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Vassiliki Nikoletopoulou & Nektarios Tavernarakis

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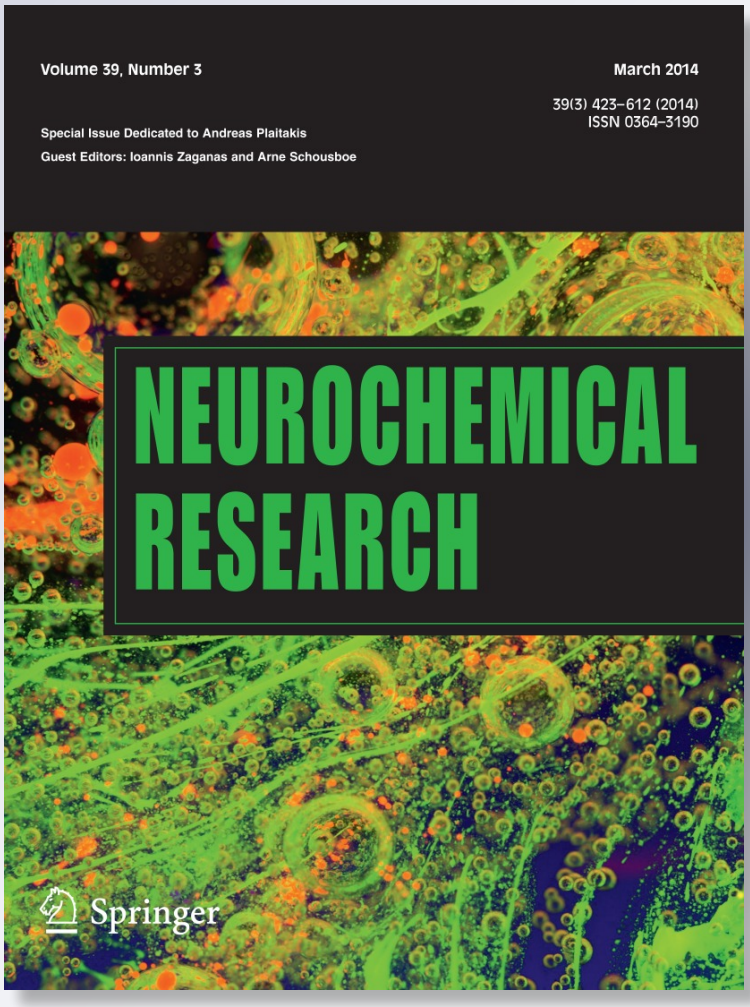

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COMMENTS

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Abbreviations

AD	Alzheimer's disease
CMT2A	Charcot-Marie-Tooth 2A
DOA	Dominant optic atrophy
DRG	Dorsal root ganglia
FCLS	French Canadian Leigh syndrome
LHON	Leber's hereditary optic neuropathy
LRP130	Leucine rich protein 130 kDa
MFN1	Mitofusin1
MFN2	Mitofusin2
mtDNA	Mitochondrial DNA
OPA1	Optic atrophy 1
PD	Parkinson's disease
PGC-1α	Peroxisome proliferator-activated receptor coactivator 1-α
RGCs	Retinal ganglion cells

Mitochondrial dysfunction is becoming appreciated as a unifying characteristic of diverse degenerative pathologies affecting distinct populations of central and peripheral neurons. Indeed, mitochondria require an intact transport and signalling network within the cell to optimally perform their function. Consequently, the mitochondrial system is highly sensitive and would likely be particularly affected in malfunctioning neurons that are losing synapses to other cells and become progressively isolated from their network before dying. In line with this notion, mitochondrial abnormalities have been linked with neuronal ageing [1] as well as with Alzheimer's disease (AD) or related tauopathies (see for example refs [2–4]) and Parkinson's disease (PD) [5].Thus, aberrant mitochondrial function is a normally anticipated consequence of neuronal degeneration.

However, is the reverse also true? Here, we discuss emerging evidence that indicates a causative involvement of mitochondria in specific cases of neurodegeneration, focusing on specific aspects of mitochondrial biogenesis and dynamics. The realization that the primary cause of some familial forms of neurodegenerative disorders lies in mutations in nuclear genes encoding mitochondrial proteins, or in mitochondrial genes, provides compelling support for the hypothesis that mitochondrial abnormalities can be causative of neuronal degeneration.

Evidence in support of this view has its roots in 1988 when Leber's hereditary optic neuropathy, a neurodegenerative disorder affecting specifically retinal ganglion cells (RGCs), was for the first time associated with pathogenic defects of mitochondrial DNA (mtDNA) [6]. This key finding commenced the so called "molecular era of mitochondrial medicine". Following this discovery, it was progressively appreciated that RGCs are particularly vulnerable to mitochondrial defects, which compromise their survival and maintenance. For example, dominant optic atrophy (DOA), the most commonly inherited optic neuropathy characterized by the specific loss of retinal ganglion cells [7], was also attributed to various mutations in the nuclear gene OPA1 [8, 9], encoding a mitochondrial dynamin-related GTPase. OPA1 functions in the formation and maintenance of the mitochondrial network by regulating mitochondrial fusion. Recent work suggests that it also functions by directly controlling the replication of mtDNA and the distribution of nucleoids [10].

In addition to RGCs, disrupted mitochondrial fusion is also responsible for the degeneration of sensory neurons in patients with axonal Charcot-Marie-Tooth disease

V. Nikoletopoulou · N. Tavernarakis (✉)
Institute of Molecular Biology and Biotechnology, Foundation for Research and Technology, 71110 Heraklion, Crete, Greece
e-mail: tavernarakis@imbb.forth.gr

(designated CMT2A). In this case, however, OPA1 is not implicated; mitochondrial dysfunction is rather due to point mutations in mitofusin-2 (MFN2). Similarly to OPA1, MFN2 is a large nuclear-encoded dynamin-like GTPase protein, anchored in the outer mitochondrial membrane by two transmembrane domains. Overexpression of several Mfn2 mutants in cultured sensory neurons, isolated from the dorsal root ganglia (DRG) of the rat, induces mitochondrial aggregation around the nucleus [11]. As a consequence, neurites are almost completely devoid of mitochondria, with few static mitochondria still present. In addition, transgenic mice over-expressing the Mfn2T105 M variant in motor-neurons, display severe motorneuron degeneration accompanied by muscular atrophy. In this case, mitochondria appear to also collapse around the nucleus and only few reach distal parts of axons [12]. Therefore, mutations affecting the fusion machinery (Fig. 1) are particularly effective in triggering degeneration of neuronal populations that are diverse in their developmental origin and function.

Correct distribution of mtDNA appears to rely upon mitochondrial fusion. For example, in MEFs lacking MFN2, MFN1 or both, a significant amount of mitochondria is devoid of mtDNA [13]. Notably, the same phenotype is found in OPA1 depleted cells. These findings indicate that mitochondrial fusion could be a mechanism facilitating mtDNA maintenance through exchange of DNA molecules between mitochondria. However, the mechanism by which germline mutations in ubiquitously expressed proteins such as OPA1 and MFN2 lead to the strictly selective degeneration of RGCs and peripheral neurons respectively, while leaving other populations intact remains largely unclear and difficult to interpret [14–16]. One possible explanation could lie in the vast morphological heterogeneity and distinct electrophysiological properties of different neurons, innately established to serve local needs for proper synaptic patterning and communication. As a result, there is a corresponding heterogeneity in the requirements for trafficking mitochondria and attending to different energy demands in different types of neurons. RGCs for example, have remarkably complex dendritic trees [17], and sensory neurons similarly have multi-dendritic arbors, making both populations very similar in this aspect of morphology, yet, idiosyncratic compared to other neurons.

Another possible explanation is that mitochondrial dynamics are modulated differentially by cell-specific mechanisms that remain poorly delineated. For example, it has been found that the OPA1 gene produces many splice variants. Some of these splicing isoforms (4/4b and 4b/5b) predominate in foetal brain, retina, heart and muscle, while splicing isoforms 4/5b and 4/4b/5b are weakly but ubiquitously expressed in all tissues [18]. The biochemical properties of these splice variants, and their proportion in different neuronal populations, remain unknown. In general, high transcript levels are observed in the retina [8], a fact which may be related to the apparent restriction of the clinical phenotype to the visual system. Moreover, there is an increasing number of new proteins with mitochondrial localization being identified (for example see Ref. [19]), and already known proteins are found to also localize to mitochondria, in addition to other cellular compartments. Therefore, as of yet unidentified modulators of the fusion machinery with distinct distribution profiles in the nervous system may be involved in the pathogenesis of DOA and CMT2A.

Notably, a new gene cluster, which is termed *Armcx* [20] and is localized on the X chromosome of eutherian mammals, encodes a new family of proteins that regulate mitochondrial dynamics, with some members exclusively

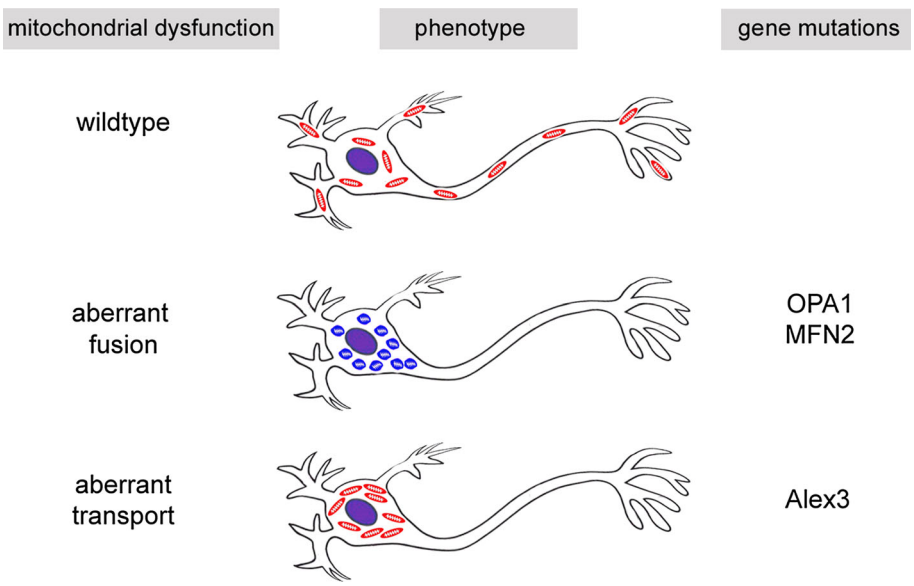

Fig. 1 Schematic representation of mitochondrial dynamics aberrations (in either fusion or transport), leading to degeneration of specific neuronal subpopulations. Mitochondria of normal shape and structure are represented in *red*, while fragmented mitochondria are shown in *blue*. *Note* that fusion and transport defects, resulting from mutations in different genes, both result in accumulation of mitochondria in the perinuclear space and prevent their distribution to neuronal processes (Color figure online)

expressed in the nervous system. Furthermore, one family member, Alex3, influences the dynamics and trafficking of mitochondria in neurons through interaction with the Kinesin/Miro/Trak2 complex, in a Ca^{2+}-dependent manner. Similarly to mutations in OPA1 and MFN2, Alex3 overexpression also alters mitochondrial distribution and morphology, resulting in aggregation of mitochondria at the perinuclear space, and impaired trafficking into processes (Fig. 1), suggesting a functional link between the processes of fusion and trafficking.

The tissue distribution and function of the remaining 5 genes present in this cluster has yet to be investigated, but offers a potentially promising avenue for gaining more insight into the complex regulation of mitochondrial function in neuronal populations. Consistent with the notion that the mitochondrial fusion/fission is coupled with trafficking mechanisms in neurons to ensure proper distribution and function of mitochondria (Fig. 1), recent studies demonstrate a direct functional link between actin-mediated mitochondrial transport and tau toxicity in neurons in vivo [21]. Specifically, tau overexpression, a common model of AD, results in elongated mitochondria in neurons that are unable to be properly transported to processes. Mechanistically, tau overexpression prevents the mitochondrial localization of a key protein driving mitochondrial fission, the dynamin-related GTPase DPR1, by stabilizing actin filaments. Importantly, reversing this mitochondrial defect rescues neurons from tau-induced toxicity in vivo, indicating that aberrant mitochondrial biogenesis may be the underlying cause of neurodegeneration in models of AD, and not a mere consequence of degeneration, which was the prevailing scheme so far. Additional evidence for a causal involvement of mitochondrial biogenesis defects in neurodegeneration stems from the analysis of mouse mutants for the peroxisome proliferator-activated receptor coactivator 1-α (PGC-1α). PGC-1α was shown to be sufficient to instruct mitochondrial biogenesis in different tissues [22, 23], hence it is considered a master regulator of this process. In all tissues investigated, PGC-1α interacts with cell-type specific transcription factors to control the transcription of key targets required for mitochondrial biogenesis.

The first mice with a germ-line deletion of the PGC-1α locus were described in 2004 [24] and were found to display several neurobehavioral defects that are indicative of striatal dysfunction, such as hyperactivity and limb clasping among others. A closer analysis of the striatum, the brain area affected in neurodegenerative diseases such as Huntington's disease with an aberrant movement component, indicated that lack of PGC-1α results in widespread spongiform lesions. Although these lesions represented mainly axonal degenerations, vacuolated neuronal bodies and gliosis were also present. Beyond the striatum, similar but less widespread degenerations were also detected in other brain regions, including in particular superficial cortical layers, the thalamus, the substantia nigra and the hippocampus. More recently, forebrain- and neuron-specific conditional PGC-1α knockout mice were generated [25]. Analysis of these animals also indicated widespread lesions across the forebrain, both confirming the germ-line mutant phenotypes and demonstrating a cell-autonomous requirement of proper mitochondrial biogenesis in neurons. Moreover, defective mitochondrial biogenesis, resulting from lack of PGC-1α functionality has also been causally implicated in the French Canadian variant of Leigh syndrome (FCLS), a disease characterized by severe neurodegeneration. Interestingly, LRP130 (leucine-rich protein 130 kDa), the protein mutated in FCLS, constitutes a necessary component of a PGC-1α-containing complex purified from mammalian cell extracts [26]. Furthermore, functional analyses demonstrated that LRP130 functions in mitochondrial biogenesis by modulating the function of PGC-1α. Specifically, LRP130 modulates PGC-1α action on several mitochondrial subunits encoded within the mitochondrion, but has no involvement in regulating the expression of mitochondrial protein encoded by nuclear genes.

Whether re-activation of the PGC-1α locus, using an inducible in vivo system, is sufficient to restore neuronal integrity in the brain remains to be elucidated. Similarly, it would be interesting to explore whether restoration of functional PGC-1α complexes in the mouse model of FCLS, by forced expression of wild type LRP130, could ameliorate the neuronal phenotypes, in which case, the mitochondrial biogenesis machinery would be a great new target to explore for developing novel therapies for neurodegenerative diseases. In conclusion, while aberrant mitochondria often ensue neuronal deterioration in a wide range of diseases, there is compelling evidence that mitochondrial dysfunction can also actively trigger neuronal degeneration in specific cases, such as the ones indicatively discussed above. The cellular context required for this still remains to be fully elucidated. Identifying new players in the regulation of mitochondrial function and effectively integrating this new information with the known heterogeneity of neurons will be crucial in deciphering the distinct impact of mitochondrial dysfunction in diverse neuronal pools.

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