MT therapy constrains scientific freedom and hinders the competitiveness of US science [20–22, 28].

I disagree with each of these arguments in favor of allowing experimental MT. Donor egg treatment provides an undervalued, but highly effective and safe alternative to MT. Donated eggs completely prevent transmission of mutant mtDNA [29]. In this treatment, a genetically similar woman undergoes controlled ovarian stimulation and egg retrieval, and then donates the resulting eggs to the woman carrying mutant mitochondria. Some believe donor egg treatment creates a baby, who is not genetically related to the recipient. In fact, because of extensive genetic similarities among humans, especially those related ethnically, donors share over 99.9% of their DNA sequences with prospective mothers [30–32]. Additionally, during donor egg treatment, the sperm still contributes 50% of the DNA to the offspring so the infant arising from donated eggs differs genetically from the infant born with the mother's own eggs by less than 0.05%. In addition, growing evidence supports the notion that genetic variation does not account for all inheritance. Environmental factors, especially the uterine environment, also play major roles in heritability (Carpinello, 2018 #12075).

Other options exist for women harboring germ-line mtDNA mutations. PGT-M has enjoyed some success in preventing transmission of mtDNA diseases [24]. Germ-line mtDNA mutations do not themselves reduce ovarian reserve, nor cause infertility [33], so controlled ovarian stimulation enables women to produce multiple oocytes, some with sufficiently low concentrations of affected mitochondria to produce unaffected offspring.

PGT-M does have limitations in its application to mitochondrial disease [24, 33]. The concentration of mutant mtDNA in biopsied trophectoderm cells may not reflect that in the inner cell mass, the precursor of the embryo proper. A small number of women produce only embryos bearing predominantly mutant mtDNA, leaving no embryos for transfer. Replication of mtDNA follows a perplexing set of rules, and embryos selected for low concentration of mutant mtDNA may selectively expand the population of mutant mitochondria during later development [2, 16, 19]. Of note, this same problem of carry over and selective expansion of affected mitochondria has been demonstrated to occur in human ESCs [34], and in the only case of MT published to date [35]. The pervasiveness of this phenomenon suggests that MT itself may fail to completely block transmission of mutant mtDNA.

Evidence to support the proposition that mtDNA encodes no important human traits, and therefore, MT does not constitute germ-line genetic engineering, also is scant. Most genome-wide association studies (GWAS) filter out the high copy number mtDNA, so they do not look for association between mtDNA gene variants and disease. Meanwhile, extensive experimental data demonstrates profound effects of mtDNA in a wide array of human conditions, including autism [36], aging [16], psychiatric diseases [7], immune response [37], response to ototoxic antibiotics [38], and risk for cardiomyopathy [39], among others. MTDNA, therefore, does contribute to many facets of "humanness" and to genetic identity, so MT does constitute germ-line genetic engineering.

Sliding down the slippery slope greased by legalization of MT

The most compelling argument to uphold the ban on MT in the USA is the near certainty that, if lifted, indications for MT will undergo mission creep, and extend inappropriately to millions of women who suffer from age-related infertility, despite compelling evidence that MT provides neither safe nor effective treatment for reproductive aging. ART in the USA remains heavily market driven and operates outside constraints provided by governmental authorities, insurance companies, or universities. The ART market in the USA also is undergoing consolidation into a few, large, consumer-oriented chains of ART centers, frequently backed by private equity. The largest enterprises are acquiring stakes in ART-related technologies. The ART market has grown mostly outside of academic medical centers, whose IRBs and bioethical review committees would provide a modicum of restraint. Even the editorial boards of most ART-related journals now are dominated by individuals with close ties to industry.

Equally concerning is that, with the current battle raging between the political right and the left in the USA, extending governmental oversight to ART, to limit the spread of unindicated use of MT, could lead to complete bans on all ART. A number of state legislatures are considering bills seeking to define embryos as human beings, which would grant them associated human rights. What will prevent regulations introduced to prevent spread of MT from restricting access to ART itself? More specifically, how would MT be restricted to experimental prevention of mitochondrial disease? If a clinical embryologist detects a single copy of mutant mtDNA in a polar body, which practically every oocyte contains, will this be sufficient to indicate MT?

Reproductive aging is the most pressing clinical challenge facing couples across the world [40]. Despite extensive research, little is understood about the biological underpinnings of reproductive aging. We do know that the oocyte is the locus of reproductive aging in women [29] and that aneuploidy plays a central role in age-related oocyte dysfunction [41]. Mice differ profoundly from humans in that their uterus and hypothalamus exhibit age-related dysfunction well before their oocytes [42]. A number of mechanisms have been proposed to explain oocyte aging in women, including disruption of long-lived proteins, such as cohesions [43], crossover inefficiency in late ovulating oocytes [44], telomere attrition [45], accumulation of ROS damage to DNA and proteins, and impairment of DNA repair [46].

Initially, accumulation of mtDNA mutations in human oocytes provided an attractive hypothesis to pull together the diverse manifestations of oocyte aging [11]. Unfortunately, compelling evidence now suggests that defective mitochondria are unlikely drivers of oocyte aging in women. Mitochondria are remarkably quiescent in oocytes and embryos, at least until the blastocyst stage [15]. They consume only low levels of oxygen and use alternative mechanisms to generate ATP, including the Warburg effect [47, 48], and the adenosine salvage pathway [49]. In a mouse model of reproductive aging, reciprocal nuclear transfer between old and young oocytes shows that the aging phenotype segregates with the nucleus not the cytoplasm [50]. Women who harbor even the most toxic mutations in mtDNA, who have produced offspring with severe mitochondrial diseases, remain fertile [33]. Indeed, pedigrees of families carrying mitochondrial diseases are remarkable for their fertility. Moreover, in a mouse model, genetic reduction of mtDNA copy number does not impact on fertilization or preimplantation embryo development [51].

Nor is manipulation of mtDNA likely to prove benign. In nature early stages of oogenesis provide an effective bottleneck, to block transmission not only of defective mtDNA but also of mtDNA whose sequences are incompatible with nuclear DNA [34]. mtDNA encodes 37 genes, including 13 genes encoding proteins critical for oxphos as well as genes critical for their translation [16]. But control of mtDNA replication has been subsumed by nuclear-encoded genes. These act on the D-loop region of the mtDNA, which not only provides origin of replications for mtDNA but also are one of the most rapidly evolving regions of the genome [16].

It is important to appreciate that effective interaction between mitochondrial and nuclear DNA is not a static, but rather a continuously evolving process [16]. mtDNA mutates at a rate ten times faster than nuclear DNA. In fact, mtDNA mutates so rapidly that variation in its sequences provides a method to trace cell lineage within somatic tissues, such as the brain [52]. These unique features of mtDNA are not mere curiosities of molecular biology—they also pose threats to the health of heteroplasmic offspring. Mixing even neutral variants of mtDNA sequence in the germ-line (called heteroplasmy) of mice produces a phenotype consisting of neurocognitive and behavioral dysfunction [9, 53]. mtDNA must be amenable to regulation by the nuclear genome. Presumably, this exigency explains the universal pattern of oocyte transmission of mtDNA. This finding also should suggest caution in attempting human experiments which attempt to bypass billions of years of evolution. Of note, interracial crosses do not provide natural experiments of heteroplasmy. Even in the setting of crosses between racially distinct individuals, oogenesis still provides a bottleneck to block transmission of incompatible mitochondrial and nuclear genomes. Experimental mixing of mitochondrial genomes during early development, after the oogonial bottleneck has completed its work, bypasses the "Muller's ratchet," and risks introducing heteroplasmy.

The US ART market provides limited ability to vet the safety and efficacy of new technologies, such as MT. History already bears this out. An early iteration of MT attempted to supplement oocytes of women who had experienced multiple IVF failures with small doses of cytoplasm extracted from donor oocytes [54, 55]. Despite the lack of proper controls and concerns about the propriety and safety of this procedure, it was introduced into clinical practice and taught at workshops at national clinical meetings, including the Annual Meeting of the American Society for Reproduction Medicine. Only when the FDA intervened did this MT frenzy abate.

Another version of MT proposed to extract mitochondria from cells cultured from ovarian biopsies [56]. Wall Street aggressively responded to the "market opportunity" posed by this experimental therapy, with apparently little concern for its safety or efficacy, by investing over $228 million in this technology before results of any clinical trial were available. When asked by investors when clinical trials would be forthcoming, the CEO of the firm offering MT responded, "the fertility (industry) just doesn't do trials" [57, 58]. Apparently, what it did do was marketing, in the form of lavish industry-sponsored symposia at national meetings, and grants to support descriptive research carried out by scientists, most

of whom sat on the fledgling company's scientific advisory board. Ultimately, the market corrected its position on the technology, with loss of virtually the entire investment [59]. The biggest loss was to society and to the scientific community, which were distracted from more fruitful avenues of research by the outsized infusion of private equity. Only after the demise of the company did results of the sole clinical trial appear in publication, reporting compelling evidence that MT impairs, not improves, fertility [60].

Conclusion

At the present time, MT is a research not a clinical procedure. Therefore, the US ban on MT research does not limit access to established therapies for mitochondrial disease. The US ban on MT research should remain in place because the US ART market does not have the requisite infrastructure to investigate it without unleashing MT on millions of poorly informed patients. Just as society does not permit research on infectious agents to be carried out in facilities lacking security to prevent spread of biohazards contained within it, society also should limit research on MT. The US IVF community operates in an environment incapable of equipoise, and lacks the will and ability to limit experimental therapies to appropriate indications. Conversely, to introduce measures to regulate ART, sufficient to restrict MT only to prevent transmission of mitochondrial disease, would risk ceding control to those who would prohibit ART altogether. At this time in history, the most appropriate path is for Americans to watch closely as British and Europeans investigate the efficacy and safety of MT, in secure regulatory environments. In the meantime, donor egg treatment provides a highly effective, safe, and widely available treatment to prevent transmission of mitochondrial disease.

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