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Mitochondrial dynamics and inherited peripheral nerve diseases

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ABSTRACT

Peripheral nerves have peculiar energetic requirements because of considerable length of axons and therefore correct mitochondria functioning and distribution along nerves is fundamental. Mitochondrial dynamics refers to the continuous change in size, shape, and position of mitochondria within cells. Abnormalities of mitochondrial dynamics produced by mutations in proteins involved in mitochondrial fusion (mitofusin-2, MFN2), fission (ganglioside-induced differentiation-associated protein-1, GDAP1), and mitochondrial axonal transport usually present with a Charcot–Marie–Tooth disease (CMT) phenotype. *MFN2* mutations cause CMT type 2A by altering mitochondrial fusion and trafficking along the axonal microtubule system. CMT2A is an axonal autosomal dominant CMT type which in most cases is characterized by early onset and rather severe course. *GDAP1* mutations also alter fission, fusion and transport of mitochondria and are associated either with recessive demyelinating (CMT4A) and axonal CMT (AR-CMT2K) and, less commonly, with dominant, milder, axonal CMT (CMT2K). OPA1 (Optic Atrophy-1) is involved in fusion of mitochondrial inner membrane, and its heterozygous mutations lead to early-onset and progressive dominant optic atrophy which may be complicated by other neurological symptoms including peripheral neuropathy. Mutations in several proteins fundamental for the axonal transport or forming the axonal cytoskeleton result in peripheral neuropathy, i.e., CMT, distal hereditary motor neuropathy (dHMN) or hereditary sensory and autonomic neuropathy (HSAN), as well as in hereditary spastic paraplegia. Indeed, mitochondrial transport involves directly or indirectly components of the kinesin superfamily (KIF5A, KIF1A, KIF1B), responsible of anterograde transport, and of the dynein complex and related proteins (DYNC1H1, dynactin, dynamin-2), implicated in retrograde flow. Microtubules, neurofilaments, and chaperones such as heat shock proteins (HSPs) also have a fundamental role in mitochondrial transport and mutations in some of related encoding genes cause peripheral neuropathy (*TUBB3, NEFL, HSPB1, HSPB8, HSPB3, DNAJB2*). In this review, we address the abnormalities in mitochondrial dynamics and their role in determining CMT disease and related neuropathies.

1. Mithocondrial dynamics

Peripheral nerves require efficient energetic metabolism to maintain their complex machinery with anterograde and retrograde transport along axons, which may be as long as one meter, and the high Schwann cell specialisation with many myelin lamellae wrapping axons. Proper mitochondrial functioning is therefore fundamental for axonal and myelin formation and maintenance. Mitochondria are surrounded by an outer and an inner membrane (OM, IM). The IM folds inward to form cristae that provide the necessary increase in surface area for the electron transport chain and energy production.

Mitochondrial dynamics define the continuous process of fusion and fission of these organelles, fundamental to regulate their shape, size and number, as well as the mitochondrial transport along axons, and the interactions with other organelles, such as the endo-

Abbreviations: AD, autosomal dominant; AR, autosomal recessive; CFEOM, congenital fibrosis of extra-ocular muscles; CMAP, compound muscle action potential; CMT, Charcot-Marie-Tooth disease; COX, cytochrome c oxidase; dHMN, distal hereditary motor neuropathy; DI, dominant intermediate; DOA, dominant optic atrophy; GST, glutathione S-transferase; HMSN, hereditary motor and sensory neuropathy; HSAN, hereditary sensory and autonomic neuropathy; HSP, heat shock protein; IM, inner membrane; iPSC, induced pluripotent stem cell; MRI, magnetic resonance imaging; mtDNA, mitochondrial DNA; NCS, nerve conduction studies; NCV, nerve conduction velocities; OM, outer membrane; RI, recessive intermediate; ROS, reactive oxygen species; SAP, sensory action potential; SMALED, spinal muscular atrophy; SPG, spastic paraplegia.

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Nomenclature

Genes/proteins

BICD2	Bicaudal D, Drosophila, homolog of, 2
BSCL2	Berardinelli–Seip congenital lipodystrophy type 2
DCTN1	Dynactin 1
DNAJB2	DNAJ/HSP40 homolog, subfamily B, member 2
DNM2	Dynamin 2
DRP1	Dynamin-related protein 1
DYNC1H1	Dynein cytoplasmic-1, heavy chain-1
FIS1	Mitochondrial fission protein-1
GDAP1	Ganglioside-induced differentiation-associated protein-1
GJB1	Gap junction protein, beta-1
HDAC6	Histone deacetylase 6
HSPB1	Heat-shock 27-kDa protein 1
HSPB3	Heat-shock 27-kDa protein 3
HSPB8	Heat-shock 22-kDa protein 8
KIF1A	Kinesin family member 1A
KIF1B	Kinesin family member 1B
KIF5A	Kinesin family member 5A
MFF	Mitochondrial fission factor
MFN1	Mitofusin-1
MFN2	Mitofusin-2
MPZ	Myelin protein zero
NEFL	Neurofilament protein, light polypeptide
OPA1	Optic atrophy-1
PMP22	Peripheral myelin protein-22
SH3TC2	SH3 domain and tetratricopeptide repeat domain-2
SPTLC1	Serine palmitoyltransferase, long-chain base subunit-1
SPTLC2	Serine palmitoyltransferase, long-chain base subunit-2
TUBB3	Tubulin beta 3

plasmic reticulum (ER) [22,30,52,76,91,104,106,124,128]. Fusion and fission have been studied in yeasts and *Drosophila melanogaster*, with the identification of critical proteins and their mammalian orthologues [31,52]. Mitochondrial fusion is regulated by dynamin-like GTPases located both in the OM, Mitofusin-1 (MFN1) and Mitofusin-2 (MFN2), and in the IM, Optic Atrophy-1 (OPA1) (Fig. 1A) [31,52,91]. MFN1 and MFN2 form homo- and hetero-oligomers in OM of two mitochondria, determining their tethering in the fusion process [51,52]. MFN1 interacts also with OPA1, important for the IM fusion and cristae shaping [51,52]. Mitochondrial fission is regulated by other proteins, including mitochondrial fission factor (MFF) and mitochondrial fission protein 1 (FIS1), acting in the OM as ligands of a cytoplasmic multimeric GTPase, also related to dynamins, named DRP1 (dynamin-related protein-1) in mammals [52]. Ganglioside-induced differentiation-associated protein-1 (GDAP1) is located in the OM and plays a role in mitochondrial fission (Fig. 1B) [52,100,101].

Anterograde and retrograde axonal transport is important for flow of macromolecules and organelles, including mitochondria, which must be properly distributed along the axon, particularly in regions of high energetic demand. In motor and sensory neurons of the peripheral nervous system, mitochondria are particularly concentrated in defined regions: the initial segment of the axon stemming from the perikaryon, in correspondence of nodes of Ranvier, at distal sites close to the neuromuscular junctions (motor neurons) or to the sensory end terminals (sensory neurons), and at site of lesion such as demyelination areas [12].

Dynein and dynactin are engaged in the axonal retrograde transport, whereas kinesins are fundamental for the anterograde transport (Fig. 2) [30,76,91,124,128]. Proteins of the cytoskeleton (microtubules and neurofilaments) and proteins involved in the transport of vesicles and membranes (such as dynamin-2) also contribute to intracellular trafficking and are important for mitochondrial transport. Heat-shock 27-kd protein-1 (HSPB1) and 22-kd protein-8 (HSPB8) are chaperones with several possible tasks. Their dysfunction causes protein misfolding and neurofilament network disruption, thus deranging axonal transport [17,74,120].

Mutations in genes encoding proteins involved in mitochondrial dynamics are associated with hereditary peripheral neuropathies: mutations affecting *MFN2* and *GDAP1* cause different types of Charcot–Marie–Tooth disease (CMT) [15,30,45,104–107,122,159], patients carrying *OPA1* mutations may have peripheral neuropathy [9,78,91,152], and abnormalities of proteins involved in axonal transport are also associated with CMT and related neuropathies [30,124,128] (Tables 1–3).

All these neuropathies are characterized by a primary axonopathy. Notably, there is no known abnormality of mitochondrial dynamics leading to demyelinating types of CMT, although other alterations of mitochondrial functioning may affect Schwann cells and result in demyelinating CMT [106], suggesting that different pathways are involved in such mitochondrial neuropathies.

2. Mitochondrial fusion and fission

2.1. MFN2 *(mitofusin-2)*

MFN2 contains a GTPase domain, two transmembrane domains, and two coil-coiled regions (HR1, HR2). HR2 domains on opposing mitochondria form an antiparallel coiled-coil bond tethering mitochondria. OM fuses by homo- and hetero-dimerization of MFN2 and MFN1 (Fig. 1) [25]. Smaller MFN2 amounts are found in the ER membrane and bind to mitochondrial MFN1 and MFN2, playing a role in Ca^{++} release from ER and its influx into mitochondria [47,90]. MFN2 is also involved, possibly through its action on Ca^{++} influx, in increasing outer membrane permeability, a step of cell apoptosis [139], and mitochondrial dynamics are engaged in the apoptotic process which includes mitochondrial fragmentation. Furthermore, MFN2 is thought to play a role in oxidative phosphorylation and gradient coupling [112]. Importantly, MFN2 anchors mitochondria to kinesin-1 through the adaptor Miro1/Milton complex (Fig. 2). Kinesin-1 binds to microtubules, and through its ATPase activity transfers mitochondria along axons toward the terminal end [12,13,76,92,93].

MFN2 is ubiquitously expressed, but *MFN2* mutations have been associated only to neurological dysfunction, and particularly to peripheral neuropathy. MFN1 might be sufficient to compensate for the MFN2 defect in most tissue, but not in peripheral nerves, where MFN1 expression is particularly low [51,52].

MFN2 is one of the many genes associated with CMT, a highly heterogeneous group of hereditary disorders sharing a core phenotype characterized by distal muscle wasting and weakness, frequent distal limb sensory loss, reduced-to-absent deep tendon reflexes, and skeletal deformities. CMT classification is based on inheritance pattern, nerve conduction studies (NCS), presence of predominant myelin or axonal abnormalities, and mutated genes, and is summarized in Table 1.

MFN2 mutations are usually associated with autosomal dominant (AD) axonal CMT2 (CMT2A) and *MFN2* is the most important axonal CMT gene, accounting for up to 20% of all CMT2 [20,23,37,38,62,89,95,125,145,158,159]. Most *MFN2*-related CMT cases show a severe phenotype, with early onset and disabling progressive course, whilst other patients have less severe disability and later onset [37,38,62,145,158,159]. About 100 sequence