

Mitochondrial dynamics—fusion, fission, movement, and mitophagy—in neurodegenerative diseases

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Neurons are metabolically active cells with high energy demands at locations distant from the cell body. As a result, these cells are particularly dependent on mitochondrial function, as reflected by the observation that diseases of mitochondrial dysfunction often have a neurodegenerative component. Recent discoveries have highlighted that neurons are reliant particularly on the dynamic properties of mitochondria. Mitochondria are dynamic organelles by several criteria. They engage in repeated cycles of fusion and fission, which serve to intermix the lipids and contents of a population of mitochondria. In addition, mitochondria are actively recruited to subcellular sites, such as the axonal and dendritic processes of neurons. Finally, the quality of a mitochondrial population is maintained through mitophagy, a form of autophagy in which defective mitochondria are selectively degraded. We review the general features of mitochondrial dynamics, incorporating recent findings on mitochondrial fusion, fission, transport and mitophagy. Defects in these key features are associated with neurodegenerative disease. Charcot-Marie-Tooth type 2A, a peripheral neuropathy, and dominant optic atrophy, an inherited optic neuropathy, result from a primary deficiency of mitochondrial fusion. Moreover, several major neurodegenerative diseases—including Parkinson's, Alzheimer's and Huntington's disease—involve disruption of mitochondrial dynamics. Remarkably, in several disease models, the manipulation of mitochondrial fusion or fission can partially rescue disease phenotypes. We review how mitochondrial dynamics is altered in these neurodegenerative diseases and discuss the reciprocal interactions between mitochondrial fusion, fission, transport and mitophagy.

INTRODUCTION

In the past decade, our view of mitochondrial dynamics has expanded from a curious phenomenon into an integral cell biological process influencing many cellular functions and ultimately survival (1,2). Once thought to be solitary and rigidly structured, mitochondria are now appreciated to constitute a population of organelles that migrate throughout the cell, fuse and divide, and undergo regulated turnover. These dynamic processes regulate mitochondrial function by enabling mitochondrial recruitment to critical subcellular compartments, content exchange between mitochondria, mitochondrial shape control, mitochondrial communication with the cytosol and mitochondrial quality control. As a result, mitochondria can readily adapt to changes in cellular requirements, whether

due to physiological or environmental imperatives. When mitochondrial dynamics is disrupted, cellular dysfunction ensues. Here we discuss the human diseases associated with abnormalities in mitochondrial dynamics.

DISEASES OF MITOCHONDRIAL FUSION: CONVERGING PHENOTYPES

Three mammalian proteins are required for mitochondrial fusion (1): Mfn1 and Mfn2 for outer membrane fusion, and OPA1 for inner membrane fusion (3,4). Mouse knockouts of each of these three genes result in embryonic lethality and mitochondrial dysfunction (5–7). Mutations in *Mfn2* cause Charcot-Marie-Tooth type 2A (CMT2A), a peripheral

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neuropathy affecting sensory and motor neurons of the distal extremities (8). Mutations in *OPA1* are the predominant cause of autosomal dominant optic atrophy (DOA), a degeneration of retinal ganglia cells that leads to optic nerve atrophy (9,10). A frequently asked question is why mutations in two proteins both required for mitochondrial fusion should cause two diseases with such different tissue specificity. Potential answers include differential expression patterns between *Mfn2* versus *OPA1*, functional differences between *OPA1* (11) and *Mfn2* (12), differences in an outer membrane fusion defect versus an inner membrane fusion defect (4) and redundancy between *Mfn1* and *Mfn2* (6,13).

Although all of these explanations may apply, more overlap in the clinical manifestations of CMT2A and DOA has emerged with the study of additional affected families. In addition to optic atrophy, some DOA patients present with additional symptoms, including peripheral motor-sensory neuropathy. Sensorineural deafness, cerebral atrophy, cerebellar ataxia, chronic progressive external ophthalmoplegia, mitochondrial myopathy and psychiatric involvement can also manifest (14,15). Similarly, some CMT patients with *Mfn2* mutations suffer from optic atrophy as well as deafness, cognitive dysfunction, cerebral and cerebellar abnormalities, vocal cord paresis, scoliosis, parkinsonism and psychiatric involvement (16–21). In addition, the same mutation (e.g. R94W) can generate a large range of phenotypes even within the same family. Therefore, modifying factors clearly play a role in determining manifestation of the diseases. In fact, one patient with an *OPA1* mutation notably does not have optic atrophy, but instead displays ptosis, hearing loss, proximal weakness, psychiatric involvement and muscle mitochondrial dysfunction (22).

In summary, mutations in either *OPA1* or *Mfn2* can impact a broad range of tissues beyond the optic and peripheral nerves. The overlapping symptoms in DOA and CMT2A families suggest that *OPA1* and *Mfn2* mutations can affect certain tissues in a similar way. Interestingly, the widespread CNS involvement and myopathies are reminiscent of mtDNA mutation syndromes. Indeed, *OPA1* ‘plus’ patients actually harbor mitochondrial DNA (mtDNA) deletions in their muscle cells, suggesting a role for mitochondrial fusion in maintaining mtDNA integrity (14,15).

IMPACT OF MITOCHONDRIAL FISSION ON FUNCTION

As in yeast (*Dnm1*), flies (*Drp1*) and plants (*DRP3B*), mitochondrial fission in mammals is mediated by a dynamin-like protein, *Drp1* (1). *Drp1* is a predominantly cytosolic protein that is recruited to mitochondria during fission. In yeast, this recruitment is clearly dependent on the mitochondrial outer membrane protein *Fis1* (2). In mammalian cells, however, knockdown of *Fis1* blocks mitochondrial fission without affecting *Drp1* localization to mitochondria (23). Recent studies have identified another tail-anchored outer membrane protein, *Mff*, which is involved in mitochondrial fission. Knockdown of *Mff* causes mitochondrial elongation and resistance to CCCP-induced fragmentation (24). Blue native gel studies show that *Fis1* and *Mff* reside in complexes of

different sizes, suggesting distinct machineries for mitochondrial fission. The potential role of *Mff* in *Drp1* recruitment to mitochondria remains to be tested.

Although no inherited diseases are known to result from mutation of these genes, one case of neonatal lethality has been attributed to a defect in *Drp1* (25). This patient carried a dominant-negative allele that caused perinuclear tangles of elongated, large-diameter mitochondria. Symptoms included optic atrophy, a notably small head with abnormal brain development and hypoplasia. Lactic acid levels were elevated in the blood and even more so in the cerebral spinal fluid (CSF). Muscle and fibroblasts showed normal respiratory function, but it seems likely that neuronal cells had electron transport chain (ETC) abnormalities, given the extreme lactic acid concentrations in the CSF and the brain structural defects. In cell culture studies, down-regulation of *Drp1* in HeLa cells causes slower cell growth, loss of mtDNA, uncoupling of the ETC, decreased cellular respiration and increased reactive oxygen species levels (26).

Therefore, like mitochondrial fusion, fission seems to be required to maintain mitochondrial function. The mechanisms, however, probably differ. Fusion is likely to protect function by providing a chance for mitochondria to mix their contents, thus enabling protein complementation, mtDNA repair and equal distribution of metabolites. Fission likely acts instead to facilitate equal segregation of mitochondria into daughter cells during cell division and to enhance distribution of mitochondria along cytoskeletal tracks. In addition, fission may help to isolate damaged segments of mitochondria and thus promote their autophagy as discussed below (27). When these protective mechanisms fail, mitochondrial fission can also promote apoptosis, an important topic that has been extensively reviewed (28).

EMERGING ASPECTS OF MITOCHONDRIAL DYNAMICS

Perturbations in mitochondrial fusion, fission, motility and turnover can lead to distinctive defects in neurons (Fig. 1). However, there is also substantial overlap in these defects, because these four processes are interdependent. The reciprocal interactions between these processes are becoming appreciated, but our molecular understanding is still sparse.

Mitophagy

Autophagy is a process whereby cellular components are degraded by engulfment into autophagosomes. Autophagosomes fuse with lysosomes, which contain hydrolytic enzymes that break down cellular components. During nutrient deprivation, the products can be recycled into more urgently needed molecules. Although autophagy plays a particularly prominent role during starvation, it also appears to have a housekeeping role in maintaining quality control by turning over organelles and degrading protein aggregates. Mitophagy denotes the degradation of mitochondria through autophagy. Although the existence of mitophagy has been known for some time, it has been unclear whether mitochondria are randomly or selectively targeted for mitophagy.

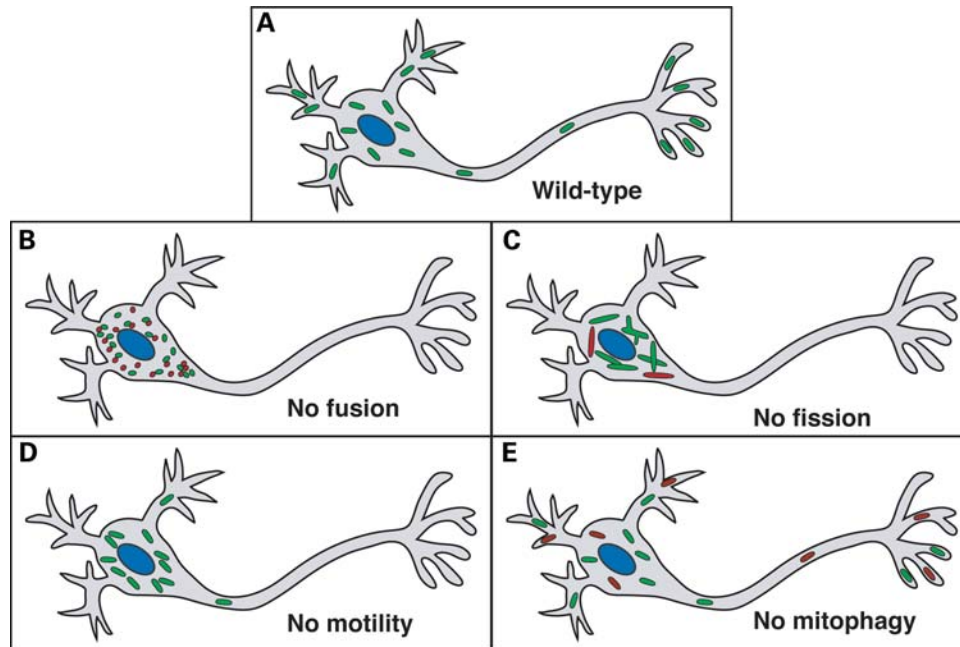


Figure 1. Defects in mitochondrial dynamics that lead to neuronal dysfunction. (A) In wild-type neurons, mitochondria travel long distances from the cell body out to dendritic and axonal termini, where they play important roles in ATP production and calcium homeostasis. (B) In the absence of fusion, the mitochondrial population fragments and a subset show ultrastructural defects and dysfunction (red). The mitochondria secondarily have transport defects that prevent proper distribution to the periphery. (C) In the absence of fission, the mitochondrial population is excessively long and interconnected, and a subset shows dysfunction (red). These large mitochondria cluster within the cell body and are not efficiently transported to the periphery. (D) Primary defects in mitochondrial motility prevent distribution of mitochondria to the periphery. (E) In the absence of mitophagy, abnormal mitochondria (red) accumulate.

Several recent findings indicate that mitophagy can selectively degrade defective mitochondria. In yeast cells, mitophagy is regulated independently from bulk autophagy (29). Mitochondria that are damaged by a laser irradiation in hepatocytes are selectively removed by mitophagy (30). Studies in pancreatic β -cells and COS7 cells show that mitochondrial fission can yield uneven products, with one depolarized daughter mitochondrion and one hyperpolarized mitochondrion (27). Such depolarized mitochondria are much less likely to fuse, have reduced levels of OPA1 protein, and are eventually autophagocytosed. This mitophagy is dependent on loss of fusion and the presence of fission, because OPA1-overexpression, Fis1 RNAi, and Drp1 dominant-negative expression all reduce levels of mitophagy. When mitophagy is thus compromised, oxidized proteins accumulate, and cellular respiration and insulin secretion decrease. It is important to note that although mitochondrial fragmentation is permissive for mitophagy, it is not a sufficient signal for mitophagy (27,31).

Mitochondrial motility

Another aspect of mitochondrial dynamics beyond fusion and fission is the motility of mitochondria. This aspect is critically important in highly polarized cells, such as neurons (32), which require mitochondria at sites distant from the cell body, but can also be crucial to cellular function in smaller cells (33). Defects in both fusion and fission have been shown to decrease mitochondrial movement. Presumably, the large tangle of highly interconnected mitochondria in fission-deficient cells prevents efficient movement, especially

into small pathways such as neuronal processes (34,35). In fusion-deficient cells, the cause of decreased motility is less clear. Empirically, however, fusion-deficient mitochondria display loss of directed movement, instead hovering in a manner reminiscent of Brownian motion (6). In neurons lacking mitochondrial fusion, both increased mitochondrial diameter due to swelling and aggregations of mitochondria seem to block efficient entry into neurites, resulting in a dearth of mitochondria in axons and dendrites (36). These defects result in improperly developed neurons or gradual neurodegeneration.

Mitochondrial transport in mammalian cells is largely microtubule based (32). Anterograde motion is driven by the kinesin-1 motor (KHC, Kif5b), which interacts with mitochondria through the outer membrane proteins Miro1 and Miro2 (37). In *Drosophila*, Milton is an adapter protein that mediates binding of Miro to kinesin. High local concentrations of calcium act through the EF hands of Miro to halt mitochondrial movement, and thus retain mitochondria at sites where ATP production and Ca^{++} buffering are needed (38–40). Loss of this Miro-dependent transport pathway in neurons results in depletion of mitochondria from dendrites and axons, resulting in neurotransmission defects during prolonged stimulation (41).

How this mitochondrial transport apparatus interacts with the fusion/fission machinery is unclear, but most likely involves indirect interactions. Deletion of Miro in yeast greatly affects mitochondrial morphology without disrupting mitochondrial fusion or fission (42). Likewise in mammalian cells, manipulation of Miro can dramatically affect mitochondrial shape (39,43,44). Disruption of dynein function, which is

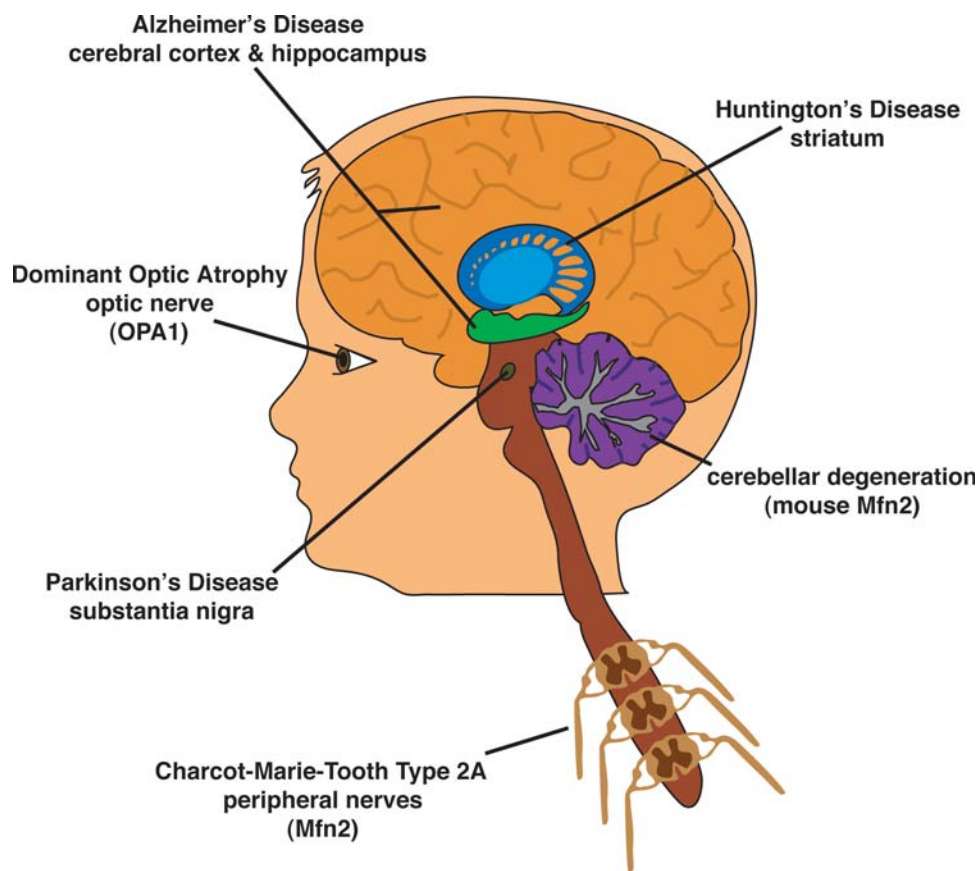


Figure 2. Neurodegenerative disease associated with defects in mitochondrial dynamics. Neuronal systems affected in neurodegenerative disease are shown. For each disease, only the primary affected regions are indicated, but there is evidence for more widespread involvement.

necessary for retrograde transport of mitochondria, sequesters Drp1 in the cytoplasm and results in perinuclear, elongated mitochondria (45). Therefore, mitochondrial fusion and fission defects secondarily impair motility, and conversely, transport defects affect mitochondrial morphology. However, the mechanisms underlying this interplay remain to be determined.

NEURODEGENERATIVE DISEASES INVOLVING MITOCHONDRIAL DYNAMICS

Aside from diseases such as DOA and CMT2A caused by perturbation of mitochondrial fusion, mitochondrial dynamics seems to impact a wide variety of human diseases through interactions with other cellular processes. Many of these diseases are neurodegenerative and affect many distinct regions of the brain as well as the peripheral nervous system (Fig. 2), again emphasizing the importance of mitochondrial function in maintaining healthy neurons.

Parkinson's disease

Progressive loss of dopaminergic neurons in the substantia nigra leads to Parkinson's disease (PD), the second most common neurodegenerative disease in humans. The most prominent PD symptoms include a resting tremor, rigidity, bradykinesia and a characteristic unsteady gait. Both chemical

and genetic lines of evidence strongly suggest mitochondrial involvement. Drugs that inhibit complex I of the ETC produce PD-like symptoms in humans and animal models. The majority of PD cases are sporadic with unclear etiology. However, ~10% of PD cases are inherited, and linkage analysis has identified a number of PD-associated genes. Two genes identified in hereditary PD are Pink1 and Parkin, both of which have been shown to be important for mitochondrial integrity (46). Pink1 is a serine/threonine kinase with an N-terminal mitochondrial targeting sequence and is localized to both mitochondria and the cytosol. Parkin is a cytosolic E3 ubiquitin ligase with two RING fingers, cysteine- and histidine-containing protein motifs that coordinate zinc ions.

Studies of mammalian Pink1 and Parkin have been complicated by the fact that mouse knockouts have little phenotype and fail to reproduce the common symptoms of PD (47–49). However, mitochondria from both knockouts demonstrate mild defects in respiration and sensitivity to oxidative stress (47,49–51). Additional studies show that loss of Pink1 can result in abnormalities in mitochondrial morphology, but the effects differ among cell types. Loss of Pink1 in human dopaminergic neurons or primary mouse neuronal cultures leads to reduced viability accompanied by abnormal, swollen mitochondria (52). Mitochondria from Pink1^{-/-} mouse striatal neurons show no gross ultrastructural changes, although a small increase in the number of large mitochondria is observed (50). Knockdown of Pink1 in COS7 cells also increases

mitochondrial size through tubulation. This effect is suppressed by hFis1 or Drp1 over-expression (53). In contrast, PD patient fibroblasts were reported to contain fragmented mitochondria (54). Similarly, knockdown of Pink1 in HeLa cells and human neuronal SH-SY5Y cells causes mitochondrial fragmentation, an effect reversed by over-expression of Parkin (54,55).

Whereas mouse knockouts of Pink1 or Parkin have subtle phenotypes, the corresponding mutants in flies show severe mitochondrial dysfunction in multiple tissues (56–59). Both mutants are remarkably similar, marked by flight muscle degeneration accompanied by swollen mitochondria with disrupted cristae. Double mutants have a similar phenotype. Parkin over-expression restores muscle integrity and flight to *pink1* mutants, but Pink1 over-expression in *parkin* mutants has no effect. These findings have led to the model that Pink1 and Parkin likely act in the same pathway, with Parkin downstream of Pink1 (56,58,59). Consistent with this model, there is biochemical evidence for a direct interaction between Pink1 and Parkin (60).

How does the Pink1/Parkin pathway regulate mitochondrial function? Recent genetic studies in flies suggest that Pink1 and Parkin act to promote mitochondrial fission or inhibit fusion (53,61,62). Over-expression of *Drp1* or down-regulation of *Marf/Mfn2* (a fly homologue of mammalian Mfns) or *OPA1* can dramatically ameliorate the phenotypes of *pink1* or *parkin* mutant flies, including flight muscle degeneration, abnormal wing posture and defects in climbing and flying. These striking observations indicate a genetic interaction between the Pink1/Parkin pathway and mitochondrial dynamics. However, some observations suggest that the relationship may not be direct. For example, the epistatic relationship of Pink1/Parkin to mitochondrial fusion and fission is not straightforward. With regard to mitochondrial morphology in muscle, *drp1*, *marf* and *opa1* mutations are epistatic to *pink1* and *parkin* mutations. In the testicular mitochondria, however, a *pink1* mutation is epistatic to an *fzo* mutation (61). Furthermore, although *pink1* or *parkin* mutants have some enlargement of mitochondria, this morphological change is accompanied by increased apoptosis and is different from that of *drp1* mutants. In addition, a synthetic lethal interaction is seen in *pink1*-null, *drp1*-heterozygous flies. These data indicate that Pink1/Parkin do not act in a simple linear pathway with either mitochondrial fission or fusion.

In the studies of PD, interpretation of the functions of Pink1 and Parkin have been complicated by the discrepancies in mitochondrial morphology defects found among various mammalian cell lines and between the fly and mammalian model systems. Such complexity is also apparent in studies of Alzheimer's disease (AD) and Huntington's disease (HD) (later). In part, these discrepancies may suggest that Pink1 and Parkin do not directly regulate mitochondrial fusion or fission in a straightforward manner. Mitochondrial morphology is highly dependent on mitochondrial physiology, and therefore it can be difficult to interpret changes in mitochondrial shape. In particular, the cause of mitochondrial fragmentation can be indirect, because it frequently accompanies mitochondrial dysfunction. In *Caenorhabditis elegans*, an RNAi screen revealed that disruption of over 80% of

mitochondrial genes leads to mitochondrial fragmentation and/or aggregation, showing that this morphological phenotype is an extremely common one and not necessarily an indication of a specific effect on mitochondrial fusion or fission (63).

Recent studies implicate Parkin in the turnover of mitochondria through mitophagy. Parkin is specifically recruited to mitochondria with low membrane potential, and these targeted mitochondria are then destroyed through the autophagosome (31). The mitochondrial accumulation of Parkin is voltage-dependent, and does not depend on changes in pH or ATP levels (64). These experiments suggest that Parkin may act as a sensor for mitochondrial integrity and trigger mitophagy upon dysfunction. It is unclear whether Pink1 is involved in this pathway. Knockdown of Pink1 in SH-SY5Y cells induces mitochondrial fragmentation, accumulation of mitochondrially-targeted autophagosomes and increased cell death (55). Inhibition of Drp1 prevents mitochondrial fragmentation and mitophagy, but exacerbates cell death. Co-expression of Parkin, though, increases mitophagy and decreases cell death while at the same time preventing mitochondrial fragmentation. In this case, mitochondrial morphology itself does not appear to be the critical component in determining cell fate. Rather, the functional state of the mitochondrial population appears to govern the cellular outcome. Taken together, these results suggest that Pink1 protects mitochondrial function, whereas Parkin promotes mitochondrial quality control by eliminating dysfunctional mitochondria. In future studies, it will be important to test whether Parkin-deficient cells from PD patients indeed have a defect in mitophagy.

Alzheimer's disease

The most common neurodegenerative disease, AD, is marked by cognitive dysfunction and memory loss caused by neuronal death in the cerebral cortex. Afflicted brains carry intracellular neurofibrillary tangles and extracellular amyloid plaques composed chiefly of beta-amyloid (A β) derived from amyloid precursor protein (APP). Although the pathological mechanism for AD is still unknown, the predominant hypothesis is that excess A β production results in cellular toxicity. Transgenic mouse models over-expressing APP lead to amyloid plaques associated with activation of inflammatory cells, localized loss of neurons, and some cognitive behavioral changes (65).

Abnormalities in mitochondrial structure are found in the brain of AD patients (66). A β can localize to mitochondria, and this interaction has been suggested to underlie in part their cytotoxic effects (67,68). Exposure of neuronal cells to conditioned medium from cells stably expressing mutant forms of APP leads to increased mitochondrial fission, loss of dendritic spines and eventually cell death (69). This increase in mitochondrial fission was traced to elevated levels of S-nitrosylated Drp1 (SNO-Drp1), which is suggested to have increase fission activity due to enhanced dimerization. Expression of Drp1(C644A), a mutant incapable of nitrosylation, prevents excessive mitochondrial fission and neuronal cell injury without interfering with normal, basal levels of mitochondrial fission. Moreover, increased levels of SNO-Drp1 were found in brain samples from AD patients and AD mouse models. These data suggest that the cytotoxic

effects of A β result, in part, from generation of nitric oxide that leads to activation of Drp1 activity.

In contrast, another study found that fibroblasts from sporadic AD patients express lower levels of Drp1 and display elongated mitochondria which form collapsed perinuclear networks (70,71). The same group, however, found that APP over-expression in M17 neuroblastoma cells resulted in predominantly fragmented mitochondria, decreased levels of Drp1 and OPA1, and a defect in neuronal differentiation (72). Over-expression of Drp1 or OPA1 could partially rescue different aspects of these defects.

Huntington's disease

Progressive loss of striatal and cortical neurons leads to cognitive and motor impairment and eventually death in patients with HD. Whereas multiple genes have been associated with PD and AD, HD is an autosomal dominant disease caused by trinucleotide expansion [cytosine, adenine, and guanine (CAG)] within a single gene, huntingtin (Htt). Disease is associated with CAG expansion leading to a stretch of glutamines beyond 35 residues in Htt. In HD patients and mouse transgenic HD models, several lines of evidence indicate that expression of mutant Htt is associated with mitochondrial dysfunction (73). For example, Htt expression correlated with elevated lactate levels, decreased mitochondrial membrane potential, decreased respiratory function through complex II, defects in mitochondrial calcium uptake, reduced mitochondrial mobility and mitochondrial ultrastructural changes. In animal models, 3-nitropropionic acid, an irreversible inhibitor of complex II, can cause HD-like symptoms. Conversely, over-expression of complex II subunits can prevent cell death in striatal neurons carrying mutant Htt.

Recent studies uncover an interplay between HD and mitochondrial dynamics. Rat cortical neurons treated with 3-nitropropionic acid have fragmentation and condensation of mitochondria which can be prevented by antioxidant treatment (74). Likewise, mitochondria in HeLa cells over-expressing a mutant Htt with a 74 glutamine repeat (Htt74Q) show fragmentation of mitochondria, reduced mitochondrial fusion, reduced ATP and increased cell death (75). Remarkably, expression of either dominant-negative Drp1 or Mfn2 not only prevents this change in mitochondrial morphology, but also restores ATP levels and attenuates cell death. Inhibition of Drp1 can also rescue the mobility of worms expressing Htt74 in muscle cells.

Because increasing fusion or reducing fission can partially rescue mutant Htt over-expression, it is possible that mutant Htt disrupts fusion and fission. However, it is unclear whether such a direct relationship exists. Mutant Htt can associate with mitochondria (76), but the biochemical function of Htt remains poorly understood. It is possible that, in some cellular environments, manipulation of fusion and fission rates can improve the physiology of mitochondria even if the initial insult is not directly on fusion or fission. Mutant Htt expression has multiple effects on mitochondrial physiology, including respiratory dysfunction and reduced transport. Htt72Q transgenic mice display a generalized transport defect in neurons (77), including abnormal movement of mitochondria (76–78). The mitochondria move more slowly, stop more frequently and travel shorter distances. Defects in

membrane potential, respiratory distress and inefficient transport can all secondarily contribute to the morphological defects associated with mutant Htt expression.

PERSPECTIVE

Taken together, the studies reviewed here clearly indicate that perturbations in mitochondrial dynamics are directly or indirectly involved in a host of human neurodegenerative diseases. However, our understanding of the mechanisms involved remains rudimentary at best. There exists much conflicting data among different disease models, especially regarding the mitochondrial morphological changes associated with disease states and the mechanisms underlying these changes. Several factors likely contribute to these discrepancies. First, the variations in mitochondrial phenotypes suggest that although PD, AD and HD clearly perturb mitochondrial dynamics, the effects are unlikely to result from simple, direct effects on the processes of fusion and fission. Second, it is becoming increasingly clear that a myriad of factors can affect mitochondrial shape. For each disease, it will be important to dissect the key underlying mechanisms.

As we learn more about how neurodegenerative diseases impact mitochondria, it is becoming clear that mitochondrial dynamics is a multi-factorial process that is integrated into cell physiology. Mitochondrial fusion and fission play prominent roles in controlling mitochondrial shape and function. However, these opposing processes have reciprocal interactions with mitochondrial transport and mitophagy. Therefore, several inter-related factors—fusion, fission, transport and turnover—form a complex interacting network that governs mitochondrial function and thereby cellular integrity. A challenge for future studies is to unravel the molecular nature of these interactions. Given that manipulation of genes controlling mitochondrial fusion and fission can ameliorate disease phenotypes, there is compelling reason to hope that efforts to artificially manipulate mitochondrial dynamics (79) will ultimately lead to new therapeutic approaches.

Conflict of Interest statement. None declared.

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NOTE ADDED IN PROOF

Mihara (80) and colleagues have recently disrupted Drp1 in mice and have provided additional evidence for the role of mitochondrial fission in neuronal development. Embryonic neurons lacking Drp1 show improper mitochondrial distribution consistent with Figure 1 and increased sensitivity to apoptosis.

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