Seminars in Cell & Developmental Biology 21 (2010) 593–598

Contents lists available at ScienceDirect

Seminars in Cell & Developmental Biology

journal homepage: www.elsevier.com/locate/semcdb

Review

OPA1 (dys)functions

Thomas Landes[a], Ingrid Leroy[a], Ambre Bertholet[a], Alan Diot[a], Farnoosh Khosrobakhsh[a], Marlène Daloyau[a], Noélie Davezac[a], Marie-Christine Miquel[a,b], Delphine Courilleau[a], Emmanuelle Guillou[c], Aurélien Olichon[d], Guy Lenaers[e], Laetitia Arnauné-Pelloquin[a], Laurent J. Emorine[a], Pascale Belenguer[a,*]

[a] *Université de Toulouse, UPS, CNRS; UMR 52412, Laboratoire Métabolisme Plasticité Mitochondries, F-31000, France*
[b] *UPMC, Paris, F-75005, France*
[c] *CNIO, Madrid, E-28029, France*
[d] *Institut Claudius Regaud, Toulouse, F-31000, France*
[e] *Institut des Neurosciences de Montpellier, F-34000, France*

ARTICLE INFO

Article history:
Available online 4 January 2010

Keywords:
Mitochondria
Apoptosis
mtDNA
ADOA
Dynamin

ABSTRACT

Mitochondrial morphology varies according to cell type and cellular context from an interconnected filamentous network to isolated dots. This morphological plasticity depends on mitochondrial dynamics, a balance between antagonistic forces of fission and fusion. DRP1 and FIS1 control mitochondrial outer membrane fission and Mitofusins its fusion. This review focuses on OPA1, one of the few known actors of inner membrane dynamics, whose mutations provoke an optic neuropathy. Since its first identification in 2000 the characterization of the functions of OPA1 has made rapid progress thus providing numerous clues to unravel the pathogenetic mechanisms of ADOA-1.

Contents

1. Introduction

Mitochondria form a highly dynamic reticulum which morphology varies according to cell types and contexts and depends on continuous fission and fusion of both mitochondrial outer (OM) and inner membranes (IM). In the past decade, genetic screens in yeast led to the identification of several evolutionarily conserved proteins essential for the maintenance of mitochondrial morphology. In mammals, FIS1 and DRP1 drive mitochondrial fission whereas fusion involves the OM proteins Mitofusin-1 and -2 (MFN1 and MFN2), and the IM-located OPA1 [1]. Accumulating data show the impact of mitochondrial dynamics on mitochondrial functions and on the physiology of the cell [2]. Furthermore these processes are essential for mammalian development and are affected in neurodegenerative diseases.

In this review, we will focus on OPA1 and discuss to which extent the recent progresses in elucidating the different functions of this dynamin could help understanding the pathological mechanisms of type 1 optic atrophy (ADOA-1 OMIM 165500). ADOA-1 is a neurological disease caused by mutations of *OPA1*, that affects retinal

* Corresponding author at: Laboratoire Métabolisme Plasticité Mitochondries, Université Paul Sabatier, BAT4R3B1, 118 route de Narbonne, 31062 Toulouse cedex 09, France. Tel.: +33 5 61 55 62 38; fax: +33 5 61 55 81 66.
E-mail address: pascale.belenguer@cict.fr (P. Belenguer).

1084-9521/$ – see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.semcdb.2009.12.012

ganglion cells (RGC) whose axons form the optic nerve, and leads to reduced visual acuity and possibly to blindness [3].

2. OPA1 expression

The *OPA1* gene encodes a mitochondrial protein localized in the inter-membrane space (IMS) and associated to mitochondrial membranes [4–7]. OPA1, and its yeast orthologues Mgm1p in *Saccharomyces cerevisiae* and Msp1p in *Schizosaccharomyces pombe*, belongs to the dynamins' family [8–11]; with which it shares three conserved regions: a GTPase domain, a middle domain and a carboxy-terminal coiled-coil domain (CC-II) also called GTPase effector domain (GED) (Fig. 1). The latter is involved in the oligomerization and activation of the dynamins. The amino-terminal region of OPA1, preceding the GTPase domain, displays a mitochondrial import sequence (MIS) followed by a predicted transmembrane domain (TM1) and a coiled-coil domain (CC-I) located downstream of alternatively spliced exons (Fig. 1).

In humans *OPA1* ORF is built from 30 exons, 3 of which (4, 4b and 5b) are alternatively spliced leading to 8 mRNA (Fig. 1) [12]. Exon 4 that is evolutionary conserved does not present any remarkable domain whereas both exons 4b and 5b that are specific to vertebrates encode hydrophobic domains (TM2a and TM2b) and the latter an additional coiled-coil region (CC-0) [13,14]. Precursors translated from the eight *OPA1* mRNA are targeted to mitochondria via their MIS which is removed upon import by the mitochondrial processing peptidase (MPP) to give rise to long isoforms (l-OPA1) [4,6]. Each l-OPA1 isoform is then subjected to a limited proteolysis generating one or two short isoforms (s-OPA1) [15]. Both short and long isoforms of OPA1 are associated to mitochondrial membranes, and it is proposed that l-OPA1 is anchored to the IM while s-OPA1, lacking TM1, is peripherally attached to the IM, a fraction of it having the possibility to diffuse in the IMS and to associate to OM [4–7,16]. Numerous and discordant studies on the generation of s-OPA1 have implicated three mitochondrial proteases recognizing two cleavage sites (Fig. 1). The rhomboid protease PARL, the mammalian counterpart of Pcp1p that cleaves Mgm1p [17], is involved in the generation of a low abundant s-OPA1 isoform soluble in the IMS [16]. However PARL does not wholly explain the processing of OPA1 since its knockdown/out does not affect the ratio of l- to s-isoforms of the dynamin [7,14,18,19]. Based on an over-expression study, the m-AAA protease paraplegin is proposed to cleave OPA1 at S1 (Fig. 1), but its knockout does not affect the processing of the protein [7,14,19]. However the contribution in OPA1 processing of two other subunits of the m-AAA complex, AFG3L1 and AFG3L2, is revealed by experiments conducted in yeast [14]. Furthermore recent data suggest that prohibitins, that regulate the activity of m-AAA proteases, modify the processing of OPA1 [20]. The i-AAA protease YME1L is responsible for cleavage at S2 (Fig. 1), and other sites [15,18]. Interestingly, l-OPA1 isoforms containing exon 4b are totally processed into short forms [15]. To make this picture more complex, the cleavage of OPA1 does not only occur in basal condition but is also induced by both apoptosis and dissipation of mitochondrial membrane potential ($m\Delta\psi$). Loss of $m\Delta\psi$ destabilizes l-OPA1 and enhances the cleavage at S1 and at other sites not including S2 [7,15,18,19]. Increased sensitivity to apoptosis of *Parl*$^{-/-}$ cells has been proposed to be due to an altered processing of OPA1 leading to the loss of the low abundant soluble s-OPA1 [16]. Nevertheless, nor PARL, nor m-AAA proteases, nor YME1L, totally account for the processing of the dynamin upon dissipation of $m\Delta\psi$ or apoptotic stimuli.

Although *OPA1* is ubiquitously expressed, it shows tissue specific expression patterns. High mRNA expression levels occur in retina, brain, liver, heart and pancreas and the relative abundance of the eight *OPA1* splice variants shows tissue specificity [9,12,21,22]. Furthermore, changes in the relative abundance of l- and s-OPA1 has been observed in various tissues [4,22].

Altogether, these data reveal that *OPA1* expression is highly regulated at both post-transcriptional and post-translational levels. The later indeed includes proteolytic processing but further studies will certainly also reveal the role of phosporylation, ubiquitination and sumoylation that regulate other actors controlling mitochondrial dynamics such as DRP1 and the yeast homologue of Mitofusins Fzo1p [1].

3. OPA1, mitochondrial fusion

Loss of function of OPA1 by RNAi or gene knockout, or of Mgm1p and Msp1p, causes fragmentation of the tubular mitochondrial reticulum [5,23–26]. Conversely, over-production of this protein promotes mitochondrial elongation in cells where mitochondria are punctuated [4,27]. Surprisingly, over-expression of the dynamin in cells with tubular mitochondria causes mitochondrial fragmentation [5,28]. However, such cells still possess a normal mitochondrial fusion activity [27,29]. The profusion activity of OPA1 is further confirmed by experiments showing that mitochondrial fusion is impaired in OPA1-depleted or *Opa1*$^{-/-}$ cells [15,26,27,29,30]. Interestingly, levels of OPA1 can differentially influence two types of fusion: a "transient fusion" that result in rapid exchange of soluble components without affecting the morphology of mitochondria and a "complete fusion" that permits the exchange of all mitochondrial components and affect mitochondrial morphology [31].

Since cleavage of l-OPA1 induced by dissipation of $m\Delta\psi$ or by apoptosis correlates with mitochondrial fragmentation [7,18,19,32], it has been initially proposed that long form of the dynamin are crucial for OPA1-mediated mitochondrial fusion while short forms are unable to fuse mitchondria [7]. This has been also proposed for Mgm1p since mitochondria from *PCP1*-deleted *Saccharomyces cerevisiae* cells lacking s-Mgm1p can fuse [33]. However, this hypothesis has not been then confirmed since both short and long forms of the dynamin are required to restore the fusion of mitochondria in *MGM1*-deleted cells [17]. Similarly, splicing variants that produce both l- and s-OPA1 have the capacity to restore defective mitochondrial fusion in *Opa1*$^{-/-}$ cells, while those that only produce s-OPA1 do not [15]. Furthermore a non-cleavable

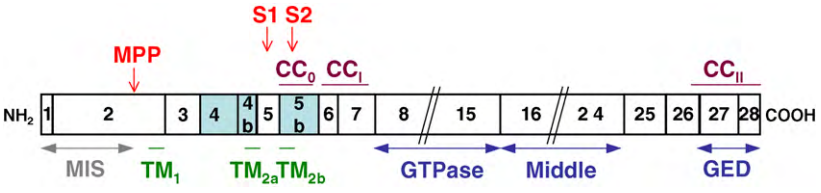

Fig. 1. Schematic representation of OPA1 structure. OPA1 shares structural features with dynamins: a GTPase domain, a Middle domain and a GTPase Effector Domain (GED) containing a coiled-coil region (CC-II). Before the GTPase domain, OPA1 displays a Mitochondrial Import Sequence (MIS) followed by a predicted transmembrane region (TM1) and a coiled-coil region (CC-I). All these domains are present in the eight splice variants of the dynamin while predicted transmembrane domains (TM2a and TM2b) and additional coiled-coil region (CC-0) are only present in spliced exons. Intra-mitochondrial proteolytic cleavage sites for Mitochondrial Processing Peptidase (MPP), Paraplegin (S1) and YME1L (S2) are indicated. Numbers correspond to OPA1 exons.