Review

Mitochondria as a central sensor for axonal degenerative stimuli

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Axonal degeneration is a major contributor to neuronal dysfunction in many neurological conditions and has additional roles in development. It can be triggered by divergent stimuli including mechanical, metabolic, infectious, toxic, hereditary and inflammatory stresses. Axonal mitochondria are an important convergence point as regulators of bioenergetic metabolism, reactive oxygen species (ROS), Ca^{2+} homeostasis and protease activation. The challenges likely to render axonal mitochondria more vulnerable than their cellular counterparts are reviewed, including axonal transport, replenishing nuclear-encoded proteins and maintenance of quality control, fusion and fission in locations remote from the cell body. The potential for mitochondria to act as a decision node in axon loss is considered, highlighting the need to understand the biology of axonal mitochondria and their contributions to degenerative mechanisms for novel therapeutic strategies.

Introduction

Neuronal soma and axons die by very different mechanisms. Axon degeneration is in many cases an autonomous process that is distinct from classical apoptosis but can be genetically regulated. Conversely, a protein that protects axons, the slow Wallerian degeneration protein (Wld^S), has no known effect on survival of the soma [1,2]. As molecular mechanisms underlying axon survival and degeneration become better understood, it is important to ask what makes them specific for axons.

Many mitochondrial dysfunctions lead to disorders in which axon degeneration is the predominant feature, or a prominent early step (Table 1). Thus, axons may face a greater challenge than neuronal soma or dendrites in maintaining sufficient functioning of mitochondria for survival. Mitochondria, long known to have multiple roles in cell death, differ strikingly between axons and soma. First, their elongated shape, at least in peripheral nerve axons, is specialized for life in a long narrow cylinder [3]. Maintenance of this shape is critical for efficient delivery by axonal transport so that even moderate swelling will block both their own transport and that of many other cargoes (Figure 1). Second, axonal mitochondria are discrete structures, in contrast to the syncytia more typically seen in many cell types. Because of this discontinuity, the delivery of material and exchange with other mitochondria may be more dependent on mechanisms such as fusion and fission. Third, their transport has to be carefully regulated to ensure that mitochondria are focused in the correct regions of the huge axonal compartment [4], which can be several hundred times larger than neuronal soma. In this way, high requirements for adenosine triphosphate (ATP) synthesis and Ca^{2+} buffering can be met.

This review considers the extent to which unique features of axonal mitochondria underlie axon-specific degeneration mechanisms, making them a nodal point for decisions on axon survival. In some cases, axons degenerate through failure to maintain a healthy mitochondrial population at literally 'arm's length' from the cell body, whereas in others mitochondria may play a more active role in axon degeneration. The latter process may be much faster, whereas a steady decline in mitochondria quality in axons may take many years and only occur when axonal transport further declines with age.

Challenges for axonal mitochondria

Mitochondrial defects are surprisingly prevalent in axon degeneration disorders (Table 1). It is interesting to consider whether this reflects properties of mitochondria that are important within axons in particular and how such properties may fit together.

Mitochondrial fusion and fission in neurodegenerative conditions

Mitochondrial fusion and fission are particularly prominent among the functions of the proteins in Table 1. Proteins controlling these processes are mutated in subtypes of peripheral neuropathy, optic atrophy and hereditary spastic paraplegia (HSP). Mitofusin 2, an outer mitochondrial membrane protein mediating fusion is mutated in the pure axonal disorder Charcot-Marie-Tooth Type 2A [5], whereas optic atrophy 1 (OPA1), which has a related role in fusing the inner mitochondrial membrane, is defective in autosomal dominant optic atrophy [6]. Paraplegin (encoded by the *SPG7* gene), which is mutated in some types of HSP, regulates control of mitochondrial size by OPA1 [7] and its absence results in giant mitochondria [8]. Ganglioside-induced differentiation-associated protein-1 (GDAP1), a protein that enhances mitochondria fragmentation, is mutated in the mixed axon/myelin disorder Charcot-Marie-Tooth Disease type 4A (CMT4A) [9].

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Table 1. Mitochondrial proteins mutated in disorders with prominent axonal degeneration[a]

Disease	Protein	Disease type	Possible protein function	Refs
Charcot-Marie-Tooth	Mitofusin 2	CMT2A	Outer mitochondrial membrane protein ER protein Axonal mitochondrial transport ER-mitochondrial tethering	[5,32,103]
	HSPB1 (HSP27)	CMT2F	Molecular chaperone Neurofilament organization Microtubule binding	[104,105]
	HSPB8 (HSP22)	CMT2L	Molecular chaperone Associated with autophagy	[106]
	Gdap1	CMT4A	Outer mitochondrial membrane protein Mitochondrial fission	[9]
Friedrich's ataxia	Frataxin	Friedrich's ataxia	Mitochondrial matrix iron chaperone Redox regulation	[22]
Hereditary spastic paraplegia	Paraplegin	SPG7	Mitochondrial ATPase	[8]
	Hsp60	SPG13	Mitochondrial chaperone Resistance to oxidative stress (?)	[107]
	Spartin	SPG20	Several protein partners, localization and functions Required for mitochondrial calcium uptake capacity	[81]
	Reep1	SPG38	Binds spastin Associates with microtubules ER-shaping and mitochondrial dynamics (?)	[108]
Optic atrophy/neuropathy	OPA1	Optic atrophy	Inner mitochondrial membrane protein Mitochondrial fusion	[6,109]
	Complex 1 subunits ND1, 4, 6	Leber's hereditary optic neuropathy	Complex I subunit of mitochondria Decrease ATP production	[110]
Parkinson's disease	Parkin	PARK2	Cytosolic E3 ubiquitin ligase Mitochondrial quality control Microtubule dynamics	[18]
	PINK1	PARK6	Mitochondrial quality control	[17]
	DJ-1	PARK7	Atypical peroxidase Regulation of oxidant defenses	[111,112]
	LRRK2	PARK8	Partial mitochondrial localization	[113]
	HTRA2	PARK13	Mitochondrial intermembrane space Pro-apoptotic	[114]
	POLG1	Parkinson's disease, Alper's syndrome	Inner mitochondrial membrane Mitochondrial DNA synthesis, replication and repair	[115]
Sensory neuropathy	Bcl-w	Small fiber sensory neuropathy	Mitochondrial localization Anti apoptotic Bcl-2 family member	[67]

[a]Abbreviations: HTRA2, high temperature requirement protein 2; LRRK2, leucine-rich repeat kinase 2; POLG1, mitochondrial DNA polymerase gamma 1; Reep1, receptor expression enhancing protein 1.

The GTPase dynamin-related protein 1 (DRP1), in addition to being associated with mitochondrial fission, is also required for neurite development or maintenance in primary culture [10]. In humans, a mutation in *DRP1* has been associated with severe and lethal defects in the nervous system [11]. Fusion and fission of axonal mitochondria may also be a primary target in toxic models, as chronic exposure to low levels of rotenone causes loss of dopaminergic neuronal processes without cell death in a process that may require mitochondrial fission [12].

Mitochondria quality control and neuronal degeneration

Quality control of mitochondria is another emerging theme, especially in Parkinson's disease (PD), where a growing body of evidence points to a 'dying back' process of early axon and synapse loss [13]. Experiments in non-neuronal cell culture suggest that accumulation of phosphatase and tensin homolog (PTEN)-induced putative kinase 1 (PINK1) on the surface of dysfunctional mitochondria acts as a signal for their removal by mitophagy [14,15]. By contrast, regular voltage-dependent proteolysis of PINK1 on healthy mitochondria maintains low levels of this protein [14]. This degradation stops if mitochondrial membrane potential falls, causing rapid accumulation of PINK1 and recruitment of Parkin leading to mitophagy. Recent data confirm that Parkin recruitment occurs in neuronal soma [16]. Genetic evidence supports a similar mechanism *in vivo* as loss-of-function mutations in PINK1 or Parkin cause PD [17,18] and *Drosophila* studies indicate that Parkin lies downstream of PINK1 [19].

Quality control becomes particularly intriguing in the context of the huge axonal arbors of dopaminergic neurons in mammalian brain [20]. Degeneration of these nerve terminals clearly precedes death of the soma [13] so any failure of quality control may occur here first. In distal axons of sensory neurons, mitochondria fragments are engulfed by microtubule-associated protein 1A/1B-light chain 3 (LC3)-positive vesicles and the resulting autophagosomes fuse with lysosomes as they move retrogradely [21]. The importance of retrograde transport is consistent with the accumulation of depolarized mitochondria in distal axons in a *Drosophila* model of Friedreich ataxia, associated with a failure of retrograde axonal transport [22]. Whether these first stages of mitophagy in axons use