Mitochondria

The role of mitochondria in health, ageing, and diseases affecting vision

A A Sadun, V Carelli

Control of mitochondrial mediated apoptosis will become a holy grail

Abu-Amro and Bosley have, in this issue (p 823),¹ published a paper relating total cellular mitochondrial DNA (mtDNA) content with a classic neuro-ophthalmological disorder, non-arteritic anterior ischaemic optic neuropathy (NAION).² NAION is widely regarded as a watershed ischaemic event to the optic nerve that occurs as a consequence of structural crowding in the optic disc (usually congenital) with compromise of the vascular supply (often from diabetes or hypertension).^{2,3}

Mitochondria are intracellular organelles that carry their own peculiar genome, a circular 16.5 kb molecule that reflects their bacterial origin.⁴ Each cell carries a variable number of mitochondria and each mitochondrion has multiple mtDNA copies. Hence, cellular mtDNA copy number is a combination of these two variables; it is normalised for the nuclear DNA content that defines the number of cells sampled. Pathogenic mtDNA mutations have been associated with maternally inherited optic neuropathy—that is, Leber's hereditary optic neuropathy (LHON).⁵ mtDNA copy number has been reported to be increased in LHON, possibly as a compensatory mechanism for the impaired mitochondrial respiration.⁶

Remarkably, Abu-Amro and Bosley found higher mtDNA content in 84% of their NAION subjects. The same authors previously reported an increased frequency of non-synonymous polymorphisms (inducing an amino acid change) in NAION patients.⁷ They hypothesised that some weak pathogenic role for these polymorphisms could predispose to NAION, and interpreted their present findings as a compensatory response similar to that seen in other mitochondrial disorders.⁸ However, in this paper no correlation is seen between increased mtDNA copy number and the presence of these polymorphisms. More importantly, most of the polymorphisms found in NAION patients are ancient, well known mtDNA variants defining specific haplogroups (mtDNA maternal lineages) of European populations.⁴ Thus, if these polymorphisms truly

contribute to the pathology of NAION, then we would expect some maternal inheritance for this disease.

Abu-Amro and Bosley measured the mtDNA copy number in leucocytes obtained from the blood of patients with the previous diagnosis of NAION and compared this to that found in age matched controls. They paralleled their findings to those noted in LHON. There are several problems with this reasoning, however. It is unlikely that the mtDNA content increases specifically to compensate for these polymorphisms insofar as no correlation was found. More likely non-specific compensation may occur to a variety of metabolic stresses such as those already known to be associated with NAION. For example, diabetes and hypertension and other risk factors known to occur in most patients with NAION produce general systemic problems such as an increase in oxidative stress. Hence, the proper control population in a search for mtDNA copy number alteration in NAION would be matched for diabetes and hypertension. Such an investigation might show that the increase in mtDNA copy number is a non-specific protective response against many forms of insult. This would mean that NAION is not a specific mitochondrial disease, though, of course, LHON is. The confounding

variable of systemic vasculopathy is what seems to associate NAION with mitochondrial compensations.

It is fascinating that mitochondria not only provide the efficient production of energy (ATP) needed by all cells, but also control a number of other metabolic pathways, including buffering of calcium and modulation of apoptosis. What does all this mean to the ophthalmologist?

Mitochondria probably have an important role in a variety of inherited and acquired diseases as well as in ageing. Mutations occur at a much faster rate to mtDNA compared to nuclear DNA.⁴ Indeed, recent theories suggest that the problem underlying ageing and several common systemic diseases is a somatic accumulation of mtDNA errors.^{4,9,10} With limited means of repair, cells may manage best by having several copies of mtDNA to complement for somatic mutations in each mitochondrion, as well as increasing mtDNA copy number with ageing or disease.¹¹ Furthermore, mitochondria fuse and exchange their mtDNA much as bacteria conjugate and exchange bits of DNA.¹² In the absence of sex, such mechanisms of DNA exchange may extend the efficiency of the system over a lifespan.

Mitochondrial dysfunction can produce several rare ophthalmological diseases. But in the next few decades, we will probably also see mitochondria as a subject of interest insofar as they may be secondly involved in the pathogenesis of a variety of other more common ophthalmological degenerative diseases. Examples of the first sort include chronic progressive external ophthalmoplegia, dominant optic atrophy, and LHON. Examples of the second sort might include disorders that are less obviously related to mitochondria such as cataracts, wound healing, glaucoma, macular degeneration, and other age related diseases. In normal ageing and,

Figure 1 Intrinsic mitochondrial control of apoptosis. ROS⁺, reactive oxygen species; MPTP, mitochondrial permeability transition pores; V_m, membrane resting potential; CytC, cytochrome C.

particularly, in degenerative disorders mitochondrial dysfunction results in defective oxidative phosphorylation and may overproduce reactive oxygen species (ROS). A common final mitochondria driven pathway to cell death may be mediated by the opening of the mitochondrial permeability transition pore (MPTP), which promotes apoptosis (see fig 1). Oxidative stress is currently assumed to be a major consequence of mitochondrial dysfunction as well as a source of further damage to mitochondrial macromolecules leading to a vicious cycle that culminates in cell death.⁴ Indeed, we have been investigating a number of acquired optic neuropathies that all share the common feature of cell death produced by mitochondrial impairment.¹³

Novel therapies will aim to correct the bioenergetic defect and limit the overproduction of reactive oxygen species, or at least mitigate their effects on the MPTP. Further therapies will seek to modulate the downstream activation of the apoptotic cascade. These anti-apoptotic or neuroprotective strategies may forestall, though not reverse, cellular death in the cornea, lens, retina, and

optic nerve. Control of mitochondrial mediated apoptosis will become a holy grail in general. But it is in ophthalmological disorders that the promise is greatest, insofar as the cells of the eye, from the cornea to the retina, are most accessible to both treatment and observation. The next two decades will be an exciting era for vision research.

Br J Ophthalmol 2006;**90**:809–810.
doi: 10.1136/bjo.2006.091884

Authors' affiliations

A A Sadun, V Carelli, Doheny Eye Institute, Departments of Ophthalmology and Neurological Surgery, Keck Medical School at USC, Los Angeles, CA, USA
V Carelli, Department of Neurological Sciences, University of Bologna, Italy

Correspondence to: Professor Alfredo Sadun, Doheny Eye Institute, Departments of Ophthalmology and Neurological Surgery, Keck Medical School at USC, Los Angeles, CA, USA; asadun@usc.edu

REFERENCES

- 1 **Abu-Amero KK**, Bosley TM. Increased relative mitochondrial DNA content in leucocytes of patients with NAION. *Br J Ophthalmol* 2006;**90**:823–5.
- 2 **Arnold AC**. Ischemic optic neuropathies. *Ophthalmol Clin North Am* 2001;**14**:83–98.
- 3 **Hattenhauer MG**, Leavitt JA, Hodge DO, *et al*. Incidence of nonarteritic anterior ischemic optic neuropathy. *Am J Ophthalmol* 1997;**123**:103–7.
- 4 **Wallace D**. A mitochondrial paradigm of metabolic and degenerative diseases, aging, and cancer: a dawn for evolutionary medicine. *Annu Rev Genet* 2005;**39**:359–407.
- 5 **Carelli V**, Ross-Cisneros F, Sadun A. Mitochondrial dysfunction as a cause of optic neuropathies. *Prog Ret Eye Res* 2004;**23**:53–89.
- 6 **Yen MY**, Chen SC, Wang AG, *et al*. Increase of mitochondrial DNA in blood cells of patients with Leber's hereditary optic neuropathy with 11778 mutation. *Br J Ophthalmol* 2002;**86**:1027–30.
- 7 **Bosley TM**, Abu-Amero KK, Ozand PT. Mitochondrial DNA nucleotide changes in non-arteritic ischemic optic neuropathy. *Neurology* 2004;**63**:1305–8.
- 8 **Poulton J**, Holt IJ. Mitochondrial DNA: does more lead to less? *Nat Genet* 1994;**8**:313–15.
- 9 **Loeb LA**, Wallace DC, Martin GM. The mitochondrial theory of aging and its relationship to reactive oxygen species damage and somatic mtDNA mutations. *Proc Natl Acad Sci USA* 2005;**102**:18769–70.
- 10 **Trifunovic A**, Hansson A, Wredenberg A, *et al*. Somatic mtDNA mutations cause aging phenotypes without affecting reactive oxygen species production. *Proc Natl Acad Sci USA* 2005;**102**:17993–8.
- 11 **Lee H-C**, Yin P-H, Lu C-Y, *et al*. Increase of mitochondria and mitochondrial DNA in response to oxidative stress in human cells. *Biochem J* 2000;**348**:425–32.
- 12 **Chen XJ**, Butow RA. The organization and inheritance of the mitochondrial genome. *Nat Rev Genet* 2005;**6**:815–25.
- 13 **Sadun AA**. Mitochondrial optic neuropathies. *J Neurol Neurosurg Psychiatry* 2002;**72**:423–5.