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Mitochondria: Joining Forces to Thwart Cell Death

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Abstract

Mitochondria are highly dynamic organelles that undergo constant cycles of fusion and fission. An additional level of regulation of mitochondrial function, which is particularly important in neurons, is their active transport along microtubules. Recent evidence suggests that the mitochondrial fusion/fission machinery, as well as the molecular motors responsible for their movement, constitute powerful regulatory control points that directly impact metabolism and regulation of cell death. This is true for not only apoptosis, but also for excitotoxicity where calcium overload is a major component of the cell death process. In this review, we will describe the molecular mechanisms regulating fusion and fission and how this impinges on cell survival in the context of acute neuronal injury.

ACCEPTED MANUSCRIPT

Introduction

As the powerhouse of the cell, mitochondria play a crucial role in energy metabolism. In addition, recent research has highlighted other aspects of mitochondrial function that play key roles in cell survival and death [1, 2]. Mitochondria are highly dynamic organelles that undergo constant cycles of fusion and fission. This dynamic behaviour of mitochondria is required for proper mitochondrial function and distribution and plays an important role in cell death. Mitochondrial dynamics also impinge on a second important mitochondrial function, calcium buffering, which regulates signal transduction pathways, metabolism and cell death. An additional level of regulation, which is particularly important in neurons, is the active transport of mitochondria along microtubules. These processes regulate not only normal function and distribution of mitochondria but also several types of cell death such as apoptosis and excitotoxicity. Below, we describe the molecular mechanism regulating fusion and fission and their impact on cell survival in the context of acute neuronal injury.

Mechanisms that regulate mitochondrial fusion and fission

In healthy cells, mitochondrial fusion and fission are ongoing processes that are essential for development and survival (reviewed in [1, 2]). For example, fission is required during cell division to properly distribute mitochondria to daughter cells [3, 4] while fusion allows rapid mixing of mitochondrial content in order to buffer localized substrate deficits or complement damaged mitochondrial DNA [5, 6]. In neurons, mitochondrial fission is essential for mitochondrial transport to their potential docking sites in axons and dendrites and is tightly associated with development of spines and synapses [7, 8]. In addition, mitochondrial dynamics play a role in the proper recruitment of mitochondria to strategic locations such as areas of high metabolic demand. This is especially important in neurons because of their peculiar morphological characteristics. At the molecular level, three key GTPases mediate mitochondrial fusion and fission events in mammalian cells (Figure 1). These include mitofusins (MFN1/2), Optic Atrophy 1 (OPA1) and Dynamin Related Protein 1 (DRP1) which are briefly described below (for a recent review, see [9]).

Mitofusins MFN1 and MFN2 are integral outer mitochondrial membrane (OMM) proteins that regulate OMM fusion. Although MFN1 and MFN2 have overlapping functions, they are also believed to have distinct roles [10-12]. MFN1 is mainly involved in the docking of two juxtaposed mitochondria while MFN2 could potentially act as a regulatory GTPase [11-14]. Specific roles for MFN2 include modulation of metabolism by affecting the electron transport chain [15, 16] and tethering of endoplasmic reticulum to mitochondria [17]. Of note, GTP hydrolysis by MFN2 is not required for fusion as a hydrolysis deficient mutant of MFN2 (MFN2_{RasG12V}) can still induce mitochondrial fusion [13, 14]. In addition, point mutations in MFN2 are associated with Charcot Marie Tooth Neuropathy type II, a peripheral nerve neuropathy causing progressive muscle weakness and muscular atrophy [18].

OPA1 OPA1, an intermembrane space protein associated with the inner mitochondrial membrane (IMM), regulates IMM fusion as well as cristae structure [19-21]. There are eight OPA1 splice variants as well as several proteases that can cleave its transmembrane domain, suggesting a complex mode of regulation. [22-24]. Recent studies have also

demonstrated that both its full-length (L-OPA1) and cleaved (S-OPA1) forms are required for IMM fusion [23, 24]. The functional importance of OPA1 was highlighted by the discovery that mutations in OPA1 lead to a severe neuropathy, autosomal dominant optic atrophy (ADOA), characterized by a progressive degeneration of optic nerve, moderate to severe loss of visual acuity, and abnormalities of colour vision [25, 26].

DRP1 DRP1 is a key regulator of mitochondrial fission that is recruited to fission sites along mitochondria and is actively involved in the scission process. Recruitment of DRP1 to mitochondria is regulated by several post-translational modifications such as phosphorylation and SUMOylation [27]. DRP1 plays an essential role in several aspects of mitochondrial function. For example, in neurons, DRP1-mediated fission allows distribution of mitochondria along dendrites and is essential for synapse development [8, 28, 29].

Mitochondrial dynamics and cell death

As outlined above, mitochondria play a vital role in cellular homeostasis, while regulation of their dynamics is central to proper mitochondrial function. Paradoxically, mitochondria also play a key role in the regulation of cell death, and mitochondrial dynamics constitute an integral part of the pathways leading to the demise of the cell. In the central nervous system, two major types of cell death occur following acute injury, apoptosis and excitotoxicity, both of which are sensitive to the modulation of the fission/fusion machinery.

Classical Apoptotic Cell death

Classical apoptotic cell death is a tightly regulated process controlled by members of the BCL-2 family of proteins. Induction of apoptosis by intracellular signals such as DNA damage or ER stress leads to the activation of the pro-apoptotic BCL-2 homologues BAX and BAK, which promote cytochrome c release from mitochondria and subsequent activation of caspases, the apoptotic proteases. Apoptosis plays an important role in injury-induced neuronal death. Indeed, biochemical hallmarks of apoptosis have been observed in cells following both focal and global ischemia [30, 31] while animals overexpressing BCL-2 are more resistant to stroke [32, 33]. One important apoptotic trigger following neuronal injury is the reactive oxygen species (ROS) that are generated during hypoxia/reperfusion. ROS cause DNA damage, leading to p53-dependent activation of apoptosis [34-36]

Multiple studies have substantiated a link between mitochondrial dynamics and the classical apoptotic pathway. For example, in neuronal cells, mitochondria undergo excessive fission in response to ROS, DNA damage, and NO, which can be prevented by the expression of MFN2 or a dominant-negative form of DRP1 (K38A) [14, 37]. Dominant-negative DRP1 also rescued cell survival under these conditions, indicating that Drp1-mediated mitochondrial fission is an early event contributing to the collapse of mitochondria and cell death. Similarly, loss of MFN1, MFN2 or OPA1 leads to mitochondrial fragmentation and increased sensitivity to cell death stimuli [20, 38, 39], while overexpression of these proteins leads to better survival in several cell types including neurons [14, 37]. Importantly, in the absence of injury, loss of MFN2 results in

neuronal loss in vitro [14], and degeneration of purkinje neurons in vivo [40], highlighting the importance of mitochondrial fusion proteins in neuronal survival.

At the molecular level, two potentially overlapping mechanisms have been proposed to explain the importance of fission during apoptosis. First, apoptotic DRP1-dependent mitochondrial fragmentation is associated with opening of the cristae structure and mobilisation of cytochrome c, which can then be rapidly released upon OMM permeabilisation [41, 42]. Consequently, interfering with mitochondrial fission using a dominant-negative DRP1 prevents the reorganization of the cristae, dampening cytochrome c release and caspase activation [41]. Second, several components of the fission/fusion machinery have been associated with the regulation of BAX/BAK activation. For example, DRP1 and MFN2 have been found in puncta with BAX and BAK [43]. In addition, overexpression of MFN2 or the MFN2_{RasG12V} mutant inhibits BAX activation and protects against cytochrome c release in cell lines and primary neurons [13, 14]. MFN2 has also been suggested to interact with the anti-apoptotic BCL-2 homologue BCL-X_L and its *c elegans* homologue CED9 [44], although the significance of this interaction for cell survival has not been addressed. Other proteins involved in mitochondrial fusion/fission also interact with BAX. For example, Endophilin B1 (Bif-1, SH3GLB1), a protein of the endophilin family that plays a role in membrane dynamics, has been shown to regulate both mitochondrial dynamics and activation of BAX [45, 46]. Interestingly, the cross-talk between mitochondrial dynamics and BCL-2 homologues seems to go both ways. Indeed, BCL-X_L was shown to enhance mitochondrial dynamics and increase mitochondrial biomass, leading to increased synapse formation in cultured primary neuron [44, 47, 48]. Similarly, deficiency of both BAX and BAK in the BAX/BAK double knockout (DKO) cells caused fragmentation of the mitochondrial network. This defect was mapped to alterations in the regulation of MFN2 [49], as BAX promoted the recruitment of MFN2 into foci associated with fission/fusion sites. Of note, a constitutively active, GTP-bound form of Mfn2 (MFN2_{RasG12V}) reinstated fusion in MFN2 knockout but not DKO cells where it also failed to redistribute to fission/fusion foci [49]. Similar clusters containing BAX/BAK, MFN2 and DRP1 have previously been described in apoptotic cells and associated with the cytochrome c release activity of BAX. It is therefore possible that the enhanced anti-apoptotic activity of MFN2_{RasG12V} relates to its inability to be recruited to the apoptotic BAX foci, which could interfere with the activation of BAX within these foci. However, this remains to be tested, as other models of BAX activation suggest that BAX-induced cytochrome c release is driven by much smaller BAX oligomers that directly permeabilize the OMM [50-52].

Excitotoxic cell death

Apoptosis is an important mode of cell death in most mammalian tissue during development and in the context of cellular damage. However, a second mode of cell death, excitotoxicity, is a major cause of neuronal loss following acute brain injury. Excitotoxicity is caused by an excessive synaptic release of the neurotransmitter glutamate, causing the overactivation of glutamate receptors. Several downstream pathways then lead to a BAX/BAK-independent form of cell death with characteristics of both apoptosis and necrosis (reviewed in [53, 54]). For example, activation of NO synthase by PSD95 downstream of the NMDA receptor leads to the generation of highly reactive peroxynitrites, causing cellular damage and cell death. Excessive calcium influx

following NMDAR overactivation also activates several potentially deleterious signalling cascades. A major effect of calcium overload is the alteration of mitochondrial function. Mitochondria act as a calcium buffer following calcium release from the endoplasmic reticulum or through cell surface receptors [55], but also respond to calcium influx by increasing their metabolism [56]. However, if mitochondrial calcium increases over a certain value, a channel freely permeable to water and ions, the permeability transition pore (PTP), is open [57]. Opening of the PTP causes swelling and rupture of the OMM in a process that is completely distinct from BAX/BAK-dependent OMM permeabilisation. This leads to the disruption of energy production and release of cytotoxic factors, such as Apoptosis-Inducing Factor (AIF) and EndoG, from mitochondria. These factors then converge on the nucleus, causing DNA fragmentation and cell death. In addition, calcium-dependent activation of μ -calpain promotes the release of AIF from mitochondria [58, 59]. Calcium overload-induced mitochondria dysfunction also leads to the formation of ROS, causing further cellular damage.

As with apoptosis, components of the fission/fusion machinery influence excitotoxic cell death. For example, NO-induced toxicity in primary cortical neurones involves mitochondrial fragmentation and is prevented by overexpression of MFN1 or dominant-negative DRP-1 [37]. Similarly, overexpression of MFN2 or OPA1 protected neurons from NMDA-induced cell death (Jahani-Asl *et al.*, submitted). However, neither downregulation of DRP1 or overexpression of MFN1 rescued NMDAR overactivation-induced toxicity [37], suggesting that mitochondrial fusion alone might not be sufficient and that other pathways, such as calcium handling by mitochondria, might be involved.

Links between calcium and mitochondrial structure and function are well documented. For example, sustained calcium release from the ER cause DRP1-dependent mitochondrial fragmentation [60], while Miro, a mitochondrial protein containing a EF-hand calcium binding domain, regulates mitochondrial transport in a calcium dependent manner. Interestingly, MFN2 has recently been shown to tether mitochondria and ER, affecting ER calcium content [17]. The close association between ER and mitochondria is indeed thought to be critical for calcium handling. A possible link between mitochondrial calcium and OPA1 activity was also recently highlighted by the observation that LETM1, a mitochondrial EF-hand-containing protein, affects OPA1 processing and mitochondrial structure [61]. Calcium-induced modulation of OPA1 activity could potentially help preserve mitochondrial structure at higher calcium load by maintaining cristae structure.

In addition to the influence of the core fission/fusion machinery, mitochondrial movements play an important role in calcium handling. Mitochondria are transported in an anterograde fashion along microtubules by the motor protein Kinesin-1, which binds to mitochondria through an adaptor complex formed of Miro and Milton [62, 63]. In the presence of high calcium levels, Kinesin-1 is dissociated from microtubules through the action of calcium-bound Miro, concentrating mitochondria at sites of high calcium concentration. This serves two purposes: it allows increased buffering of calcium by mitochondria and also increases local ATP production to help pump calcium out of the cell. The significance of this was highlighted by the observation that a Miro mutant that did not respond to calcium increased NMDA toxicity. Overexpression of Miro can also increase mitochondrial length, which could further help buffering calcium [63]. However, as mitochondrial fission is required for proper distribution of mitochondria to synaptic terminals, the balance between fission, fusion and mitochondrial movements rather than

activation of one or the other is likely to be the critical readout. This is exemplified by the mitochondrial phenotype in Alzheimer's disease neurons, where both fission and fusion proteins are affected, resulting in a reduced axonal distribution of mitochondria [64]. In that context, expression of DRP1 improved synaptic function following Amyloid- β treatment by promoting the redistribution of mitochondria to synapses.

Concluding Remarks

In summary, a strong link has been uncovered in recent years between cell death and mitochondrial dynamics. Several questions remain however, especially with regards to excitotoxicity where the interplay between fission/fusion and mitochondrial movements is likely to play a critical role. For example, it still remains to be determined whether fusion *per se* is protective, or if other cytoprotective roles of fusion proteins (such as signalling functions) are the dominant factor. The balance between fission and fusion also needs to be taken in account, as fission is required to distribute mitochondria to their proper location within the cell. Given these caveats, modulation of these pathways will likely have far-reaching consequences beyond the regulation of calcium signalling described here, but that warrant further research.

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Figure Legends

Figure 1. **Regulation of mitochondrial fission/fusion**

(A) Mitofusins (Mfn1 and Mfn2) are located on the outer mitochondrial membranes (OMM) and regulate fusion of the OMM. Mfns interact on apposing mitochondria to mediate their tethering (Arrow 1). This results in OMM fusion (Arrow 2). OPA1, an intermembrane space GTPase which is found in association with the inner mitochondrial membrane (IMM), mediates fusion of IMM (Arrow 3). (B) The key regulator of mitochondrial fission is Dynamin Related Protein 1 (DRP1). DRP1 is a cytosolic GTPase which is recruited to the mitochondria at the site of scission (Arrow 1). DRP1 forms a ring like structure on the mitochondria surface. The energy from the GTP hydrolysis drives constriction of the membranes (Arrow 2).

