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Mitochondrial dynamics, transport, and quality control: A bottleneck for retinal ganglion cell viability in optic neuropathies☆

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ABSTRACT

Retinal ganglion cells, the neurons that selectively die in glaucoma and other optic neuropathies, are endowed with an exceedingly active metabolism and display a particular vulnerability to mitochondrial dysfunction. Mitochondria are exquisitely dynamic organelles that are continually responding to endogenous and environmental cues to readily meet the energy demand of neuronal networks. The highly orchestrated regulation of mitochondrial biogenesis, fusion, fission, transport and degradation is paramount for the maintenance of energy-expensive synapses at RGC dendrites and axon terminals geared for optimal neurotransmission. The present review focuses on the progress made to date on understanding the biology of mitochondrial dynamics and quality control and how dysregulation of these processes can profoundly affect retinal ganglion cell viability and function in optic nerve diseases.

1. Introduction

The retina is among the most metabolically active tissue in the body and, as such, requires a precise regulation of energy production proportional to consumption. Mitochondria play a crucial role in meeting the high metabolic demand of retinal neurons by maintaining a constant energy supply through oxidative phosphorylation. Adenosine triphosphate (ATP) is generated by the electron transport chain complexes located within the cristae folds of the inner mitochondrial membrane (IMM) (Smeitink et al., 2001). In addition to energy production, mitochondria are essential for regulating a number of processes essential for neuronal functions including metabolic balance, intracellular calcium homeostasis, production of reactive oxygen species (ROS), and apoptotic signaling. With their high energy demand, complex dendritic arbors, and long axons, it is not surprising that retinal ganglion cells (RGCs) are particularly vulnerable to mitochondrial dysfunction. Indeed, inherited mitochondrial defects are associated with a number of optic neuropathies including Leber's hereditary optic neuropathy (LHON) and autosomal dominant optic atrophy (ADOA), which are characterized by selective RGC death (Brown et al., 2002; Alexander et al., 2000; Delettre et al., 2000; Carelli et al., 2004). Glaucoma, the most common optic neuropathy and the leading cause of irreversible blindness worldwide (Carelli et al., 2004), has not been linked to mutations that result in mitochondrial dysfunction. However, accumulating evidence indicates that age-related mitochondrial defects play a central role in the pathogenesis of glaucoma (Jarrett et al., 2010; Kong et al., 2009; Osborne et al., 2014; He et al., 2009; Joe and Tomarev, 2010; Abu-Amero and Bosley, 2006; Banerjee et al., 2013; Lee et al., 2012; Sundaresan et al., 2015; Bailey et al., 2014; Williams et al., 2017).

Mitochondria are extremely dynamic organelles that are constantly changing their shape, size, and location in response to cellular and environmental cues. The balance between fission and fusion determines the morphology of mitochondria and allows rapid adaptation to meet the energetic demand of neurons (Rambold et al., 2011; Gomes et al., 2011; Strauss et al., 2008). Mitochondrial biogenesis is the process that results in increased number and/or volume of *de novo* mitochondria (Jornayvaz and Shulman, 2010), while mitophagy involves clearing of damaged mitochondria and it is a critical component of mitochondrial quality control in physiological conditions (Ding and Yin, 2012; Palikaras et al., 2016). Mitochondrial transport and mobility ensure the presence of these organelles at sites of high energy consumption such as the synapses at dendrites and axonal terminals, which are far removed from the cell body (Vos et al., 2010; Mattson and Liu, 2002). The interplay between fission, fusion, biogenesis, degradation, and transport continually remodels and rebuilds the mitochondrial network. These

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dynamic processes ensure a healthy population of mitochondria throughout the complex morphological structure of RGCs, and allow these neurons to rapidly adapt to the steep changes in energy demand. The present review focuses on the progress made to date on understanding how the intricate balance between mitochondrial biogenesis, dynamics, transport, and degradation affect RGC viability and function. Impairment of any one of these components is predicted to result in an insufficient energy supply, which would have grave consequences on the energetically demanding RGC. Therefore, we will discuss how mitochondria are affected in optic neuropathies, including glaucoma, and present these findings in the realm of other neurodegenerative diseases. We also highlight the areas where there is a paucity of information and point to the challenges ahead to exploit mitochondria-based therapeutics for optic neuropathies.

2. The peculiar vulnerability of RGCs to mitochondrial dysfunction

RGCs are exquisitely vulnerable to mitochondrial deficits as evidenced from numerous diseases triggered by mutations in genes essential for mitochondrial function. Point mutations in the mitochondrial DNA, which impair subunits of the respiratory chain complex I, account for approximately 90% of LHON cases (Brown et al., 2002). Although these mutations are present in all cells of the body, only RGCs are compromised and die as the disease progresses. Approximately 75% of ADOA cases, the most common inherited optic neuropathy, are caused by mutations in *OPA1*, a gene encoding a dynamin-related protein in the IMM that regulates mitochondrial dynamics (Alexander et al., 2000; Delettre et al., 2000). Similar to LHON, OPA1 is ubiquitously expressed, but only RGCs are selectively lost in ADOA patients. Since glaucoma is a complex, multifactorial disease, the contribution of mitochondrial dysfunction to the disease process has been considerably more challenging to decipher. Although the onset of glaucoma is typically later than LHON or ADOA, these diseases share a similar phenotype characterized by the selective and progressive death of RGCs. Oxidative stress attributed to a complex I-linked decrease in ATP production, similar to mitochondrial pathology in LHON, has been documented in ocular hypertension models and samples from glaucoma patients (Van Bergen et al., 2015; Abu-Amero et al., 2006). For example, a recent study demonstrated mitochondrial dysfunction and alterations in oxidative phosphorylation pathways in aging DBA/2J mice (Williams et al., 2017). Indeed, ocular hypertension induced an age-dependent decline in retinal NAD^+ and glutathione, and oral supplementation of vitamin B3/nicotinamide (NAM), a precursor of NAD +, was neuroprotective (Williams et al., 2017). Of interest, transformed lymphocytes from glaucoma patients exhibit complex I activity impairment and slow proliferation suggestive of defects in mitochondrial oxidative phosphorylation (Van Bergen et al., 2015). The negative impact of chronic oxidative stress and ROS on RGC in glaucoma is the subject of excellent previously published reviews (Osborne and Del Olmo-Aguado, 2013; Izzotti et al., 2006; Chrysostomou et al., 2013; Baltmr et al., 2010; Yildirim et al., 2005) and will not be discussed here. Importantly, the risk of developing glaucoma increases with age (Rochtchina et al., 2002; Mitchell et al., 1996; Leske et al., 1994; Dielemans et al., 1994) and accumulating evidence suggests that there is increased mitochondrial dysfunction in aging individuals (Bratic and Larsson, 2013; Cui et al., 2012; Trifunovic and Larsson, 2008). Indeed, it has been proposed that somatic mitochondrial DNA mutations and polymorphisms accumulate with age and contribute to mitochondrial damage in glaucoma (Jeoung et al., 2014; Yu-Wai-Man et al., 2011).

3. Special metabolic requirements of RGCs

Why are RGCs particularly susceptible to mitochondrial damage? There is no clear-cut answer to this question, but a possible explanation rests on the acute energy demand of these neurons combined with their unique morphology. The RGC soma reside in the ganglion cell layer within the retina, their elaborate dendritic arbors project into the inner plexiform layer to establish synaptic contacts with other retinal neurons, and the long axons extend through the optic nerve to form distal terminals and connect with cellular partners in the brain. At the active sites of both intraretinal and brain synapses, an astonishing amount of energy is required to synthesize neurotransmitters, organize synaptic vesicles, restore ion gradients, and buffer calcium (Vos et al., 2010; Mattson and Liu, 2002). In humans, there is an estimated one million axons per optic nerve that extend a distance of 50 mm to transmit signals from the retina to the brain (Mikelberg et al., 1989). Energy in the form of ATP is required to transport cargoes bidirectionally along RGC axons. The unmyelinated portion of the RGC axon within the retina requires more energy for the generation of an action potential due to absence of saltatory conduction, relative to the myelinated segment distal to the lamina cribrosa (Wang et al., 2003). Based on this, it is not surprising that considerably more mitochondria populate the unmyelinated portion of RGC axons, concentrated primarily in varicosities, compared to the myelinated segment in a number of species including humans (Wang et al., 2003; Mutsaers and Carroll, 1998; Bristow et al., 2002). Recently, elevated intraocular pressure was shown to result in increased cross-sectional surface of the RGC axons accompanied by reduced numbers of mitochondria per optic nerve unit area (Cooper et al., 2015). Decreased mitochondrial density is predicted to greatly limit the energy supply required to maintain RGC axons, particularly in conditions of chronic stress.

An additional challenge is the steep energy requirement for the maintenance of complex RGC dendritic arbors which harbour millions of synapses. A recent study using *in vivo* time-lapse confocal recordings demonstrated that mitochondria in RGC dendrites are extremely mobile during development and become almost motionless as synapses mature (Faits et al., 2016), confirming the sustained energy demand at these sites. Intriguingly, pathological RGC hyperactivity, a common feature of retinal degeneration and optic nerve injury (Ward et al., 2014; Morquette et al., 2014), reverted mitochondria to a high mobility status (Faits et al., 2016) suggesting an important need for energy mobilization after injury. In summary, the unique cytoarchitecture of RGCs combined with its highly compartmentalized energy requirements, which add enormous pressure to maintain a vast and highly dynamic mitochondrial population, converge to make these neurons especially vulnerable to deficits in mitochondrial function.

4. At the origin: mitochondrial biogenesis

The various structural and functional components of mitochondria are encoded by both nuclear and mitochondrial genes. The majority of mitochondrial proteins are encoded by the nuclear genome including complexes I, III, IV, and V, which are all essential components of the mitochondrial respiratory chain (Neupert, 1997). *De novo* synthesis of mitochondria is a complex process that depends on both the translation of the mitochondrial- and nuclear-encoded proteins required for the assembly of the mitochondrial compartments, as well as the replication of the mitochondrial DNA. The main site of mitochondrial biogenesis is postulated to occur in close proximity to the nucleus because this topological arrangement ensures that only properly replicated molecules are incorporated in all mitochondria (Davis and Clayton, 1996).

A tight regulation of the process of biogenesis is required to maintain an adequate number of mitochondria within the cell. The level of biogenesis in each cell varies in response to numerous environmental stimuli. For example, the expression of peroxisome proliferator-activated γ coactivator 1α (PGC-1α), a master regulator of mitochondrial biogenesis (Fernandez-Marcos and Auwerx, 2011), increases in RGCs as well as in retinal and optic nerve astrocytes in response to metabolic or oxidative stress (Noh et al., 2013; Guo et al., 2014). Increased mitochondrial biogenesis is postulated to be an adaptive measure to ensure that damaged mitochondria are replenished (Piantadosi et al.,