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Minireview

Mouse models of dominant optic atrophy: What do they tell us about the pathophysiology of visual loss?

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ABSTRACT

Dominant optic atrophy (DOA) is the most common inherited optic neuropathy affecting one in every 12,000 people. It presents with bilateral visual loss, central visual fields defects, colour vision disturbance and optic disc pallor. *OPA1* has been identified as the responsible gene and its locus mapped to chromosome 3q28-q29. Mutations in this gene are responsible for the clinical phenotype in over 70% of patients with DOA. Histopathological studies in tissues from patients reveal loss of retinal ganglion cells but the paucity of viable human tissue has raised the importance of an animal model to study the pathophysiology of the disease. In the last decade considerable work has gone into the generation of animal, most notably mouse, models of Opa1 DOA. Two murine models of DOA have been published, designated B6;C3-*Opa1*^{Q285STOP} and B6;C3-*Opa1*$^{329\text{-}355del}$ and they provide valuable insights with respect to neurological and visual phenotyping, mitochondrial dysfunction, optic nerve and axonal changes, retinal ganglion cell depletion and dendritic atrophy. Here we summarise the current state of knowledge of the mechanisms of disease based on data from these models of Opa1 DOA.

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1. Introduction

Mitochondria are dynamic organelles with an essential bioenergetic function. They continually undergo fusion and fission, in a process that is held in equilibrium by various mitochondrial shaping proteins, for fission; Drp1 and Fis1 (Frank et al., 2001; Lackner & Nunnari, 2009; Liesa, Palacin, & Zorzano, 2009; Yu, Fox, Burwell, & Yoon, 2005) and for fusion; the mitofusins (Mfn1 and Mfn2) and Opa1 (Chen & Chan, 2006; Chen et al., 2003; de Brito & Scorrano, 2009; Song, Ghochani, McCaffery, Frey, & Chan, 2009). Mutations in *OPA1* result in the disease dominant optic atrophy (DOA), which is characterised by a mild to moderate progressive loss of visual acuity, central visual field defects, colour vision defects and temporal optic disc pallor. Although the importance of Opa1 protein in controlling mitochondrial fusion is well known the mechanisms by which *OPA1* mutations cause DOA have yet to be elucidated.

1.1. OPA1 and dominant optic atrophy

Mutations in *OPA1* lead to DOA, (Alexander et al., 2000; Delettre, Lenaers, Pelloquin, Belenguer, & Hamel, 2002) the most common optic neuropathy, with an estimated prevalence of 1:12,000 (Carelli, Ross-Cisneros, & Sadun, 2002) rising to 1:10,000 in certain populations (Delettre et al., 2002). DOA typically presents in the first decade of life as bilateral visual loss with pallor of the optic disc, centrocecal visual field scotoma and tritanopia (Delettre et al., 2002; Votruba, Moore, & Bhattacharya, 1998). Visual loss may be slowly progressive. There is considerable intra- and interfamilial variability in severity of visual loss ranging from legally blind to asymptomatic carriers. Some pedigrees have associated clinical features such as ptosis, myopathy and progressive external ophthalmoplegia. Histological assessment from donor eyes shows thinning of the retinal ganglion cell layer suggesting degeneration of retinal ganglion cells (RGCs). Demyelination has been observed in the optic nerve, chiasm and tract (Kjer, Jensen, & Klinken, 1983; Milea et al., 2010). The shape of the optic nerve has been reported to be characteristic (Fournier, Damji, Epstein, & Pollock, 2001; Votruba, Thiselton, & Bhattacharya, 2003) and the size of the optic nerve head is reduced (Barboni et al., 2010).

Over 200 different *OPA1* mutations have been reported to date (Ferré, Amati-Bonneau, Tourmen, Malthiery, & Reynier, 2005; Olichon et al., 2006). Isolated mutations in the *OPA1* gene have also been shown to cause a 'DOA plus syndrome', in which optic atrophy is accompanied by sensorineural deafness, ataxia, axonal sensory-motor polyneuropathy, chronic progressive external ophthalmoplegia and mitochondrial myopathy with cytochrome c oxidase negative and Ragged Red Fibres (Amati-Bonneau et al., 2009; Huang, Santarelli, & Starr, 2009; Milone, Younge, Wang, Zhang, & Wong, 2009; Yu-Wai-Man et al., 2010). Remarkably, it has recently emerged that, in rare cases, *OPA1* mutations can be

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associated with hearing loss, ptosis and oculomotor deficits in the absence of any detectable optic atrophy (Milone et al., 2009).

1.2. The Opa1 protein

The *OPA1* gene codes for the protein OPA1, a dynamin-like mitochondrial related guanosine triphosphatase (GTPase) and a 100 K member of the GTPase superfamily (Hinshaw & Schmid, 1995). OPA1 is homologous with the yeast (*Saccharomyces cerevisae*) gene Mgm1 (Olichon et al., 2002) and is located primarily on the mitochondrial inner membrane. Mgm1/Opa1 has multiple functions, playing a central role in the maintenance of mitochondrial morphology and mitochondrial networks through its effects on endocytosis, vesicular traffic and coated vesicle formation (Hinshaw & Schmid, 1995). It also influences mitochondrial motility (including mitochondrial fission and fusion) to ensure an appropriate distribution of mitochondria and adequate supplies of ATP within the cytosol. OPA1 is thought to play a protective role as an anti-apoptotic GTPase by limiting the detrimental impact of apoptotic stimuli (Davies et al., 2007). The OPA1 protein is expressed ubiquitously throughout the body with high levels in the retina, brain (Aijaz, Erskine, Jeffery, Bhattacharya, & Votruba, 2004; Misaka, Miyashita, & Kubo, 2002) liver and heart. Given the critical importance of OPA1 to so many cellular activities it is interesting that OPA1 mutations manifest primarily as DOA (Davies & Votruba, 2006).

1.3. Mouse models of dominant optic atrophy

Ocular and CNS tissue from patients with DOA is scarce and the published histology of DOA has come from a very small number of elderly patients with severe disease (Johnston, Gaster, Smith, & Tripathi, 1979; Kjer et al., 1983). This limitation has created a pressing need for an animal model of DOA. Such a model must combine the genetic and clinical characteristics of DOA in animals that are suitable for genetic analysis. Mice are widely used as genetic disease models due to the relative ease of genetic manipulation and high homology to the human genome. The murine retina shows relatively good homology to the human retina rendering the mouse suitable for modelling a wide range of human visual diseases with a genetic basis (Smith, John, Nishina, & Sundberg, 2002). However, there is a range of anatomical limitations, and it should be recognised that although the murine eye is a good model for human eye disease it is by no means perfect. Despite this, much has been learnt from mouse models of human genetic eye disease. In the last 5 years two mouse models of Opa1 DOA (based on OPA1 haploinsufficiency) have been published: the B6;C3-*Opa1*^{Q285STOP} Opa1 mutant mouse (Davies et al., 2007) and the B6;C3-*Opa1*$^{329\text{-}355del}$ Opa1 mutant mouse (Alavi et al., 2007). Both display a broad correlation with the human DOA phenotype. (The two models are compared and contrasted in Table 1.)

2. Mouse models of dominant optic atrophy

2.1. Generation of the B6;C3-*Opa1*^{Q285STOP} and B6;C3-*Opa1*$^{329\text{-}355del}$ *Opa1 mutant mice*

Both the B6;C3-*Opa1*^{Q285STOP} mutant mouse (Davies et al., 2007) and the B6;C3-*Opa1*$^{329\text{-}355del}$ mutant mouse (Alavi et al., 2007) were generated after screening an ENU-mutagenized DNA library of mouse DNA (Ingenium, Martinsried, Germany) for mutants with sequence changes in *Opa1*.

The B6;C3-*Opa1*^{Q285STOP} *Opa1* mutant mouse was generated by screening an ENU-mutagenized DNA archive from C3HeB/FeJ males for point mutations in *Opa1* exons 1, 8, 9, 10, 12 and 28, selecting a heterozygous nonsense mutation in exon 8, which codes for a C–T transition at 1051 bp (Q285STOP). This mutation causes protein truncation at the beginning of the dynamin GTPase, close to the location of a number of human disease mutations (c.868C>T (R290 W) and c.869G>T (R290Q) (Ferré et al., 2005)). The Opa1 mutant mouse line (B6;C3-*Opa1*^{Q285STOP}) was produced through *in vitro* fertilization with mutant sperm and C57Bl/6 J females to produce a heterozygous, *Opa1*±, mouse. The founder (F1) generation was then systematically outcrossed to C57Bl/6 J up to at least G4. The pdeβ (RD1 mutation), carried by the C3H line, was excluded by systematic genotyping and breeding. Heterozygous *Opa1*± mice were intercrossed to generate generation cohorts.

The B6;C3-*Opa1*$^{329\text{-}355del}$ Opa1 mutant mouse was also generated by screening an ENU-mutagenized DNA library of mouse DNA and this time identifying a splice site mutation in murine *Opa1* intron 10*:* c.1065+5G → A. Using a purebred C3HeB/FeJ outcross on C57Bl/6 a mouse model for DOA carrying this splice site mutation in the *Opa1* gene was created. The mutation is close to three reported human mutations (c.1065+2T>C, c1065+2T>G and c.1065+3A>C (Ferré et al., 2005)) and results in skipping of exon 10 in the OPA1 gene causing an in-frame deletion of 27 amino acid residues in the dynamin GTPase domain.

Both models show ∼50% reduction in *Opa1* transcript in retinal tissue and a ∼50% reduction in Opa1 protein across a range of tissues, suggesting that haploinsufficiency underlies the pathophysiological mechanism. Both the B6;C3-*Opa1*^{Q285STOP} and B6;C3-*Opa1*$^{329\text{-}355del}$ mutant mouse are embryonic lethal when homozygous; at <E13.5 in the B6;C3-*Opa1*^{Q285STOP} mutant mouse (Davies et al., 2007) and ca. E8.5 (between E3.5 and E12) in the B6;C3-*Opa1*$^{329\text{-}355del}$ mutant mouse (Alavi et al., 2007).

2.2. Visual, neurological and neuromuscular abnormalities

Visual function in the B6;C3-*Opa1*^{Q285STOP} mutant mouse has been assessed with a rotating optokinetic drum (OKN) using high (2°, corresponding to 0.25 cycles/degree) to low (4° and 8°, 0.125 and 0.0625 cycles/degree) resolution gratings. Two studies (Davies et al., 2007; Yu-Wai-Man et al., 2009) have looked at visual function at 6, 12, 13 and 18 month old mice. Significantly decreased mean tracking frequencies from 12 months in *Opa1*± mice were detected at high and low spatial frequencies. Furthermore, reduced detection of the low resolution gratings was documented from 18 months onwards in *Opa1*± mice.

Given the ubiquitous expression of Opa1 (Alexander et al., 2000) an Opa1 deficiency may be expected to adversely affect other organ systems, especially those with high levels of mitochondria and high metabolic demands. Detailed (non ocular) phenotyping of the B6;C3-*Opa1*^{Q285STOP} mouse model by SHIRPA neurological testing has revealed subtle systemic neurological and neuromuscular abnormalities (Davies et al., 2007), such as decreased locomotor activity.

There are several reported neurological and metabolic abnormalities in the B6;C3-*Opa1*$^{329\text{-}355del}$ mutant mouse phenotype (Alavi et al., 2009). SHIRPA testing showed that over a half of the Opa1 mutant mice had an abnormal clutching reflex with a third (11 males and 2 females) suffering a tremor by 22 months of age. Opa1 mutant mice also performed significantly worse than controls on the Rotarod; a rotating rod used to test the physical performance of rodents. Although Opa1 mutant mice maintained a normal food intake they were significantly lighter than controls regardless of sex. Post-mortem examination revealed significantly less body fat than controls though the muscle fibre morphology was unaffected. The extra-ocular phenotype reported in the B6;C3-*Opa1*$^{329\text{-}355del}$ mutant mouse has recently been supported by findings on Rotarod in the B6;C3-*Opa1*^{Q285STOP}. This also applies to the tendency for B6;C3-*Opa1*^{Q285STOP} mutants to have lower

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