

Mitochondrial disorders and the eye

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Abstract: The clinical significance of disturbed mitochondrial function in the eye has emerged since mitochondrial DNA (mtDNA) mutation was described in Leber's hereditary optic neuropathy. The spectrum of mitochondrial dysfunction has become apparent through increased understanding of the contribution of nuclear and somatic mtDNA mutations to mitochondrial dynamics and function. Common ophthalmic manifestations of mitochondrial dysfunction include optic atrophy, pigmentary retinopathy, and ophthalmoplegia. The majority of patients with ocular manifestations of mitochondrial disease also have variable central and peripheral nervous system involvement. Mitochondrial dysfunction has recently been associated with age-related retinal disease including macular degeneration and glaucoma. Therefore, therapeutic targets directed at promoting mitochondrial biogenesis and function offer a potential to both preserve retinal function and attenuate neurodegenerative processes.

Keywords: mitochondria, disease, retina, eye, aging, neuroprotection

Introduction

The importance of optimal mitochondrial function for ocular health has been clear since the first mitochondrial DNA (mtDNA) disease mutation was discovered in Leber's hereditary optic neuropathy (LHON).¹ Other syndromic mtDNA diseases often have retinal involvement together with variable central nervous system pathology. A second major disease grouping classified as "mitochondrial" disease is due to mutations in nuclear genes that result in mitochondrial dysfunction, including autosomal dominant optic atrophy (ADOA), Friedreich's ataxia, Mohr-Tranebjaerg syndrome, and Charcot-Marie-Tooth disease subtype CMT2A. These disorders commonly display optic neuropathy together with variable central nervous system involvement, and have been described in detail elsewhere.^{2,3} The neuro-ophthalmic manifestations of mitochondrial diseases have also been extensively reviewed by Newman et al.⁴

With our increased awareness, the spectrum of "mitochondrial disease" has expanded from describing mtDNA disease, to diseases secondary to improper function of any protein located in the organelle resulting in abnormal mitochondrial function. Moreover, mitochondrial dysfunction is attracting growing attention as contributing to the pathogenesis of many common sporadic age-related neurodegenerative diseases, including Alzheimer's disease, Parkinson's disease, and glaucoma.⁵⁻⁸ While controversy exists as to whether mitochondrial impairment in these diseases is primary or secondary to upstream disease pathways, the mitochondrion is emerging as pivotal in disease pathogenesis and as an important target of novel therapeutic approaches.

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The eye can therefore be viewed as a model for energetic impairment in the central nervous system, often being the first neuronal tissue affected by mitochondrial failure. The eye may become a model of therapeutic experimentation, with direct implications for degenerative brain diseases. Here we discuss the variable ocular involvement in inherited mitochondrial diseases, the possible role of mitochondrial dysfunction in the common age-related ophthalmic diseases, including glaucoma and age-related macular degeneration, and finally we review emerging therapeutic approaches to improving mitochondrial function.

Mitochondria and neurons

The accurate cliché of the mitochondrion being the “powerhouse of the cell” has been complicated by the growing recognition that this organelle is a central node of key cellular pathways governing not only intermediary metabolism, but also stress responses and cell death.⁹ We first consider the traditional energetic role of the organelle and the effects on retinal neurons resulting from mtDNA mutations.

Neurons require large amounts of adenosine triphosphate (ATP) supplied by the mitochondria. Energetic needs are greatest at dendritic regions where ATP-dependent ion pumping reinstates the plasma membrane electrical potential consequent to impulse transmission.¹⁰ Neuronal anatomy, with long processes extending from the cell body where mitochondria are synthesized, requires the purposeful transport of organelles along axons and dendrites to the sites of ATP usage. This transport is accomplished by energy-dependent bidirectional transport along microtubules. Kinesin moves mitochondria in the anterograde direction, whereas retrograde transport is via dynein motors.¹¹ Mitochondrial network dynamics is a growing area in mitochondrial research, with the discovery of genes involved in the constant fission and fusion of organelles. The optic atrophy 1 (autosomal dominant) gene (*OPA1*), the most common gene mutated in ADOA, encodes a dynamin-related GTPase of the mitochondrial inner membrane that directs fusion of this membrane. Why disruption of mitochondrial dynamics due to loss of OPA1 function results in specific loss of retinal ganglion cells remains unknown.

The simplistic idea that different degrees of energetic impairment lead to a hierarchy of neuronal populations being adversely affected does not adequately explain the pathological changes in the central nervous system in mitochondrial diseases. Retinal ganglion cells appear to be one of the most sensitive neurons to mitochondrial failure, although the reasons for this susceptibility remain unclear.

mtDNA and oxidative phosphorylation

Mitochondrial DNA is a circular, double-stranded DNA molecule residing in the mitochondrial matrix. It is the only non-nuclear DNA in mammalian cells, coding 13 of the approximately 90 protein subunits of the oxidative phosphorylation complexes. The majority of the protein machinery required for mitochondrial replication, transcription, translation, and assembly is encoded by nuclear genes,¹² whilst mtDNA contributes a 12SrRNA, a 16SrRNA, and 22 tRNAs.¹³ The oxidative phosphorylation pathway produces the majority of ATP for use in all cells. It comprises five multisubunit enzyme complexes: complex I, the NADH:ubiquinone oxidoreductase (>45 subunits, seven from mtDNA); complex II, the succinate dehydrogenase (four nuclear subunits); complex III, the ubiquinone:cytochrome c oxidoreductase (11 subunits, one from mtDNA); complex IV, cytochrome c oxidase (13 subunits, three from mtDNA); and complex V, H⁺ATP synthase (15 subunits, two from mtDNA). Electrons enter the respiratory chain at either complex I from the oxidation of NADH or complex II from oxidation of FADH₂. As pairs of electrons travel via redox centers in complexes I, III, and IV, protons are extruded into the intermembrane space where the proton gradient is harnessed by complex V to phosphorylate ADP to ATP.¹⁴

Dysfunction of oxidative phosphorylation consequent to mtDNA or nuclear gene mutations can result in a reduction in maximal ATP production rate and increased reactive oxygen species production by complexes I and III,^{15,16} heightening oxidative stress within the cell.¹⁷ mtDNA is highly susceptible to damage by reactive oxygen species due in part to the lack of protective DNA binding histones,¹⁸ limited DNA repair mechanisms,^{19,20} and the close proximity of mtDNA to the site of production of reactive oxygen species, the oxidative phosphorylation machinery. And unlike nuclear genes, mtDNA exists in hundreds to thousands of copies per cell, is replicated throughout life, and is maternally inherited. The extent to which mtDNA mutations produce pathologic changes in tissues depends on the balance between normal and mutant mtDNA populations in cells and tissues (heteroplasmy) and the resilience of tissues to impairment of oxidative phosphorylation (threshold effect), resulting in varied phenotypes and affected tissues in mitochondrial diseases.^{21,22} The differential expression of components of the electron transport chain in various tissues and the segregation of mitochondria during development²³ has also been implicated in tissue-specific diseases.²⁴

mtDNA haplogroups

The mtDNA genome accumulates mutations at a much higher rate than nuclear DNA, and during human evolution certain mutation groups (haplogroups) have evolved and become fixed in specific populations.²⁵ A haplogroup is a cluster of stable background mtDNA polymorphisms in individuals from a common female ancestor.²⁶ Specific mtDNA haplogroups have been associated with pseudoexfoliative glaucoma,^{27,28} primary angle-closure glaucoma,²⁹ age-related macular degeneration,^{30–32} and LHON.^{32–40}

The implication of these associations is that the mtDNA sequence background may influence the clinical phenotype of a disease by subtle effects on oxidative phosphorylation function.⁴⁰ Interestingly, haplogroup associations in healthy populations have been demonstrated to influence maximum oxygen consumption, where healthy males carrying haplogroup J had lower efficiency of the electron transport chain and ATP production,⁴¹ which may explain the increased prevalence of the J haplogroup in LHON patients.⁴⁰ At a molecular level, the haplogroup may influence the cellular response to stress, because LHON cells with point mutations m.11778G>A or m.14484T>C from mtDNA haplogroup J had markedly increased susceptibility to a neurotoxic metabolite compared with the same mutations on different mtDNA haplogroup backgrounds, such as the U and H haplogroups.⁴² Certain haplogroups also delay the assembly kinetics of complexes I, II, and IV into oxidative phosphorylation supercomplexes,⁴³ where this cooperative stability is required to maintain efficient respiration.⁴⁴

Mitochondrial dynamics

If mitochondrial distribution in neurons is impaired, local energetic crisis may occur even if oxidative phosphorylation remains optimal. Within the eye, the optic nerve is structurally unique, consisting of retinal ganglion cell axons originating in the unmyelinated retinal nerve fiber layer which turn 90 degrees through a series of perforated collagen plates, known as the lamina cribrosa, at the optic nerve head, where mitochondrial density decreases as myelination begins.^{45–51}

Mitochondrial shape and distribution are regulated by two opposing processes, ie, fission and fusion. Fission is mediated by dynamin-related protein 1 and fission 1 (mitochondrial outer membrane) homolog (*Saccharomyces cerevisiae*), whilst fusion is regulated by OPA1, mitofusin-1, and mitofusin-2. These processes are vital to maintain adequate mixtures of mtDNA^{52,53} and to respond to localized metabolic demands.⁵⁴ Changes in the expression of fission/fusion proteins alter mitochondrial shape and size, and may promote or inhibit

apoptotic signals leading to neuronal death. Neuronal cells have markedly high expression levels of dynamin-related protein 1 and OPA1 compared with non-neuronal cells.⁵⁵ Furthermore, knockdown of endogenous dynamin-related protein 1 significantly increases the mitochondrial length in all cell types, but only selectively causes apoptosis of cortical neurons,⁵⁵ indicating the sensitivity of specific neuronal populations to loss of control of mitochondrial dynamics.

Mitochondrial fission/fusion proteins and their regulators are associated with optic nerve loss. *OPA1* mutation is the commonest cause of ADOA.^{2–4} Mutations in the outer membrane profusion protein, mitofusin-2, in Charcot-Marie-Tooth disease^{56,57} impair nerve conductive velocity in peripheral neurons, and lead to subacute optic atrophy in some pedigrees.⁵⁸ Evidence is emerging that involvement of single nucleotide polymorphisms of mitofusin-1 and mitofusin-2 genes is present in normal tension glaucoma.⁵⁹ Presenilin-associated rhomboid-like protease (PARL) regulates mitochondrial fusion⁶⁰ and processes OPA1 into a soluble form.⁶¹ The T191C genetic variation of PARL in normal populations exhibited significant effects on mitochondrial content levels.⁶² Single nucleotide polymorphisms of PARL have been associated with glaucoma, LHON, and mutations causing Parkinson's disease.^{59,63,64}

Altering the fission-fusion balance has profound effects on mitochondrial function and structure. With pharmaceutical or genetic inhibition of fusion, there is a collapse of mitochondrial energy production as mitochondria consume ATP⁶⁵ which alters mitochondrial distribution toward fission,^{54,66} promoting apoptosis.^{65,67} Converse to mitochondrial fission, promoting mitochondrial fusion increases mitochondrial energy production⁶⁸ which may be protective against injury.^{69,70} Increased mitochondrial fusion has been demonstrated to protect cells from autophagy by boosting mitochondrial cristae volume and enhancing mitochondrial ATP synthase activity.⁶⁵ Upregulation of OPA1 in mouse models was protective against retinal ganglion cell death in a glaucoma mouse line, DBA2 J,⁷¹ and may be an important cellular defense mechanism against glaucomatous optic neuropathy.⁷²

Mitochondrial diseases and optic neuropathies

LHON is characterized by degeneration of retinal ganglion cells and their axons. LHON is the most common inherited mtDNA disease, and over 90% of cases are due to mutations in one of three mtDNA-encoded oxidative phosphorylation complex I genes, ie, G11778A/ND4, T14484C/ND6, and

G3460A/ND1.²⁻⁴ These mtDNA mutations lead to decreased complex I enzyme rates⁷³ and lowered ATP production,⁷⁴ which are hypothesized to sensitize retinal ganglion cells to apoptosis.^{2,3} Patients typically have normal vision until the age of 15–35 years, when a rapid loss of central vision occurs in one eye, then the second eye within one year. Visual loss progresses to 20/200 or worse, with visual field testing revealing central or centrocecal scotomas.³ Axonal loss in the papillomacular bundle results in temporal atrophy of the optic nerve head. While maternal inheritance provides a strong diagnostic clue, penetrance of LHON is variable within kindreds, and males are overrepresented, with 80%–90% of affected individuals being male.⁴

ADOA, also known as Kjer's optic neuropathy,⁷⁵ also leads to vision impairment due to selective and specific degeneration of retinal ganglion cells and their axons in the optic nerve.^{3,76,77} ADOA results from haploinsufficiency of the mitochondrial fusion protein, OPA1.⁷⁸ In ADOA, there is evidence of decreased mtDNA content⁷⁹ and an increased prevalence of mtDNA mutations in severe cases of ADOA (ADOA+) where multiple deletions of mtDNA were identified.^{80,81} In addition to its role in maintaining mitochondrial cristae structure,^{68,82-84} other functions of OPA1 may include ensuring adequate "mixing" of mtDNA.⁵⁴ Small hydrophobic peptide fragments from cleaved OPA1 may also contribute to mtDNA nucleoid attachment to the inner mitochondrial membrane, promoting mtDNA replication and distribution.⁸⁵

Disrupted mtDNA distribution, or cristae structure, is predicted to have secondary impacts on oxidative phosphorylation due to either inadequate mtDNA transcription or lack of inner membrane surface area for oxidative phosphorylation complex anchoring. It has been reported that decreased oxidative phosphorylation capacity in ADOA patients with OPA1 mutations correlates with relatively poor visual acuities, while related mutation carriers with normal vision appeared to have relatively preserved oxidative phosphorylation function.⁸⁶ This suggests that patients with preserved vision may harbor genetic variants that allow some compensation of oxidative phosphorylation function.

Syndromic mtDNA diseases with ocular involvement

Retinopathy

Several syndromic central nervous system diseases are also known to result from mtDNA mutations. While optic neuropathy is an occasional finding in these disorders, a pigmentary retinopathy is the commonest retinal pathology.

This is best illustrated in the neurogenic atrophy and retinitis pigmentosa syndrome, which results from point mutations in the mtDNA ATPase-6 gene, commonly T8993G. Patients typically present with retinitis pigmentosa with or without optic neuropathy, and can develop dystonia.⁸⁷ Mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes (MELAS) can result from many mtDNA point mutations, although the most common is the A3243G mutation in the tRNA^{Leu} gene. MELAS patients present with stroke-like episodes that lead to frequent retrochiasmal visual loss, but often also have pigmentary retinopathy without optic atrophy.⁸⁸ The spectrum of disease arising from the A3243G point mutation is also evidenced by its contribution to the pathogenesis of maternally inherited diabetes and deafness.^{89,90} This is a multisystemic disease characterized by sensorineural deafness, retinal abnormalities, and diabetes, commonly arising in the third to fourth decade of life.^{89,91} The retinal abnormalities, typically occurring in maternally inherited diabetes and deafness, are bilateral in the majority of cases, and involve two main phenotypes, as described by Rath et al.⁹² The most common phenotype involves circumferential perifoveal atrophy with retinal pigment epithelium hyperpigmentation sparing of the fovea. The second phenotype is a pattern dystrophy characterized by relative sparing of the fovea, with diffuse granularity and pigment clumping, and retinal pigment epithelium within the retinal vascular arcades. However, despite the degree of atrophy, visual acuity is preserved, with a good prognosis.⁹³

Chronic progressive external ophthalmoplegia

Chronic progressive external ophthalmoplegia is a phenotype of mitochondrial myopathy with ophthalmic involvement. The presenting signs are of bilateral ptosis, which generally precedes development of ophthalmoplegia. Whilst visual acuity is preserved, progressive fibrosis of the extraocular muscles can manifest as diplopia.⁴ Eyelid muscles are also affected and can contribute to exposure-related corneal disease. Chronic progressive external ophthalmoplegia is attributed to sporadic mutations, nuclear inherited mutations, and maternally inherited mutations of mtDNA. Most cases of chronic progressive external ophthalmoplegia arise sporadically from large-scale rearrangement of mtDNA resulting in defective oxidative phosphorylation.^{4,94} Nuclear inherited chronic progressive external ophthalmoplegia is attributed to multiple large-scale mutations in mtDNA affecting mtDNA replication and repair.⁴ Maternally inherited chronic progressive external ophthalmoplegia

commonly arises from point mutations in mtDNA tRNA genes.⁹⁵ The Kearns-Sayre syndrome is the severest form of chronic progressive external ophthalmoplegia, where the presenting feature is usually ptosis and ophthalmoplegia. Kearns-Sayre patients often develop a pigmentary retinopathy together with cardiac conduction defects and severe neurological signs, including ataxia.⁹⁶

Mendelian mitochondrial syndromes with ocular involvement

Several nuclear gene mitochondrial disorders have optic neuropathy as a secondary feature. These are considered briefly here because they result from mutations in mitochondrial proteins that indirectly interfere with oxidative phosphorylation, and so can add further insights into energetic failure and retinal pathogenesis.

Friedreich's ataxia results from a GAA trinucleotide repeat expansion in the *frataxin* gene. Frataxin is a mitochondrial protein involved in Fe-S cluster assembly, disruption of which results in excessive mitochondrial iron levels and loss of retinal ganglion cells, giving rise to optic neuropathy and ataxia.^{2,4,97} The oxidative phosphorylation pathway relies on the redox ability of Fe, via multiple Fe-S clusters, to perform electron transfer and thus energy transduction. Four of the five oxidative phosphorylation complexes contain either or both heme prosthetic groups or Fe-S clusters. The pattern of retinal ganglion cell loss in Friedreich's ataxia is more diffuse than that seen in LHON and ADOA, not preferentially involving the papillomacular bundle but involving the optic radiations, and is slowly progressive.^{2,98,99}

Mohr-Tranebjaerg syndrome is an X-linked recessive disease characterized by deafness, dystonia, and optic atrophy.¹⁰⁰ It is caused by mutation of the deafness/dystonia peptide, also called TIMM8A.¹⁰¹ TIMM8A is one of several proteins forming the translocase of the inner membrane complex, which together with the translocase of the outer membrane forms the machinery of mitochondrial protein import.^{102,103} Because the oxidative phosphorylation complexes are among the most abundant of mitochondrial proteins, perturbation of protein import is likely to impact on the oxidative phosphorylation pathway, although mitochondrial studies in patients have not yet been reported. Retinal ganglion cell loss appears to be similar to that reported for Friedreich's ataxia, with diffuse involvement of the optic radiations.^{104,105}

Hereditary spastic paraplegia is a disease grouping that can result from mutations in a number of nuclear genes. It is characterized by progressive spasticity of the lower

limbs, frequently complicated by the presence of optic atrophy. One of these variants is caused by mutations in the *SPG7* gene coding for paraplegin, an AAA-type metallo-protease of the mitochondrial inner membrane. Mutation of paraplegin has been reported to cause impairment of oxidative phosphorylation complex I, providing a pathogenetic link to LHON.¹⁰⁶ Pathological descriptions of the optic nerve have not been reported.

As mentioned above, when discussing mitochondrial dynamics, Charcot-Marie-Tooth disease subtype CMT2A has been associated with mutations in the mitochondrial fusion protein, mitofusin-2.¹⁰⁷ Charcot-Marie-Tooth disease is a common inherited peripheral neuropathy; the variant CMT2A also displays an optic neuropathy that typically develops a decade after onset of the neuropathy. Visual decline progresses rapidly, with bilateral central scotomas evident on fundus examination, reminiscent of LHON.^{2,4} Mitofusin-2 is a GTPase similar in structure to OPA1, but is located in the mitochondrial outer membrane. No consistent oxidative phosphorylation phenotype has been identified, although studies are limited.² Pathological reports indicate a pattern of retinal ganglion cell loss similar to LHON, with preferential involvement of the papillomacular bundle.⁵⁸

Oxidative phosphorylation defects and preferential retinal ganglion cell pathology

The very common but far from invariant finding of preferential retinal ganglion cell loss in mitochondrial diseases raises fascinating questions for pathogenesis. From the early "metabolic maps" provided by Kageyamia and Wong-Riley,⁴⁸ who pioneered histochemical reaction for the oxidative phosphorylation complex IV (cytochrome oxidase) to map mitochondrial density in the retina, it was clear that inner segments of the photoreceptor have the highest degree of enzymatic activity, followed by the inner and outer plexiform layers and the cell bodies of the retinal ganglion cells, and their axons forming the nerve fiber layer. Yet only in a minority of mitochondrial disease patients are the photoreceptors affected, such as found in the pigmentary retinopathies seen in MELAS, neurogenic atrophy, and retinitis pigmentosa, and Kearns-Sayre syndromes. The lack of outer retinal involvement in ADOA and CMT2A, disorders of mitochondrial fission/fusion, is circumstantial evidence that only neurons with long axons suffer from disordered mitochondrial fission and fusion.

Within the mtDNA diseases, how can different defects in the same pathway (oxidative phosphorylation) most commonly give rise to loss of retinal ganglion cells, yet

sometimes cause photoreceptor loss in the absence of optic neuropathy? This may in part be explained by the high metabolic activity of the retinal pigment epithelium which forms the retina-brain barrier and is richly endowed with mitochondria.¹⁰ Oxidative stress may be heightened by the high local oxygen concentrations due to proximity to the choroid and the daily outer segment phagocytosis by the retinal pigment epithelium that leads to accumulation of the phototoxin, *N*-retinyl-*N*-retinylidene ethanolamine. It is possible that the point mutations responsible for MELAS, neurogenic atrophy, and retinitis pigmentosa syndromes, and the mtDNA deletions associated with Kearns-Sayre syndrome/chronic progressive external ophthalmoplegia result in heightened oxidative stress compared with the LHON mutations. Experimentally, when retinal pigment epithelium oxidative phosphorylation is specifically ablated in postnatal mice using a cre-lox tFAM knockdown approach, the retinal pigment epithelium undergoes dedifferentiation and a secondary photoreceptor degeneration results.¹⁰⁸ Histopathological studies in limited cases of mtDNA-linked pigmentary retinopathy suggest a secondary disruption of photoreceptors consequent to retinal pigment epithelium failure.⁴

Both LHON and ADOA can occur in more complex forms, with variable central nervous system involvement. Extraocular features of “LHON plus” syndromes include spastic dystonia, ataxia, or even more severe encephalopathies. It is interesting that mtDNA mutations identified in these cases are usually in complex I genes, are different from the primary LHON mutations, and have more severe defects in oxidative phosphorylation.^{109–111} It has become clear that ADOA can also be associated with extraocular features, with up to one in six *OPA1*-linked ADOA patients showing variable combinations of sensorineural deafness, ataxia, peripheral neuropathy, and ophthalmoplegia.¹¹²

The clinical and biochemical evidence therefore supports the concept that subtle oxidative phosphorylation defects, especially in complex I genes, result in preferential retinal ganglion cell loss. More severe oxidative phosphorylation defects result in more severe disease, typically affecting the brainstem, basal ganglia or cerebellum, with or without optic neuropathy. The common involvement of sensorineural deafness and peripheral neuropathy in such patients reiterates the theme of neurons with long axons being more vulnerable to mitochondrial dysfunction. Refer to Table 1 for a summary of mitochondrial disorders with ocular involvement which outlines the complexity of preferential retinal ganglion cell pathology.

Age-related neurodegeneration, mitochondria, and the retina mtDNA somatic mutation, oxidative phosphorylation, and aging

A lingering disadvantage of the semiautonomous nature of mitochondria in long-lived organisms is the necessity for continual replication of the mitochondrial genome. This leads to an age-related loss of mtDNA integrity, and a consequent decline in oxidative phosphorylation in postmitotic tissues.^{113,114} mtDNA is highly susceptible to damage from reactive oxygen species due to lack of DNA repair and protection mechanisms.^{18,20} Acquired mtDNA mutations through aging and oxidative stress are increasingly being attributed to diseases of the aging eye and brain.^{115,116} Evidence of increased point mutations, large-scale rearrangements, and mtDNA depletions has been demonstrated in age-related macular degeneration, subtypes of ADOA, and subtypes of glaucoma.

In subtypes of glaucoma, there is evidence of increased mtDNA mutations in peripheral blood and the trabecular meshwork, particularly in patients with primary open angle glaucoma,^{117–119} pseudoexfoliation glaucoma,¹⁰⁵ and congenital glaucoma.¹²⁰ Interestingly, mtDNA mutations did not occur, or were in very low abundance in other glaucoma subtypes (pigmented, juvenile, acute, neovascular, and chronic closed angle glaucoma),^{119,121} once again highlighting a combination of risk factors precipitating retinal ganglion cell loss.

Mouse models that accumulate high levels of mtDNA mutations owing to impairments in mitochondrial polymerase γ proofreading function have been shown to develop phenotypes consistent with accelerated aging. Our group recently demonstrated that mice with neuronal-specific mitochondrial polymerase γ mutations have increased mtDNA deletions and point mutations in their retinas, which increase the sensitivity of the retinal ganglion cell-dominant inner retinal function to acute intraocular pressure injury.¹²² This insult is known to produce mechanical, metabolic, and oxidative stress in the retina.⁷ These findings indicate that an accumulation of mtDNA mutations is associated with impairment in neural function and reduced capacity of neurons to resist external stress *in vivo*, suggesting a potential mechanism whereby the aging central nervous system can become more vulnerable to neurodegeneration.

Glaucoma

Glaucoma is a neurodegenerative disease of the optic nerve characterized by accelerated death of retinal ganglion cells and their axons, leading to progressive visual field loss.

Table 1 Mitochondrial diseases with ocular involvement

| Disease | Mutation | Impact on mitochondrial function | Ocular phenotype | Retinal ganglion cell affected? | Photoreceptor affected? |
|--|---|---|---|---------------------------------|-------------------------|
| Leber's hereditary optic neuropathy | mtDNA encoded complex I subunits ND1,4,6 | OXPHOS complex I defects | Central or centrocecal scotomas and axonal loss in the papillomacular bundle of rapid onset; temporal atrophy of the optic nerve head | Yes | No |
| Autosomal dominant optic atrophy | Over 220 mutations identified, primarily in <i>Opa1</i> gene | Regulation of cristae morphology and OXPHOS impairment | Insidious onset, slowly progressive disease with bilateral vision loss; central, centrocecal, paracentral scotomas, and generalized color-perception deficits | Yes | No |
| Neurogenic atrophy and retinitis pigmentosa syndrome | mtDNA mutation most commonly T8993G in ATPase-6 gene | OXPHOS complex V defect | Retinitis pigmentosa, cone-rod photoreceptor dystrophy, with or without optic neuropathy | Yes | Yes |
| Mitochondrial encephalopathy, lactic acidosis and stroke-like episodes | Most commonly A3243G mtDNA mutation in the tRNA ^{Leu} gene | Multiple OXPHOS defects | Stroke-like episodes, retrochiasmal visual loss, pigmentary retinopathy without optic atrophy | No | Yes |
| Maternally inherited diabetes and deafness (MIDD) | Most commonly A3243G mtDNA mutation in the tRNA ^{Leu} gene | Multiple OXPHOS defects | Discontinuous circumferential perifoveal atrophy with sparing of the fovea Alternatively, a pattern dystrophy characterized by RPE changes surrounding vascular arcades with relative sparing of the fovea | No | Yes |
| Chronic progressive external ophthalmoplegia | Large-scale rearrangements of mtDNA Maternal inherited CPEO: point mutations in mitochondrial tRNA genes | Multiple OXPHOS defects | Bilateral ptosis, ophthalmoplegia Progressive fibrosis of extraocular muscles Pigmentary retinopathy, optic neuropathy, corneal opacity, cataracts may occur also | Yes | Yes |
| Kearns-Sayre syndrome | Large-scale rearrangements of mtDNA | Multiple OXPHOS defects | Severe subtype of CPEO, with ptosis, ophthalmoplegia, and pigmentary retinopathy, plus specific extraocular systemic criteria | Yes | Yes |
| Friedreich's ataxia | GAA trinucleotide repeat expansion in the <i>frataxin</i> gene | Impairment of iron-sulfur containing mitochondrial proteins including OXPHOS complex I, II, and III | Optic atrophy and degeneration of optic radiations Slowly progressive or occasionally LHON-like subacute optic neuropathy | Yes | No |
| Mohr-Tranebjaerg syndrome | Deafness/dystonia peptide DDPI/TIMM8A | Mitochondrial protein import, secondary OXPHOS defects | Visual dysfunctions from loss of the visual cortex, optic atrophy and degeneration of retinal inner nuclear layer | Yes | No |
| Hereditary spastic paraplegia | Mutations in numerous nuclear genes, for example <i>SPG7</i> (paraplegin) | Impairment of OXPHOS complex I | Pathological descriptions of the optic nerve have not been reported | Yes | No |
| Charcot-Marie-Tooth disease subtype CMT2A | <i>Mfn2</i> | Mitochondrial outer membrane fusion defects | Subacute onset of optic atrophy and subsequent slow recovery of visual acuity | Yes | No |

Abbreviations: OXPHOS, oxidative phosphorylation; CPEO, chronic progressive external ophthalmoplegia; LHON, Leber's hereditary optic neuropathy.

Two major risk factors are aging and increased intraocular pressure.^{123,124} Around 30%–40% of patients do not present with intraocular pressures above population means, indicating that glaucoma is a complex disease, and age-related mitochondrial failure has been hypothesized to play a role.^{125–127}

Despite some clinical similarities, the pattern of retinal ganglion cell loss is considerably different in glaucoma to that seen in LHON and ADOA. In the latter diseases, the small fibers of the papillomacular bundle are preferentially affected, resulting in temporal atrophy and central vision loss. In primary open angle glaucoma, peripapillary atrophy classically leads to an arcuate, peripheral vision loss. However, this cannot be taken as evidence for a lack of oxidative phosphorylation involvement in some patients with glaucoma. As noted earlier for the nonsyndromic mitochondrial optic neuropathies, different patterns of optic nerve, retinal, and wider visual system pathology can result from mitochondrial dysfunction.

Age-related macular degeneration

Age-related macular degeneration is a late-onset neurodegenerative disease that shares several clinical and biological features associated with Alzheimer's disease. In most cases, age-related macular degeneration involves the buildup of protein plaques, known as drusen, in the central macular region of the retina. Stress stimuli including oxidative stress, aging, genetic factors, and inflammation may drive both age-related macular degeneration and Alzheimer's disease pathogenesis,¹²⁸ including the depositing of protein plaques in the retina or brain. Similarities in these two diseases are also seen with polymorphisms in the risk factor gene, *APOE*, being associated with age-related macular degeneration,^{129,130} as well as Alzheimer's disease.^{131,132} The *APOE* gene regulates the homeostasis of triglycerides and cholesterol,¹³³ and loss of function of *APOE* has been linked to the deposit of senile plaques, mainly comprised of the amyloid beta peptide,¹³⁴ which build up in drusen^{135,136} and also colocalize with another risk factor for age-related macular degeneration, ie, complement protein.^{137,138} Evidence indicates the genotype of *APOE* may dictate the risk of Alzheimer's disease and other chronic disorders, largely due to its impact on oxidative stress modulation.¹³⁹

Age-related macular degeneration is divided into two major forms, ie, the “wet” form caused by leakage from choroidal neovascularization into the subretinal space, and the more common “dry” form associated with buildup of drusen in the macula.¹⁴⁰ There is an increased prevalence of large-scale mtDNA rearrangements and deletions in both the blood¹⁴¹ and retinas^{142,143} of patients with age-related macular degeneration. There are also increased rates of single nucleotide

polymorphisms in the noncoding mtDNA control region (d-loop) in retinas with age-related macular degeneration,³⁰ which has been observed in Alzheimer's disease and other oxidative stress conditions.¹⁴⁴ It is likely that an increased rate of mtDNA deletions and single nucleotide polymorphisms diminishes the number and density of mitochondria, which may partially explain the decreased mitochondrial density observed in age-related macular degeneration retinas.¹⁴⁵ The various components affecting mitochondrial function and the dynamics and mechanisms by which they contribute to mitochondrial disorders of the eye are summarized in Figure 1.

Diagnostic approaches

In some cases, a clinical phenotype can be a strong predictor of the underlying molecular features. In both LHON and ADOA, evaluation of history, optic nerve head morphology, and optic nerve function can be predictive of disease.¹⁴⁶ However, both ADOA and LHON may be misdiagnosed as glaucoma on optic nerve head examination alone, and training programs may aid in accurate diagnosis of glaucoma¹⁴⁷ and other optic neuropathies.¹⁴⁸ When a mutation is suspected in retinal degenerative conditions, several considerations for patient counseling must be investigated. These include a positive family history of disease, typical clinical ophthalmic features for known mitochondrial diseases (including retinal and optic disc appearance, and optic nerve head appearance),¹⁴⁸ and laboratory investigations^{149,150} which all aid identification of genetic involvement.

The complexity of mitochondrial disorders is enhanced by the dual genetic coding of mitochondrial oxidative phosphorylation from both nDNA and mtDNA. The mode of inheritance of mitochondrial disease can be maternal, autosomal dominant, autosomal recessive, or X-linked, which complicates genetic counseling for suspected patients and families.¹⁵¹ Mitochondrial DNA mutations, either heritable or acquired through aging and as a consequence of oxidative stress, may underlie retinal ganglion cell loss. Identifying the type of mtDNA mutation is challenging, because mutations may be either heritable at known positions (eg, in LHON) or due to single nucleotide polymorphisms, point mutations, or large-scale deletions and rearrangements. Diagnosis of mtDNA mutation also faces the challenge that different tissues may harbor different levels of mutant and wild-type mtDNA (heteroplasmy).²¹ In LHON patients, varying levels of heteroplasmy of mutant mtDNA were identified between hair follicles and blood cells,¹⁵² and a LHON patient had higher levels of mutant mtDNA in their retina and optic nerves than in their blood cells at post mortem.¹⁵³ In age-related

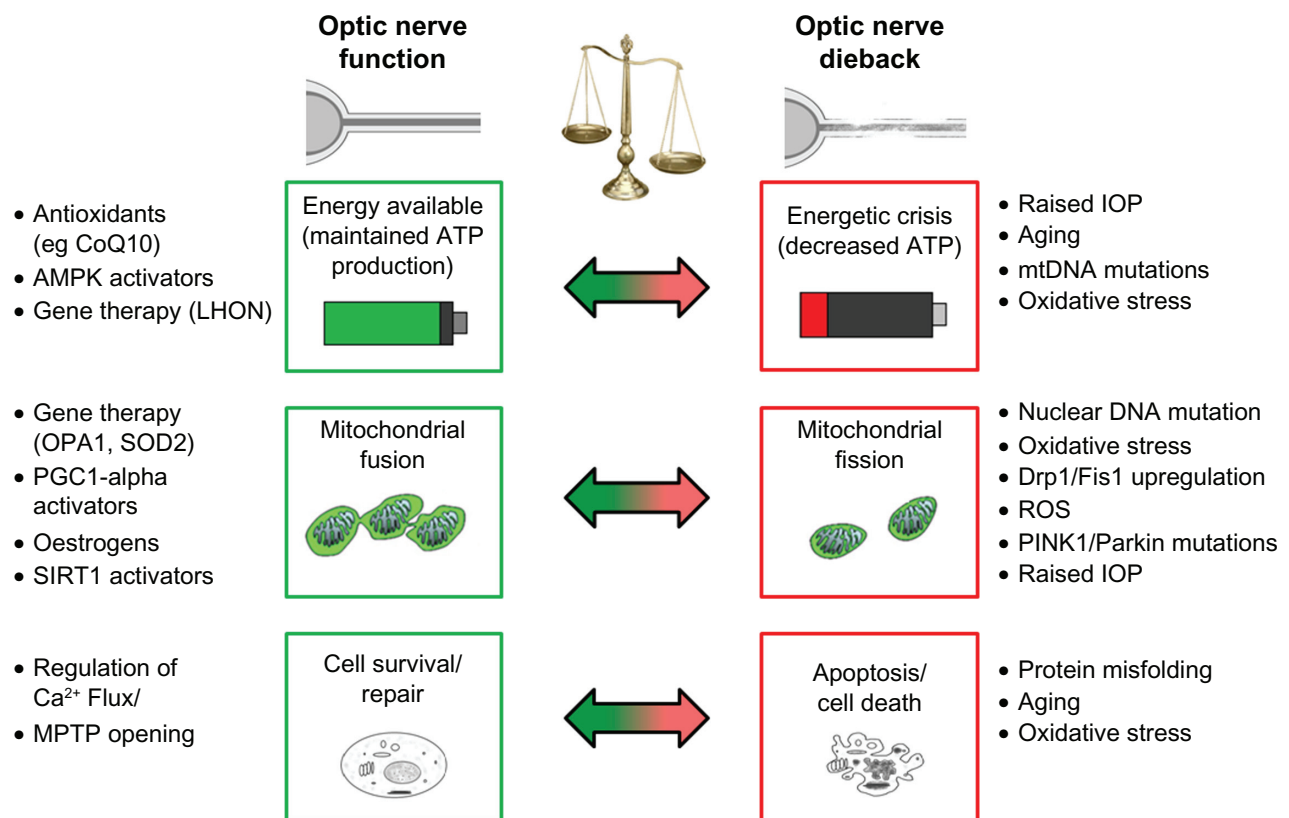


Figure 1 Factors contributing to optic nerve degeneration.

Note: The spectrum of mitochondrial dysfunction in the eye has emerged through understanding of the contribution of multiple stressors leading to mitochondrial failure and optic nerve loss. While controversy continues as to whether mitochondrial impairment in these diseases is primary or secondary to upstream disease pathways, the mitochondrion is emerging as a central culprit in cell death. Therapeutic developments aimed at boosting mitochondrial function are gathering pace. These approaches are likely to be of benefit not only in retinal disease, but also in diseases of the aging brain due to the growing evidence for a role of mitochondrial decline in age-related neurodegeneration.

macular degeneration, post mortem analysis of retinas and peripheral blood demonstrated a greater accumulation of rearrangements and deletions of mtDNA in retinas.¹⁴¹

Aside from genetic screening, functional laboratory investigations may give clues to the underlying pathogenesis of the mitochondrial disease. Typical laboratory investigations require sampling of biopsy tissue (eg, leucocytes, muscle, fibroblasts) for functional mitochondria studies.^{149,150} Detailed oxidative phosphorylation enzymatic studies may be undertaken from the tissue or cell line, but technique standardization is required^{149,154} due to interlaboratory variation in methods.¹⁵⁵ Mitochondrial function can also be determined noninvasively. Phosphorus magnetic resonance spectroscopy is well suited to gathering clinical data on skeletal muscle energetics, and is a very sensitive index of mitochondrial function which has been used to study bioenergetic defects in ADOA and LHON.^{3,81,156–158}

Coupled with a positive clinical appearance, a better molecular understanding of the mitochondrial involvement in conditions of the eye will guide therapeutic development. We believe the future holds several avenues of therapeutic

potential to ameliorate mitochondrial dysfunction, which are outlined below.

Avenues for neuroprotection

Gene therapy in the eye

Since the retina and optic nerve are part of the central nervous system, yet are relatively accessible, this provides an attractive opportunity to study the regenerative responses of adult neuronal cells to gene therapy. Current means of gene delivery may be via the use of replication-deficient viral vectors, recombinant plasmids, or electroporation. Gene replacement of defective genes (eg, LHON complex I), the therapeutic use of antioxidant genes (eg, superoxide dismutase, SOD) and increasing expression of haploinsufficient proteins (eg, OPA1 in ADOA) are currently under investigation. These may also hold promise in the treatment of other degenerative conditions, including glaucoma and optic neuritis. Haploinsufficiency of the OPA1 protein is the underlying pathogenic mechanism of retinal ganglion cell loss in human ADOA patients,⁷⁸ and OPA1 haploinsufficiency negatively affects retinal ganglion cell survival and function in animal models.^{159–161}

Increasing OPA1 expression is being investigated as a means to ameliorate retinal ganglion cell loss. In cultured cells, the protective effect of increased OPA1 expression prevented cells undergoing apoptosis^{82,162} and protected against excitotoxicity.¹⁶³ Adenovirus-associated virus vector (AAV2) transfection of *OPA1* into glaucomatous DBA/2 J mouse retinas protected against loss of retinal ganglion cells, with protection persisting up to two months after transfection.⁷¹

Retinal ganglion cells are under constant oxidative stress, and boosting antioxidant defenses or providing neurotrophic factors may support retinal ganglion cell survival. Cells with the G1178A LHON mutation suffer increased oxidative stress levels.⁷⁷ AAV-mediated delivery of mitochondrial *SOD* (*SOD2*) improved cell survival when cells were cultured in galactose media where cells are forced to rely on oxidative phosphorylation for all ATP production.¹⁶⁴ When the *SOD2* concept was transferred into an animal model with severe complex I defects in the retina induced by ribozyme-mediated knockdown of a nuclear complex I gene, the same group demonstrated protection of optic nerve fibers by preventing early apoptosis of retinal ganglion cells.¹⁶⁵ There have also been extensive animal trials on the AAV-mediated delivery of trophic factors (eg, ciliary neurotrophic factor) in promoting retinal ganglion cell growth and axonal regeneration in optic nerve transection or optic nerve crush models.¹⁶⁶

The ability to reverse, correct, or replace an inherited genetic mutation is a potential strength of gene therapy. Homologous recombination has not been convincingly demonstrated to occur in mtDNA, which has prevented the correction of heritable mtDNA mutations.^{167–170} This has also challenged modeling of mtDNA diseases in rodents and has required alternate approaches. LHON-like phenotypes were induced either by the intravitreal injection of rotenone, a toxic complex I inhibitor,^{171–173} or by delivery of mutant human ND subunits into the retina by either electroporation¹⁷⁴ or AAV-mediated delivery.¹⁶⁴

Various groups are now exploring the concept of replacing mutant complex I genes by allotropic rescue in animal models.^{172,174,175} This concept involves the introduction of recoded human mtDNA genes, with an added mitochondrial import presequence into the nuclear genome of rodents by AAV delivery. However, these experiments face the uncertainty of whether introducing human mitochondrial genes into rodent cells would result in functional improvement of oxidative phosphorylation. Mismatching of nuclear and mitochondrial encoded oxidative phosphorylation subunits in cybrid models takes advantage of evolutionary divergence, which is sufficient to cause mitochondrial dysfunction.^{176–178}

Thus, the successful delivery of human ND4 subunits into the mitochondrion does not necessarily provide a functional benefit to the murine mitochondria, nor does it guarantee correct assembly into functional oxidative phosphorylation complexes. These findings have also raised questions on whether AAV delivery of highly hydrophobic complex I subunits would be correctly assembled into mitochondrial membranes *in vivo*.^{3,179–181}

Although some of these results appear promising, much caution needs to be in place before commencing human trials because there are a number of concerns relating to the safety of gene rescue.^{179,182} To date, no human trials have commenced with AAV-mediated gene delivery into the retina, although patient selection and recruitment is actively taking place for LHON gene therapy trials, and a cohort of patients has already been identified and selected for suitability of inclusion in these trials.¹⁸³

Regulation of hormonal agents

Phenylbutyrate is a histone deacetylase inhibitor currently being used as a treatment in Parkinson's disease due to its neuroprotective properties against oxidative cell death.^{184–187} The action of phenylbutyrate is mediated partly via activation of the protein DJ1, which was protective against mouse models of neurodegeneration induced by treatment with the oxidative phosphorylation complex I inhibitors rotenone or 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine.^{187,188} Phenylbutyrate treatment prior to ischemic intraocular pressure elevation (>100 mmHg) in the rat retina also protected against retinal ganglion cell loss and preserved retinal thickness.¹⁸⁹ The activation of DJ1 by phenylbutyrate stabilized nuclear factor erythroid 2-related factor, a master regulator of antioxidant transcription response,¹⁹⁰ as well as working in parallel with the pink/PARKIN pathway to protect mitochondrial function in the presence of oxidative stress.^{191,192}

In response to histone deacetylase inhibition, estrogen receptor alpha ($ER\alpha$) is activated and the DNA binding capacity of $ER\alpha$ is increased.¹⁹³ Deacetylation of $ER\alpha$ is also regulated by histone deacetylase 8 and sirtuin 1 homolog, which act together as independent enhancers of $ER\alpha$ activity.¹⁹³ Mitochondrial biogenesis involves signaling via numerous transcription factors and transcriptional coactivators, one being estrogen-related receptor (ERR) 8α , that works in concert with the peroxisome proliferator-activated receptor gamma ($PPAR\gamma$) coactivator ($PGC1\alpha$) family.¹⁹⁴ Estrogen receptor signalling may be a means to activate mitochondrial transcription^{195,196} via estradiol treatment,¹⁹⁷ which upregulates

mtDNA-encoded complex IV genes.^{198,199} Estrogens may have a vital role in maintaining mitochondrial function during stress, and have been shown to ameliorate the LHON complex I defect by enhancing mitochondrial biogenesis and improving mitochondrial energy production.²⁰⁰ The putative antioxidant role of estrogens has also been supported by evidence from cybrid cell lines of LHON treated with 17 β -estradiol, which demonstrated increased antioxidant SOD, stabilization of the mitochondrial membrane potential,²⁰¹ and more efficient mitochondrial biogenesis.³ Estrogens also contribute to the regulation of glucose metabolism and insulin sensitivity via activation of ER α .^{202,203} The effect of estrogens on pathways regulating cellular energy levels has been demonstrated by the ability of 17 β -estradiol to phosphorylate and activate AMP-activated protein kinase (AMPK), the master initiator of cellular catabolism, independently of AMP level.²⁰⁴

As such, estrogens and novel nonhormonal analogs are of interest to protect neurons against acute brain injury and chronic neurodegeneration,²⁰⁵ and the evidence suggests a protective mechanism against increased intraocular pressure in rodents.²⁰⁶ There is also evidence that estrogen therapy (with estradiol) was able to increase retinal blood flow in rodent models,²⁰⁷ as well as improving optic nerve head topography and optic nerve head blood flow in postmenopausal women on hormone replacement therapy,²⁰⁷ which may protect the retina against injury. 17 β -estradiol treatment also conferred neuroprotection in hippocampal neurons exposed to glutamate excitotoxicity by regulation of mitochondrial calcium load.²⁰⁸

Regulation of mitochondrial biogenesis as a therapeutic target

The preservation of healthy mitochondrial function in neurodegeneration has guided emerging mitochondrial therapies towards examining mitochondrial biogenesis as a therapeutic target. Several reviews have highlighted the mechanisms of mitochondrial biogenesis and its role in neuroprotection.^{209–212}

One master transcriptional regulator of mitochondrial biogenesis is PPAR γ coactivator (PGC1 α).²¹³ PGC1 α regulates mitochondrial homeostasis through upregulation of mitochondrial biogenesis, respiration, and controlling the utilization of substrates for energy production.²¹⁴

The PPARs are ligand-controlled upstream regulators of PGC1 α activity involved in transcription of genes responsible for fatty acid transport and mitochondrial oxidation. Synthetic PPAR agonists have been developed for the management of type 2 diabetes (PPAR γ agonists, eg, thiazolidinediones),

and lipid disorders (PPAR α agonists, eg, fibrates). The thiazolidinedione class of medications has demonstrated a neuroprotective effect of two PPAR γ ligands (troglitazone and 15d-PGJ2) in glutamate-induced cytotoxicity in a rat neuronal precursor cell culture model.²¹⁵ PPAR γ agonists also demonstrated a role in neurorecovery following transient ischemic injury.^{216–218}

Given the high energy demand yet poor nutrient storage capability of central nervous system neurons,²¹⁹ it is not surprising that regulation of cellular energy is pivotal in the context of mitochondrial dysfunction in disorders of aging and the eye. AMPK is an evolutionary preserved cellular “calorimeter” common to all eukaryotes that acts as a cellular switch to activate catabolic pathways and turns off anabolic pathways.^{220,221} AMPK is intimately related to mitochondrial oxidative phosphorylation because the energy-sensing process is sensitive to changes in the ratio of cellular AMP to ATP.²²² Low ATP levels activate AMPK by phosphorylation of AMPK at Thr172 in the kinase domain,²²³ and AMPK is implicated in promoting mitochondrial biogenesis through PGC1 α . The glitazone class of medication has been shown to phosphorylate and thereby activate AMPK in muscle by increasing the AMP:ATP ratio.²²⁴ Activated nuclear AMPK complexes are able to phosphorylate mitochondrial transcriptional coregulators directly, including PGC1 α .²²⁵ The potential for pharmacological activation of AMPK in promoting mitochondrial biogenesis and conferring neuroprotection has been suggested by *in vitro* studies using metformin, a biguanide commonly used in the management of type 2 diabetes.^{226,227} This highlights several mechanisms by which regulation of PGC1 α can exert neuroprotection in the central nervous system.

The silent information regulator T1 (SIRT1) is also influential in mitochondrial function, biogenesis, and neuroprotection. SIRT1 is an enzyme that belongs to the sirtuin gene family. It acts as a metabolic sensor and mediates the regulation of oxidation and energy homeostasis genes through NAD⁺-dependent deacetylation of transcription factors.²¹⁴ Independent of deacetylase activity, sirtuins have been implicated in mitochondrial function through antioxidant properties²²⁸ and regulation of oxidative stress genes.²²⁹ Furthermore, SIRT1 activation deacetylates PGC1 α , thereby activating mitochondrial biogenesis.²³⁰ SIRT1 has also demonstrated immunomodulatory neuroprotection of retinal ganglion cells in models of autoimmune optic neuritis.²³¹ These mechanisms of SIRT1 activation have therefore set the foundation for potential neuroprotective interventions.

Calorie restriction is one such established method of improving mitochondrial biogenesis,²³² respiration,²³³ and reduction of reactive oxygen species production through upregulation of SIRT1.²³⁴ Calorie restriction has been shown to facilitate retinal ganglion cell recovery in acute intraocular pressure challenge and ischemia-reperfusion models.²³⁵ Glucose restriction has been shown to activate AMPK, which then activated the gene for the NAD synthetic enzyme, Nampt.²³⁶ This highlighted an important convergence between AMPK and SIRT1 in mitochondrial biogenesis (Figure 2).²³⁷ Similarly, resveratrol, a plant polyphenol, mimics the effects of calorie restriction, primarily through activation of SIRT1, but also activation of AMPK in several tissues.^{238,239} It has demonstrated neuroprotective effects in acute and chronic central nervous system injury.^{53,240,241} Additionally, the antioxidant properties of resveratrol were shown to reduce the production of reactive oxygen species and inflammatory markers in the trabecular meshwork in primary

open angle glaucoma,²⁴² and to protect against hydrogen peroxide-induced retinal pigment epithelial cell dysfunction that occurs with age-related macular degeneration.²⁴³

Antioxidant and reactive oxygen species scavenging

Oxidative stress is a common feature of mitochondrial disease, and evidence points toward a pathogenic involvement in diseases of the eye, as discussed above. Ameliorating oxidative stress may be a potential therapeutic avenue to explore to protect the eye against the adverse effects of aging and mitochondrial dysfunction. There is evidence clinically that antioxidant and vitamin supplementing may benefit mitochondrial diseases, with most promise in the use of coenzyme Q₁₀ and its derivatives, eg, idebenone. The rationale behind their use is to replace naturally depleted stores, to bypass defective electron transfer, and these agents also have naturally occurring antioxidant properties.²⁴⁴ In the body, their use may lead to lowering of

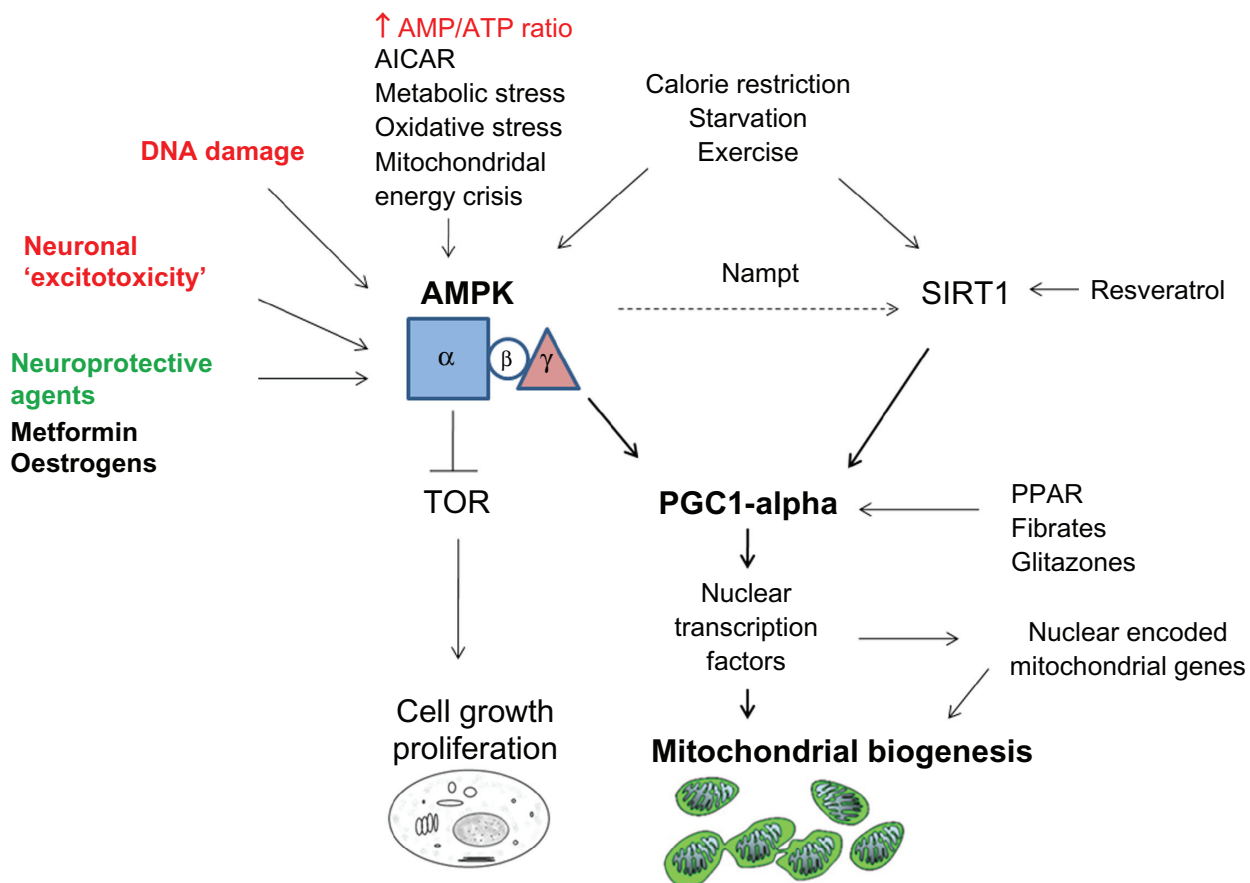


Figure 2 Role of AMPK in neuroprotection. **Note:** AMP-Activated protein kinase (AMPK) is a heterotrimeric enzyme that activates catabolic pathways and turns off anabolic pathways in response to increased AMP/ATP ratio (hypoxia, glucose deprivation, OXPHOS inhibition), Ca²⁺ mediated neuronal excitotoxicity, DNA damage. Low ATP levels activate AMPK by phosphorylation of AMPK at Thr172 in the kinase domain (in the alpha subunit). Once activated, AMPK inhibits ATP consumption, inhibits protein synthesis (by inhibiting Target of Rapamycin, TOR), and inhibits fatty acid and cholesterol synthesis. AMPK can drive mitochondrial biogenesis by phosphorylation of mitochondrial transcriptional coregulators including PGC-1 α ; and indirectly promote SIRT1 activity via regeneration of NAD⁺ through the enzyme Nampt. Emerging neuroprotective avenues for AMPK activation act via increasing AMP/ATP ratio (Glitazones), Metformin, and Estradiol.

plasma lactate levels and reducing oxidative stress.²⁴⁵ The use of coenzyme Q₁₀ and derivatives is being investigated in children with various mitochondrial disorders²⁴⁶ as well as more specifically in patients suffering MELAS²⁴⁷ and Parkinson's disease.²⁴⁸ Idebenone, a short-chain derivative of coenzyme Q₁₀, has been used to slow the progression of Friedreich's ataxia,^{249,250} and in conjunction with vitamin B2 and vitamin C to treat LHON. In a clinical trial of 28 LHON patients (14 placebo, 14 treatment), idebenone treatment has been demonstrated to speed the visual recovery period in LHON from 34 months to 17 months²⁵¹ and has proved effective in improving vision in an isolated patient case²⁵² but not in two other patients.²⁵³ Another large Phase II clinical trial involving up to 84 patients to test the effectiveness of idebenone in LHON is underway where an improvement in mean visual acuity is the primary outcome.²⁵⁴ A trial of idebenone in reducing vision loss in ADOA reported potential benefits in some patients, where five out of seven patients experienced improvement in vision.²⁵⁵ These data support the use of idebenone in the treatment of primary mitochondrial optic neuropathies, and may provide potential as a therapeutic in glaucoma and other mitochondrial optic neuropathies.

Conclusion

The most common ophthalmic manifestation of primary mitochondrial disease is optic atrophy, followed by pigmentary retinopathy and ophthalmoplegia. The majority of mitochondrial disease patients will have variable central nervous system involvement, with ataxias, sensorineural deafness, and peripheral neuropathies being among the most frequently encountered signs. A growing appreciation for the potential role of age-related mitochondrial dysfunction has focused increasing attention on the possible role of mitochondria in the common age-related retinal diseases, age-related macular degeneration and glaucoma. Therapeutic developments aimed at boosting mitochondrial function are gathering pace.

The retina is both a key target of mitochondrial pathology and an ideal model system to test neuroprotective and neuroregenerative therapies. It is likely that advances in retinal neuroprotection via modulation of mitochondrial function will have implications for age-related neurodegenerative brain diseases.

Disclosure

The authors report no conflicts of interest in this work.

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