Mitochondrion 36 (2017) 66–76

Contents lists available at ScienceDirect

Mitochondrion

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

Mitochondrial dysfunction underlying outer retinal diseases

Evy Lefevere[a], Anne Katrine Toft-Kehler[b], Rupali Vohra[b], Miriam Kolko[b], Lieve Moons[a,*], Inge Van Hove[a]

[a] Neural Circuit Development and Regeneration Research Group, Department of Biology, KU Leuven, Leuven, Belgium
[b] Department of Neuroscience and Pharmacology, Faculty of Health Sciences, Center for Healthy Aging, University of Copenhagen, Copenhagen, Denmark

ARTICLE INFO

Keywords:
Mitochondria
Photoreceptors
Retinal pigment epithelium
Age-related Macular Degeneration
Kearns-Sayre Syndrome
Neuropathy Ataxia Retinitis Pigmentosa Syndrome

ABSTRACT

Dysfunction of photoreceptors, retinal pigment epithelium (RPE) or both contribute to the initiation and progression of several outer retinal disorders. Disrupted Müller glia function might additionally subsidize to these diseases. Mitochondrial malfunctioning is importantly associated with outer retina pathologies, which can be classified as primary and secondary mitochondrial disorders. This review highlights the importance of oxidative stress and mitochondrial DNA damage, underlying outer retinal disorders. Indeed, the metabolically active photoreceptors/RPE are highly prone to these hallmarks of mitochondrial dysfunction, indicating that mitochondria represent a weak link in the antioxidant defenses of outer retinal cells.

1. Introduction

Mitochondria are crucial and ubiquitous intracellular organelles and the major source for cellular energy production through oxidative phosphorylation, thereby providing most of the adenosine triphosphate (ATP) requirements of eukaryotic cells (Schrier and Falk, 2011; Yu-Wai-Man et al., 2011) (see Fig. 1). These energy producing organelles consist of an outer and inner membrane that defines two distinct compartments, more specifically an intermembrane space and an internal matrix space (Yu-Wai-Man et al., 2011). Mitochondrial oxidative phosphorylation resides in the inner mitochondrial membrane, in which the invaginations, called cristae, greatly improve the surface area for ATP generation. The electron transport chain in the inner membrane is the site of oxidative phosphorylation and consists of a five-complex chain of polypeptides, in which the first four complexes oxidize NADH and $FADH_2$ through a controlled series of redox reactions, while complex V phosphorylates ADP to ATP (Fig. 1). Ubiquinone, also known as coenzyme Q (Co Q), and cytochrome complex (cyt C) are cofactors of the electron transport chain that act as electron shuttles and importantly contribute to the mitochondrial respiratory chain function. Defects in these complexes and/or cofactors may lead to diminished mitochondrial ATP production and an increased formation of reactive oxygen species (ROS) (Fraser et al., 2010). Next to their main function as ATP producers, mitochondria fulfill important critical functions to preserve cell integrity and survival, by means of scavenging ROS, mitochondrial dynamics (fission and fusion), the regulation of calcium homeostasis, nucleotide metabolism, and the biosynthesis of amino acids, cholesterol and phospholipids (Falk, 2010; Schrier and Falk, 2011). As such, malfunctioning of this critical organelle leads to severe impairment of tissue homeostasis and cellular dysfunction, mainly characterized by defects in bio-energetic processes and mitochondrial dynamics, increased apoptosis and augmented oxidative stress, but also by accumulation of mutated mitochondrial DNA (mtDNA) (Procaccio et al., 2014; Golden and Melov, 2001). Notably, mitochondria have their own genome, semi-autonomously replicating and transcribing their mtDNA in the internal matrix space (Druzhyna et al., 2008). The structural proteins that form the oxidative phosphorylation system are encoded by both mtDNA and nuclear DNA (nDNA), indicating the importance of both genomes in the structure and function of the mitochondrial respiratory complexes (Calvo et al., 2006; Fraser et al., 2010). The increment in oxidative stress and associated mitochondrial disturbances are vastly associated with increasing age (Raha and Robinson, 2000). Indeed, the free radical theory as the most outspoken hypothesis to explain ageing together with mitochondria as the

Abbreviations: CNS, central nervous system; NARP, Neuropathy Ataxia Retinitis Pigmentosa; KSS, Kearns-Sayre Syndrome; MILS, Maternally Inherited Leigh Syndrome; AMD, Age-related Macular Degeneration; MIDD, Mitochondrial Syndrome of Maternally Inherited Diabetes and Deafness; MELAS, Mitochondrial Myopathy, Encephalopathy, Lactic Acidosis, and Stroke like episode; RP, Retinitis Pigmentosa; CPEO, Chronic Progressive External Ophthalmoplegia; SPG15, spastic paraplegia type 15; mtDNA, mitochondrial DNA; nDNA, nuclear DNA; ATP, adenosine triphosphate; RPE, retinal pigment epithelium; CFH, complement factor H; ROS, reactive oxygen species; bcl-2, B-cell lymphoma 2; BAX, like protein 4; SD-OCT, spectral domain optical coherence tomography; SOD, superoxide dismutase

* Corresponding author at: Neural Circuit Development and Regeneration Research Group, Animal Physiology and Neurobiology Section, Department of Biology, KU Leuven, Naamsestraat 61, Box 2464, B-3000 Leuven, Belgium.
E-mail address: Lieve.moons@kuleuven.be (L. Moons).

http://dx.doi.org/10.1016/j.mito.2017.03.006
Received 15 July 2016; Received in revised form 6 March 2017; Accepted 27 March 2017
Available online 29 March 2017

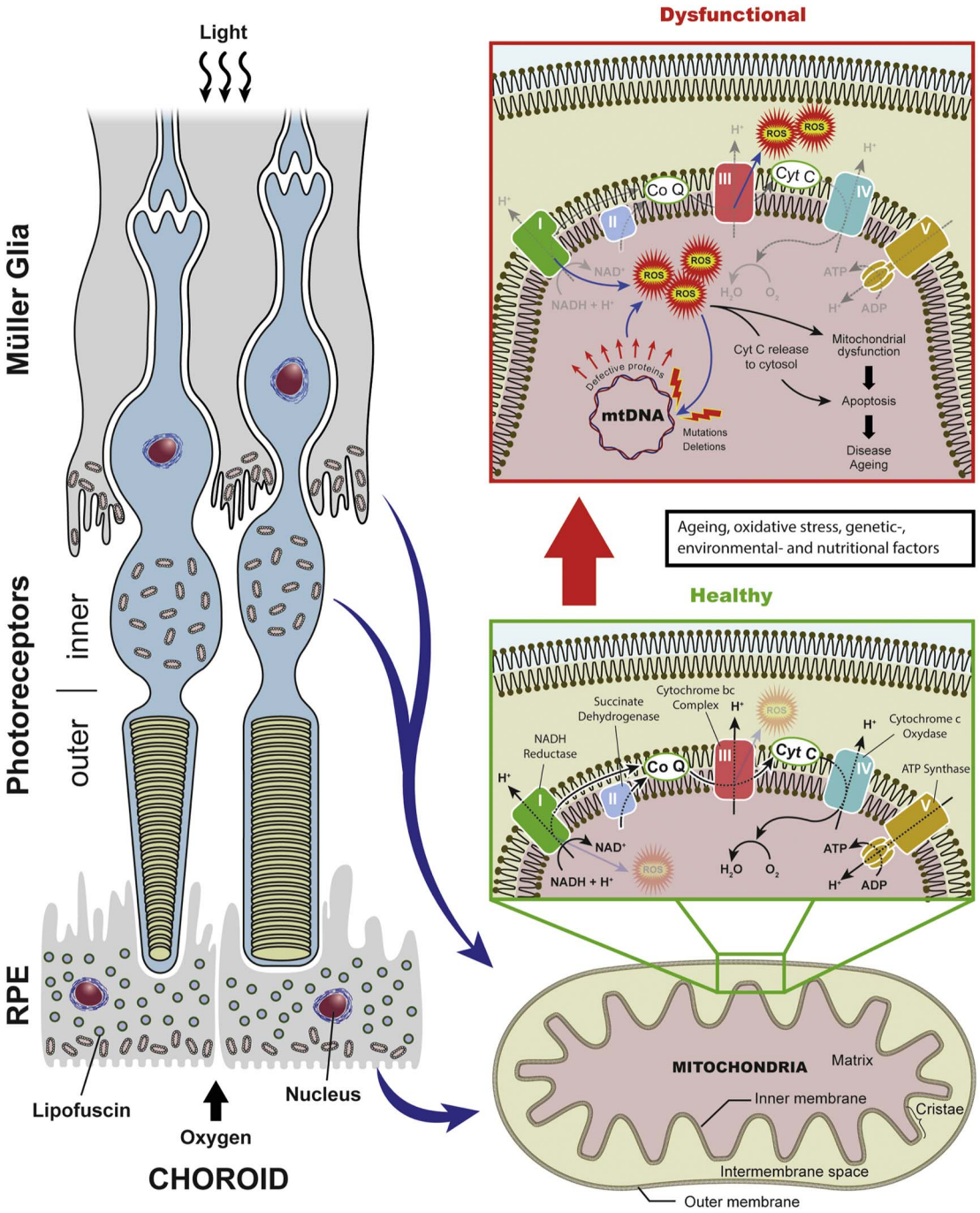

Fig. 1. Healthy versus dysfunctional mitochondria in the outer layers of the mammalian retina.As indicated on the left picture, the Müller glia, photoreceptors and retinal pigment epithelium (RPE) cells are closely interacting. The photoreceptors face the apical microvilli-rich surface of the RPE that continuously support photoreceptor function through interactions with their outer segments. This RPE/photoreceptor complex resides in a highly oxidative environment as it is constantly exposed to light and local oxygen. The chromophore lipofuscin in the RPE is capable of generating a wide array of reactive oxygen species (ROS). However, the mitochondria in the outer retina represent the major source of endogenous ROS. The picture schematically shows the cellular localization of mitochondria in the outer retinal cells, i.e. in Müller glia, in photoreceptor and RPE cells. The mitochondria concentrate at the external end of the Müller glia, in the inner segments of the photoreceptors and at the basal side of the RPE cells. In the right picture, a magnification of the mitochondrial membranes shows in detail the oxidative phosphorylation pathway where the proton gradient across the inner membrane, formed by complex I-V, successfully converts ADP to ATP in healthy conditions. Ubiquinone, also known as coenzyme Q (Co Q), and cytochrome complex (cyt C) are cofactors of the electron transport chain that act as electron shuttles and importantly contribute to the mitochondrial respiratory chain function. After several insults, the oxidative phosphorylation system fails in efficiently pumping protons leading to decreased generation of ATP and augmented ROS production. Complex I and III mainly provoke augmented ROS levels, which cause oxidative damage to mitochondrial DNA (mtDNA) leading to defective mitochondrial proteins and membranes. Mitochondrial oxidative stress can also accelerate the release of cyt C to the cytosol, thereby activating apoptosis. As such, increased ROS leads to mitochondrial dysfunction and apoptosis and highly contributes to outer retinal pathologies.

principle source of ROS, suggests that ageing in mammals is highly correlated with an accumulation of deteriorated mtDNA and a decrease in respiratory chain function, as a result of hyperproduction of intracellular ROS (Trifunovic and Larsson, 2008; Payne and Chinnery, 2015). Although mitochondrial dysfunction with age is well described, also other processes/proposed theories may cause cellular ageing, such as heterochromatin formation, endoplasmic reticulum stress, telomere attrition, etc. (Liu, 2014; Musumeci et al., 2017; Chandrasekaran et al., 2016). Nevertheless, mitochondria are suggested to serve a prominent role in the complicated web of processes leading to cellular and