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Review

Mitochondrial dynamics and disease, OPA1

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Abstract

The mitochondria are dynamic organelles that constantly fuse and divide. An equilibrium between fusion and fission controls the morphology of the mitochondria, which appear as dots or elongated tubules depending the prevailing force. Characterization of the components of the fission and fusion machineries has progressed considerably, and the emerging question now is what role mitochondrial dynamics play in mitochondrial and cellular functions. Its importance has been highlighted by the discovery that two human diseases are caused by mutations in the two mitochondrial pro-fusion genes, *MFN2* and *OPA1*. This review will focus on data concerning the function of OPA1, mutations in which cause optic atrophy, with respect to the underlying pathophysiological processes.

Keywords: Mitochondria; Optic atrophy; Dynamin; Apoptosis; OPA1

1. Introduction

Cellular proliferation requires the biogenesis and transmission of the intracellular organelles. Biogenesis of the mitochondria, the major and essential role of which is to provide cellular energy by oxidative phosphorylation, results from the growth and division of pre-existing organelles [1]. Since the mitochondrial DNA (mtDNA) specifies only the mitochondrial translation machinery, and a limited number of proteins implicated in the respiratory chain, the nuclear genome makes an essential contribution to the biogenesis, transmission and function of the mitochondria.

The metabolic functions of the mitochondria have been studied for many years, but it is only recently that the morphology of the mitochondrial network, in relation with the functioning and transmission of this organelle, has been started to be reconsidered. Major advances in this domain have been made possible by the isolation of yeast mutant strains deficient for the transmission, maintenance and organization of the mitochondria. Their characterization has led to the proposal that the morphology of the mitochondrial network depends on the equilibrium between two antagonistic forces acting on the

Abbreviations: mtDNA, mitochondrial DNA; GED, GTPase effector domain; MIS, mitochondrial import sequence; HS, hydrophobic segment; MPP, Mitochondrial processing peptidase; IMS, inter membrane space; IM, inner membrane; OM, outer membrane; PEG, polyethylene glycol; mito-PAGF, mitochondrial matrix targeted photoactivable Green Fluorescent Protein; ADOA, autosomal dominant optic atrophy; LHON, Leber hereditary optic neuropathy; ORF, open reading frame; RGC, retinal ganglion cells; MELAS, mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes; LS, Leigh syndrome; KSS, Kearns–Sayre syndrome; NARP, neuropathy, ataxia, and retinitis pigmentosa; MERRF, myoclonic epilepsy associated with ragged-red fibers

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Table 1
Mitochondrial shaping proteins in mammals and yeast

Human proteins	*S. cerevisiae* homologs	Location	Function
OPA1	Mgm1	IMS, IM/OM, peripheral/integrated	Fusion
Mfn1/2	Fzo1	OM integrated	Fusion
	Ugo1	OM integrated	Fusion
DRP1/DLP1	Dnm1	Cytosol, OM peripheral	Fission
hFis	Fis	OM integrated	Fission
	Mdv1	Cytosol, OM peripheral	Fission
	Caf4	Cytosol, OM peripheral	Fission
MTP18		IMS, mitochondrial membranes integrated	Fission
	Mdm33	IM integrated	IM fission ?
	Mdm10	OM integrated	Tubulation
	Mdm12	OM integrated	Tubulation
	Mdm31	IM integrated	Tubulation
	Mdm32	IM integrated	Tubulation
	Mmm1	OM/IM-spanning	Tubulation
	Mmm2	OM integrated	Tubulation
Endophilin B1		Cytosol, dynamic association with mitochondria	OM remodeling
Mitofilin	YKR016W	IMS	Cristae remodeling
ATP synthase	ATP synthase	IM, F0-integrated/ F1-peripheral	Cristae remodeling

fission and the fusion of mitochondrial membranes (Table 1). For example, the state of the mitochondrial outer membrane is determined by both fission, driven by the dynamin Dnm1p, and fusion, controlled by the GTPase Fzo1p. The description of other elements of the outer membrane involved in the control of mitochondrial dynamics has recently been refined by the identification of genetic and biochemical partners of Dnm1p and Fzo1p. Most of these proteins are conserved in higher eukaryotes where they fulfill similar functions (Table 1). The dynamics of the inner membrane, and the mechanisms involved in the modeling of the cristae, which are now considered to be dynamic tubular projections of the inner membrane [2], are not well characterized. OPA1, and its yeast counterparts, Mgm1p and Msp1p, are believed to control these processes. Furthermore, recent studies have implicated Mitofilin [3] and ATP synthase [4] as critical organizers of the cristae morphology (Table 1).

Numerous reviews addressing the critical role of mitochondrial dynamics in determining mitochondrial morphology are available (see the reviews listed in [5] and the related issues in this volume), while its requirement in the function of the mitochondria and at the cellular level is considerably less well characterized [6]. However, the importance of mitochondrial dynamics has been highlighted recently by the discovery that two inherited human diseases are caused by mutations in two mitochondrial fusion genes [7–9]. This review will focus on data concerning the function of one of these genes, *OPA1*.

2. From yeast to ADOA

2.1. Mgm1p/Msp1p/OPA1, a conserved mitochondrial dynamin

Mgm1$^+$ was first identified in a genetic screen for nuclear genes required for the maintenance of mtDNA in the budding yeast *S. cerevisiae* [10]. We then isolated its orthologues, *Msp1*$^+$ in the fission yeast *S. pombe* [11] and *OPA1* in humans [7], and showed that the function of this gene has been conserved during evolution since expression of OPA1 can complement the loss of *msp1*$^+$ in *S. pombe* [12].

Mgm1p, Msp1p and OPA1 are members of the dynamin family [7,10,11,13–16]. They consist of an N-terminal mitochondrial import sequence (MIS), followed by short hydrophobic stretches, a coiled-coiled domain, a GTPase domain, a middle domain, and a C-terminal coiled-coil domain known as the GTPase Effector Domain (GED) (Fig. 1). The MIS targets the protein to the mitochondria and is cleaved by the mitochondrial processing peptidase (MPP) upon import [17–21]. While the sub-mitochondrial localization of this dynamin has long been the subject of controversy, it is now accepted that all three homologues are localized to the inter-membrane space (IMS) [17,19,22–26]. Nevertheless, some discrepancies still persist concerning the relationship of these dynamins with the mitochondrial membranes. Mgm1p has been shown to be either peripherally associated with, or integrated into, the inner or outer membranes (IM or OM respectively) [17,22,24,27], while Msp1p is anchored in the IM [18]. OPA1 has been shown to co-sediment with both mitochondrial membranes and to interact more or less tightly with the IM [19,21,26]. Further studies are needed to clarify this point, keeping in mind that the existence of several forms of these dynamins could explain these controversial findings [19,21,22,27,28]. In particular, a short form of Mgm1p, carrying a deletion in the N-terminal region, is generated by the action of the mitochondrial rhomboid-type protease Pcp1p [17,29,30]. While generation of the long MMP-matured and the short rhomboid-matured forms of this dynamin seems to be a feature that is conserved in both budding and fission yeasts (our unpublished data), and although the mammalian PARL can replace its yeast Pcp1p counterpart [29], it is not clear if OPA1 is similarly processed by a rhomboid

Fig. 1. Schematic representation of the domain structure of OPA1. OPA1 shares a number of structural features with proteins of the dynamin family. These include a GTPase domain containing the three consensus GTP binding sequences (red bars) and the dynamin signature (red hatched bar), a middle domain and a C-terminal coiled-coil region which may correspond to a GTPase effector domain (GED). Only dynamin itself contains a pleckstrin homology domain (PH) that binds lipids, while the association of OPA1 with mitochondrial membranes could be related to the presence of two hydrophobic segments (HS) located immediately after the N-terminal mitochondrial import sequence (MIS). The C-terminal regulator prolin rich domain (PRD) is also found only in the conventional dynamins. In OPA1, a N-terminal coiled-coil region (CC) is located immediately before the GTPase domain. Yeast orthologues of OPA1, Mgm1p and Msp1p, display the same structural organization.

protease. Nevertheless, human OPA1 has 5 isoforms [19] that may originate from the 8 alternatively spliced mRNA variants [28] and/or proteolytic or yet unknown post-translational modifications.

Loss of Mgm1p, Msp1p or OPA1 by either gene deletion or RNAi experiments in yeast and mammalian cells respectively leads to fragmentation of the mitochondrial tubules [22,25,26,31]. This could be due to an increased rate of mitochondrial division or a decrease in the capacity of the mitochondria to fuse. The later hypothesis was indeed first evidenced in *S. cerevisiae* zygotes formed by mating *MGM1* null mutants which are unable to mix their mitochondrial contents [23,24], and then in OPA1-depleted mammalian cells by PEG [32] or mito-PAGF [33] fusion assays [34,35]. Accordingly, while abolishing the function of the dynamin Dnm1p, the major actor of mitochondrial fission in *S. cerevisiae*, blocks mitochondrial fragmentation resulting from the loss of Mgm1p it does not restore the fusion-induced defect [23,24]. OPA1 may work together with the mitofusins (Mfn), large GTPases involved in OM fusion [36–39], to promote mitochondrial fusion. Consistent with this idea, OPA1 was shown to require Mfn1 (and not Mfn2) to induce mitochondrial tubulation [34]. Furthermore, biochemical interactions involving the pro-fusion Ugo1p were reported to occur between Mgm1p and Fzo1p (the Mfn orthologue) [23,30,40] in *S. cerevisiae*. However, this has yet to be demonstrated in mammalian cells that presumably lack an *UGO1* homologue. This interaction may serve to physically coordinate the dynamics of IM and OM.

Surprisingly, while OPA1 and its yeast counterparts are believed to promote fusion of mitochondrial membranes, over-expression of the dynamin in HeLa and Cos-7 cells causes mitochondrial fragmentation [20,26] (our unpublished data). This paradox may be explained by a non-specific effect due to over-expression of a membrane protein in the tubular mitochondrial network. However, recent data showing that MEFs overexpressing OPA1 fused their mitochondria as efficiently as untransfected cells indicates that the mitochondrial fragmentation seen in these cells is not due to lack of fusion [41]. Furthermore, over-expression of OPA1 promoted mitochondrial elongation in cells in which the mitochondria are naturally fragmented [19, 34]. Taken together, these observations may point to the existence of surveillance mechanisms which, while allowing local membrane dynamics, maintain the mitochondrial network within a morphological state compatible with its function in a given cell type. Thus in HeLa and Cos7 cells, constitutive over-expression of functional OPA1 could trigger an overwhelming fission response by increasing mitochondrial fusion.

Electron microscopic analysis showed that the fragmented mitochondria from Mgm1p- or OPA1-depleted cells have an altered internal structure [24,26,31]. Disorganized cristae with irregular shapes and volumes, some of which showed enlarged mitochondrial junctions, were often observed, together with reticular elongated cristae running parallel to the longitudinal axis of the mitochondria and occasionally forming stacks. Such alterations provide evidence that dynamin, the great part of which is located inside and not at the rims of the mitochondria [18,22,26,31], has a major function in structuring the membranes of the cristae. However, *dnm1* inactivation reverses the changes seen in the organization of the cristae in *mgm1*-deleted yeast, indicating that the role of Mgm1p in the structural organization of the cristae may be an indirect effect of its function in mitochondrial fusion [24].

Interestingly, some of the defects induced in the cristae by loss of OPA1 are reminiscent of those occurring in the mitochondria of apoptotic cells. Loss of the conserved mitochondrial dynamin leads to cell death both in yeast and in mammalian cells [11,25,31]. This cell death has been attributed to the loss of mtDNA in the petite negative *msp1*$^{+}$-deleted fission yeast [25], while an *mgm1* null mutant that lacks respiratory function can still grow by fermentation on glucose medium [10]. In mammalian cells, downregulation of OPA1 gives rise to an extreme sensitivity to exogenous proapoptotic stimuli and an increase in the rate of spontaneous apoptosis, and facilitates the release of cytochrome c from the mitochondria both in vivo and in vitro [31,35,42].

Much data have now been accumulated with regard to OPA1 and its yeast counterparts, but the function of this protein remains unclear (Fig. 2). Is OPA1 a global regulator of mitochondrial dynamics or does it function primarily at the level of the IM and/or the cristae? Is OPA1 strictly involved in fusion and can the suggested effects on mitochondrial fragmentation [26] of this member of a pro-fission protein family be definitively ruled out? Does OPA1 have a direct role in apoptosis and what are the underlying molecular mechanisms? Answering these questions will be complicated since these processes are very intricate, and since numerous forms of this dynamin, each of which may have specific localizations and functions, are present in the cell. This later point is well exemplified in yeast, where both the long form of Mgm1p,

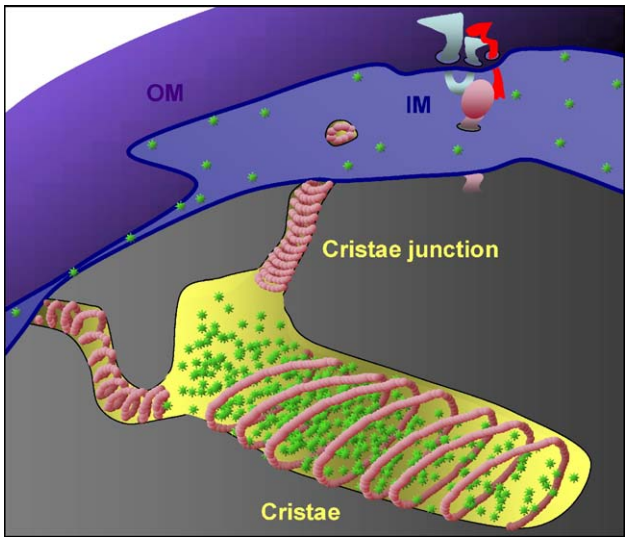

Fig. 2. Possible roles for OPA1. OPA1 (in pink) anchored to the inner membrane (IM) could controls its dynamic in coordination with the dynamic outer membrane (OM) by interacting either directly or indirectly with Mfn2 (in grey). Oligomerized OPA1 could structure the cristae or could control the cristae junction opening, sequestering cytochrome *c* (in green) in intra-cristae compartment.

proposed to be involved in fusion, and the short form, presumably involved in mtDNA maintenance, are essential [17,30]. Furthermore, we have recently shown that differently spliced OPA1 variants have distinct roles in mitochondrial dynamics and apoptosis (unpublished data). Since mutations in OPA1 are associated with autosomal dominant optic atrophy (ADOA) [7,8], a cause of inherited blindness, a better understanding of the functions of this dynamin is crucial to gain further insight into the pathological processes associated with this disease.

2.2. ADOA

Autosomal dominant optic atrophy (MIM #165500) is the most common form of inherited optic neuropathy, with a frequency of 1:12 000 to 1:50 000 [43,44]. This disease is characterized by an insidious onset of visual impairment in early childhood with moderate to severe loss of visual acuity, temporal optic disc pallor, abnormalities of color vision and caecocentral visual field scotoma [45–47] (Fig. 3). ADOA shows variable expression, both between and within families, ranging from an asymptomatic state to a legal blindness [47]. Electrophysiological and histopathological studies have suggested that the underlying defect is retinal ganglion cell (RGC) degeneration leading to atrophy of the optic nerve [45,48], as observed in Leber's hereditary optic neuropathy (LHON), a maternally transmitted disease caused by mitochondrial DNA mutations [49].

Until now four gene loci have been designated for ADOA, namely OPA1 (3q28–29), OPA3 (19q13.2–13.3), OPA4 (18q12.2–12.3) and OPA5 (22q12.1–q13) [50–53]. Among these, the most common is OPA1, which was found by us and others to be attributable to mutations in the *OPA1* gene [7,8]. Ninety-six OPA1 gene mutations, mainly family-specific, have been described so far [54]. The OPA1 mutations, of which 66, 29 and 5% are substitutions, deletions and insertions respectively, are spread throughout the coding sequence of the gene, but most are localized in the GTPase domain and in the 3′ end of the coding region, whereas the 5′ region is little affected (Fig. 4). No obvious correlation between genotype and phenotype could be detected [55–57], suggesting a role for other genetic or environmental modifying factors. One deletion of the entire *OPA1* gene has been identified, strongly suggesting that the mechanism underlying type 1-ADOA is haploinsufficiency [58]. However, evaluation of the mutation spectrum suggests more than one pathogenetic mechanism for the disease. Some mutations may be semi-dominant, because one compound heterozygote patient has been reported to have more severe symptoms than his simple-heterozygote parents [57].

3. Can studies of Mgm1p/Msp1p/OPA1 help us to understand type 1-ADOA?

3.1. Is haploinsufficiency the only cause of type 1-ADOA?

Two of the numerous different *OPA1* mutations, one corresponding to a deletion of the entire gene and the other virtually the entire ORF (Trp2Stop), provide evidence that haploinsufficiency is the cause of the disease [57,58]. Accordingly, almost 50% of the OPA1 mutations cause premature truncations of OPA1 and nearly 40% are located within the GTPase domain, possibly leading to the loss of function of this dynamin. Nevertheless, we and others have demonstrated that expression of GTPase mutants of Mgm1p and Msp1p in yeasts (and OPA1 in MEFs) containing a wild type allele of the appropriate dynamin induces mitochondrial fragmentation [23,25,27,34] by a dominant negative effect. A dominant negative mechanism is well documented for dynamins with deficient GTPase activity [59,60]. This is related to the ability of the mutated dynamin to form oligomers with the wild type protein and thus to interfere with its GTPase activity. Our preliminary results from an examination of the mitochondrial morphology in primary skin fibroblasts from patients bearing a missense substitution in the GTPase domain of OPA1 indicate that a dominant negative effect may be involved in the pathogenesis of type 1-ADOA. In cells from this patient, the mitochondria appeared to be considerably more fragmented than in fibroblasts from control individuals (our unpublished data). Thus, the integration of GTPase mutated OPA1 into oligomers with wild type OPA1 may decrease the GTPase activity of the dynamin and thus the fusion competency of the mitochondria. GTPase activity has indeed been shown to be necessary for the function of Mgm1p/OPA1 in mitochondrial fusion [23,24,26,34]. However, while oligomerization of Mgm1p has been deduced using a genetic approach [23], no data concerning the ability of OPA1 to oligomerize, and the effect of oligomerization on its GTPase activity are available. However, when taken together, the available results fit with both the hypotheses that have been proposed as the pathophysiological processes underlying dominantly inherited diseases. Among the 96 OPA1 mutations identified, those occurring in the GTPase domain would exert a dominant negative effect, while the C-terminal truncations, by removing the potential GED domain and thus abolishing the oligomerization-stimulated activity of the dynamin, would cause haploinsufficiency. It is of importance to clarify this point for future therapeutic implications. Further investigations of the effects of OPA1 mutations on cells from type 1-ADOA patients, as well as a biochemical characterization of wild type and pathogenic alleles of OPA1 will be highly informative.

3.2. Is type 1-ADOA really tissue specific?

Even though it is not the only reported case, the tissue specificity of type 1-ADOA is surprising for a disease for which the genetic origin is a nuclear gene encoding a ubiquitously expressed mitochondrial protein. While most abundant in the retina, the OPA1 mRNA is widely distributed in mammalian tissues [7,8,57]. OPA1 protein is also present in several tissues [19,61], and it is not exclusively localized to the RGC since OPA1 immuno-labelling was detected in the ganglion cell layer as well as in the outer and inner plexiform layers and in the inner nuclear layer in adult retinal tissues from mammals [61–64], although discrepancies still persist on the cell types involved.

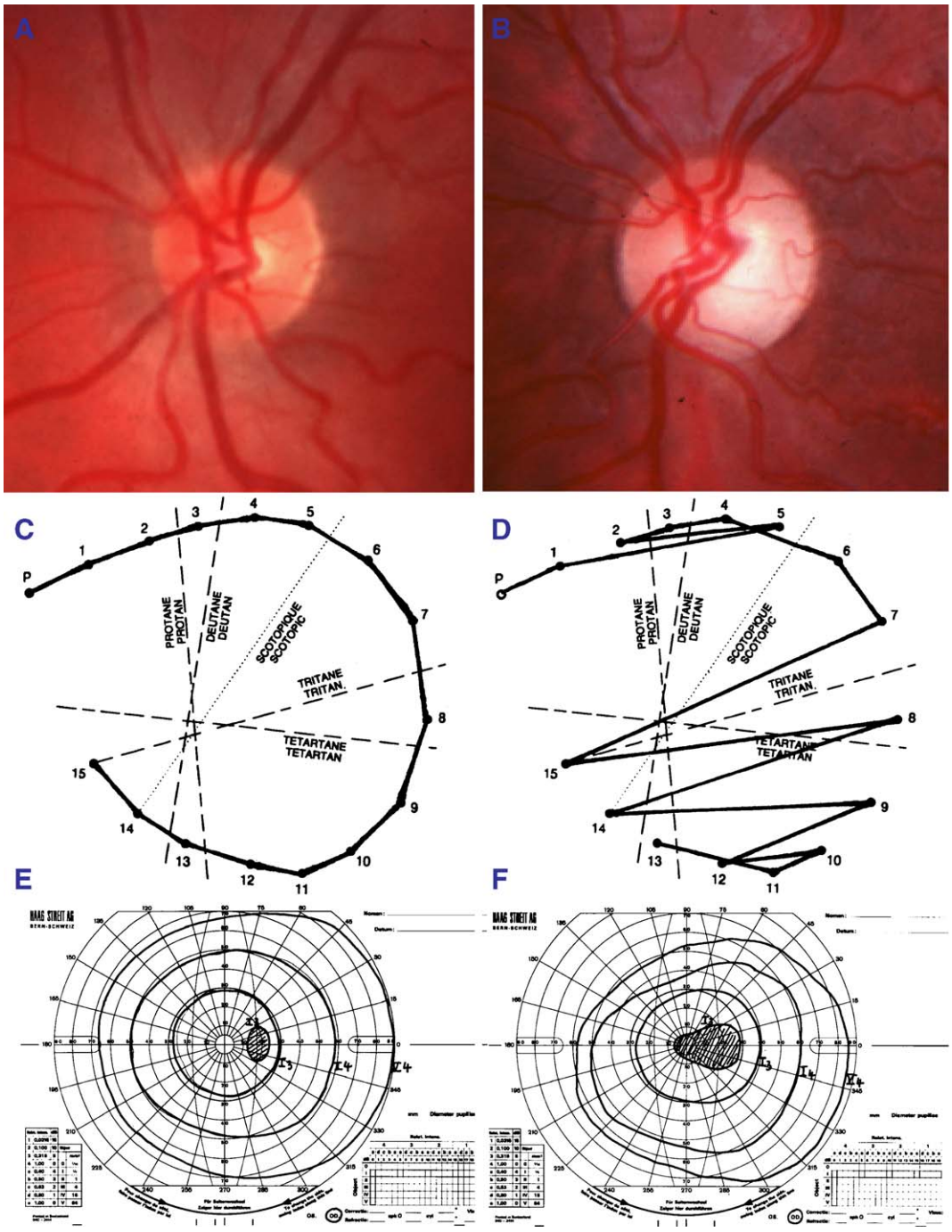

Fig. 3. Ophthalmologic diagnosis of ADOA. Results of an ADOA patient bearing an OPA1 mutation (B, D, F) are compared with those of a normal individual (A, C, E). (A–B) Eye fundus photographs showing that the patient's optic nerve disc is pale and that pallor predominates in the temporal side. (C–D) Color vision was tested using the 15-hue Farnsworth's panel. The circling line indicates that the normal individual was able to harmoniously classify the 15 hues while the patient made a disorganized classification with a confusion in the blue-yellow axis (tritanopia). (E–F) Dynamic perimetry using a Goldman apparatus to test the visual field. In the normal individual, the blind spot is present as a small hatched area while in the patient it extends to the central visual field to form a centrocaecal scotoma (hatched area). Three lines of equal retinal sensitivity (isotopers) are represented.

The presence and subcellular distribution of OPA1 in the optic nerve is somewhat controversial, since OPA1 was not detected in the rat optic nerve [62], though it is highly expressed in the mouse optic nerve axons [63]. Surprisingly, OPA1 is expressed in the myelinated regions of the human optic nerve, which show a decreased number of mitochondria as compared to the somata of the RGC, where biogenesis of mitochondria occurs, and to the fiber layer containing unmyelinated axons before the lamina cribosa [61].

Since OPA1 is widely expressed in many tissues the reason that RGC are primarily affected by OPA1 mutations remains unknown. Nevertheless, the somewhat specific distribution of the mRNA and protein variants of OPA1 [19,28] may suggest the involvement of a specific form of this dynamin in the

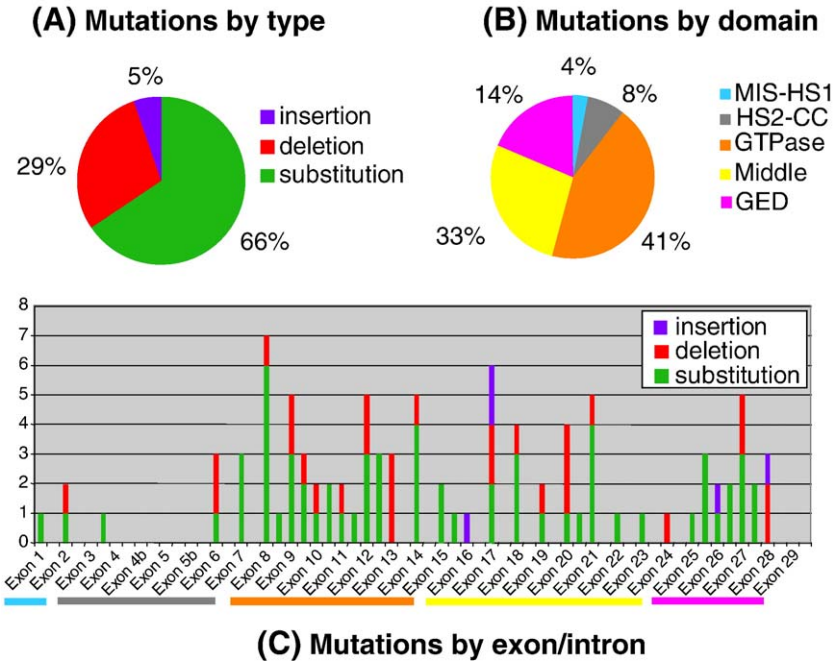

Fig. 4. Mutation spectrum of OPA1. Distribution of the 96 mutations of OPA1 according to their type (A), domain (B) and location (C). In B, only mutations affecting exons are considered and domains correspond to those described in Fig. 1. In C, spaces between two consecutive exons correspond to introns and colored bars under exons indicate their belonging to OPA1 domains.

pathogenesis of type 1-ADOA. On the other hand, recent reports of sensorineural hearing loss associated with dominant optic atrophy caused by the R445H mutation in OPA1 in several unrelated families [65–68] indicate that the RGC are not the only cell types affected in type 1-ADOA. The widespread distribution of OPA1 in the sensory and neural cochlear cells of the guinea pig supports the hypothesis of the involvement of the auditory nerve in OPA1 dysfunction. Fibroblasts from patients bearing the R445H allele were shown to contain highly fragmented mitochondria [68]. It is not clear why the R445H mutation, located within the GTPase domain, cause a broader spectrum of disease whereas other mutations identified to date are associated with optic atrophy alone. Comparative biochemical and biological characterizations of this particular allele should help us to understand the molecular basis of this ADOA "plus" syndrome, as will careful examination of auditory performance in type 1-ADOA patients and screening for *OPA1* mutations in patients suffering sensorineural hearing loss. Furthermore, clinical studies are currently being undertaken to determine if type 1-ADOA patients show muscular, cardiac and neuronal extra-ocular deficits that could signal a more generalized mitochondrial dysfunction (C. Hamel and G. Lenaers, personal communication).

3.3. Does RGC degeneration occur via an apoptotic process?

There are multiple parallels that link the two major neurodegenerative disorders of the RGC, type 1-ADOA and LHON. A set of elegant experiments investigating LHON cybrid death pathways in glucose free/galactose medium (which reduces the rate of glycolytic flux, thereby forcing cells to utilize oxidative metabolism) has shown that the three common LHON mutations which affect complex I (the ND1, ND4, and ND6 subunits) cause an increased sensitivity to caspase-independent apoptotic cell death [69–71]. Considering that we and others have demonstrated that downregulation of OPA1 induces spontaneous apoptotic cell death and sensitizes cells to exogenous apoptotic stimuli [31,35], it is tempting to propose that apoptosis may represent the pathophysiological process leading to the degeneration of the RGC in type 1-ADOA. Preliminary results that we have obtained using skin fibroblasts from patients bearing pathogenic GTPase and GED OPA1 mutations support this hypothesis. These cells show an increased sensitivity to staurosporine-induced cell death when compared to fibroblasts from controls individuals (our unpublished data).

Thus, the mitochondrial dysfunction common to both LHON and type 1-ADOA seems to be a predisposition of the neuronal cells to apoptotic death. In LHON this feature has been proposed to be mediated by a deficient complex I, which impairs the efficiency of the respiratory chain, thereby lowering ATP synthesis and increasing ROS production [49]. A similar mechanism could occur in type 1-ADOA, since drops in the mitochondrial membrane potential and cellular respiration occur in cells where OPA1 expression has been downregulated [31,41]. Interestingly, recent results obtained from primary cultures from type 1-ADOA patients [68] fit with the in vivo data obtained using ^{31}P magnetic resonance spectroscopy that demonstrate defective ATP synthesis in skeletal muscle from these patients [72]. Nevertheless, in type 1-ADOA the primary defect would be attributed to the role of OPA1 in mitochondrial dynamics and/or the structural organization of the cristae.

Several studies have indicated that mitochondrial morphology changes during apoptosis induced by different agents such

as staurosporine, cisplatin, and etoposide, resulting in small round organelles [73,74]. Furthermore, inhibition of the mitochondrial fission machinery and upregulation of mitochondrial fusion reduce cell death, suggesting a role for mitochondrial fragmentation in apoptosis [31,35,74–76]. The underlying effect of OPA1 on apoptosis could thus be its pro-fusion activity. RNAi experiments have shown that loss of OPA1 induces spontaneous apoptotic death or an increase in sensitivity to exogenous pro-apoptotic stimuli, together with fragmentation of the mitochondrial network [31,34,35,42]. Taken together these results suggest that loss of fusion activity leaves the fission forces unopposed resulting in excessive mitochondrial fission and cell death. On the other hand, we and others have shown that loss of OPA1 induces a drastic change in the structure of the cristae [26,31,42]. It has been proposed that only 15% of the total cytochrome *c* is available in the intermembrane space, with the remainder being sequestered in the narrow junctions within the cristae [77]. Downregulation of OPA1 has been shown to induce spontaneous cytochrome *c* release, and to accelerate the release of cytochrome *c* induced by apoptotic stimuli [31,42]. Hence, downregulation of OPA1 has been proposed to account for the rapid and complete cytochrome *c* release observed during apoptosis. Thus, the reorganization of the cristae mediated by the loss of OPA1 could represent the mechanism underlying the effect of this dynamin on apoptosis. Recent experiments showing that OPA1 is co-released with cytochrome *c* from the mitochondria before their fragmentation support this hypothesis [42]. On the contrary, the finding that the morphology of the cristae is restored to normal upon *dnm1* inactivation in *mgm1*-deleted yeast contradict this hypothesis [24]. The recent discovery that OPA1 needs Mfn1 to control mitochondrial dynamics [34] may help us to discriminate between these two models. Nevertheless, interesting data could reconcile both hypotheses since they lead to the proposition that, through DRP1 (the dnm1 orthologue)-mediated signaling, fission is coupled to the remodeling of the cristae [78]. Further analyses are required to support these different hypotheses, and promise exciting breakthroughs in the near future both with regard to the pathogenesis of type 1-ADOA, and with regard to mitochondrial dynamics and their relationship to apoptosis.

4. Discussion

In 1988 Wallace identified the first substitution in the mtDNA causing a genetic disorder which was originally described by Leber in 1871, thereby beginning the list of optic neuropathies linked to mitochondrial dysfunctions [79–81]. The discovery, in the year 2000, that the genetic cause of the most common group of ADOA is *OPA1*, a nuclear gene encoding a mitochondrial dynamin [7,8], together with the finding that *OPA3*, the third gene identified as involved in primary optic atrophies, encodes an IM protein [52,82], definitively demonstrates that the optic nerve is highly dependent on mitochondrial functions. This raises the interesting possibility that the yet unidentified causative genes for ADOA (OPA4, MIM605293 and OPA5, [53]), as well as for the rare isolated autosomal recessive optic atrophies (ROA, MIM258500), encode mitochondrial proteins. Mitochondrial dysfunctions may be suspected not only in the primary optic atrophies, in which degeneration of the optic nerve is the main and often the only clinical feature of the disease, but also in primary optic atrophies accompanied by secondary defects, often neurological. This is well exemplified in the Costeff syndrome (MIM258501), a neuro-opthalmologic disease caused by recessive mutations in *OPA3* [83]. Furthermore, secondary optic atrophy is also frequently reported as one of the clinical features of multisystem disorders associated with mtDNA mutations including MELAS (MIM5400000), LS (MIM256000), KSS (MIM 530000), NARP (MIM 551500), MERRF (MIM545000). In addition, certain acquired dietary (vitamin B12 or folic acid deficiencies) or toxic (ethambutol, chloramphenicol uses) optic neuropathies have also been reported to be associated with mitochondrial dysfunctions.

What makes the optic nerve so vulnerable to mitochondrial dysfunction? One common hypothesis for why neurons are so sensitive to mitochondrial dysfunction is that they have a high demand for energy in regions that may be at a considerable distance from the cell body, where the biogenesis of the mitochondria occurs. Bioenergetic defects may be deleterious for the conduction of action potentials, as well as for mitochondrial transport, and may thus result in nonfunctional synapses, axonal degeneration and ultimately cell death. Due to the high energy demand required for the conduction of electrical impulses through the anterior unmyelinated portion of the axons, and the long course of the axons, the RGC may be a bioenergetically weak element of the central nervous system. Since OPA1 expression is ubiquitous, and since it was recently proposed that neither the pattern nor the abundance of OPA1 mRNA and protein variants are specific to RGC [64], a plausible hypothesis as to why these neurons may be more vulnerable to OPA1 inactivation could be a particular susceptibility to mitochondrial membrane disorders inducing mitochondrial dysfunction or mislocalization. While the former point is in agreement with reports that describe altered mitochondrial ATP synthesis and respiration in OPA1-inactivated cells [41,68,72], the latter may relate to the particular distribution of the mitochondria in RGC. These show an accumulation of mitochondria in the cell bodies and in the intraretinal unmyelinated axons, where they accumulate in the varicosities, and a relative paucity of mitochondria in the myelinated parts of axons [84–86]. Furthermore, the effect of mitochondrial dynamics on the correct intracellular distribution of the mitochondria and its influence on neuronal plasticity and function was recently highlighted by inactivation of *DRP1* in live hippocampal neurons [67]. Link between axonal transport of mitochondria [87] and mitochondrial dynamics was also enlighted by a recent study showing that Drosophila mutants lacking DRP1 failed to populate the distal axon with mitochondria, affecting the mobilization of the synaptic vesicle reserve pool [88,89]. Considering the sum of these data, it is not surprising that mutations in the pro-fusion protein Mfn2 cause a peripheral neuropathy [9].

A better understanding of the role of mitochondrial dynamics in mitochondrial and cellular function is essential to evaluate the physiological and physiopathological impact of these processes. Finally, it can be predicted that identification of other molecular constituents of the fission and fusion machineries would be helpful in identification of genes responsible for optic atrophy and more generally for neurodegenerative disorders.

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