Mitochondrion 35 (2017) 44–53

Contents lists available at ScienceDirect

Mitochondrion

journal homepage: www.elsevier.com/locate/mito

Mitochondrial dysfunction in ocular disease: Focus on glaucoma

Khalid Kamel[a], Michael Farrell[b], Colm O'Brien[a,*]

[a] Institute of Ophthalmology, Mater Misericordiae University Hospital, Dublin, Ireland
[b] Neuropathology, Beaumont Hospital, Dublin, Ireland

ARTICLE INFO

Keywords:
Mitochondria
mtDNA
Oxidative stress
Glaucoma

ABSTRACT

Mitochondrial dysfunction commonly presents with ocular findings as a part of a systemic disorder. These ophthalmic manifestations can be the first sign of a mitochondrial abnormality, which highlights the key role of a comprehensive ophthalmic assessment. On the other hand, a number of visually disabling genetic and acquired eye diseases with no curative treatment show abnormal mitochondrial function. Recent advances in mitochondrial research have improved our understanding of previously unexplained ocular disorders utilising better diagnostic approaches. Further studies on mitochondrial dysfunction and novel modalities of treatment will help to improve outcomes of these conditions. In this review article we discuss the clinical picture of common mitochondrial-related eye diseases, diagnostic approaches and possible treatment options including a very recent interesting report about gene therapy, with a particular focus on glaucoma.

1. General introduction

Combined adult and paediatric mitochondrial disease is now estimated to have a prevalence of at least 1:5000 (Schaefer et al., 2004). Mitochondrial disorders have received more attention as a contributing factor to many age-related neurodegenerative diseases including Parkinson disease and Alzheimer disease (Crouch et al., 2007; Schapira and Gegg, 2011). This might be explained through impaired oxidative stress generated by mitochondrial dysfunction in cellular senescence and aging (Bhatia-Dey et al., 2016; Moiseeva et al., 2006).

Several eye conditions have been linked to abnormalities of the mitochondria, whether as a mutation in the mitochondrial DNA (mtDNA) or a malfunction in its energy producing respiratory chain. Examples include Leber's hereditary optic neuropathy (LHON), autosomal dominant optic atrophy (ADOA), pigmentary retinopathy, chronic progressive external ophthalmoplegia (CPEO), together with age-related macular degeneration (AMD) and glaucoma, also age related. As ocular manifestations are prominent in mitochondrial disease, ophthalmologists may be considered as first line physicians to discover adult mitochondrial dysfunction with subsequent prompt diagnosis, management and counseling.

1.1. Mitochondrial bioenergetics

Mitochondria are the main energy producing organelles in the human cell. They achieve this function through a number of pathways including: oxidative phosphorylation (OXPHOS), glycolysis, the Krebs cycle, glutaminolysis, pentose phosphate pathway and β-oxidation of fatty acids. All these pathways work in harmony to maintain optimal ATP levels and energy status in the cell. As each pathway has a spare capacity outwith the resting state, a number of regulatory mechanisms allow the different pathways to compensate for each other under conditions of increased energy demand.

Mitochondria are sensitive to stress, and respond dynamically to surrounding microenvironmental change. With the advent of high-throughput technology in measuring cellular respiration together with the development of specific mitochondrial inhibitors, a detailed bioenergetic profile of cells can be obtained. This can help as an early sensor to diagnose and predict the prognosis of various chronic and complex diseases with dysfunctional metabolism (Dranka et al., 2011; Hill et al., 2012; Nicholls et al., 2010). A potential new biomarker that can serve as a single integrated measure to quantify bioenergetic health is the Bioenergetic Health Index (BHI) (Chacko et al., 2014).

Basal respiration is considered a threshold below which the cell cannot meet energy demands by oxidative phosphorylation. Consequently, glycolysis is then stimulated to meet the energy needs. The difference between the basal and maximal respiration is called the reserve respiratory capacity. Under conditions of oxidative stress, the reserve capacity is depleted, and if the basal respiratory threshold is breached, cell death occurs (Dranka et al., 2011; Dranka et al., 2010; Giordano et al., 2012; Hill et al., 2009; Sansbury et al., 2011; Schneider et al., 2011).

MtDNA is a double stranded circular molecule which encodes 13 out of 90 essential polypeptides of the respiratory chain, the rest are

* Corresponding author.
E-mail address: cobrien@mater.ie (C. O'Brien).

http://dx.doi.org/10.1016/j.mito.2017.05.004
Received 25 October 2016; Received in revised form 8 March 2017; Accepted 8 May 2017
Available online 09 May 2017

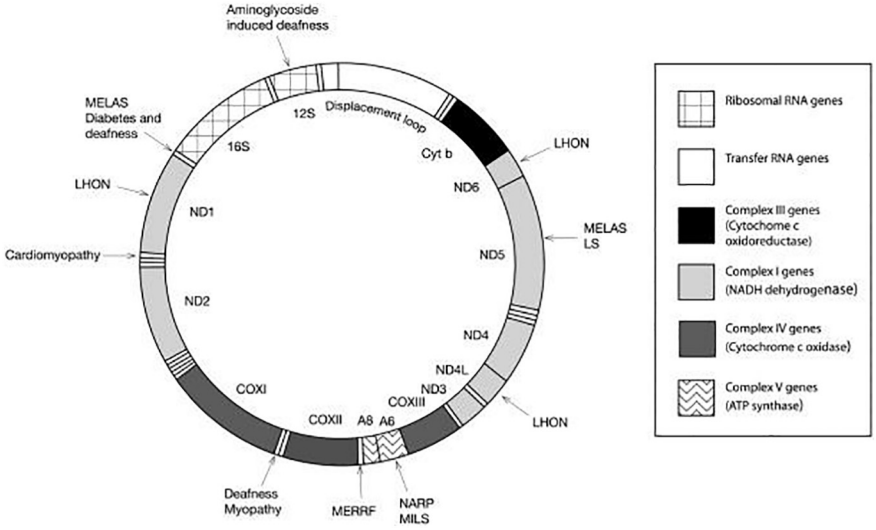

Fig. 1. Diagram of the human mitochondrial genome and sites of mutations leading to different ocular and non-ocular mitochondrial associated diseases. Adapted from "Seminars in medicine of the Beth Israel Hospital, Boston. Mitochondrial DNA and disease" by Johns.

encoded by nuclear genes (Saraste, 1999). In mammals, these include seven (ND1-6, 4L) of the approximately 45 polypeptides of enzyme Complex-I, one (cytochrome *b*) of the 11 polypeptides of Complex-III, three (COI-III) of the 13 polypeptides of Complex-VI (cytochrome *c* oxidase) and two (ATP6 and 8) of the approximately 15 polypeptides of Complex-V (ATP synthase) (Wallace, 2013) (Fig.1).

MtDNA polypeptides are essential to the electron and proton wiring systems responsible for mitochondrial energy production. In OXPHOS, electrons flow from reduced to oxidized status down the electron transport chain that is embedded in the mitochondrial inner membrane. As the electrons traverse Complexes I, III, IV, the energy produced is utilized to pump protons from the mitochondrial matrix to the intermembrane space across the inner membrane. This creates an electrochemical gradient that is acidic (positive) on the outside and alkaline (negative) on the inside (Mitchell, 1961). The resulting 0.2 V capacitance is the potential energy driving virtually all human biological processes. If cellular breathing stops, the membrane potential collapses, energy production ceases and death ensues (Wallace, 2005, 2007, 2011).

The potential energy stored in the mitochondria can be used to take up Ca^{++} from the cytosol, modulate cellular reactive oxygen species production, transport proteins and substrates in and out of the mitochondria and most importantly, generate ATP by Complex-V, which is the chemical energy carrier that energizes cellular reactions in the cytosol (Mitchell, 1961).

Surprisingly enough, the efficiency by which the transported electrons are converted into ATP differs between human individuals from different regional populations. Some are highly efficient at converting caloric energy into a proton gradient and consequently generating ATP. As a result, these individuals need to burn only the least number of calories for the required ATP, and thus generate the minimum heat for the ATP used (tightly coupled). In contrast, others less efficient at this process burn more calories for the same amount of ATP and thus produce more body heat (loosely coupled). Epigenetically, this altered coupling efficiency can be modulated, for example by altering the sequence of the mtDNA and thus changing proton pumping efficiency (Mishmar et al., 2006; Ruiz-Pesini et al., 2004) or by induction of uncoupling protein 1 in brown fat (Puigserver et al., 1998). This variation can be beneficial in different climatic conditions. In tropical and temperate environments, it is more advantageous to be more tightly coupled to produce the maximum ATP with less heat. On the other hand, it would be more beneficial in the arctic to be loosely coupled so that more heat is generated to maintain body temperature. This type of adaptive variation which is due to mtDNA changes is supported by the observation that climatic differences correlate with mtDNA variations rather than with nuclear DNA variations (Balloux et al., 2009).

MtDNA codes for the proteins which are essential to the coupling of the electron transport to proton pumping and thus ATP production. All four electron transport chain complexes that include mtDNA-coded polypeptides (I, III, IV, and V) either generate or use the proton gradient. In contrast, Complex-II which transports electrons but does not pump protons is composed of four nDNA polypeptides. The proton permeability of Complexes I, III, IV and V must be balanced with each other. If any of them leaks protons, then the electrochemical gradient (which is a capacitor) can short, and this would be detrimental. Hence, the 13 polypeptides of the mtDNA represent an integrated electrical circuit in which each polypeptide must possess a coupling efficiency compatible with the other 12 mtDNA polypeptides (Wallace, 2007).

1.2. Mitochondrial dysfunction

Nuclear DNA (nDNA) is transmitted by autosomal dominant or recessive pattern, unlike mtDNA which is transmitted by maternal inheritance. There are multiple identical copies of mtDNA present within each mitochondrion (polyploid), with several thousand copies in each cell. Normally, all copies of mtDNA are identical in a single individual (homoplasmy). Mutation in one copy may lead to two populations of wild and mutated mtDNA that co-exist within the same cell (heteroplasmy). The mitochondria are distributed together with its mtDNA between the two daughter cells during replication, and the amount of mutated mtDNA differs in each daughter cell in a process called 'Replicative Segregation'. The clinical manifestations of a mitochondrial disease are only evident when the degree of mutated mtDNA exceeds a certain bioenergetic threshold, thereby leading to phenotypic variation which in turn is dependant on the ratio of mutant to wild type cellular mtDNA. The random distribution of mutated mtDNA between daughter cells explains the age and tissue variability of clinical manifestations observed in mitochondrial disorders (DiMauro and Schon, 2003; McKenzie et al., 2004). The presence of an mtDNA mutation in a group of patients with a specific disease entity does not necessarily indicate a primary or a pathogenic role for that mutation, unless certain criteria have been applied (Chinnery et al., 1999).

The dysfunction of oxidative phosphorylation secondary to nDNA or mtDNA mutations can lead to a reduction of maximal ATP production and increased reactive oxygen species (ROS) generation. The increased