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Short Review:

Mitochondrion and its related disorders: Making a comeback*

Xian-ning ZHANG[1,2,3], Ming QI[1,2]

([1]*Zhejiang University-Adinovo Center for Genetic and Genomic Medicine, Zhejiang University, Hangzhou 310058, China*)

([2]*James D. Watson Institute of Genome Sciences, Zhejiang University, Hangzhou 310058, China*)

([3]*National Education Base for Basic Medical Sciences, Zhejiang University, Hangzhou 310058, China*)

E-mail: zhangxianning@zju.edu.cn; qiming_14618@yahoo.com

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Abstract: The great majority of genetic disorders are caused by defects in the nuclear genome. However, some significant diseases are the result of mitochondrial mutations. Because of the unique features of the mitochondria, these diseases display characteristic modes of inheritance and a large degree of phenotypic variability. Recent studies have suggested that mitochondrial dysfunction plays a central role in a wide range of age-related disorders and various forms of cancer.

Key words: Mitochondria, Mitochondrial disorder, Mutation
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Life is the interplay between structure, energy, and information, yet the role of energy deficiency in human disease has been poorly explored by modern medicine (Wallace, 2005). The mitochondria are involved in energy production through the oxidative phosphorylation (OXPHOS) metabolic pathways, and are thus critically important for cell survival (Chan, 2006; Wallace, 2007).

An average eukaryotic cell contains 10^3~10^4 copies of mitochondria. A mitochondrion is a semi-autonomous, self-reproducing organelle in the cytoplasm of eukaryotic cells and has multiple copies of circular double-stranded mitochondrial DNA (mtDNA) of 16569 base pairs (bp) in man—actually 16568 bp, and 3107del is maintained in the sequence as a gap, "X" (Andrews *et al*., 1999; Http://www.mitomap.org/mitomap_rCRS.gb.txt). The human mitochondrial genome consists of approximately 1500 genes, 37 encoded by the maternally inherited mtDNA and the remainder encoded in the nuclear DNA (nDNA) (Ryan and Hoogenraad, 2007). The mtDNA genome is very compact, containing little repetitive DNA. The 37 encoded genes include 2 ribosomal RNA (rRNA), 22 transfer RNA (tRNA) and 13 peptides involved in OXPHOS. The nuclear genome encodes up to 200 factors required for the maintenance and expression of mtDNA or for the assembly of OXPHOS protein complexes. Mutations in many of these nuclear genes can also lead to disorders with the phenotypic characteristics of mtDNA diseases (Liang and Wong, 1998; Luoma *et al*., 2004; Zeviani and Carelli, 2007).

The transcription of mtDNA takes place in the mitochondrion, independent of the nucleus. The mitochondrial genome mutates at a rate about 10-fold greater than nDNA does (Hudson *et al*., 2005). The diseases that result from mutations in mtDNA show distinctive patterns of inheritance due to three features of mitochondrial chromosomes: replicative segregation, homoplasmy and heteroplasmy, and maternal inheritance. When a mutation arises in a cellular mtDNA, it creates a mixed intracellular population of mutant and normal molecules known as heteroplasmy. As a cell divides, it is a matter of chance whether the mutant mtDNA are partitioned into one daughter cell or another. Thus, over time the percentage of mutant mtDNA in different cell lineages can drift toward either pure mutant or normal

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(homoplasmy), a process called as replicative segregation. The phenotype associated with an mtDNA mutation will depend on the relative proportion of normal and mutant mtDNA in the cells of a particular tissue. As a result, mitochondrial disorders are generally characterized by reduced penetrance, variable expression, and pleiotropy. Hereditary mitochondrial diseases are transmitted only through the maternal line, since spermatozoa contain hardly any mitochondria. Paternal inheritance of mtDNA disorder has been well documented in only one instance (Schwartz and Vissing, 2002).

Each tissue type requires a certain amount of mitochondrially produced ATP for normal function. Organ system with large ATP requirements and high thresholds, for example, the brain, heart, skeletal muscle, eye, ear, liver, pancreas and kidney, tend to be the ones most seriously affected by mitochondrial diseases. The first inherited pathogenic mtDNA mutations were discovered in 1988, when Wallace *et al*. (1988) reported the mtDNA mutation that causes Leber hereditary optic neuropathy (LHON, OMIM 535000), a form of middle life blindness, and subsequently the mutation that causes myoclonic epilepsy and ragged red fiber disease (MERRF, OMIM 545000), a progressive epilepsy with muscle weakness. Since then, a large number of mtDNA mutations have been linked to familial symptoms, including forms of blindness, deafness, dementia, stroke-like episodes, migraines, movement disorders, cardiomyopathy, renal dysfunction, diabetes, various forms of cancer, etc. (Wallace, 2005; Zeviani and Carelli, 2007). Three types of mutations have been identified in mtDNA: (1) Missense mutations in protein-coding mtDNA genes that alter the activity of an OXPHOS protein. mtDNA missense mutations can be associated with two common ophthalmologic manifestations, optic atrophy and retinitis pigmentosa; (2) Single-base mutations in tRNA or rRNA genes that impair mitochondrial protein synthesis. The example diseases are MERRF and MELAS (mitochondrial encephalomyopathy, lactic acidosis and strokelike episodes, OMIM 540000); (3) Rearrangements that consist of duplications and deletions of the mtDNA molecule. These can produce Kearns-Sayre disease (muscle weakness, cerebellar damage, and heart failure, OMIM 530000), Pearson syndrome (infantile pancreatic insufficiency, pancytopenia, and lactic acidosis, OMIM 557000), and chronic progressive external ophthalmoplegia (CPEO). The disease-causing mutations seen in mtDNA include more than 50 point mutations and more than 100 deletions or duplications.

Since the mitochondria use OXPHOS to convert dietary calories into usable energy, generating reactive oxygen species (ROS) as a toxic by-product, mitochondrial dysfunction plays a central role in a wide range of age-related disorders and various forms of cancer (Wallace, 2007; Xia *et al*., 2007; Zeviani and Carelli, 2007). Increased amount of rearrangements (deletions/small duplications) and point mutations of mtDNA have been reported during aging in several mammalian species. Studies of different tissues have shown that the somatic mtDNA mutations are not always evenly distributed but can accumulate clonally in single cells and cause a severe respiratory chain deficiency in these cells. It is probable that clonal expansion of pathogenic mtDNA mutations in individual cells will lead to their loss with age, but it is unclear how this phenomenon will affect organismal survival (Trifunovic *et al*., 2004).

The tissue-specific manifestations of these diseases may result from the varying energetic roles and needs of the different tissues. The variation in the individual and regional predisposition to degenerative diseases and cancer may result from the interaction of modern dietary caloric intake and ancient mitochondrial genetic polymorphisms (Pospisilik *et al*., 2007). Therefore the mitochondria provide a direct link between our environment and our genes, and the mtDNA variants that permit our forbears to energetically adapt to their ancestral homes are influencing our health today (Calvo *et al*., 2006; Wallace, 2007).

References

Andrews, R.M., Kubacka, I., Chinnery, P.F., Lightowlers, R.N., Turnbull, D.M., Howell, N., 1999. Reanalysis and revision of the Cambridge reference sequence for human mitochondrial DNA. *Nat. Genet.*, **23**(2):147. [doi:10.1038/13779]

Calvo, S., Jain, M., Xie, X., Sheth, S.A., Chang, B., Goldberger, O.A., Spinazzola, A., Zeviani, M., Carr, S.A., Mootha, V.K., 2006. Systematic identification of human mitochondrial disease genes through integrative genomics. *Nat. Genet.*, **38**(5):576-582. [doi:10.1038/ng1776]

Chan, D.C., 2006. Mitochondria: Dynamic organelles in disease, aging, and development. *Cell*, **125**(7):1241-1252.

[doi:10.1016/j.cell.2006.06.010]

Hudson, G., Keers, S., Man, P.Y., Griffiths, P., Huoponen, K., Savontaus, M.L., Nikoskelainen, E., Zeviani, M., Carrara, F., Horvath, R., *et al*., 2005. Identification of an X-chromosomal locus and haplotype modulating the phenotype of a mitochondrial DNA disorder. *Am. J. Hum. Genet.*, **77**(6):1086-1091. [doi:10.1086/498176]

Liang, M.H., Wong, L.J., 1998. Yield of mtDNA mutation analysis in 2000 patients. *Am. J. Med. Genet.*, **77**(5): 395-400. [doi:10.1002/(SICI)1096-8628(19980605)77:5<395::AID-AJMG8>3.0.CO;2-M]

Luoma, P., Melberg, A., Rinne, J.O., Kaukonen, J.A., Nuponen, N.N., Chalmers, R.M., Oldfors, A., Rautakorpi, I., Peltonen, L., Majamaa, K., *et al*., 2004. Parkinsonism, premature menopause, and mitochondrial DNA polymerase gamma mutations: Clinical and molecular genetic study. *Lancet*, **364**(9437):875-882. [doi:10.1016/S0140-6736(04)16983-3]

Pospisilik, J.A., Knauf, C., Joza, N., Benit, P., Orthofer, M., Cani, P.D., Ebersberger, I., Nakashima, T., Sarao, R., Neely, G., *et al*., 2007. Targeted deletion of AIF decreases mitochondrial oxidative phosphorylation and protects from obesity and diabetes. *Cell*, **131**(3):476-491. [doi:10.1016/j.cell.2007.08.047]

Ryan, M.T., Hoogenraad, N.J., 2007. Mitochondrial-nuclear communications. *Annu. Rev. Biochem.*, **76**(1):701-722. [doi:10.1146/annurev.biochem.76.052305.091720]

Schwartz, M., Vissing, J., 2002. Paternal inheritance of mitochondrial DNA. *N. Engl. J. Med.*, **347**(8):576-580. [doi:10.1056/NEJMoa020350]

Trifunovic, A., Wredenberg, A., Falkenberg, M., Spelbrink, J.N., Rovio, A.T., Bruder, C.E., Bohlooly, Y.M., Gidlof, S., Oldfors, A., Wibom, R., Törnell, J., Jacobs, H.T., Larsson, N.G., 2004. Premature ageing in mice expressing defective mitochondrial DNA polymerase. *Nature*, **429**(6990):417-423. [doi:10.1038/nature02517]

Wallace, D.C., 2005. A mitochondrial paradigm of metabolic and degenerative diseases, aging, and cancer: A dawn for evolutionary medicine. *Annu. Rev. Genet.*, **39**(1):359-407. [doi:10.1146/annurev.genet.39.110304.095751]

Wallace, D.C., 2007. Why do we still have a maternally inherited mitochondrial DNA? Insights from evolutionary medicine. *Annu. Rev. Biochem.*, **76**(1):781-821. [doi:10.1146/annurev.biochem.76.081205.150955]

Wallace, D.C., Singh, G., Lott, M.T., Hodge, J.A., Schurr, T.G., Lezza, A.M., Elsas, L.J.2nd, Nikoskelainen, E.K., 1988. Mitochondrial DNA mutation associated with Leber's hereditary optic neuropathy. *Science*, **242**(4884): 1427-1430. [doi:10.1126/science.3201231]

Xia, C., Meng, Q., Liu, L.Z., Rojanasakul, Y., Wang, X.R., Jiang, B.H., 2007. Reactive oxygen species regulate angiogenesis and tumor growth through vascular endothelial growth factor. *Cancer Res.*, **67**(22):10823-10830. [doi:10.1158/0008-5472.CAN-07-0783]

Zeviani, M., Carelli, V., 2007. Mitochondrial disorders. *Curr. Opin. Neurol.*, **20**(5):564-571.