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Review

Cell signaling and mitochondrial dynamics: Implications for neuronal function and neurodegenerative disease

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ABSTRACT

Nascent evidence indicates that mitochondrial fission, fusion, and transport are subject to intricate regulatory mechanisms that intersect with both well-characterized and emerging signaling pathways. While it is well established that mutations in components of the mitochondrial fission/fusion machinery can cause neurological disorders, relatively little is known about upstream regulators of mitochondrial dynamics and their role in neurodegeneration. Here, we review posttranslational regulation of mitochondrial fission/fusion enzymes, with particular emphasis on dynamin-related protein 1 (Drp1), as well as outer mitochondrial signaling complexes involving protein kinases and phosphatases. We also review recent evidence that mitochondrial dynamics has profound consequences for neuronal development and synaptic transmission and discuss implications for clinical translation.

Contents

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Introduction

Mitochondrial dysfunction occurs in a wide range of neurological disorders including Alzheimer disease (AD), amyotrophic lateral sclerosis (ALS), Huntington disease (HD), Parkinson disease (PD), and a subset of spinocerebellar ataxias (SCA). For the most part, however, it remains unknown as to whether neurodegeneration in these disorders is triggered by mitochondrial dysfunction, or whether mitochondrial dysfunction results from the disease state.

While excellent recent reviews have highlighted links between mitochondrial dysfunction and disease (Cho et al., 2010; Martin, 2010; Morais and De Strooper, 2010; Moreira et al., 2010; Pandey et al., 2010; Patten et al., 2010; Pickrell and Moraes, 2010; Rodolfo et al., 2010; Schon and Przedborski, 2011; Witte et al., 2010), this review focuses on cellular signaling pathways that impact mitochondrial morphology and transport and potential dysregulation of these signaling pathways in neuronal injury and disease.

Mitochondrial shape and function, and ultimately cellular homeostasis, is determined by balanced mitochondrial fission and fusion events. Research over the last decade has led to an appreciation of the complexity of the cellular signaling mechanisms that sculpt the mitochondrial network in response to changing needs of the cell and the organism. Below, we discuss how dynamic protein–protein interactions and posttranslational modifications control the rate of fission and fusion of mitochondria and review our current understanding of the role of mitochondrial dynamics in neuronal development and function.

Regulation of mitochondrial fission

Drp1 structure/function

Dynamin-related protein 1 (Drp1, encoded by the human DNM1L gene) is a large GTPase that cycles between the cytosol and the outer mitochondria membrane (OMM), where it oligomerizes into spiral-shaped structures to physically pinch a single mitochondrion into two (Hoppins et al., 2007). Drp1 contains four domains: 1) an N-terminal GTPase domain which harbors the enzymatic activity, 2) a middle domain (MID) necessary for oligomerization, 3) an alternatively spliced variable domain (VD) that contains most posttranslational modification sites, and 4) a C-terminal GTPase effector domain (GED) which interacts with the GTPase domain (Fig. 1A). According to recently published crystal structures of dynamin-1 (Faelber et al., 2011; Ford et al., 2011), the α-helices of the MID and GED form a "stalk" domain, two of which interact in a criss-cross fashion to assemble a Drp1 dimer (Figs. 1B and C). Similar to dynamin at clathrin-coated vesicles (Hoppins et al., 2007; Praefcke and McMahon, 2004), the catalytic cycle of Drp1 is thought to occur in four discrete steps. First, Drp1 is recruited from the cytosol to the OMM. Second, Drp1 oligomerizes to form spirals around the OMM. Third, GTP is hydrolyzed to GDP to power constriction of the Drp1 oligomer. Fourth, the Drp1 oligomer disassembles and Drp1 is released back into the cytosol.

Drp1 is subject to alternative splicing, with one alternative exon separating subdomains A and B of the GTPase domain, and tandem

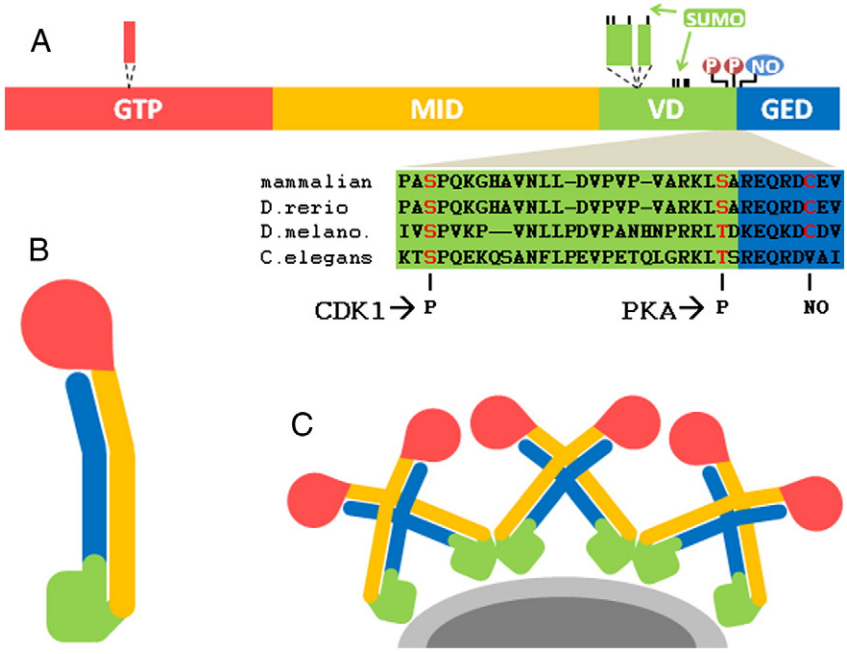

Fig. 1. Posttranslational regulation of dynamin-related protein 1 (Drp1). A) Based on sequence similarity to dynamin, the Drp1 coding sequence can be subdivided into four domains (GTP, GTPase domain; MID, middle domain; VD, variable domain; GTPase effector domain, GED). Shown are insertion points for alternatively spliced coding sequences and sites of posttranslational modification (P, phosphorylation; NO, S-nitrosylation; SUMO, sumoylation). The sequence alignment highlights the phylogenetic conservation of the S-nitrosylation and phosphorylation sites. B) Fold model of a Drp1 monomer based on crystal structures of dynamin-1 (Faelber et al., 2011; Ford et al., 2011). MID and GED form an extended stalk that separates the GTPase from the variable domain and mediates dimerization and higher order assembly of Drp1. C) Model of Drp1 fission complex assembly (segment of helix with three Drp1 dimers shown in cross-section). Adjacent rungs of the Drp1 helix interact via GTPase domains.