MITOCHONDRIAL GENETICS IN AMD

The powerhouse of the cell holds potential for the treatment of age-related disease.

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Mitochondria are organelles crucial for the homeostasis of cells. The numbers of mitochondria within a cell can vary from just a few to several thousand, depending on the energy requirements of that cell. Each mitochondrion is compartmentalized to contain an intermembrane space between the outer and inner membranes; cristae, which are invaginations of the inner membrane; and an inner matrix that contains proteins, ribosomes, transfer RNA (tRNA), and mitochondrial DNA (mtDNA) (Figure 1).

It has long been recognized that mitochondria are the equivalent of batteries in human cells. If they fail or give out, then homeostasis is lost, cells cannot function efficiently, and tissues eventually become susceptible to aging disorders and death. This is a widely recognized phenomenon, with more than 8,000 published articles in the literature on the topic of mitochondria and aging and more than 22,000 on the topic of mitochondria and diseases.

The maternally inherited mtDNA is a double-stranded, closed, circular mtDNA that codes for 37 genes yielding 13 proteins essential for oxidative phosphorylation, 22 tRNAs, and two ribosomal RNAs. Recently described mitochondria-derived peptides, such as humanin and MOTS-c, are encoded from the 16S-rRNA and 12S-rRNA regions of the mtDNA genome and have protective properties against cell death.1,2 Interestingly, there are more than 1,500 mitochondrial proteins that are encoded by the nuclear DNA and imported into the mitochondria.

HAPLOGROUPS AND RETINAL DISEASE

The geographic origins of populations can be classified by maternal lineages according to nucleotide accumulation patterns called haplogroups within mtDNA. The oldest haplogroups are from Africa, and from these the European, Asian, and Native-American haplogroups have evolved over thousands of years. Each haplogroup has an accumulation of specific single nucleotide polymorphism (SNP) variants that represent that group (Table).

Some age-related diseases, including age-related macular degeneration (AMD), are being correlated to specific...
haplogroups. For example, studies show that three European haplogroups, J, T, and U, are associated with AMD,\(^3\) while the H haplogroup has a protective effect against developing the disease.\(^7\) In addition, the J and U haplogroups are associated with large soft drusen and retinal pigment abnormalities, which are characteristics of AMD.\(^3\)

There are also some individual mtDNA SNPs associated with AMD. For example, the SNP A4917G, which is within the NADH dehydrogenase subunit 2 of complex I, is an independent predictor of AMD,\(^4\) and individuals with SNP A11812G of the MT-ND4 gene and SNP A14233G of the MT-ND6 gene, both located in respiratory complex I, are at 2.5 times greater risk of advanced AMD than age-matched controls.\(^6\) Finally, patients with late AMD have shown a strong association with noncoding mtDNA D-loop SNPs.\(^5\) Some of the mtDNA SNP variants representing the different haplogroups can lead to nonsynonymous amino acid changes, with some substitutions making the mtDNA more susceptible to damage than other SNP patterns. This ultimately may decrease the efficiency of mitochondria and thereby affect the visual functioning of the highly metabolic retinal tissues. For future clinical studies, just as many investigations are analyzing for high-risk AMD nuclear genes, perhaps it would be wise to evaluate mtDNA haplogroup patterns in patient populations.

Although associations have been found between mtDNA haplogroups and diseases, it has been difficult to understand how the mtDNA variants affect the behavior of cells. Fortunately, the transmitochondrial cytoplamic hybrid (cybrid) model (cell lines containing identical nuclei but mtDNA from different individuals) has become available to answer many of these questions. Using human retinal pigment epithelium (RPE) cybrid cell lines, it has been shown that different mtDNA haplogroups send retrograde signaling to the nucleus that changes transcription levels of nuclear genes related to complement, inflammation, apoptosis, and epigenetics, all of which are important pathways involved in numerous cellular functions and disease processes, including AMD.\(^9\)-\(^12\)

### HOW WE KNOW MITOCHONDRIA ARE INVOLVED WITH AMD

Histologic, molecular, and genetic studies have shown that mitochondria are involved with AMD. Transmission electron microscopy studies have demonstrated that the RPE cells of AMD retinas have damaged, fragmented, and ruptured mitochondria.\(^13\) Using specific histologic stains, it has been shown that AMD retinas have higher levels of DNA damage compared with age-matched normal retinas.\(^15\)-\(^17\) Molecular studies testing for mtDNA damage have shown increased numbers of lesions and fragmentations throughout the mtDNA genome in the RPE cells of human donor AMD eyes.\(^16,18,19\) However, the neuroretinal tissues of these AMD eyes have intact mtDNA and nDNA.\(^19\) More recently, it has been shown that, if AMD patients possess the high-risk CFH allele (C), then they have significantly more mtDNA damage compared with patients who have the wild-type allele (T).\(^20\)

### MITOCHONDRIA AS A TARGET FOR THERAPY IN AMD

Recent studies have provided evidence supporting the hypothesis that defects in the mitochondria are hallmark pathologic events in AMD. With increased mtDNA damage, there are higher levels of reactive oxygen species formation, leading to oxidative damage, lower production of adenosine triphosphate (ATP), and, ultimately, cell death (Figure 2). Unlike with nuclear DNA, the mitochondria do not have efficient repair systems for damaged mtDNA. Once this damage takes place, therefore, the cascade of events can spiral forward unchecked.

Consequently, there is growing interest in identifying mitochondria-targeting drugs that can protect the mtDNA and prevent the occurrence of damage in the first place. This is true for not only for ocular diseases but
also for neurodegenerative and cardiovascular diseases, cancers, diabetes, and obesity. Mitochondria are becoming the targets for an entire new field of drug development. The future will likely include clinical trials using mitochondria-targeting drugs for retinal diseases, and this will be an exciting, novel area of research with great therapeutic potential.


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