Paternal comeback in mitochondrial DNA inheritance

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Since the discovery of mtDNA in 1963 (1), it has been a common notion that inheritance of this small, but very essential, piece of DNA occurs in a strict maternal manner. One reason for this is that the paternal contribution of sperm mitochondria to the fertilized egg is about 1,000-fold less than the number of mitochondria present in the oocyte. In addition to this, there seem to be selective mechanisms, which are still poorly understood, that target paternal mtDNA for destruction. Sperm mitochondria are marked with ubiquitin, which likely facilitates this deselection of paternal mtDNA molecules (2), and paternal mtDNA molecules are usually undetectable after the four- to eight-cell stage after fertilization (3). It is therefore interesting that Luo et al. (4) in PNAS report on biparental inheritance in three families, which challenges the notion of strict maternal transmission of mtDNA to offspring.

Nuclear and mitochondrial DNAs have separate evolutionary origins. The circular mtDNA genome is derived from bacteria and founded the basis for multicellular organisms when single, eukaryote cells engulfed proteobacteria ∼1.5 billion y ago, according to the endosymbiotic theory (5). Although mtDNA is thought to be transmitted by strict maternal inheritance in humans, paternal inheritance of mtDNA has been described for several insects such as fruit flies (6, 7), honey bees (8), and periodical cicadas (9) and in chickens (10) and several mammals such as mice (11, 12), sheep (13), and cloned cattle (14).

Impact of mtDNA Inheritance on Genetic Counseling, Forensic Science, and Anthropology

Strict maternal inheritance of mtDNA has great importance for genetic counseling of women carrying pathogenic mtDNA mutations. For affected men, counseling is easy, because they do not pass mtDNA mutations on to offspring. Genetic counseling of women carrying pathogenic mtDNA mutations is more complicated than for most Mendelian inherited diseases, because the mutation load of an mtDNA variant in oocytes will always be unknown, and therefore it is close to impossible to predict whether and how offspring will be affected. The notion of strict maternal inheritance also has great impact on other aspects of natural science. mtDNA is preserved much better after death than nuclear DNA and therefore plays a great role in forensic analyses. For instance, mtDNA analyses were pivotal in identifying the remains of the last Russian tsar, Nicholas II, and his family (15). mtDNA analyses are also key in anthropology, biogeographic investigations, and human migration studies. They permit an examination of the relatedness of populations, and, as an example, have been key in mapping the geographic footprint of the Vikings (16). The finding of a single patient carrying both his father's and mother's mtDNA in 2002 therefore received much attention and potentially challenged the assumptions made about strict maternal mtDNA inheritance in anthropologic and forensic sciences (17). In the subsequent almost two decades following this discovery, however, human paternal mtDNA inheritance could not be found in patients with mitochondrial diseases (18) and healthy persons (19), and although mixed mtDNA haplotypes were found in several studies, suggestive of biparental mtDNA inheritance, they were generally dismissed as contamination or sample mix-up (20). The study by Luo et al. (4) therefore revitalizes the existence of paternal inheritance of mtDNA. They demonstrate biparental inheritance of mtDNA in healthy persons, and the findings are convincing because it was demonstrated in three independent families, in several generations of these families, and by using whole-DNA sequencing performed by two different laboratories.

A puzzling finding in the paper by Luo et al., though, is the very uniform level of heteroplasmy in individuals from the same family. Such stability of two different mtDNA molecules from generation to generation is unprecedented in patients carrying wild-type and mutated mtDNA species. A plausible explanation for this could be amplification of nuclear elements of mtDNA, if the mtDNA sequences tested

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by Luo et al. were localized to one chromosome. The authors do not rule out this possibility.

Potential Mechanisms Underlying Paternal Inheritance of mtDNA

If nuclear elements of mtDNA cannot explain the apparent biparental inheritance, then perhaps the greatest new finding in the paper by Luo et al. (4) is the clear evidence of a dominantly inherited pattern of biparental mtDNA inheritance. It is the first time that a hint at the potential mechanism for paternal mtDNA inheritance in humans has been proposed based on data. Not only must this dominantly inherited nuclear variant disable the selective destruction of paternal mtDNA during embryogenesis, but the high level of paternal mtDNA found in the persons with biparental mtDNA inheritance also suggests a selective replication of paternal vs. maternal mtDNA in the persons with biparental inheritance of mtDNA. If the selective replication of paternal mtDNA molecules did not occur, then the paternal mtDNA content would be very low, because of the skewed maternal/paternal mtDNA ratio in the fertilized oocyte. Therefore, Luo et al. (4) suggest genes involved in mtDNA replication and copy number are involved in permitting paternal mtDNA transmission. Attention in the coming years will be directed at finding this or these nuclear factors that govern strict maternal inheritance, which potentially could be solved in the families reported by Luo et al. (4) by whole-genome sequencing of members of the three families. Inspiration as to what genes to look for could come from looking at the yeast genome, as paternal inheritance of mtDNA is common in these cells (21). The data presented in the original case of paternal inheritance of mtDNA did not suggest a mechanism by which paternal mtDNA was transmitted (17). The case was also different from that of the healthy persons reported by Luo et al. (4) in that the paternal mtDNA carried a deleterious 2-bp deletion of the ND2 gene (17). It can be speculated that the mutation could interfere with the normal function of the nuclear gene(s), proposed by Luo et al. (4), that eliminate paternal mtDNA, or perhaps alternative mechanisms allowing paternal mtDNA inheritance are at play. In any case, elucidating these mechanisms is key, not only to understanding human molecular genetics better but also to identifying potential therapeutic targets for future treatment of patients with mitochondrial diseases. Although the new findings by Luo et al. (4) do not change the fact that paternal inheritance of mtDNA is the exception, understanding the mechanisms underlying this form of inheritance may prompt development of ways to manipulate paternal mtDNA transmission in women carrying deleterious mtDNA mutations.

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