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D. melanogaster, mitochondria and neurodegeneration: small model organism, big discoveries

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ABSTRACT

In developed countries, increased life expectancy is accompanied by an increased prevalence of age-related disorders like cancer and neurodegenerative diseases. Albeit the molecular mechanisms behind the clinically, pathologically and etiologically heterogeneous forms of neurodegeneration are often unclear, impairment of mitochondrial fusion–fission and dynamics emerged in recent years as a feature of neuronal dysfunction and death, pinpointing the need for animal models to investigate the relationship between mitochondrial shape and neurodegeneration. While research on mammalian models is slowed down by the complexity of the organisms and their genomes, the long latency of the symptoms and by the difficulty to generate and analyze large cohorts, the lower metazoan *Drosophila melanogaster* overcomes these problems, proving to be a suitable model to study neurodegenerative diseases and mitochondria-shaping proteins. Here we will summarize our current knowledge on the link between mitochondrial shape and models of neurodegeneration in the fruitfly. This article is part of a Special Issue entitled 'Mitochondrial function and dysfunction in neurodegeneration'.

Introduction

Neurodegenerative diseases are a group of diseases characterized by progressive loss of specific neuronal populations (dopaminergic, gabaergic or motor neurons). Depending on which cellular type of central and/or peripheral nervous system is affected, neurodegeneration can lead to motor, behavioral or cognitive symptoms. Most of these diseases are sporadic, but 5–10% of total cases are of genetic origin. Mapping the alleles associated with the familial cases of neurodegeneration greatly helped in the identification of molecular mechanisms underlying these devastating disorders; however, we are very far from the elucidation of the pathogenetic mechanisms, and even more from effective therapies that can interfere with the natural history of these diseases (Mandemakers et al., 2007).

Neurons are highly active cells whose main function is to transmit nerve impulses from one part of the body to another one in a regulated and coordinated way. To accomplish their function, neurons require a large amount of energy, which has to be provided from the soma to the far synapse mostly by mitochondria (Kann and Kovacs, 2007). Regulation of neuronal functions depends on neurotransmitters and hormones which influence them by interacting with receptors, and by modulating ion channels and pumps. Certain facets of neurodegeneration therefore depend on two main cellular functions which are intimately related to energy production and to quality control of proteins: altered protein quality control is often associated with endoplasmic reticulum (ER) stress (Rao and Bredesen, 2004). On the other hand, primary or secondary mitochondrial dysfunction can result in production of oxygen reactive species (ROS), ATP depletion, impaired organelles dynamics and trafficking and ultimately in reduced energy supply for the neuron (Costa and Scorrano, 2012; Liesa et al., 2009; Oettinghaus et al., 2012).

These two pathogenic mechanisms are often linked one to each other. Studies of the past few years highlighted the emerging role of mitochondria dynamics in maintenance of functional neurons (Chen et al., 2007). Dysregulation of mitochondria-shaping proteins expression or activity impacts not only on mitochondrial morphology, but also on mitochondrial biogenesis and bioenergetics (Gomes et al., 2011; Pich et al., 2005), distribution (Baloh et al., 2007) and calcium

Abbreviations: AD, Alzeheimer's disease; ADOA, Autosomal dominant optic atrophy; AP, Amyloid plaque; APP, Amyloid precursor protein; Aβ, Amino acids amyloid β-peptides; CaMKIIa, Calcium/calmodulin dependent protein kinase II alpha; CMTIIa, Charcot–Marie–Tooth type IIa neuropathy; DA, Dopaminergic neurons; Drp1, Dynamin-related protein 1; EP, Endocytosis pool; ER, Endoplasmic reticulum; ERG, Electroretinogram; Fis1, Fission 1; Fzo1, Fuzzy onion 1; GAL4, Galactose yeast transcriptional activator; IAP, Inhibitor of apoptosis; iAAA, Inner membrane ATPases associated with various cellular activities with IMS–facing catalytic center; IFM, Indirect flight muscle; IOC, Interoomatidial cells; mAAA, Inner membrane ATPases associated with various cellular activities with matrix-facing catalytic center; Marf, Mitochondrial assembly regulator factor; Mff, Mitochondrial fission factor; Mfn, Mitofusin; MnTaB, Mn(III)tetrakis(4-Benzoic acid)porphyrin Chloride; Oma1, Overlapping activity with mAAA protease 1; OMIM, Online Mendelian inheritance in man; OPA1, Optic atrophy 1; Parl, Presenilin-associated rhomboid-like; PD, Parkinson's disease; Psn, Presenilin; RGC, Retinal ganglion cell; ROS, Oxygen reactive species; RP, Reserve pool; RRP, Ready releasable pool; TH, Tyrosine-hydroxylase; TUNEL, Terminal deoxynucleotidyl transferase dUTP nick end labeling; UAS, Upstream activating sequence; VDRC, Vienna *Drosophila* RNAi center.

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homeostasis (de Brito and Scorrano, 2008; Szabadkai et al., 2004). Thanks to the use of animal models, we are starting to understand how this leads to neuronal dysfunction and loss (Alavi et al., 2007; Costa et al., 2010; Davies et al., 2007; Ishihara et al., 2009). However, the interplay between mitochondrial shape and function is extremely complex and the current discovery rate is slowed down by the complexity of murine models. A valid alternative is represented by *Drosophila melanogaster* that has been successfully employed to lay the basis for several key findings in the field of neurodegeneration.

In this review we will focus on recent discoveries of the role of mitochondrial dynamics in neurodegeneration that were identified by using *Drosophila melanogaster* as a model system.

Mitochondria shaping proteins in Drosophila melanogaster

Mitochondrial shape in living cells is very heterogeneous and can range from small spheres to interconnected tubules (Bereiter-Hahn and Voth, 1994). The morphological plasticity of mitochondria results from the ability of this organelle to undergo fusion and fission, which are regulated by a family of mitochondrial shaping proteins. We will now outline the main players in the fruitfly: for the sake of clarity, we will compare them to the known players in mammals (Table 1).

Mitochondrial fusion is promoted by large trans-membrane dynamin-related proteins. Optic Atrophy 1 (OPA1, UniProt O60313) resides in the inner mitochondrial membrane and is involved in mitochondrial fusion, as well as in the regulation of cristae biogenesis and remodeling (and therefore of cytochrome c release during apoptosis) (Cipolat et al., 2004, 2006; Frezza et al., 2006). In *H. sapiens*, 8 different OPA1 isoforms are retrieved (Delettre et al., 2001; Olichon et al., 2002; Satoh et al., 2003), which are differentially posttranslationally processed in at least five different protein forms (Delettre et al., 2001; Duvezin-Caubet et al., 2007; Ishihara et al., 2006; Olichon et al., 2003, 2007) by a complicated and yet not completely understood network of proteases that include iAAA, mAAA, paraplegin, Oma1, and Parl (Cipolat et al., 2006; Duvezin-Caubet et al., 2007; Griparic et al., 2007; Head et al., 2009; Ishihara et al., 2006; Song et al., 2007). While a detailed description of the processing of Opa1 is out of the scope of this review, it is useful to remind that the concerted action of these proteases results in the production of long and short forms of the protein (Ishihara et al., 2006) that are both required for correct function of the protein and therefore for mitochondrial fusion, as well as of a soluble form that albeit quantitatively scarce, participates in the formation of the Opa1-containing oligomers that stabilizes the cristae during apoptosis (Frezza et al., 2006). *Drosophila* OPA1 homologue (dOpa1, UniProt A1Z9N0) shares 51.2% similarity with the human orthologue. In fruitflies, Opa1 gene is transcribed into 2 isoforms, that are processed into a short form by *Drosophila* presenilin-associated rhomboid-like (PARL) homologue rho-7 (McQuibban et al., 2006; Rahman and Kylsten, 2011), a protease that is conserved during evolution from yeast to mammals (Hill and Pellegrini, 2010). Most studies on dOPA1 analyzed mutant flies where the function of the protein had been ablated by a genomic P-element/transposon insertion (Shahrestani et al., 2009; Tang et al., 2009; Yarosh et al., 2008) and will be described in detail the next chapter. Recently it was also reported that downregulation of dOpa1 in the heart results in dilated cardiomyopathy, with severe alteration of contractility (Dorn et al., 2011).

Partner of Opa1 in the regulation of mitochondrial fusion are mitofusins (Mfns), which are located in the outer mitochondrial membrane. Mammals possess two Mfns, Mfn1 (UniProt Q8IWA4) and Mfn2 (UniProt O95140). MFN1 and MFN2 act in trans on opposing membranes by bridging mitochondria, maintaining a distance of 95 Ångstrom between the two membranes (Koshiba et al., 2004). However, the two Mfns do not seem to display redundant functions. The control of mitochondrial oxidation (Bach et al., 2003) and the anti-proliferative effect by Mfn2 (Chen et al., 2004) are not shared by Mfn1. Moreover, while mitochondrial fusion mediated by the inner mitochondrial membrane Opa1 requires Mfn1 (Cipolat et al., 2004), Mfn2 is enriched in subdomains of the outer membrane of mitochondria in close apposition to the ER and directly links mitochondria to the ER (de Brito and Scorrano, 2008). Finally, mutations in MFN2 are associated with the peripheral Charcot–Marie–Tooth type IIa (CMTIIa) neuropathy (Zuchner et al., 2004).

Drosophila played an instrumental role in the birth of the field of mitochondrial dynamics, since the first protein able to influence mitochondrial morphology was indeed a mitofusin discovered in

Table 1
Mitochondria-shaping proteins in *D.melanogaster*. Mammalian mitochondria-shaping proteins and their respective *Drosophila* homologues are listed. The main functional domains, expression in different fruitfly's organs and tissues, observed phenotypes and disease to which proteins are related are described.

Protein	Domains	*Drosophila* homologue	Expression data in post-embryonic organs or tissues	Phenotypes	Disease
OPA1	GTPase, GTPase effector (GED)	Opa1-like, CG8479	adult eye, adult central nervous system, larval/adult hindgut, larval/adult fat body, adult spermathecae	Lethality, cardiomyopathy, Rough and glossy eye	Autosomal Dominant Optic Atrophy (ADOA)
MFN2, MFN1	GTPase, Heptad repeats (HR)	Marf, Mitochondrial assembly regulatory factor, CG3869	adult head, adult eye, adult central nervous system, adult crop, larval/adult midgut, larval/adult hindgut, larval/adult Malpighian tubules, adult heart, adult fat body, adult salivary gland, larval trachea, adult spermathecae, adult male accessory gland, larval/adult carcass	Lethality, cardiomyopathy	Charcot–Marie–Tooth type IIa (CMT2A)
DRP1	GTPase, GED	Drp1, CG3210	larval/adult central nervous system, larval Malpighian tubules, larval salivary gland, adult testis	Lethality, Defective Nebenkern, Mitochondrial distribution, Impaired neurotransmission	Alzeheimer's, Huntington's, ADOA, CMT2A
FIS1	tetratricopeptide repeat(TPR)-like motifs	Fis1, CG17510	adult head, adult eye, larval/adult central nervous system, adult crop, larval/adult midgut, larval/adult hindgut, larval/adult Malpighian tubules, adult heart, larval/adult fat body, larval/adult salivary gland, larval trachea, adult female reproductive system, adult male reproductive system, larval/adult carcass	Mitochondrial dynamics	
MFF	DUF800	Tango11, CG30404	larval/adult central nervous system, larval Malpighian tubules, larval fat body, larval salivary gland, adult ovary	Mitochondrial and peroxisomes fission	