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Impairing the Mitochondrial Fission and Fusion Balance: A New Mechanism of Neurodegeneration

Andrew B. Knott[1] and **Ella Bossy-Wetzel**[1,*]

[1] Burnett School of Biomedical Sciences, College of Medicine, University of Central Florida

Abstract

Mitochondrial dysfunction is a common characteristic of all neurodegenerative diseases. However, the cause of this dysfunction remains a mystery. Here, we discuss the potential role of mitochondrial fission and fusion in the onset and progression of neurodegenerative diseases. Specifically, we propose that an imbalance in mitochondrial fission and fusion may underlie both familial and sporadic neurodegenerative disorders. There is substantial evidence that links disruption of the mitochondrial fission and fusion equilibrium, resulting in abnormally long or short mitochondria, to neurodegeneration. First, hereditary mutations in the mitochondrial fusion GTPases optic atrophy-1 (OPA1) and mitofusin-2 (Mfn2) cause neuropathies in humans. In addition, recent findings report increased mitochondrial fission in Parkinson's disease (PD) models and induction of mitochondrial fission by two proteins, PTEN-induced kinase 1 (PINK1) and Parkin, which are mutant in familial forms of PD. Furthermore, mutant huntingtin, the disease-causing protein in Huntington's disease (HD), alters mitochondrial morphology and dynamics. Rotenone, a pesticide and inducer of PD symptoms, and amyloid-β (Aβ) peptide, which is causally linked to Alzheimer's disease (AD), initiate mitochondrial fission. Finally, mitochondrial fission is an early event in ischemic stroke and diabetic neuropathies. In sum, a growing body of research suggests that a better understanding of mitochondrial fission and fusion and the regulatory factors involved may lead to improved treatments and cures for neurodegenerative diseases.

Keywords

Huntington's disease; Parkinson's disease; GTPases; OPA1; Mitofusins; Drp1; PINK1; Parkin

Role of Mitochondria in Neurons

Neurons are highly specialized cells that face unique challenges in carrying out their important physiological functions. First, neurons are active cells and thus require large amounts of energy. Furthermore, some neurons have extremely long processes, with axons extending up to one meter in motor neurons. Thus, neurons must transmit energy across long distances. Finally, neurons are highly interactive cells whose major function is communication. Thus, neurons have a tightly regulated signaling system that relies on delicate balances of ions in synapses and the efficient functioning of ion channels, receptors, and pumps.

Mitochondria help neurons meet the challenges they face. Mitochondria provide most of the energy for neurons through oxidative phosphorylation and are thus critical to neuronal function. Mitochondria provide the energy for ATP-dependent entities and processes such as

*Corresponding author: Ella Bossy-Wetzel, Ph.D., University of Central Florida, Burnett School of Biomedical Sciences, College of Medicine, 4000 Central Florida Blvd., Orlando, FL 32816, Tel.: +(407) 823 4756, Fax: +(407) 823 0956, E-mail: ebossywe@mail.ucf.edu.

ion channels, receptors, and pumps, vesicle release, and recycling of neurotransmitters.[1-3] Importantly, mitochondria have the ability to fuse, divide, and migrate to provide energy throughout the extended neuronal processes. In addition to their role in energy production, mitochondria often accumulate at synapses and play an important role in synaptic maintenance through their ability to buffer Ca^{2+}. Thus, considering how much neurons depend on mitochondria, it should come as no surprise that there is a strong link between mitochondrial dysfunction and neurodegenerative diseases.

Mitochondrial Dysfunction in Neurodegeneration

Mitochondrial dysfunction is an early event in virtually all common neurodegenerative diseases, including Huntington's disease (HD), Parkinson's disease (PD), Alzheimer's disease (AD), amyotrophic lateral sclerosis (ALS), stroke, and epilepsy.[4] More recent findings suggest that mitochondrial dysfunction may also play a role in psychiatric disorders including bipolar disorder and depression.[5,6] Indicators of mitochondrial dysfunction observed in neurodegenerative diseases include ultrastructural changes, respiratory complex inhibition, decreased ATP production, increased free radical production, mtDNA deletions, impaired Ca^{2+} buffering, and loss of mitochondrial membrane potential.[4]

Much of the recent research on HD has focused on mitochondrial dysfunction. HD mice exhibit early defects in respiration and ATP production.[7] In addition, 3-nitroproprionic acid (3-NP), a mitochondrial complex II inhibitor, produces HD-like symptoms and mutant huntingtin itself seems to disrupt complex II activity.[8] Mutant huntingtin also seems to disrupt mitochondrial Ca^{2+} buffering [9,10] and cause mitochondrial ultrastructural changes in HD patient lymphoblasts.[11] Finally, several recent studies suggest that peroxisome proliferator-activated receptor gamma co-activator 1 alpha (PGC-1α), a master transcriptional regulator of many mitochondrial proteins including those associated with oxidative stress defense and respiration, is underactive in HD and this decreased activity may contribute to mitochondrial impairment.[12-14]

Several observations suggest a link between mitochondrial dysfunction and PD. First, inhibitors of mitochondrial respiratory chain complex I, such as rotenone and MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine), cause PD symptoms.[15,16] In addition, mutant proteins in familial forms of PD, including alpha-synuclein, LRRK2, Parkin, PINK1, and DJ-1, associate with the mitochondrial membranes and may play a role in ROS production and/or defense.[17-21] Finally, a mutation in the protein HTRA2/OMI, which resides in the intermembrane space, causes familial PD and expression of the mutated gene in cultured cells causes a loss of mitochondrial membrane potential and mitochondrial swelling.[22]

Oxidative damage is an early event in AD.[23] In addition, amyloid-β peptide inhibits cytochrome c oxidase activity and increases reactive oxygen species (ROS) production.[24,25] Both of these observations suggest a link between mitochondrial dysfunction and AD, because oxidative stress, cytochrome c, and ROS are associated with mitochondria. In addition, recent research indicates that a widespread reduction in glucose metabolism rates across many brain regions is an indicator of future conversion to AD in age-associated cognitive decline patients.[26]

Mitochondrial Fragmentation and Neurodegeneration

While mitochondrial dysfunction is evident in neurodegeneration, its precise role in disease progression is unclear and the mechanism(s) of its origin are not well understood. One potential cause of mitochondrial dysfunction is uncontrolled mitochondrial fission. Disruption of the carefully orchestrated balance between mitochondrial fission and fusion, promoting either excessive fusion or fission, can negatively affect cell function and viability.

Fission/fusion defects may limit mitochondrial motility, decrease energy production, promote oxidative stress, lead to mtDNA deletion, and impair Ca^{2+} buffering, all of which could lead to neuronal death. Research suggests that many of the mitochondrial defects associated with HD, PD, and AD could result, at least in part, from disruption of the fission/fusion mechanisms.

Mechanisms of Mitochondrial Fission and Fusion

Mitochondria are dynamic organelles that actively divide and fuse to mix metabolites and mtDNA copies to adjust to the constantly changing energy demands of the cell. A group of conserved, large dynamin-related GTPases maintains the critical balance between mitochondrial fission and fusion. Drp1 is a key mediator of mitochondrial fission.[27,28] Fis1 in yeast and its mammalian homologue hFis1 are also involved in mitochondrial fission, likely playing a role in Drp1 recruitment to the mitochondria.[29,30] While the precise mechanism of mitochondrial fission in mammals remains a mystery, genetic studies in yeast provide a potential model. The favored model of mitochondrial fission suggests that Drp1 assembles into rings or spirals surrounding the mitochondrial outer membrane with the help of hFis1 and other unknown cofactors and regulators.[31] GTP hydrolysis is thought to cause a conformational change in Drp1 that drives the mitochondrial outer membrane fission event.

In contrast to fission, mitochondrial fusion requires both outer and inner membrane components. Mitofusins 1, 2 (Mfn1, 2) facilitate outer membrane fusion in mammals likely through trans interactions that promote membrane curvature and fusion.[32-34] Studies suggest that the GTPase OPA1 is the main mediator of inner membrane fusion and maintenance of mtDNA in mammals.[35-40] The mechanism of inner membrane fusion is unknown, but findings indicate that two distinct isoforms of OPA1, produced by proteolytic cleavage, are necessary for successful fusion events.[41-43]

Linking Mitochondrial Fragmentation to Neurodegeneration

Mutations in fusion GTPases cause neurodegenerative diseases and mitochondrial dysfunction in mice and humans.[44-46] For example, Mfn2 mutations cause Charcot-Marie-Tooth subtype 2A (CMT2A), a human peripheral neuropathy.[47,48] Patients with CMT2A exhibit muscle weakness and axonal degeneration of motor and sensory neurons. OPA1 mutations cause autosomal dominant optic atrophy (ADOA), the most common form of optic atrophy characterized by progressive blindness and degeneration of retinal ganglion cells and the optic nerve.[49-51] New studies have also identified novel mutations in OPA1 that result in 'ADOA-plus' phenotypes characterized by mtDNA instability, deafness, and movement disorders in addition to traditional ADOA symptoms.[39,52] Since mutations in mitochondrial fusion proteins, which result in increased mitochondrial fragmentation, cause neurodegenerative disease, there is good reason to hypothesize that mitochondrial fragmentation may contribute to the pathology of diseases such as PD, AD, and HD.

First, rotenone, a pesticide that causes PD symptoms in mice and humans, induces mitochondrial fission.[53] In addition, Aβ peptide seems to induce mitochondrial fragmentation.[53] Furthermore, while the role of transcriptional dysregulation in HD (via PGC-1α) has been the focus of much recent attention, the direct effects of mutant huntingtin on mitochondria, such as ultrastructural changes, morphological alterations, and calcium handling defects,[9,11] may result from excessive mitochondrial fission. Interestingly, mutant huntingtin seems to bind directly to the mitochondrial outer membrane in transgenic mice 9 and forms large foci similar to Drp1.[27,28] Further supporting the role of mitochondrial fission in HD, Chang and coworkers recently reported that mutant huntingtin aggregates impair mitochondrial motility and trafficking.[54] Their imaging data show mitochondria that

resemble those that have undergone irreversible fission. However, because of limitations in their image analysis, the authors could not conclude if they were observing a simple change in mitochondrial morphology, fission, or both.

One final observation that may suggest a link between mitochondrial fragmentation and neurodegeneration is the fragmentation of other organelles, such as Golgi and endoplasmic reticulum (ER), in neurodegenerative diseases. For example, Golgi fragmentation occurs *in vivo* in human AD and ALS patients 55 and it seems that Golgi fragmentation acts downstream of mitochondrial fragmentation and may play a causal role in neuronal cell death initiation.56 Thus, it is interesting to consider the possible connection between and hierarchy of different organelle fragmentations in neurodegeneration. Chronic organelle fragmentation, including mitochondria, may be a central pathway of neurodegeneration. Where these events fall in the neurodegenerative cascade and their potential causative role remain unclear and are topics for future research.

How is Fission Turned On?

Because we now suspect that excess mitochondrial fission is an important and early event in neurodegenerative disease, it is important to understand what can activate the fission machinery. New findings indicate that oxidative and nitrosative stress appear to be important inducers of mitochondrial fission.53›57 In addition, research suggests that DNA damage 57›58 and elevated glucose levels may stimulate mitochondrial fission.59›60 Finally, recent studies continue to indicate that aberrant activation of cell cycle components in post-mitotic neurons may play an important role in the regulation of the mitochondrial fission machinery, such as Drp1.

The deleterious effects of oxidative stress resulting from increased levels of reactive oxygen species (ROS), including DNA, membrane, and protein damage, are well recognized. However, recent research indicates that oxidative stress also stimulates mitochondrial fission. Jahani-Asl and coworkers recently reported that hydrogen peroxide treatment of cultured cerebellar granule neurons induced mitochondrial fragmentation within one hour of treatment.57 In addition, we recently found that nitric oxide caused pronounced mitochondrial fission in neurons prior to the onset of neuronal loss and in a mouse model of stroke.53 Interestingly, expression of Mfn or dominant negative Drp1 in cultured neurons is protective against oxidative insults.53›57

DNA damage is another event that can trigger mitochondrial fission. Importantly, research has shown that DNA damage is a common physiological event after stroke and trauma and contributes to neuronal loss.58 Recently, Jahani-Asl and coworkers found that neurons exposed to the topoisomerase camptothecin, which mimics physiological DNA damage, exhibit increased mitochondrial fragmentation beginning 3-6 hours after exposure and have a profoundly altered mitochondrial pool by 12 hours.57 Interestingly, mitochondrial fragmentation begins well before nuclear degradation and neuronal death, indicating that mitochondrial fission (triggered by DNA damage) precedes and may contribute to neuronal death in stroke and trauma models.

High glucose levels during diabetes result in neuronal injury and diabetic neuropathies.59 Thus, it is important to consider the effect of high glucose on mitochondrial function. Recent research by Leinninger and coworkers indicates that dorsal root ganglion neurons (DRGs) exposed to high glucose exhibit mitochondrial dysfunction, oxidative stress, and fragmented mitochondria.59 In addition, high glucose levels increase Drp1 expression and affect its localization to mitochondria in DRGs. Diabetic rats also exhibit increased Drp1 expression. 59 In addition, high glucose causes increased Drp1/Bax complexes, which have been shown to mediate apoptotic mitochondrial fragmentation.61¯63 Thus, it is reasonable to speculate

that increased mitochondrial fission plays an important role in the pathology of diabetic neuropathies.

As one might expect, mitochondrial fission is a regular event during cell division,64 allowing dividing cells to maintain an adequate supply of the energy-producing organelles. Thus, it should come as no surprise that components of the cell cycle machinery help regulate mitochondrial fission. For example, mitosis-promoting factor (MPF, Cdk1/cyclin B) phosphorylates Drp1 and seems to stimulate mitochondrial fragmentation.65 Interestingly, several studies indicate that cell cycle proteins such as cyclin-dependent kinases (Cdks) are upregulated in neurodegenerative disease. For example, there is increased expression of cell cycle regulators in brain samples of PD 66 and AD (reviewed by Herrup). 67 In addition, MPTP, a neurotoxin that causes PD-like symptoms, induces a significant increase in Cdk2 and Cdk4 expression in CGNs.68 Furthermore, thrombin, a serine protease associated with AD symptomology,69,70 induces Cdk4 activity in cortical neurons.71 Importantly, a broad-spectrum Cdk inhibitor (FLAV) and Cdk4 inhibitors protect neurons from MPTP- and thrombin-induced cell death, respectively.68,71 Finally, transient cerebral ischemia in rats up-regulates Cdk4 and inhibition of Cdk4 activity is highly neuroprotective. 72

Taken together, these findings indicate some correlation between neurodegenerative disease and increased activity of cell cycle proteins. However, whether this correlation represents aberrant activation of the cell cycle or a simple dysfunction in protein expression is unclear. Most importantly, we must further explore the possible link between activation of cell cycle proteins and increased mitochondrial fission in neurodegenerative diseases. While the phosphorylation of Drp1 by Cdk1 is a clear link between mitochondrial fission and the cell cycle, the relevance of the observed increases in Cdk activity in disease models to mitochondrial fission, if any, remains a question for future research.

In sum, oxidative stress, DNA damage, high glucose levels, and aberrant cell cycle activity are all potential triggers of mitochondrial fission in neurons. However, the relative importance to disease pathology of fission in each of these distinct situations remains unclear and further research is necessary to help identify the most promising treatment avenues. For example, while antioxidant therapies are a conceptually appealing answer to oxidative stress, antioxidant treatment in humans has many potential limitations. First, such treatments are reactive and likely cannot undo damage accumulated before treatment begins. Second, oxidative stress is a complex mechanism, mediated by many different types of reactive molecules that, in addition to their toxic capabilities, have important physiological functions. The therapeutic potential of cell cycle inhibitors is less clear and the potential value of reversing mitochondrial fission in diabetic neuropathies and diseases associated with DNA damage is uncertain. Finally, the therapeutic potential of mitochondrial fission inhibitors, such as the newly identified mdivi-1 (mitochondrial division inhibitor-1) that selectively blocks Drp1 activity and retards apoptosis by inhibiting mitochondrial outer membrane permeability, in the treatment of human neurodegenerative disease is an important question for future research.73 Thus, while many questions remain unanswered, the prevalence of mitochondrial fission as an early event in neurodegenerative diseases warrants further exploration of all of these areas for development of potential treatments.

How Might Disease-Specific Proteins Interfere With the Fission/Fusion Machinery?

Because there is good reason to believe that mitochondrial fragmentation plays an important role in the development and progression of neurodegenerative diseases, it is important to consider the possible ways in which disease-specific proteins may interfere with the fission/

fusion machinery. Recent research has provided both concrete and circumstantial links between disease-specific proteins and mitochondrial fission and fusion. Disease-specific proteins potentially associated with fission/fusion include proteins mutated in familial PD, PINK1, Parkin, α-synuclein (α-Syn), and HTRA2/OMI, and the mutant protein that causes HD, mutant huntingtin (mtHtt).

The most concrete link between disease-specific proteins and the mitochondrial fission/fusion system is the ability of the PINK1/Parkin pathway to promote mitochondrial fission in drosophila.74 Further supporting the importance of mitochondrial fission in disease pathology, Poole and coworkers found that reduced mitochondrial fission caused the loss of tissue and mitochondrial integrity in PINK1/Parkin mutants and stimulating fission by expressing Drp1 or blocking OPA1 was protective.74 Interestingly, heterozygous Drp1 mutations were lethal in PINK1/Parkin mutants, but were not lethal in PINK1/Parkin wildtype drosophila. This raises the possibility that PINK1, a kinase, and/or Parkin, an E3-ubiquitin ligase, may regulate Drp1 through phosphorylation or ubiquitination. Previous research suggests that both phosphorylation and ubiquitination play a role in the activation of Drp1.65›75

These results underscore an often overlooked concept – the importance of the mitochondrial fission/fusion balance to organismal viability. Though we have yet to determine if these findings in drosophila correlate to human PD, this study shows us that mitochondrial fission, while often painted in a negative light because of its role in cell death, is vital for proper mitochondrial function because it facilitates mitochondrial distribution and proliferation and perhaps provides a mechanism for isolation and packaging of damaged mitochondrial components for clearance by autophagy.76 Along this line, we have previously shown that nitric oxide-induced fission can be reversible and is associated with autophagosome activity.53 In addition, a new study indicates that Drp1 interaction with the anti-apoptotic molecule Bcl-xL stimulates synaptic formation.77 Finally, further illustrating the importance of mitochondrial fission to human health and development, Waterham and coworkers recently identified a lethal mutation in the mitochondrial fission protein Drp1 in a newborn human patient that presented with microcephaly, lactic acidemia, and optic atrophy.78

In addition to the link between familial PD mutations and mitochondrial fission in a drosophila model, several other observations suggest a potential role for other disease-specific proteins in the modification of the mitochondrial fission and fusion apparatus. For example, mtHtt localizes to the mitochondrial outer membrane and forms large clusters.9 This localization pattern is similar to the localization of the fission protein Drp1 prior to mitochondrial fission. In addition, the loss of mtDNA, the defective transport of mitochondria, and the reduction in mitochondrial length seen in HD are all characteristic of mitochondrial fission/fusion imbalance.54 Finally, the possible relationship between PD mutant proteins α-Syn and HTRA2/OMI and mitochondrial fission and fusion factors has not been adequately explored, despite the observed localization of both proteins to mitochondria and the prominent role of mitochondrial dysfunction in disease pathology.79›80

In sum, there is sufficient evidence to suggest that the mutant molecules that cause neurodegenerative diseases may modulate, directly or indirectly, the mitochondrial fission and fusion machinery. Further exploration of these potential interactions may help us better understand the pathology of both familial and sporadic neurodegenerative diseases and may speed the development of new and more effective treatments.

Impact and Outlook

Here we have proposed that mitochondrial fission and fusion imbalance is a common and causal event in many neurodegenerative diseases. While mitochondrial fission and fusion is not a new concept, its role in the initiation and progression of neurodegenerative disease has not been adequately explored. A better understanding of the fission/fusion GTPases, their structure, function, and the mechanisms of their activation and regulation, will allow for the development of treatments and therapies to target the mitochondrial fission/fusion system.

The link between mitochondrial fission and fusion imbalance and neurodegenerative diseases continues to grow stronger. First came the discovery that mutations in the mitochondrial fusion GTPases OPA1 and Mfn2 cause ADOA and CMT2A, respectively. Next, there is growing evidence suggesting that mutant proteins that cause more common diseases such as HD and familial forms of PD interact with fission/fusion GTPases and/or disrupt the fission/fusion balance. If we are able to further establish and characterize these potential links, the final task will be to determine the role of these proteins and their interactions in sporadic disease forms and develop treatments directed at these new targets.

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