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Review

The interplay of neuronal mitochondrial dynamics and bioenergetics: Implications for Parkinson's disease

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ABSTRACT

The dynamic properties of mitochondria (mitochondrial fission, fusion, transport biogenesis and degradation) are critical for neuronal function and health, and dysregulation of mitochondrial dynamics has been increasingly linked to the pathogenesis of Parkinson's disease (PD). Mitochondrial dynamics and bioenergetics are interconnected, and this is of particular importance in neurons, which have a unique bioenergetic profile due to their energetic dependence on mitochondria and specialized, compartmentalized energetic needs. In this review, we summarize the interplay of mitochondrial dynamics and bioenergetics, and its particular relevance for neurodegeneration. Evidence linking dysregulation of mitochondrial dynamics to PD is presented from both toxin and genetic models, including newly emerging details of how PD-relevant genes PTEN-induced kinase 1 (PINK1) and Parkin regulate fission, fusion, mitophagy and transport. Finally, we discuss how neuronal bioenergetics may impact PD-relevant regulation of mitochondrial dynamics, and possible implications for understanding the role of mitochondrial dynamics in PD.

Contents

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Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disorder, but the etiology is still unknown. Only a fraction of all cases (~10%) are suspected to be associated with known heritable genetic mutations, with most cases classified as idiopathic. Pathologically, PD is classically characterized by degeneration of the pigmented dopaminergic neurons of the substantia nigra, the loss of which is responsible for the PD-associated movement disorders, in addition to degeneration of other neuronal populations. Hallmarks of PD-affected neurons include evidence of excessive oxidative stress, protein damage, and, most importantly, mitochondrial dysfunction.

For over three decades, research into PD has recognized the key involvement of dysfunctional mitochondria in disease pathophysiology (for review, see Beal, 2007; Lin and Beal, 2006; Schapira, 2006). Evidence that mitochondrial bioenergetic dysfunction is an important pathogenic component in PD arises, for example, from studies linking dysfunction of mitochondrial electron transport chain (ETC) complex I to PD (Blandini et al., 1998; Haas et al., 1995; Krige et al., 1992; Parker et al., 1989; Schapira et al., 1989), as well as from findings that many of the genes whose mutations cause familial PD are involved in mitochondrial function and homeostasis (Greenamyre and Hastings, 2004; Martin et al., 2011). More recently, growing evidence suggests that defects in regulation of the *dynamic* properties of mitochondria — including fission, fusion, transport, biogenesis, and degradation through autophagy (mitophagy) — may be involved in PD pathogenesis. Regulation of mitochondrial dynamics is critical for maintaining properly functioning mitochondria, protecting mitochondrial DNA (mtDNA), and distributing mitochondria to synapses to allow proper synaptic function (Dickey and Strack, 2011; Gegg et al., 2009; Li et al., 2004; Li et al., 2008; MacAskill et al., 2009; Mironov, 2009; Nakada et al., 2001; Ono et al., 2001; Parone et al., 2008; Stowers et al., 2002; Westermann, 2012), and dysregulation of these properties has been associated with both toxin and genetic models of PD.

As contemporary research elucidates the role of mitochondrial homeostasis in neuron health and neurodegeneration, it is clear that bioenergetic status is also intertwined with mitochondrial dynamics. Interaction of bioenergetics with mitochondrial dynamics likely has particular relevance to neurons, since neurons are unique in their bioenergetic dependence on mitochondrial oxidative phosphorylation (OxPhos) for ATP production, rather than glycolysis, and their exit from the cell cycle. Thus, mitochondrial bioenergetic–dynamic interactions are likely particularly important in understanding the selective neuropathogenesis in PD. In this review, we will discuss the relevance and importance of mitochondrial dynamics to neuronal health, and their interactions with bioenergetics. We will provide an overview of what is known about mitochondrial dynamics with regard to PD, focusing on a neuronal bioenergetics perspective, and will assess some of the key questions remaining within this field.

A brief review of mitochondrial dynamics

As noted above, the dynamic properties maintaining mitochondrial homeostasis include mitochondrial fission, fusion, biogenesis, degradation through mitophagy, and transport, henceforth collectively referred to as “mitochondrial dynamics”. These mitochondrial processes interact to maintain ETC function and electrical connectivity of mitochondria; prevent build-up of damaged proteins; protect mtDNA integrity; control mitochondrial turnover; and regulate cell death mechanisms (Bereiter-Hahn and Jendrach, 2010). In addition, in neurons, fission and fusion are critical for proper synapse formation and function (Li et al., 2004, 2008). While a large body of the work on mitochondrial dynamics and the machinery involved was originally carried out in yeast, many of the involved proteins have homologues in mammalian cells, and most, if not all, dynamic processes are evolutionarily conserved (Okamoto and Shaw, 2005; Palmer et al., 2011b). The machinery and specific mechanisms involved in mitochondrial fission, fusion, transport, and mitophagy have been reviewed fully elsewhere (Detmer and Chan, 2007; Palmer et al., 2011b; Wang and Klionsky, 2011) and will be reviewed only briefly here.

Fission of mitochondria, requiring coordinated division of the inner and outer mitochondrial membranes, is in part mediated in mammalian cells via the cytosolic GTPase Dynamin-related protein 1 (Drp1) (Palmer et al., 2011b). In yeast, the Drp1 homologue, Dnm1, translocates to the outer mitochondrial membrane (OMM) via recruitment by the outer membrane protein Fis1 (Mozdy et al., 2000). However, the role of Fis1 in mammalian cells is still not fully elucidated. While mammalian Fis1 has been shown to interact with Drp1, some reports suggest that knockdown of Fis1 still allows for recruitment of Drp1 and subsequent fission (Lee et al., 2004; Wasiak et al., 2007; Yoon et al., 2003). Recently, other OMM proteins have been identified as possible recruiters of Drp1, including mitochondrial fission factor (Mff) and mitochondrial dynamics proteins 49 and 51 kDa (MiD49, MiD51) (Otera et al., 2010; Palmer et al., 2011a). Other recently described proteins have been suggested to mediate fission, including the inner mitochondrial membrane (IMM) protein MTP18, whose ability to promote fission is dependent on Drp1 expression; and the OMM protein ganglioside-induced differentiation-associated protein1 (GDAP1) (Niemann et al., 2005; Tondera et al., 2005).

Mediating complete fusion of mitochondria requires coordination between proteins on both the IMM and OMM. Outer membrane fusion is mediated by the dynamin-like GTPases mitofusin-1 and -2 (Mfn1 and Mfn2) (Cerveny et al., 2007). Fusion of the inner membrane is mediated by optic atrophy protein (Opa1) (Griffin et al., 2006). Fusion can occur either as a complete event (with a prolonged length of time preceding an associated fission event) or as a transient event (followed almost instantaneously by fission), termed “kiss-and-run” (Liu et al., 2009).

Transport of mitochondria within a cell is also of particular importance in neurons, as it is necessary for synaptic formation and function, via proper distribution of mitochondria throughout neurites. Anterograde axonal transport of mitochondria along microtubules is mediated by association of mitochondria with kinesin family motor proteins KIF1Bα and KIF5, while retrograde transport of mitochondria is mediated by interaction with cytosolic dynein (reviewed in Hirokawa et al., 2010; Hollenbeck and Saxton, 2005). Several facilitator proteins have also been identified for anterograde transport, including the proteins Miro and Milton/TRAK1|2/OIP196|98/GRIF-1 (henceforth referred to as Milton) (Cai et al., 2011; Guo et al., 2005; Stowers et al., 2002). These proteins form an adapter complex between KIF5 and the mitochondrion (Cai et al., 2011; Hirokawa et al., 2010). Via this complex, Miro regulates mitochondrial transport in axons in both a calcium-dependent manner and a Miro-abundance-dependent manner (Liu et al., 2012; MacAskill et al., 2009; Wang and Schwarz, 2009; Wang et al., 2011c).

Damaged or dysfunctional mitochondria, specifically those unable to undergo fusion or repair themselves, undergo macroautophagic degradation, called mitophagy, in which they are engulfed by an autophagosome and ultimately digested via the autophagy-lysosome pathway (Twig and Shirihai, 2011; Twig et al., 2008a; Wang and Klionsky, 2011). Mitophagy has been well characterized in yeast, with the *autophagy-related gene 32* protein, Atg32, serving as the mitochondrial receptor for autophagy, which then interacts with Atg8 and Atg11 to recruit mitochondria to the autophagic vacuole. The mammalian counterpart of Atg8 is the autophagic membrane protein LC3 (Wang and Klionsky, 2011). Though the mammalian homologue of Atg32 has yet to be identified, recent studies show that the mitochondrial outer membrane protein Nix can interact with LC3 and mediate mitophagy (Kanki, 2010).

In contrast to the above, however, the specific mechanisms responsible for the generation of new mitochondria, termed biogenesis, are not well characterized. Markers of increased or ongoing biogenesis can be examined, however, including generation of new mtDNA, increased mitochondrial biomass, and expression of proteins involved in bioenergetic regulation, such as components of the ETC (Amiri and Hollenbeck, 2008; Arnold et al., 2011; Oliveira, 2011). Biogenesis has also been inferred from levels of the transcriptional co-activator PGC-1α, which regulates expression of many genes involved in metabolism and mitochondrial bioenergetics (Arany et al., 2005; Fan et al., 2004; Handschin et al., 2003; Lin et al., 2005). Biogenesis has been less well studied directly in neurons, but there is evidence of biogenesis occurring both in cell bodies and in axons (Amiri and Hollenbeck, 2008).

The interplay of mitochondrial dynamics and bioenergetic status: particular relevance to neurons

The variance in and dynamic nature of mitochondrial size, shape, and position has been observed for nearly 100 years (Lewis and Lewis, 1914). The different morphologies and ultrastructural profiles of mitochondria have long been known to correlate to the differing bioenergetic demands of the tissues they occupy, and neuronal mitochondria are distinct from those of other tissues in morphology, interconnectivity, and location (reviewed in Benard and Rossignol, 2008; Kuznetsov et al., 2009; Mironov, 2009). Thus, it would not be surprising that regulation of fission, fusion, biogenesis and degradation would also differ among tissues. Only recently have advances in organelle labeling and live-cell imaging allowed for the detailed characterization of phenomena such as fission, fusion, degradation, biogenesis, and interactions with other cellular organelles, such as ER, among different cell types (Friedman et al., 2011; Mitra and Lippincott-Schwartz, 2010).

Bioenergetics and mitochondrial dynamics are intertwined

Mitochondrial networks are constantly undergoing remodeling via cycles of fission and fusion (Westermann, 2012). Bioenergetic state, in part, dictates and even drives the fission–fusion balance of mitochondrial dynamics (Twig et al., 2008b). This can be observed in immortalized cell lines, where transition from a glycolytic to OxPhos-dependent state elicits dramatic changes in mitochondrial network morphology when compared to their glycolytic counterparts (Rossignol et al., 2004). Conversely, multiple studies have demonstrated that defects in mitochondrial respiration can result in fragmented mitochondria and truncated networks (reviewed in Knott et al., 2008; Nakamura and Lipton, 2010). In turn, alterations in mitochondrial dynamics can also alter the bioenergetic state of both individual mitochondria and of the cell. Genetic mutation and/or inhibition of fission and fusion machinery result in dysfunctional mitochondrial networks, morphology, respiration, and homeostasis (Alexander et al., 2000; Arnoult et al., 2005; Barsoum et al., 2006; Griparic et al., 2004; Palau et al., 2009; Van Bergen et al., 2011; Zuchner et al., 2004). Thus, the cell and its mitochondria depend on an intricate balance of bioenergetics and mitochondrial dynamics. Below are some examples of how fission, fusion, and biogenesis can influence, and be influenced by, mitochondrial and cellular bioenergetic status.

Fusion and mitochondrial bioenergetic status

Mitochondrial fusion has been shown to require an intact mitochondrial membrane potential (Legros et al., 2002; Mattenberger et al., 2003). Inability to fuse following depolarization or damage may result from damage-mediated regulation of fusion-mediating proteins. OPA1 is cleaved, or otherwise reduced in abundance, following mitochondrial damage (Duvezin-Caubet et al., 2006; Ishihara et al., 2006; Song et al., 2007), and both Mfn1 and 2 are targets for ubiquitination and proteasomal degradation following mitochondrial depolarization by proton ionophores (Gegg et al., 2010; Glauser et al., 2011; Rakovic et al., 2011; Tanaka et al., 2010). It is also possible that ultrastructural conformational changes within mitochondria, that alter interactions of inner and outer membranes following depolarization (Benard and Rossignol, 2008; Biermans et al., 1990; Knoll and Brdiczka, 1983) affect the proper coordination of fusion machinery.

Fission and mitochondrial bioenergetic status

Fission, by comparison, appears to progress regardless of mitochondrial membrane potential, but is upregulated following mitochondrial damage. Mitochondrial insults, including depolarization, oxidation or nitrosylation, and ETC inhibition, have been shown to trigger rapid, Drp1-dependent mitochondrial fragmentation (reviewed in Nakamura and Lipton, 2011; Sauvanet et al., 2010). Unregulated fission contributes to the population of depolarized mitochondria (Twig et al., 2008a), with mitochondrial fragmentation a proposed precursor to apoptosis and cell death, particularly in neurodegeneration (Knott and Bossy-Wetzel, 2008; Knott et al., 2008). Somewhat unexpectedly, both inhibition and enhancement of fission, through alterations in levels of fission proteins, have been reported to reduce mitochondrial membrane potential (Dickey and Strack, 2011; Parone et al., 2008). These types of bioenergetic changes may have particular importance in compartmentalized neurons, where mitochondrial membrane potential fluctuations were shown to be the downstream effectors of fission/fusion-mediated regulation of synaptogenesis and dendrite complexity (Dickey and Strack, 2011).

Fusion–fission and mitochondrial homeostasis

In addition, the fusion–fission cycle appears to be involved in regulating degradation and repair of bioenergetically-impaired mitochondria (Liu et al., 2009; Twig et al., 2008a). Fission events that follow transient fusion events were reported to result in one polarized and one relatively depolarized daughter mitochondrion (Twig et al., 2008a). Often, the more-depolarized mitochondrion was destined for one of two fates: either fusion with a polarized mitochondrion or mitophagic degradation (Twig et al., 2008a). Fusion can also rescue mitochondria from accumulated mtDNA mutations and damaged proteins, and can protect against accumulation of depolarized mitochondria (Nakada et al., 2001; Ono et al., 2001; Twig and Shirihai, 2011). Thus, the fusion–fission cycle serves to maintain a healthy mitochondrial population and preserve bioenergetic function, where fusion can serve as a "rescue" pathway (Twig and Shirihai, 2011).

Biogenesis and degradation in bioenergetic homeostasis

Bioenergetic changes are also closely interconnected to mitochondrial biogenesis and degradation. Energy deprivation, resulting in decreased ATP levels coupled with an increased AMP/ATP ratio, activates the metabolic sensor AMP-activated protein kinase

(AMPK). AMPK then phosphorylates downstream targets to activate energy-conserving pathways (reviewed in Weisova et al., 2011). Recently, it was reported that starvation-induced mitophagy was dependent on activation of AMPK (Egan et al., 2011). On the other hand, AMPK activation is *also* necessary for mitochondrial biogenesis to occur after energy deprivation (Bergeron et al., 2001; Hardie, 2004; Hardie and Sakamoto, 2006). Thus, bioenergetic changes may link coordination between mitochondrial dynamic functions. Although activation of AMPK is known to be protective in models of neurotoxicity (Weisova et al., 2011), the role of this pathway in mitochondrial dynamics in neurons has not been elucidated.

The bioenergetic profile of neurons and neuronal dependence on mitochondrial dynamics: implications for neurodegeneration

The goal of maintaining a functional population of healthy mitochondria becomes more complicated in neurons, largely owing to their cellular morphology and bioenergetic demands. In the cellular world, neurons are unique, possessing a characteristic morphology with extensive neuritic projections, existing in a post-mitotic state, and depending on mitochondrial OxPhos respiration as their primary source of energy production (reviewed in Attwell and Laughlin, 2001; Mironov, 2009; Rolfe and Brown, 1997). 20% of the body's total oxidative metabolism is carried out by the central nervous system, with neurons generating as much as 95% of their ATP exclusively from mitochondrial OxPhos (reviewed in Attwell and Laughlin, 2001; Erecinska and Silver, 1994; Mironov, 2009; Rolfe and Brown, 1997). Failure to maintain this bioenergetic status is suggested to play a primary role in neuronal death and disease (Beal, 2007; Lin and Beal, 2006).

Preserving health in this existence is dependent upon the proper maintenance of a healthy population and distribution of functional mitochondria. Neurons have both a highly interconnected network located in the soma, and a series of separated, individual mitochondria that travel up and down the narrow, extensive axons and dendrites. This neuritic mitochondrial population is tasked with providing energy for synaptic development and function (reviewed in Ly and Verstreken, 2006; Mironov, 2009; Zinsmaier et al., 2009), and for cellular processes far removed from the cell body. Further, multiple studies have demonstrated that dysregulation of transport, fission, or fusion greatly alters synapse formation and function (Li et al., 2004; Li et al., 2008; Verstreken et al., 2005). Thus, the neuron's own morphology and function dictate an important role for mitochondrial distribution in maintaining bioenergetic status in all parts of the cell, which requires a delicate balance of mitochondrial dynamics.

Not surprisingly, then, dysfunction of mitochondrial dynamics has been directly linked to neurodegeneration. Loss-of-function mutations in Mfn2 are associated with Charcot–Marie–Tooth neuropathy type 2A (CMT2a) (Zuchner et al., 2004), and OPA1 fusion protein mutations that disable the GTPase domain cause autosomal dominant optic atrophy (ADOA) (Alexander et al., 2000). Recent interest has expanded beyond peripheral neuropathies to investigating the potential role of mitochondrial dynamics dysfunction in neurodegenerative diseases associated with aging (Chen and Chan, 2009; Han et al., 2011; Knott and Bossy-Wetzel, 2008). The strongest evidence of a role for dysregulation of mitochondrial dynamics is in Parkinson's disease, where evidence for the key role of dysfunctional mitochondrial dynamics is rapidly growing (Van Laar and Berman, 2009).

Evidence of a role for mitochondrial dynamics in PD pathogenesis

As previously mentioned, mitochondrial dysfunction has long been linked to the pathophysiology of PD, but it is more recently that dysregulation of mitochondrial *dynamics* has been implicated in the disease. Although the specific roles that alterations in mitochondrial dynamics play in PD pathophysiology remain unknown, both toxin models of PD and genetic links are providing clues to the interplay of mitochondrial function, mitochondrial dynamics, and PD pathogenesis.

PD-relevant environmental toxins and mitochondrial dynamics

Mitochondrial ETC dysfunction, in particular, complex I inhibition, has long been a focus of PD research, owing largely to the discovery of systemic mitochondrial respiration complex dysfunction in PD patients (Blandini et al., 1998; Haas et al., 1995; Krige et al., 1992; Parker et al., 1989; Schapira et al., 1989). Environmentally-encountered toxins, such as the meperidine analog MPTP (found as a contaminant in synthetic heroin) and the pesticide rotenone, induce respiration inhibition at complex I of the ETC, and mimic the pathology of PD in in vivo animal models (Martinez and Greenamyre, 2012). These compounds have also been found to alter mitochondrial dynamics in vitro.

In vitro exposure to the toxic metabolite of MPTP, MPP+, causes DRP1-dependent mitochondrial fragmentation in neuronally-derived SH-SY5Y cells and primary rat dopaminergic neurons (Wang et al., 2011d). Mitophagy was also increased in primary neurons following MPP+ (Zhu et al., 2007). In neuronally-differentiated dopaminergic PC12 cells and isolated squid axoplasm, MPP+ exposure results in altered neuritic mitochondrial velocities, with reduced anterograde transport, while increasing retrograde transport (Cartelli et al., 2010; Morfini et al., 2007). Thus, MPTP toxicity is relevant to, and influences several aspects of, mitochondrial dynamics preceding cell death.

Both acute and chronic exposures to rotenone affect not only ETC function, but also mitochondrial dynamics. When applied acutely to both non-neuronal and primary cortical neurons in culture, high concentrations of rotenone induce mitochondrial fission (Barsoum et al., 2006; Plecita-Hlavata et al., 2008). In primary neurons, acute rotenone-induced cell death was ameliorated by increasing fusion or inhibiting fission via exogenous overexpression of Mfn1 or dominant-negative Drp1, respectively (Barsoum et al., 2006). Subacute rotenone was reported to alter mitochondrial transport dynamics in neurites of differentiated SH-SY5Y cells (Borland et al., 2008). In addition, rotenone can alter microtubules (Choi et al., 2011; Ren et al., 2009; Srivastava and Panda, 2007), and this could potentially affect not only transport, but also fission/fusion, since mitochondrial fission proteins interact with tubulin (Estela et al., 2011).

Chronic, lower-dose, nonlethal rotenone in vitro treatment models, which more closely mimic the in vivo model treatment paradigm (Betarbet et al., 2000), have also been established in cultured cell lines and primary cells (Arnold et al., 2011; Sherer et al., 2001; Sherer et al., 2002). Chronic rotenone was found to alter mitochondrial calcium signaling dynamics and basal mitochondrial membrane potential of undifferentiated SH-SY5Y cells (Sherer et al., 2001). We developed a chronic low-dose rotenone in vitro model using primary rat cortical neurons and the dopaminergic PC6-3 cell line (Arnold et al., 2011). Using techniques to directly observe fission and fusion in living cells, we found evidence of early, likely compensatory, increases in mitochondrial fusion, followed by later increases in fission in neurons (Arnold et al., 2011). We also found that inhibiting mitochondrial fission protected against the loss of neurites in differentiated PC6-3 cells (Arnold et al., 2011). The collective results of these studies suggest that mitochondrial dynamics of fission, fusion, transport, and mitophagy are altered in response to PD-related toxins such as rotenone, and also implicate fission in an early pathological role in toxin-induced cell death in PD models.

Genetic models of PD and mitochondrial homeostasis

Many of the genes associated with familial forms of PD, including α-synuclein, DJ-1, leucine-rich repeat kinase 2 (LRRK2), Parkin, and PTEN-induced putative kinase 1 (PINK1), have been found to influence mitochondrial energetic function in various pathways (Greenamyre

and Hastings, 2004; Martin et al., 2011). These same PD genes have also been linked to maintenance of mitochondrial dynamics, suggesting that dysregulation of mitochondrial function *and* homeostasis may be a common pathogenic mechanism in PD. Here we will discuss their known impacts specifically on mitochondrial dynamics.

α-Synuclein

Mutations in the α-synuclein gene locus *SNCA* result in an autosomal dominant inheritance of parkinsonism (Kruger et al., 1998; Polymeropoulos et al., 1997; Singleton et al., 2003; Zarranz et al., 2004). Largely a cytosolic and presynaptic protein, the specific function of α-synuclein is not well understood. Studies have found it can interact with the mitochondria (Li et al., 2007; Nakamura et al., 2011), and that α-synuclein can be imported into the mitochondria, where it can interact with and inhibit Complex 1, potentially affecting mitochondrial bioenergetic function and oxidative stress (Devi et al., 2008). α-Synuclein expression can also influence mitochondrial susceptibility to ETC inhibitors, including MPP+ and rotenone (Orth et al., 2003; Wu et al., 2009), and transgenic mouse models have demonstrated various mitochondrial abnormalities, including increased oxidative damage to mitochondrial proteins and DNA, decreased ETC complex function, and increased susceptibility to mitochondrial inhibitors (Martin et al., 2006; Poon et al., 2005; Song et al., 2004). With regard to mitochondrial dynamics, overexpression of α-synuclein was reported to inhibit mitochondrial fusion, leading to fragmented mitochondria, whereas α-synuclein knockdown led to elongated mitochondria (Kamp et al., 2010). Evidence suggests that the α-synuclein-induced fragmentation occurs from direct interaction of the protein with mitochondrial membranes and is not dependent on fission protein Drp1 (Nakamura et al., 2011). Further, the fragmentation preceded a loss of mitochondrial OxPhos function, suggesting that α-synuclein–mitochondrial interaction influences mitochondrial dynamics *prior to* functional alterations (Nakamura et al., 2011). Most notably, α-synuclein-induced fragmentation was rescued by overexpression of the wildtype forms of PD-related proteins PINK1, Parkin, or DJ-1 (Kamp et al., 2010), linking multiple PD genes to common mechanistic effects on mitochondrial dynamics. Lastly, overexpression of the PD-linked A53T α-synuclein mutation was reported to increase mitophagy both in primary neurons and DA neurons in vivo (Chinta et al., 2010; Choubey et al., 2011), suggesting a need for increased mitochondrial turnover in association with the PD-linked mutant protein.

DJ-1

Mutations in the DJ-1 gene are associated with autosomal-recessive parkinsonism (Bonifati et al., 2003). DJ-1 has been shown to be a multifunctional protein with antioxidant, transcriptional-regulation, and possibly peroxiredoxin-like activities (Andres-Mateos et al., 2007; Blackinton et al., 2009a; Ramsey and Giasson, 2008). Typically a cytosolic protein, oxidation of a cysteine at position 106 regulates translocation of DJ-1 to mitochondria, and is crucial to its functions within mitochondria (Blackinton et al., 2009b; Canet-Aviles et al., 2004). In fibroblasts, DJ-1 mutant or knockout decreased mitochondrial membrane potential and increased fragmentation of mitochondria (Krebiehl et al., 2010), similar to recent findings in human neuroblastoma cells (Wang et al., 2012a). In primary astrocytes, loss of DJ-1 reduced mitochondrial motility, as well as mitochondrial fusion in cell bodies, but not processes (Larsen et al., 2011). Knockdown also enhanced the mitochondrial depolarization response to rotenone in astrocytes (Larsen et al., 2011), and reduced the protective effect astrocytes exert over rotenone-exposed neurons in culture (Mullett and Hinkle, 2009). Loss of DJ-1 in cortical neurons caused shortened mitochondrial morphology along with reduced fusion (Irrcher et al., 2010; Krebiehl et al., 2010), and increased mitophagy (Thomas et al., 2011). Notably, changes in mitochondrial morphology after loss of DJ-1 were prevented by PD-related proteins PINK1 and Parkin (Irrcher et al., 2010), again suggesting a common functional pathway.

Leucine-rich repeat kinase 2 (LRRK2)

Mutations in the LRRK2 gene, which cause an autosomal-dominant form of parkinsonism, account for the largest fraction of heritable forms of PD, and have also been associated with sporadic cases of PD (Paisan-Ruiz et al., 2004; Tsika and Moore, 2012; Zimprich et al., 2004). LRRK2 is a large, multi-domain protein kinase whose normal biological function is as yet unknown (Tsika and Moore, 2012). In mammalian brain and primary rat neurons, LRRK2 is found throughout the cytoplasm, localized to various membrane structures and organelles, including lysosomes, endosomes, endoplasmic reticulum, Golgi complex, and the outer mitochondrial membrane (Alegre-Abarrategui et al., 2009; Biskup et al., 2006; Dodson et al., 2012). Not surprisingly, LRRK2 has been shown to modulate various organelle functions throughout the neuron, including neurite morphology, autophagy, and mitochondrial homeostasis, which have been thoroughly reviewed elsewhere (Martin et al., 2011; Tsika and Moore, 2012). Here, we will focus on several known effects of LRRK2 on mitochondrial function and dynamics.

Primary fibroblasts from LRRK2-mutant PD patients exhibit multiple markers of mitochondrial dysfunction, including reduced membrane potential, lower ATP levels, and increased length and interconnectivity (Mortiboys et al., 2010). Ramonet et al. (2011) found that, in addition to dopaminergic degeneration, aged transgenic mutant LRRK2 mice exhibited increased numbers of damaged and soma-aggregated mitochondria, and evidence of increased mitophagy, in cerebral cortex tissue (Ramonet et al., 2011). Recently, overexpression of WT and PD-relevant mutant LRRK2 in SHSY5Y cells and primary rat cortical neurons was similarly shown to decrease mitochondrial membrane potential and ATP levels, while increasing ROS levels (Wang et al., 2012b). This study also suggests that LRRK2 may directly modulate mitochondrial fission and fusion rates, since overexpression of WT and mutant LRRK2 led to increased mitochondrial fragmentation in both SH-SY5Y cells and primary rat cortical neurons (Wang et al., 2012b). LRRK2 was found to reduce the rate of mitochondrial fusion, while also directly interacting with and enhancing mitochondrial recruitment of the fission protein Drp1 (Wang et al., 2012b). Notably, the detrimental effects of LRRK2 and its mutants could be rescued by overexpression of dominant-negative Drp1 or WT-Mfn2, suggesting that LRRK2 effects mitochondrial function via fission/fusion pathways (Wang et al., 2012b). Interestingly, the observed increased fragmentation is in contrast to the elongation observed in patient fibroblasts (Mortiboys et al., 2010; Wang et al., 2012b). Thus, further study will be required to elucidate the specific role of LRRK2 in regulating fission and fusion rates in varying cell types. Together, these studies suggest that LRRK2 influences multiple aspects of mitochondrial homeostasis, including respiration, transport, mitophagy, and fission–fusion dynamics.

PTEN-induced putative kinase 1 (PINK1) and Parkin

The strongest evidence linking PD-related genes to regulation of mitochondrial dynamics and homeostasis comes from studies of PINK1 and Parkin. Mutations in PINK1 and Parkin both cause autosomal-recessive forms of PD (Kitada et al., 1998; Valente et al., 2004). PINK1, in contrast to the other PD-related proteins, is a mitochondrially-targeted protein with kinase activity, whereas Parkin encodes a largely cytosolic E3 ubiquitin ligase (Valente et al., 2004; Zhang et al., 2000). Both PINK1 and Parkin have been shown to regulate mitochondrial function and mitochondrial dynamics. Parkin was originally shown to associate with the mitochondrial membrane, and, when overexpressed, was shown to improve mitochondrial function and ameliorate dysfunction in models of mitochondrial stress (Darios et al., 2003; Jiang et al., 2004; Mouatt-Prigent et al., 2004). Similarly, loss of PINK1 protein or function in models negatively affects mitochondrial membrane potential, ETC complexes I and IV, ATP production, calcium dynamics, morphology, mtDNA levels, and mitophagy (Abramov et al., 2011; Clark et al., 2006; Dagda et al., 2009; Exner et al., 2007; Gegg et al., 2009; Grunewald et al., 2009; Morais et al., 2009; Park et al., 2006; Wang et al., 2011b).

Both PINK1 and Parkin have also been suggested to upregulate mitochondrial biogenesis (Gegg et al., 2009; Kuroda et al., 2006). For Parkin, a potential mechanism for this upregulation was recently described. Parkin was found to downregulate an upstream repressor of PGC-1α, the transcriptional coactivator involved in upregulation of mitochondrial biogenesis (Shin et al., 2011). Conditional knockout of parkin in adult mice led to repression of PGC-1α (Shin et al., 2011). However, a recent study found that fibroblasts from Parkin-associated familial PD patients, representing a life-long loss of functional Parkin, exhibited PGC-1α *overexpression*, though the protein's downstream function was blocked (Pacelli et al., 2011). Thus, the role of Parkin in regulating PGC-1α over a lifetime has not yet been fully elucidated.

Though independently recognized and studied for their impacts on mitochondrial function, morphology, and biogenesis, studies within the last decade have demonstrated that PINK1 and Parkin participate in a pathway together regulating mitochondrial fission, fusion, degradation, and transport, lending further evidence for a central role of mitochondrial dynamic dysfunction in PD (summarized in Fig. 1). Work in *Drosophila* models first demonstrated that individual fly lines expressing mutants of the proteins exhibited remarkably similar mitochondrial pathology (Clark et al., 2006; Greene et al., 2003; Park et al., 2006; Pesah et al., 2004). Genetic interaction studies in *Drosophila* and mammalian cells have ultimately revealed a shared pathway, in which mitochondrial PINK1 operates upstream of Parkin regulating mitochondrial morphology and function (Clark et al., 2006; Deng et al., 2008; Exner et al., 2007; Narendra et al., 2010b; Park et al., 2006, 2008; Poole et al., 2008; Vives-Bauza et al., 2010; Yu et al., 2011). Below we discuss the involvement of PINK1–Parkin pathway in mediating these mitochondrial processes. We address what is known and what remains to be elucidated to determine the role of these pathways in PD neurodegeneration, and we discuss the impact of and implications for neuronal bioenergetics.

PINK1/Parkin and fission/fusion balance: fostering fission or fusion? The early work in *Drosophila* that uncovered the link between PINK1 and Parkin suggested that the PINK1/Parkin pathway under normal conditions promoted mitochondrial fission and/or inhibited fusion. Knockdown of either protein appeared to result in clumped, swollen mitochondria in flight muscles and dopaminergic neurons (Clark et al., 2006; Deng et al., 2008; Park et al., 2006, 2008; Poole et al., 2008). The mitochondrial morphologies were suggestive of hyperfusion, or inhibited fission, and were ameliorated by overexpression of the fission mediator Drp1 or knockdown of Mfn. In loss-of-function models, overexpression of Parkin ameliorated the effects of PINK1 loss, but overexpression of PINK1 in the presence of Parkin loss did not, demonstrating that PINK1 was upstream of Parkin in regulating a pathway that appeared to promote fission and/or inhibit fusion (Deng et al., 2008; Park et al., 2008; Poole et al., 2008). As work moved into mammalian cells, however, opposite effects were sometimes found. Work in immortalized mammalian cell lines and primary cultures demonstrated that transient knockdown of PINK1 or Parkin resulted in Drp1-mediated fragmentation (Dagda et al., 2009; Exner et al., 2007; Lutz et al., 2009), consistent with a pro-fusion effect of PINK1 and Parkin. On the other hand, a recent study reported that in primary hippocampal and dopaminergic rat neurons, overexpression of either PINK1 or Parkin exhibited increased fragmented mitochondria, whereas PINK1 knockdown resulted in elongation of mitochondria, an

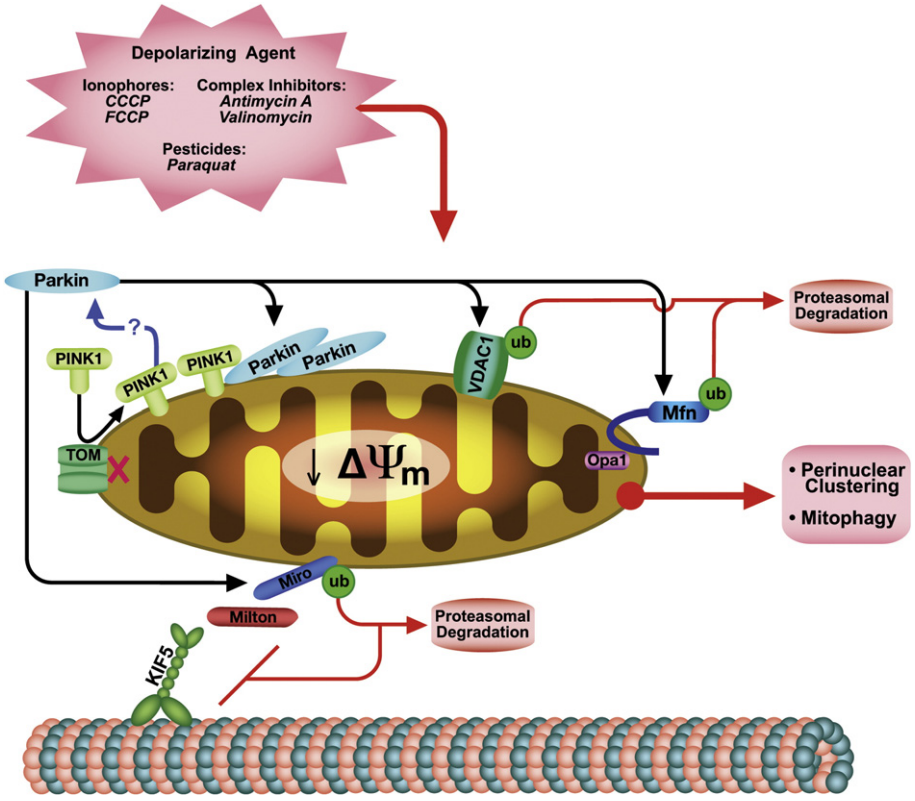

Fig. 1. Mitochondrial PINK1–Parkin pathway activation and action. Following a depolarizing insult, mitochondrial import is inhibited, allowing for the accumulation of full-length PINK1 on the outer mitochondrial membrane (OMM). This triggers translocation of cytosolic Parkin to the mitochondrial outer membrane through an unknown mechanism (blue line). Upon translocation, Parkin begins to ubiquitinate substrates on the OMM, including VDAC1, Miro, and mitofusins (Mfn), which are subsequently targeted for proteasomal degradation. Degradation of Miro also blocks the assembly of the Miro–Milton–Kinesin (KIF5) complex for anterograde transport. These events are then followed by targeting of the depolarized mitochondrion for mitophagy. The above information is summarized from references discussed in the text.

effect reversed by overexpression of Parkin or Drp1 (Yu et al., 2011), consistent with a pro-fission, or anti-fusion, effect.

It is possible that the differences observed between fly models and mammalian cells may, in part, involve a temporal effect of PINK1 or Parkin loss, as Lutz et al. (2009) found that mitochondrial morphological deficits were compensated for after prolonged protein knockdown. However, PD patient fibroblasts expressing PINK1 mutations also exhibited increased fragmentation (Exner et al., 2007). Another explanation may be a difference in regulation of mitochondrial dynamics by the PINK1/Parkin pathway based on cell-tissue type and/or cellular bioenergetic status (Cai et al., 2012; Lutz et al., 2009; Sterky et al., 2011; Van Laar et al., 2011).

Supporting a role for Parkin in *inhibiting* fusion, recent studies have now shown that the fusion proteins Mfn1 and Mfn2, are targets for ubiquitination by Parkin and subsequent proteolytic degradation, providing a potential mechanism by which the PINK1/Parkin pathway can, in fact, inhibit fusion (Karbowski and Youle, 2011). Both overexpression of Parkin or translocation of Parkin to depolarized mitochondria leads to increased ubiquitination and decreased levels of Mfn1 and 2, in both *Drosophila* and mammalian cells (Gegg and Schapira, 2011; Gegg et al., 2010; Glauser et al., 2011; Poole et al., 2010; Rakovic et al., 2011; Ziviani et al., 2010). Inhibition of fusion in the setting of mitochondrial depolarization may serve as a mechanism to foster both fission and subsequent mitophagic degradation of severely damaged mitochondria, serving as an attempt at preserving cellular bioenergetic integrity. Although one study found an opposite regulatory effect, that Parkin can also ubiquitinate and degrade the fission protein, Drp1, *promoting*, rather than inhibiting, fusion (Wang et al., 2011a), other studies have not found Parkin regulation of Drp1 levels (Poole et al., 2010; Tanaka et al., 2010). How these ubiquitination pathways factor into Parkin-mediated regulation of mitochondrial fission and fusion in *neurons* has not yet been fully elucidated.

The role of the PINK1–Parkin pathway in mitophagy — a bioenergetic connection in neurons. A study by Narendra et al. (2008) uncovered perhaps the most critical function of the PINK1–Parkin shared pathway. They found that in mammalian cells exposed to a mitochondria-depolarizing protonophore, CCCP, Parkin was rapidly recruited to severely depolarized mitochondria and facilitated their targeting for autophagic degradation via mitophagy (Narendra et al., 2008). Since that study, they and others have shown that Parkin is recruited to mitochondria following the outer-membrane surface stabilization of functional PINK1, which is normally rapidly imported into the mitochondria through TOMM20 and degraded via mitochondrial proteases, including MMP, PARL, m-AAA, and ClpXP (Greene et al., 2012; Jin et al., 2010; Meissner et al., 2011). Under conditions of depolarization, however, PINK1 is no longer imported or cleaved. The signal(s) that ultimately recruit Parkin to the PINK1-laden damaged mitochondria are not known, but functional PINK1 is required for recruitment, and functional Parkin is required for directing the mitochondria towards mitophagy (Geisler et al., 2010; Narendra et al., 2010b; Vives-Bauza et al., 2010). Once recruited, Parkin directly ubiquitinates multiple substrates, including the OMM proteins VDAC (an ion-specific voltage-dependent diffusion pore that is also part of the permeability transition pore), transport regulator Miro (an OMM protein and component of the Miro–Milton complex), and Mfn1 and 2 (the OMM fusion proteins) (Gegg and Schapira, 2011; Gegg et al., 2010; Geisler et al., 2010; Glauser et al., 2011; Narendra et al., 2010a; Poole et al., 2010; Rakovic et al., 2011; Tanaka et al., 2010; Ziviani et al., 2010). Parkin also interacts with Ambra and recruits p62, both autophagy-associated machinery, ahead of mitophagy (Geisler et al., 2010; Van Humbeeck et al., 2011a; Van Humbeeck et al., 2011b), though the exact role of these interactions in initiating mitophagy, in particular p62 recruitment and VDAC ubiquitination, are not clear (Narendra et al., 2010a). It is proposed that dysfunction of this critical pathway could lead to an accumulation of dysfunctional or severely damaged mitochondria, ultimately contributing to increased cellular stress and neuronal pathogenesis in PD.

Parkin-mediated mitophagy has been extensively characterized in immortalized cell lines and fibroblasts since first being described by Narendra et al. (2008). But only within the past couple of years have studies begun to examine the pathway in neurons in detail. In immortalized and other glycolytic cells, global instantaneous depolarization, as with CCCP, or depolarization or damage from mitochondrial ETC inhibitors can induce rapid translocation of Parkin followed by prolonged mitophagy, eventually leading to a complete clearance of mitochondria in some cells (reviewed in Narendra and Youle, 2011). Immortalized cybrid cell lines carrying lethal mtDNA deletions, which exhibit dysfunctional ETC assembly and decreased membrane potential, also demonstrated mitochondrial Parkin recruitment ahead of mitophagy (Gilkerson et al., 2012). However, the bioenergetic profiles of these cells are not readily comparable to the OxPhos-dependent neurons. We sought to test if the PINK1–Parkin mitophagy pathway would operate similarly in mitochondria-dependent neurons. Interestingly, CCCP exposure of up to 6 h does not initiate Parkin translocation or mitophagy in neurons (Van Laar et al., 2011). The restriction of Parkin translocation to mitochondria appears, in part, to be regulated by bioenergetics, as normally glycolytic cells, both yeast and mammalian, forced into OxPhos dependence, also demonstrate a lack of Parkin translocation and mitophagy (Kanki and Klionsky, 2008; Van Laar et al., 2011). Further, we found that protecting against CCCP-induced ATP loss in neurons allowed for partial, but not complete, Parkin-mitochondria translocation in neurons, suggesting that ATP loss plays a partial role in the bioenergetic regulation of Parkin translocation in neurons. Recently, Cai et al. (2012) confirmed that in mouse cortical neurons, CCCP exposure of up to 6 h did not trigger Parkin translocation, but that only after prolonged exposure (24 h) to CCCP did Parkin translocate to mitochondria and evidence of mitophagy appear. These results suggest that the neuronal mitophagic response to an acute, excessive mitochondrial stressor is a slow and regulated process. On the other hand, an in vivo model of reporter mice, exhibiting mitochondrial respiration dysfunction in DA neurons via mtDNA deletion, showed only Parkin-*independent* accumulation and elimination of mitochondria specifically in affected DA neurons (Sterky et al., 2011). Thus, Parkin may not always be involved in neuronal mitophagy under conditions of slowly accumulating mitochondrial damage, which may be important to consider in progressive neurodegenerative disease.

The type of stressor may also dictate the neuronal mitophagy response. The mitochondrial complex III inhibitor, antimycin A, was recently purported to trigger Parkin localization to axonal mitochondria in primary rat hippocampal neurons (Wang et al., 2011c). Parkin-mitochondria translocation was also shown to occur after exposure to the depolarizing agent valinomycin, a pore-generating ionophore, in DA neurons derived from iPS cells (Seibler et al., 2011), though the bioenergetics of cultured differentiated iPS cells as compared to primary neurons has not been evaluated. Adding further complexity, evidence suggests that neuron cell bodies, dendrites, and axons may have distinct responses to mitochondrial damage. For example, it has been suggested that Parkin-associated mitophagy occurs in cell bodies and dendrites, but perhaps not in axons (Cai et al., 2012).

Together, these data suggest that neuronal bioenergetics likely influence the regulation of mitochondrial degradation. The rapid loss of ATP after a global mitochondrial insult in neurons compared to other cells may prevent full-scale Parkin-associated mitophagy from occurring. However, selective damage to a small pool of mitochondria may allow selective mitophagy. Surprisingly, a sizable population of neuronal mitochondria show evidence of relative recovery of membrane potential after prolonged, 24 h CCCP exposure (Cai et al., 2012), suggesting the possibility that bioenergetic compensatory changes in neurons after prolonged exposure to a mitochondrial depolarizing agent may be occurring to allow mitophagy to occur. The significance

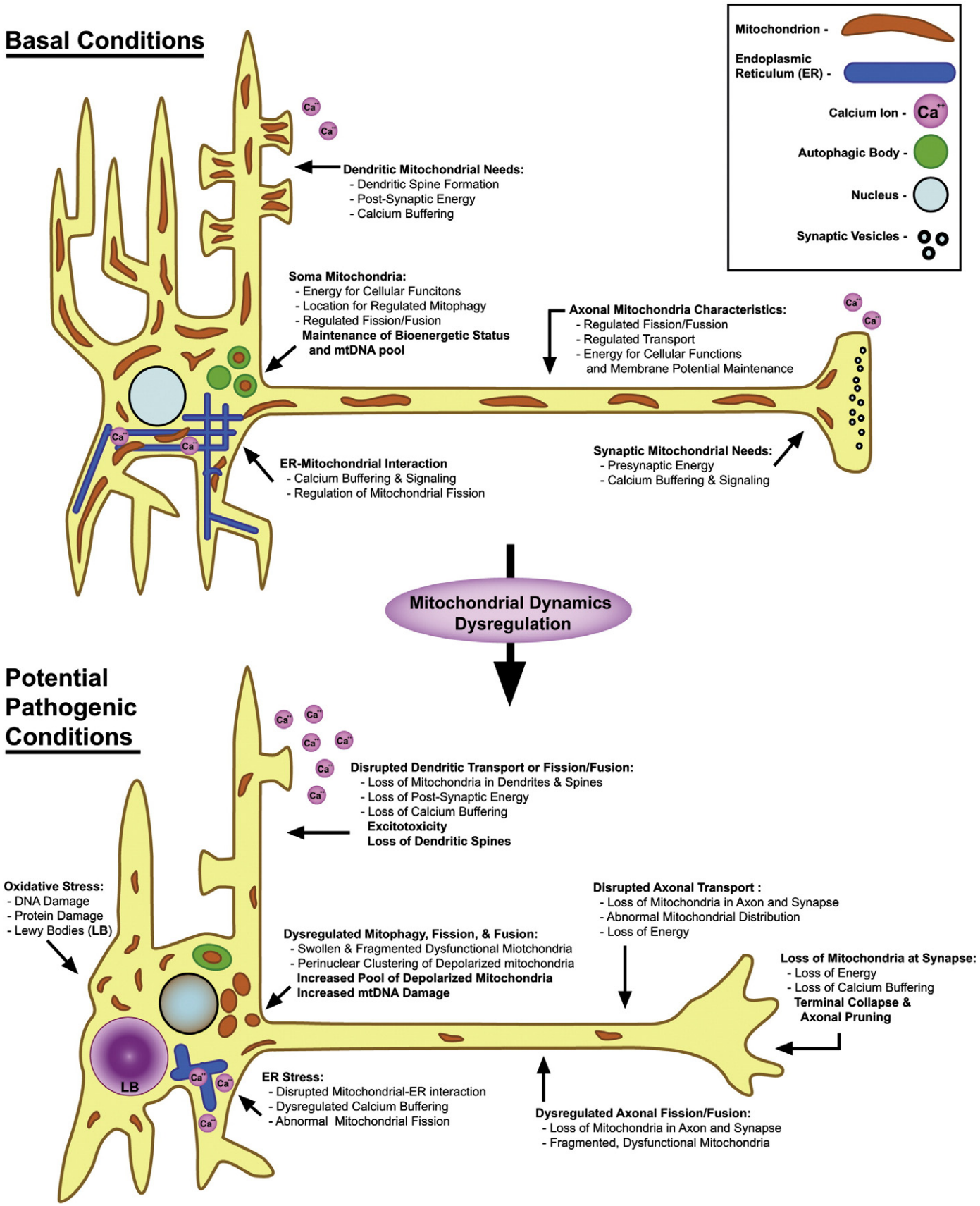

Fig. 2. Effects of dysfunction of mitochondrial dynamics in neurons. The top panel diagrams a normally functioning neuron, outlining specific compartmentalized aspects of mitochondrial dynamics in the cell body, dendritic regions, and axons/synapses. The bottom panel shows potential neuropathologic consequences of localized dysregulation of mitochondrial dynamics.

of this for neurodegeneration is as yet unknown. Alternatively, the signaling mechanisms for recruiting Parkin to mitochondria in neurons after depolarization may be regulated differently, though this is as yet unexplored. Evidence suggests that mitochondrial turnover in neurons is quite slow compared to other cells, on the order of weeks (Menzies and Gold, 1971; Wang et al., 1997), and thus, greater regulation of mitophagy in neurons likely occurs. This would seem to be beneficial in cells with long, isolated axonal environments, dependent on mitochondrial function.

PINK1–Parkin and transport

The most recently identified role for the PINK1–Parkin pathway is in regulating the axonal transport of neuronal mitochondria. The mitochondrial GTPase Miro is an OMM protein that interacts with the adapter protein Milton, forming a complex for interaction with the kinesin motor protein KIF5 (Hirokawa et al., 2010). Miro is also calcium-responsive, either releasing KIF5 or disconnecting KIF5 from the microtubule in the presence of high calcium, allowing for the recruitment to and ultimate halting of mitochondria at calcium-rich regions in the neuron (Hollenbeck and Saxton, 2005; MacAskill et al., 2009; Wang and Schwarz, 2009). Initially, PINK1 was found to form a complex with Miro and Milton (Weihofen et al., 2009). More, recently, two studies have shown that Miro abundance, and consequently trafficking of mitochondria, are regulated in a PINK1–Parkin dependent manner (Liu et al., 2012; Wang et al., 2011c). Overexpression of PINK1 or Parkin in *Drosophila* motor neurons and primary rodent hippocampal neurons resulted in decreased overall motility of axonal mitochondria, associated with a loss of Miro. Upon PINK1 or Parkin overexpression, or Parkin-induced recruitment to mitochondria, Miro was ubiquitinated by Parkin and targeted for proteasomal degradation, forcing disassembly of the Miro–Milton–Kinesin complex and altering axonal transport of mitochondria (Liu et al., 2012; Wang et al., 2011c). Additional mechanisms for PINK1 and Parkin to regulate mitochondrial transport may occur through potential interactions of Parkin with microtubules, regulating microtubule stability (Yang et al., 2005).

Regulation of transport by the PINK1–Parkin pathway also carries implications for neuronal bioenergetics. It is possible that halting axonal movement of depolarized mitochondria would prevent a potentially harmful accumulation of non-functional mitochondria at high-energy-demand regions of the neurites (Liu et al., 2012; Wang et al., 2011c). Liu et al. (2012) also show that loss of Miro facilitates Parkin-mediated mitophagic degradation of depolarized mitochondria, suggesting that the PINK1–Parkin pathways of regulating transport and mitophagy may converge to regulate overall mitochondrial homeostasis. It is likely that regulation of mitochondrial fission/fusion, transport, and degradation is interrelated, which may be the reason that PD-related genes and toxins influence many different aspects of mitochondrial dynamics.

Bioenergetic specialization within compartments of neurons: does this affect PD-relevant regulation of mitochondrial dynamics?

Aside from the general bioenergetic status of neurons compared to other, more-glycolytic cells, the unique morphology of neurons may also be a factor in regulating mitochondrial dynamics in neurons, particularly those aspects regulated by the PINK1–Parkin pathway. Neurons are highly morphologically polarized, and as such, are divided into three primary constituent compartments — the dendrites, the soma, and the axon. Though once thought to be solely dependent on the soma for molecular supplies, it is now known that biological and bioenergetic functions throughout the axons and dendrites are highly compartmentalized and specialized to their unique needs, including localized synthesis and degradation of proteins (Piper and Holt, 2004; Steward and Schuman, 2003), axon- and dendrite-specific transport (Hirokawa et al., 2010; Namba et al., 2011), calcium regulation and ER functions, and localized ATP requirements (Hollenbeck and Saxton, 2005; MacAskill et al., 2009; Mironov, 2009; Wang and Schwarz, 2009).

This specialized compartmentalization in neurons would likely make the regulation of mitochondrial homeostasis more complex than other cells, and evidence is emerging that suggests this is indeed the case. Mitochondrial transport is clearly specialized regionally within neurons to provide appropriately targeted distribution and is regulated by metabolic factors, including localized concentrations of calcium and ADP (Cai et al., 2011; Hirokawa et al., 2010; Mironov, 2009). Mitochondrial fission and fusion in axons and distal dendrites occur less frequently than that observed in other cell types or cell bodies (Berman et al., 2009). In addition, the endoplasmic reticulum (ER) was recently found to play a role in mitochondrial fission (Friedman et al., 2011), and ER morphology and function may differ in the somatodendritic compartment compared to distal axons (Ramirez and Couve, 2011). More recently, Cai et al. (2012) found that Parkin-associated mitophagy occurred in somatodendritic compartments of neurons, but not in axons. Related to this, Parkin-mediated mitophagy after mitochondrial depolarization was only observable in neurites when mitochondrial transport was halted (Cai et al., 2012). Parkin, after translocation to mitochondria, ubiquitinates Miro, targeting it for degradation, which inhibits anterograde mitochondrial axonal flux, resulting in net retrograde mitochondrial movement (Liu et al., 2012; Wang et al., 2011c). One could hypothesize that the specificity of this in axons may serve to keep damaged mitochondria out of highly energy-dependent axonal terminals. In PD, which has been hypothesized to begin in axon terminals (e.g., see Braak et al., 2004), these differences may have important implications for neuropathogenesis. How compartmentalized dysfunction in mitochondrial dynamics might factor into neurodegeneration is summarized in Fig. 2.

Conclusions: mitochondrial dynamics, neuronal bioenergetics, PD, and the potential impact on therapies

As discussed above, mitochondrial dynamics have been proposed to serve as a control mechanism for mitochondrial integrity and, ultimately bioenergetic status maintenance (Twig et al., 2008b; Twig and Shirihai, 2011; Van Laar and Berman, 2009; Westermann, 2012). In addition, basal bioenergetics within specific cells can also dictate the response of mitochondrial dynamics when faced with a stressor (Kanki and Klionsky, 2008; Van Laar et al., 2011), and that response can be affected differentially by the type of stressor (Narendra and Youle, 2011). With regard to PD, a significant body of evidence supports a role for dysregulation of mitochondrial dynamics in disease pathophysiolgy. Yet, neurons may uniquely regulate mitochondrial dynamic pathways in response to mitochondrial stressors, which may ultimately be important in PD-relevant pathways (Arnold et al., 2011; Cai et al., 2012; Sterky et al., 2011; Van Laar et al., 2011).

Given that neurons have specific and unique bioenergetics, it is likely that understanding these interactions in neurons will lead to a better understanding of how dysregulation of mitochondrial dynamics could lead to neurodegeneration in PD and could have implications for potential neuroprotective therapies. For example, exercise-induced fluctuations in energy demands lead to altered fission and fusion protein expression in skeletal muscle coinciding with alterations in oxidative phosphorylation efficiency (Ding et al., 2010). Interestingly, exercise has proven to be neuroprotective in PD animal models of neurodegeneration (Ahlskog, 2011), though evidence of neuroprotection in patients has yet to be shown. It is possible that changes in regulation of mitochondrial dynamics in neurons might have real implications early in PD pathogenesis. Continued elucidation and better understanding of bioenergetics and mitochondrial dynamics within PD pathogenesis, then, may lead to better therapies that target earlier stages of the disease.

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