HHS Public Access

Author manuscript

Mol Cell Neurosci. Author manuscript; available in PMC 2016 May 01.

Published in final edited form as:

Mol Cell Neurosci. 2015 May ; 66(0 0): 62–71. doi:10.1016/j.mcn.2015.02.008.

Pathologic and Therapeutic Implications for the Cell Biology of Parkin

Rakshita A. Charan and **Matthew J. LaVoie**

Ann Romney Center for Neurologic Diseases, Department of Neurology Brigham and Women's Hospital and Harvard Medical School, Boston, USA

Abstract

Mutations in the E3 ligase parkin are the most common cause of autosomal recessive Parkinson's disease (PD), but it is believed that parkin dysfunction may also contribute to idiopathic PD. Since its discovery, parkin has been implicated in supporting multiple neuroprotective pathways, many revolving around the maintenance of mitochondrial health quality control and governance of cell survival. Recent advances across the structure, biochemistry, and cell biology of parkin have provided great insights into the etiology of parkin-linked and idiopathic PD and may ultimately generate novel therapeutic strategies to slow or halt disease progression. This review describes the various pathways in which parkin acts and the mechanisms by which parkin may be targeted for therapeutic intervention.

Keywords

Parkin; PD; mitophagy; apoptosis; therapy; neurodegeneration

Introduction

Of all neurodegenerative disorders, Parkinson's disease (PD) is the second most prevalent affecting about 9.5 per 1,000 of the population aged at least 65 or older (Dauer and Przedborski 2003, Hirtz, Thurman et al. 2007). Since the first identification of a monogenic, inherited form of PD in 1997, researchers have made great strides in elucidating the biochemical pathways that underlie this disease. Yet the precise etiologies of inherited and sporadic PD still remain unknown. Patients present with a wide range of pathological symptoms that include bradykinesia, resting tremor, postural instability and rigidity (Wirdefeldt, Adami et al. 2011). The classic pathological manifestations of the disease include the loss of dopaminergic neurons in the substantia nigra pars compacta and the accumulation of intracellular cytoplasmic aggregates called Lewy bodies (Forno 1996). However, it is now appreciated that both the pathology and symptomology extend far

Corresponding Author: Matthew J. LaVoie Associate Professor, Department of Neurology Brigham and Women's Hospital and Harvard Medical School, 77 Ave Louis Pasteur, HIM 762 Boston, MA-02115 Phone: 617-525-5185 Fax: 617-525-5252.

beyond the nigrostriatal system (Hornykiewicz and Kish 1987, Kupsky, Grimes et al. 1987, Braak, Ghebremedhin et al. 2004, Langston 2006, Jain 2011). Unfortunately, available treatments to date are mostly geared towards the movement disturbances while the non-nigral features of PD are less well addressed.

The majority of PD cases are idiopathic, but about 5-10% of the cases have a known underlying genetic basis (Dawson and Dawson 2003). Leucine-rich repeat kinase 2 (LRRK2) and α-synuclein are associated with autosomal dominant forms of PD, whereas parkin, PINK1 (PTEN-induced kinase 1), DJ-1 and ATP13a2 are associated with autosomal recessive forms. Of these, mutations in the gene encoding parkin are the most common cause of autosomal recessive PD, comprising about 50% of all recessive forms of the disease (Lucking, Durr et al. 2000). While the biochemical function of some proteins implicated in PD are not known (e.g. α-synuclein, DJ-1, LRRK2), parkin is a well-established ubiquitin E3 ligase whose crystal structure was recently solved (Riley, Lougheed et al. 2013, Trempe, Sauve et al. 2013, Wauer and Komander 2013). The wealth of information surrounding parkin structure and function, and particularly the strides made in the last two years, make parkin biology an attractive target for therapeutic intervention in sporadic PD, where wild-type parkin expression is preserved but may be functionally compromised or amenable to facilitation. In this review, we will detail the various molecular pathways affected by parkin, as well as the possible upstream and downstream interactors that could be targeted not only for PD, but also for other neurodegenerative diseases.

Parkin and Parkinsonism

Over a decade and a half ago, parkin was identified by the investigation of a chromosomal deletion in Japanese patients diagnosed with autosomal recessive-juvenile Parkinson's disease (AR-JP) (Matsumine, Saito et al. 1997, Kitada, Asakawa et al. 1998). Patients diagnosed with AR-JP exhibited the same characteristic symptoms as those with typical late-onset PD and were L-DOPA responsive, but postmortem analyses revealed the surprising lack of expected Lewy bodies (Takahashi, Ohama et al. 1994, Mori, Kondo et al. 1998, Yokochi 2000). Later studies, however, did report the presence of Lewy bodies in the substantia nigra and the locus coeruleus of patients with compound heterozygous parkin mutations (Farrer, Chan et al. 2001, Pramstaller, Schlossmacher et al. 2005, Sharp, Marder et al. 2014). Patients with AR-JP possessed large deletions in chromosome 6 within in the coding region of parkin (Matsumine, Saito et al. 1997, Kitada, Asakawa et al. 1998). However, later studies revealed that parkin mutations were found not only in early-onset AR-JP, but also in late-onset PD (Oliveira, Scott et al. 2003). Following the discovery of this genetic disruption, it was shown that the gene product was a RING domain E3 ubiquitin ligase (Shimura, Hattori et al. 2000, Zhang, Gao et al. 2000). Parkin is a large (1.3Mb) gene that is translated to a 465 amino-acid protein that is expressed in various tissues including the heart, testis and skeletal muscle. It is also abundantly expressed in the brain, especially the substantia nigra (Kitada, Asakawa et al. 1998, Huynh, Dy et al. 2001). There have been over 200 mutations in parkin identified in patients which span all domains of the protein (Corti, Lesage et al. 2011) and include point mutations, exon rearrangements and small deletions (Mata, Lockhart et al. 2004). Given that some of the disease-associated mutations abrogate translation of a functional protein, it has been presumed that the more subtle

missense mutations would likewise cause loss-of-function, and some experimental evidence would support this assertion (Henn, Gostner et al. 2005, Sriram, Li et al. 2005, Schlehe, Lutz et al. 2008, Bosco, LaVoie et al. 2011). However, not all the mutations may directly affect E3 ligase activity, as it has been argued that some point mutations lead to decreased solubility and the propensity for aggregation of the protein (Henn, Gostner et al. 2005, Schlehe, Lutz et al. 2008), which may be particularly true of the truncated mutants.

New Insights from Parkin Structure

Parkin is a multi-domain protein, belonging to a class of RING domain E3 ligases. Parkin is unusual in that it has two RING domains, an inverted RBR (RING-InbetweenRING-RING) domain and an ubiquitin-like motif (Ubl) within its N-terminus (Sakata, Yamaguchi et al. 2003). It also contains a unique parkin-specific domain (UPD) containing the RING0 domain (Kahle, Leimer et al. 2000, Hristova, Beasley et al. 2009). The crystal structure of parkin was recently solved by multiple groups (Riley, Lougheed et al. 2013, Trempe, Sauve et al. 2013, Wauer and Komander 2013), and these impressive efforts have provided valuable insights into the behavior of parkin in the cell (Dove and Klevit 2013). These structures agreed in finding that parkin exists natively in an auto-inhibited state; the N-terminal region of parkin is folded over the RING1 and RING2 domains, occluding the active site, which requires a conformational change in order to execute an ubiquitination reaction (Riley, Lougheed et al. 2013, Trempe, Sauve et al. 2013). The structure also reveals how specific mutations in parkin affect its enzymatic activity and its folding capacity. Interestingly, even though PD-associated parkin mutations are widespread and not confined to any particular domain of the protein, they can be categorized according to predicted effects on zinc binding and protein folding, catalytic efficiency, or association with E2s, substrates, or cofactors (Trempe, Sauve et al. 2013).

Solubility: Role for parkin deficiency in sporadic PD?

Parkin contains 35 cysteine residues, making up almost 8% of the protein, which is high when considered against the proteomic average of 2% (Bosco, LaVoie et al. 2011, Dove and Klevit 2013). This characteristic is likely at least partially responsible for the protein's susceptibility to stress-induced aggregation or misfolding (Bosco, LaVoie et al. 2011). Studies have also shown that various PD-linked stressors including oxidative, nitrosative and dopamine stresses altered parkin structure, making it more insoluble (Winklhofer, Henn et al. 2003, LaVoie, Ostaszewski et al. 2005, Wang, Tan et al. 2005, Meng, Yao et al. 2011). Perhaps consistent with these *in vitro* studies, there is an age-dependent decrease in parkin solubility in human brain (Pawlyk, Giasson et al. 2003). Parkin solubility was also found to be decreased in brain tissue from sporadic PD and Diffuse Lewy Body disease patients compared to otherwise healthy controls (LaVoie, Ostaszewski et al. 2005, Wang, Ko et al. 2005, Kawahara, Hashimoto et al. 2008, Lonskaya, Desforges et al. 2013), as well as in the blood of PD patients (Vinish, Prabhakar et al. 2010). Interestingly, soluble parkin levels were also significantly decreased in cortices from post-mortem Alzheimer's disease (AD) patients, compared to healthy controls (Lonskaya, Shekoyan et al. 2013). This study also reported that insoluble parkin co-localized with intracellular amyloid beta. Collectively, these findings suggest that stress-induced or ageing-dependent decreases in soluble, active

parkin in the brain may serve as a biochemical phenocopy of loss-of-function mutations in the protein, and contribute to risk of idiopathic PD.

Animal models

Several *in vivo* models have been generated to date to understand the molecular pathways affected due to loss of a functional parkin protein. In *C. elegans*, knocking out the parkin homolog led to increased susceptibility to apoptosis (Ved, Saha et al. 2005). Parkin-null Drosophila exhibited severe mitochondrial defects and spontaneous apoptosis in muscle, and rendered the male knockout flies sterile (Greene, Whitworth et al. 2003). Moreover, genetic interaction studies indicated that both parkin and PINK1 proteins were participants of the same pathway with PINK1 upstream of parkin, as exogenous parkin expression could partially rescue PINK1 knockout phenotype, but no rescue of the parkin phenotype was observed with PINK1 expression (Clark, Dodson et al. 2006, Park, Lee et al. 2006). Similar to Drosophila, iPSC-derived neurons generated from isolated dermal fibroblasts from human patients with homozygous PARK2 mutations displayed abnormal mitochondrial morphology, increased density of the abnormal mitochondria, and aberrant mitochondrial clearance (Imaizumi, Okada et al. 2012), implicating parkin in maintaining mitochondrial health in human neurons.

Despite the intriguing phenotype of the parkin-null fly, parkin knockout mice do not display the severe mitochondrial defects expected in brain and do not display a conspicuous parkinsonian phenotype (Goldberg, Fleming et al. 2003, Perez and Palmiter 2005). Though, neurons obtained from parkin KO mice did display susceptibility to apoptotic stress, consistent with the pro-apoptotic phenotype in fly (Johnson, Berger et al. 2012, Muller-Rischart, Pilsl et al. 2013, Charan, Johnson et al. 2014). Thus, there is a notable disparity across animal models that would indicate that the biochemical pathways influenced by parkin perhaps express some species specificity, or that compensatory redundancies may exist in some organisms but not others.

Functions attributed to Parkin in PD

Multiple mitochondrial functions have been ascribed to parkin that can collectively be categorized under mitochondrial quality control and integrity, suggesting a broad role for parkin in mitochondrial health and cell survival. It is worth noting that at rest, parkin is predominantly localized within the cytosol and may regulate many of these mitochondrial processes from a distance, whereas the relocalization of parkin to the mitochondria is an important step in its role in mitochondrial turnover.

Mitochondrial clearance via mitophagy

Autophagy is an essential and highly regulated intracellular mechanism that allows for the clearance of misfolded, mutated proteins as well as entire organelles by their sequestration and degradation in autophagolysosomal compartments (Mizushima 2007). Since parkin is an E3 ligase, earlier studies indicated that parkin might be involved in the ubiquitination of substrates in order to target them for classic degradation via the ubiquitin-proteasome system (UPS) (Tanaka, Suzuki et al. 2001). Later, parkin was also shown to play a role in a

more direct mechanism of facilitating mitochondrial clearance via autophagy, termed mitophagy (Narendra, Tanaka et al. 2008). Upon stress-inducing mitochondrial depolarization by the uncoupling agent CCCP (carbonyl cyanide *m*-chlorophenyl hydrazone), another PD-related gene PINK1 stabilizes on the mitochondrial membrane, acting as a beacon for parkin to translocate to the mitochondria (Narendra, Jin et al. 2010). Recently, it was shown that phosphorylation of parkin by PINK1, as well as by PINK1-dependent phosphorylation of ubiquitin, was required to activate its E3 ligase activity (Kane, Lazarou et al. 2014, Kazlauskaite, Kondapalli et al. 2014, Koyano, Okatsu et al. 2014, Ordureau, Sarraf et al. 2014). Upon this translocation, parkin initiates ubiquitination of the outer mitochondrial membranes and recruitment of the proteasome, thus marking them for UPS and autophagic destruction (Narendra, Tanaka et al. 2008, Chan, Salazar et al. 2011, Yoshii, Kishi et al. 2011). This was confirmed by the rapid recruitment of LC3 and the LC3-binding adapter protein p62 at the mitochondria (Narendra, Jin et al. 2010, Yang and Yang 2013, Ashrafi, Schlehe et al. 2014). Several outer mitochondrial membrane proteins such as TOM20 (translocase of outer membrane 20), VDAC (voltage-dependent anion channel) and Bcl-2 have been shown to be directly associated with parkin (Chen, Gao et al. 2010, Chan, Salazar et al. 2011). A component of the autophagic machinery, Ambra1 (activating molecule in Beclin1-regulated autophagy) was also identified to interact with parkin and promote mitochondrial clearance (Van Humbeeck, Cornelissen et al. 2011). A robust, large-scale analysis of all the parkin ubiquitylome during mitophagy identified 1654 proteins that ubiquitinated at the mitochondria (Sarraf, Raman et al. 2013).

Though mitophagy has been routinely studied in immortalized cell-lines, parkin-dependent mitophagy in neurons remains less well understood. There has been a large disparity across studies assessing endogenous neuronal parkin translocation to the mitochondria upon mitochondrial depolarization (Grenier, McLelland et al. 2013). Several factors such as bioenenergetics and culture conditions are thought to affect the process of mitophagy (Van Laar, Arnold et al. 2011, Yao, Gandhi et al. 2011, Amadoro, Corsetti et al. 2014). Studies in our lab have also demonstrated that parkin-mediated mitophagy was a variable process, and depended on multiple factors, including cell-type, level of parkin expression, and the resolution of the techniques used to assess translocation and mitophagy (Charan, Johnson et al. 2014). Notably, using high-resolution microscopy aided by microfluidics, parkin-dependent mitophagy could be readily observed in neuronal axons (Ashrafi, Schlehe et al. 2014), perhaps providing the most convincing demonstration of neuronal mitophagy to date (Lu 2014). Thus, PINK1 and parkin-dependent mitophagy is one of the mechanisms by which parkin maintains mitochondrial quality control, but how defects in this process contribute to selective cell loss and PD pathology remains to be fully understood.

Regulation of Apoptosis

Several functions of parkin implicate coordinated functions of both parkin and PINK1, frequently requiring the stabilization of PINK1 at the mitochondria. However, the anti-apoptotic function of parkin would appear to be PINK1-independent. The inhibition of cytochrome c release and subsequent apoptosis by parkin is not associated with a stabilization of PINK1 nor the translocation of parkin to the mitochondria (Berger, Cortese et al. 2009) that occurs only under depolarized conditions (Narendra and Youle 2011),

providing a clear distinction from the events preceding mitochondrial turnover (Johnson, Charan et al. 2012). The neuroprotective role of parkin has been widely documented since the cloning of the gene. Parkin has been shown to prevent cell death under several different conditions such as ER stress (Bouman, Schlierf et al. 2011), proteotoxic stress (Imai, Soda et al. 2000), dopamine stress (Jiang, Ren et al. 2004), mitochondrial toxins (Rosen, Veereshwarayya et al. 2006, Henn, Bouman et al. 2007), apoptotic stress (Darios, Corti et al. 2003, Berger, Cortese et al. 2009, Johnson, Berger et al. 2012, Charan, Johnson et al. 2014), increased Wnt signaling (Rawal, Corti et al. 2009) as well as alpha-synuclein toxicity (Petrucelli, O'Farrell et al. 2002, Lo Bianco, Schneider et al. 2004). One of the mechanisms by which parkin is neuroprotective is through inhibition of cytochrome c release from the mitochondria (Darios, Corti et al. 2003, Berger, Cortese et al. 2009). Our group demonstrated the parkin-mediated prevention of Bax translocation from the cytoplasm to the mitochondria, and the regulation of this individual parkin substrate was able to fully account for the control over cytochrome c release and cell death (Johnson, Berger et al. 2012). Further studies, including additional work from our group and others have since confirmed the ubiquitination (Johnson, Berger et al. 2012, Sarraf, Raman et al. 2013) and regulation (Muller-Rischart, Pilsl et al. 2013, Charan, Johnson et al. 2014) of Bax by parkin, and that parkin is neuroprotective under apoptotic stress conditions (Muller-Rischart, Pilsl et al. 2013, Charan, Johnson et al. 2014).

Ectopic expression of parkin has been shown to be protective in many different cell-types, suggesting that the anti-apoptotic role of parkin could be applied universally. Moreover, from a functional point-of view, the PINK1-dependent and PINK1-independent pathways of parkin are interlinked and may not be mutually exclusive (Johnson, Charan et al. 2012). Indeed, our group has shown that HEK293 (human embryonic kidney 293) cells overexpressing parkin could undergo CCCP-induced mitophagy as well as robust parkin-dependent ubiquitination of Bax with comparable efficiency (Charan, Johnson et al. 2014), negating the likelihood that these respective functions are cell-type dependent.

Parkin and the Bcl-2 family

In line with evidence of parkin-dependent regulation of cytochrome c release and apoptosis, it is not surprising that parkin has been shown to interact with several members of the Bcl2 family. The Bcl2 family plays a critical role in maintaining the delicate balance between survival and programmed cell death. Parkin was shown to interact with anti-apoptotic Bcl-2 protein to modulate autophagy (Chen, Gao et al. 2010), as well as interact with pro-apoptotic Bax to regulate cytochrome c release induced apoptosis (Johnson, Berger et al. 2012). Parkin also interacts with regulatory members of the Bcl2 family such as Nix, an outer mitochondrial membrane protein that is a BH3 domain-only member of the Bcl-2 family (Ding, Ni et al. 2010). Nix is thought to play a role in facilitating parkin recruitment to the mitochondria to initiate mitochondrial clearance (Ding, Ni et al. 2010). Another BH3 domain-only protein Bnip3 was also shown to play a role in the mitochondrial recruitment of parkin and induce mitophagy (Lee, Lee et al. 2011), and recently argued to be a substrate of parkin (Gao, Chen et al. 2015). Overall, this suggests a very close partnership between parkin and the Bcl2 family members in the maintenance of cellular health. Indeed, our group showed that swapping the BH3 domain of the substrate Bax with the BH3 domain of a non-

substrate, Bcl-xl, led to a loss of recognition of Bax by parkin (Charan, Johnson et al. 2014). Collectively, these data suggest a critical role for the BH3 domain to facilitate the association of parkin and Bcl2 proteins, and that the precise conformation of each BH3 domain might be a determinant for binding.

Mitochondrial Morphology by Fission/Fusion

The interplay between mitochondrial fission and fusion plays a critical role in the metabolic behavior of mitochondria (Liesa and Shirihai 2013) and is likely highly important for the isolation and clearance of unhealthy mitochondria (Detmer and Chan 2007, Molina, Wikstrom et al. 2009, Exner, Lutz et al. 2012). Perturbation of the fusion and fission equilibrium has been implicated in PD (Santos and Cardoso 2012, Van Laar and Berman 2013) as well as several other neurodegenerative disorders such as AD, amyotrophic lateral sclerosis (ALS) and Huntington's disease (HD) (Chaturvedi and Flint Beal 2013). Fusion is largely regulated by outer mitochondrial membrane proteins such as OPA1 (optic atrophy 1), mitofusin 1 (Mfn1) and mitofusin 2 (Mfn2) (Chen, Detmer et al. 2003, Cipolat, Martins de Brito et al. 2004). Fission on the other hand, is mediated by the GTPases Drp1 that relocalizes to the tip of mitochondria from the cytoplasm, and Fis1 at the mitochondria, causing the pinching off of the mitochondrion to form two daughter mitochondria (Smirnova, Griparic et al. 2001, James, Parone et al. 2003, Loson, Song et al. 2013). Interestingly, the parkin substrate Bax has also been implicated in the fission/fusion relationship as it is found along fission sites during apoptosis (Karbowski, Lee et al. 2002) but has a pro-fusion functionality that can be divorced from its apoptotic function (Suen, Norris et al. 2008, Whelan, Konstantinidis et al. 2012). Several studies suggest PINK1 and Parkin play a regulatory role in the mitochondrial fusion/fission pathway (Lutz, Exner et al. 2009, Park, Lee et al. 2009, Poole, Thomas et al. 2010). Mfn2 was shown to be a substrate of both PINK1 and parkin (Poole, Thomas et al. 2010, Chan, Salazar et al. 2011, Chen and Dorn 2013). Phosphorylation of Mfn2 by PINK1 mediated parkin recruitment and subsequent ubiquitination in cardiac mitochondria of Drosophila, initiating its autophagic clearance (Chen and Dorn 2013). Moreover, parkin has been reported to regulate the translocation of Drp1 to the mitochondria to promote fission (Lutz, Exner et al. 2009) as well as ubiquitinate it to promote its degradation via the proteasome (Wang, Song et al. 2011).

As stated earlier, parkin-deficient flies displayed swollen and dysfunctional mitochondria (Greene, Whitworth et al. 2003), which may indicate a defect in the fission pathway. Thus, it was hypothesized that the PINK1-parkin pathway promotes the fission pathway and inhibits the fusion pathway in order to facilitate unhealthy mitochondrial clearance by mitophagy in Drosophila (Deng, Dodson et al. 2008). In contrast, in mammalian models knockdown of parkin led to increased fragmentation, suggesting an increase in the fission pathway along with a decrease in mitochondrial membrane potential (Lutz, Exner et al. 2009). This discrepancy across species in the role of parkin during fission/fusion is still unclear, however, several explanations including as bioenergetics, tissue-specificity and temporal differences may be at play (Pilsl and Winklhofer 2012).

Transcriptional Regulation

Though parkin is an E3 ligase with the primary function of ubiquitin transfer to substrates, there have been a few studies that implicate parkin more broadly in transcriptional regulation of proteins. A transcriptional repressor of PGC-1alpha (PPAR gamma coactivator-1alpha) named PARIS (PARkin Interacting Substrate) was identified as a substrate of parkin E3 ligase activity (Shin, Ko et al. 2011). Parkin was also identified as a transcriptional repressor of the transcription factor p53 (da Costa, Sunyach et al. 2009), and suggested to be regulated downstream of p53 (Zhang, Lin et al. 2011), implicating a dual role in tumor suppression. Interestingly, presenilin-1 and presenilin-2, proteins implicated in familial AD and downstream targets of p53, were also identified to be transcriptional targets of parkin activity (Duplan, Sevalle et al. 2013). In some cases, the transcriptional regulation by parkin was found to be independent of its E3 ligase activity, and by a direct physical interaction with the promoter (da Costa, Sunyach et al. 2009, Alves da Costa and Checler 2012, Duplan, Sevalle et al. 2013). The precise mechanism of this regulation remains unknown and further study is required to discover other transcriptional targets of parkin and understand this potential aspect of parkin function.

Universal role of parkin

Cardiac health

Parkin KO mice do not display spontaneous loss of dopaminergic neurons nor show deficits in motor activity. However, studies have shown that parkin KO mice have several cardiac deficits. Parkin deficient mice have decreased recovery of cardiac contractility after sepsis activation, and impaired mitophagy after myocardial infarction (Kubli, Quinsay et al. 2013, Kubli, Zhang et al. 2013, Piquereau, Godin et al. 2013). This resulted in decreased survival and larger infarct sizes when compared to wild type controls. Proteins implicated in interacting with parkin also impinge upon cardiac health. Deficiency of the parkin substrate Mfn2 in the cardiomyocytes of both Drosophila and mice led to mitochondrial dysfunction and cardiomyopathy (Chen and Dorn 2013). Loss of the parkin interacting protein Nix/BNIP3 in the heart also caused accumulation of dysfunctional mitochondria and cardiac dysfunction (Dorn 2010). Moreover, dysregulation of mitochondrial fission through Drp1 inhibition in rat hearts protected them against ischemia and reduced cell death (Ong, Subrayan et al. 2010). Therefore, the cell biology of parkin, and its homeostatic functions clearly exert important physiological influence outside the brain. Interestingly, there is a significantly increased incidence of cardiomyopathy in aged patients with PD as compared to non-PD patients (Zesiewicz, Strom et al. 2004). Though cardiac sympathetic denervation is more common in PD patients, this study did not account for factors that may bias the results, such as PD medications thought to contribute to heart disease and more routine doctor visits that would provide early diagnosis.

Role in cancer

Though at the opposite ends of the spectrum in terms of cellular health, there have been many epidemiological studies linking parkin with altered risks for cancer (Checler and Alves da Costa 2014, Xu, Lin et al. 2014). Parkin was thought to act as a tumor-suppressor gene because of its location in chromosome 6, implicated as a hotspot in several human

cancers (Garber 2010), and deletions in the PARK2 locus and parkin mutations were found in a wide variety of tumors (Cesari, Martin et al. 2003, Veeriah, Taylor et al. 2010). Recently, a vast study of about 5000 tumors showed that deletions in parkin were the most commonly occurring deletions, comprising of almost 30% of all tumors studied (Bartek and Hodny 2014, Gong, Zack et al. 2014). On the surface, these results do seem counterintuitive to the anti-apoptotic and mitochondrial quality control functions of parkin. However, this study speculated that parkin plays a role in regulating the cell cycle, and that loss of parkin function leads to perturbations in the cell cycle pathway by the accumulation of one of its substrates, Cyclin E (Staropoli, McDermott et al. 2003), allowing cells to continually divide (Veeriah, Morris et al. 2010, Gong, Zack et al. 2014). However, another study found no significant correlation between parkin mutation carriers and cancer history when compared to non-carriers (Alcalay, Clark et al. 2012). Therefore, the link between the tumor-suppressor properties of parkin and the neuroprotective properties of parkin warrant further investigation.

Role in other diseases

The balance between programmed cell-death and mitochondrial homeostasis needs to be highly regulated and any perturbation along this axis can have adverse effects on cell survival. Unsurprisingly, given its role in both these pathways, parkin has been linked to several other disorders such as AD (Burns, Zhang et al. 2009), autism (Glessner, Wang et al. 2009), multiple sclerosis (Witte, Bol et al. 2009), leprosy (Mira, Alcais et al. 2004) and inclusion body myositis (Rosen, Veereshwarayya et al. 2006). Accumulation of dysfunctional mitochondria and increases in cytochrome c release and apoptosis were linked to disrupted parkin function in diabetic kidney disease (DKD) (Zhan, Usman et al. 2014). It was also shown that parkin has a role to play in the normal production and secretion of insulin by pancreatic beta cells, defects in which cause diabetes mellitus (Jin, Kim et al. 2014). Interestingly, the viral infection by Hepatitis C also uses the parkin-dependent mitophagy pathway to prevent apoptosis and increase the life of infection (Kim, Syed et al. 2014).

A few parkin substrates belong to signaling pathways involved in regulation of critical functions ranging from endocytosis to inflammation. These include Eps15 (epidermal growth factor receptor substrate 15), involved in EGFR signaling and trafficking (Fallon, Belanger et al. 2006), beta-catenin, a component of the Wnt pathway that regulates cell proliferation (Rawal, Corti et al. 2009), and TRAF2 (TNF-receptor associated factor 2) and NEMO (NF-κB essential modifier), members of the NF-κB pathway that has a central role in development and immunity (Henn, Bouman et al. 2007, Muller-Rischart, Pilsl et al. 2013). Parkin function is also implicated in cardiac recovery after sepsis (Piquereau, Godin et al. 2013), and during neuroinflammation (Frank-Cannon, Tran et al. 2008, Tran, Nguyen et al. 2011). Thus, the integrity of parkin function is critical for the regulation of various cellular functions, defects in which can promote pathology.

Parkin targeted therapy for PD and other neurodegenerative diseases

As the life expectancy of our society dramatically increases, the burden of PD rises considerably. It is estimated that by the year 2030, the number of individuals above the age

of 50 affected with PD in the world would rise to between 8.7 and 9.3 million (Dorsey, Constantinescu et al. 2007). Thus, it is imperative to find and implement successful therapeutic strategies in order to develop new treatments for this disorder. Moreover, protein aggregation due to defects in protein clearance and mitochondrial disturbances are central features in many neurodegenerative diseases (Bossy-Wetzel, Schwarzenbacher et al. 2004, Ross and Poirier 2004, Chen and Chan 2009, Bosco, LaVoie et al. 2011, Chaturvedi and Flint Beal 2013), thus targeting parkin-dependent survival pathways and mitochondrial quality control could potentially be therapeutically relevant far beyond PD. We outline a few of the possible mechanisms by which parkin function could be augmented or activated to therapeutic advantage.

Targeting mitochondrial health

Maintenance of mitochondrial health in the cell is proving to be a very crucial component in the preservation of neuronal function. Oxidative stress has been long thought to be one of the contributing factors in mitochondrial dysfunction and in the pathogenesis of PD. Studies have shown that exposure to oxidative stress causes decreased solubility of parkin, impairing its function (Bosco, LaVoie et al. 2011). To date, there have been several compounds generated and studied that reduce oxidative stress and improve mitochondrial function, and some of them such as creatine and CoQ10 are already being tested in clinical trials (Chaturvedi and Beal 2013, Jin, Kanthasamy et al. 2014), albeit with not much success reported. A different aspect of reducing oxidative stress in PD models also being studied is targeting activation of the Nrf2 pathway using synthetic triterpenoids (Kaidery, Banerjee et al. 2013). Nrf2 is a transcription factor that regulates the antioxidant response element (ARE) and confers cellular protective from oxidative insult (Lee, Shih et al. 2003). This targeted activation of the Nrf2 pathway would be a promising approach for the amelioration of stress-induced pathologies. Other molecules such as resveratrol and uric acid have also been implicated in the prevention of oxidative stress and promoting mitochondrial and cellular health in PD (Davis, Grandinetti et al. 1996, Cipriani, Chen et al. 2010, Chen, Burdett et al. 2013, Ferretta, Gaballo et al. 2014).

Another approach could be to target PINK1 since PINK1 and parkin are components of the same pathway regulating the turnover of damaged mitochondria, and the stabilization of PINK1 on the mitochondria is an essential step for the recruitment of parkin in order to carry out its ubiquitination function (Narendra, Jin et al. 2010). A recent study found that an ATP analog, kinetin triphosphate, increased PINK1 stabilization at the mitochondria, thus promoting higher parkin recruitment and decreased cell death (Hertz, Berthet et al. 2013). This would be an interesting methodology to find small molecules that would facilitate parkin recruitment to the mitochondria, thus increasing the efficiency of clearance of damaged mitochondria in idiopathic patients in whom parkin expression is preserved. Moreover, the recent discovery of the requirement of PINK1 to phosphorylate ubiquitin in order to activate parkin (Kane, Lazarou et al. 2014, Kazlauskaite, Kondapalli et al. 2014, Koyano, Okatsu et al. 2014) also highlights the benefits of targeting PINK1. Augmenting the PINK1 kinase activity could in turn promote phosphorylation of ubiquitin and parkin and increase its activity.

There are several post-translational changes that are thought to inactivate parkin. Modifications such as nitrosylation (Chung, Thomas et al. 2004, Yao, Gu et al. 2004), methamphetamine induced conjugation of 4-hydroxy-2-nonenal (4-HNE) to parkin (Moszczynska and Yamamoto 2011) and the irreversible dopamine-induced covalent modifications (LaVoie, Ostaszewski et al. 2005) are known to affect parkin activity. Reduction of these post-translational modifications with drugs such as melatonin (Reiter, Korkmaz et al. 2008) and taurine (Askwith, Zeng et al. 2012) are thought to reduce nitrosative stress, and Vitamin E implicated in inhibiting parkin changes (Moszczynska and Yamamoto 2011) could be further explored to support parkin activity.

Reducing parkin auto-inhibition: Catalytically active parkin

The crystal structure of parkin confirmed that under basal conditions, parkin lies in an auto-inhibited state (Riley, Lougheed et al. 2013, Trempe, Sauve et al. 2013, Wauer and Komander 2013). Since parkin overexpression during aging was shown to protect for proteotoxic stress, improve mitochondrial health and increase life-span (Rana, Rera et al. 2013), there would be a certain advantage to increase parkin activity during aging. Screening for small molecules that would bind and induce a conformational change in parkin to expose its catalytic domain would mimic overexpression of parkin and promote mitophagic turnover of damaged mitochondria and prevent cell death. Even modest allosteric modulators could be of potential benefit.

Phosphorylation of parkin appears to be a prerequisite for its ubiquitination activity. Parkin is phosphorylated by the mitochondrial kinase PINK1 at Ser65 (Kondapalli, Kazlauskaite et al. 2012) (Shiba-Fukushima, Imai et al. 2012, Iguchi, Kujuro et al. 2013), however, other serines have also been identified as phosphorylation sites in parkin (Yamamoto, Friedlein et al. 2005, Rubio de la Torre, Luzon-Toro et al. 2009). Phosphorylation of parkin by other kinases at other sites may also be part of a greater network of proteins regulation of its ligase activity (Yamamoto, Friedlein et al. 2005, Rubio de la Torre, Luzon-Toro et al. 2009). Given that cytosolic parkin has been implicated in virtually all non-mitophagic functions and substrates of parkin, there are likely other kinases that play a role in parkin activation. Understanding the precise role that kinases play in the activation and possibly repression of parkin E3 ligase activity will be essential to its pharmacological manipulation.

DUBs

Ubiquitination and clearance of proteins via the UPS is highly regulated and many mechanisms have evolved to keep protein destruction in check. One of the ways protein turnover is regulated is through deubiquitinating enzymes. Deubiquitinases (DUBs) are enzymes that remove ubiquitin molecules from proteins marked for degradation, thus reversing ubiquitination and removing the signal for subsequent degradation of the target protein. Recently, several studies were published assessing the role of DUBs associated with parkin function. USP15 and USP30 were identified as playing a role in parkin-mediated mitophagy (Bingol, Tea et al. 2014, Cornelissen, Haddad et al. 2014, Cunningham, Baughman et al. 2015). These studies reported that the overexpression of the respective DUB prevented parkin-mediated mitophagy and mitochondrial clearance. Bingol et al showed that knocking down USP30 enhanced mitochondrial clearance and promoted parkin-

mediated mitophagy, while Cornelissen and colleagues showed that knockdown of the Drosophila homolog of USP15 rescued the mitochondrial and behavioral defects in parkin null flies. The fact that a DUB could rescue a parkin null fly, suggests compensatory E3 ligases in this model organism. Another deubiquitinating enzyme USP8/UBPY was discovered to play a critical role in parkin-mediated mitophagy preferentially removing the K6-linked ubiquitin chains from parkin, affecting its translocation, and subsequent degradation of substrates via mitophagy (Durcan, Tang et al. 2014).

Thus, one could hypothesize that targeting these DUBs to inhibit their activity would enhance parkin function and facilitate removal of unhealthy mitochondria and promote cell survival. Indeed, an earlier study showed that a small molecule inhibitor of another DUB, Usp14, enhanced proteasomal function and promoted protein turnover (Lee, Lee et al. 2010), confirming the drugability of these proteases and the proof-of-concept of their potential efficacy. The discovery of these parkin associated DUBs proffer an exciting opportunity to promote mitochondrial clearance and reduce accumulation of toxic substrates.

Compensatory E3 ligase

Transfer of an ubiquitin moiety to a protein is a multi-step process requiring the functions of an ubiquitin activating (E1), ubiquitin conjugating (E2) and the ubiquitin ligase (E3) enzymes, which confer the substrate specificity of this cascade. A recent curated database showed that human cells contain 2 E1s, 29 E2s and 563 E3 enzymes (Bhowmick, Pancsa et al. 2013). This system of ubiquitination resembles a pyramidal structure, enabling a highly regulated process and conferring functional diversity and complexity (Bhowmick, Pancsa et al. 2013). There have been multiple E2 enzymes thought to be associated with parkin. The enzymes UbcH7 and UbcH8 as well as the ER-associated E2s Ubc6 and Ubc7 have all been identified as binding partners (Imai, Soda et al. 2000, Shimura, Hattori et al. 2000, Zhang, Gao et al. 2000, Imai, Soda et al. 2001, Shimura, Schlossmacher et al. 2001). Thus, these E3 ligases may have unique or shared substrates within the cell, making it interesting to postulate having an E3 ligase that could compensate for the lack of parkin function. Since PD is primarily an aging disorder, one can hypothesize that one E3 ligase may compensate for another masking symptoms early in life, and the capacity to compensate for parkin deficiency may decrease with age. This observation could also account for the lack of a parkinsonian phenotype in parkin KO mice, since parkin function might be uniquely redundant with another E3 ligase in mice. Future studies, especially in mice, to study the E3 ligases compensating for lack of parkin function would be exciting to target it and generate redundancy to some degree in humans.

Conclusion

Current treatments for PD primarily involve only the management of motor symptoms, but do not address disease progression or the numerous non-nigral features of the disorder. Parkin plays an integral role within the cell and the wealth of information we now have regarding parkin biology and biochemistry far exceeds what we now know about many other neurologic disease related genes. Importantly, the far majority of PD patients have intact expression of a functional parkin protein and given the numerous homeostatic functions

implicated for this protein, activating parkin may represent a disease modifying approach. The solved crystal structure of parkin, recent links between phosphorylation and parkin activation, and the characterization of antagonistic DUBs that can likewise be pharmacologically targeted, all pave the ground forward for translational efforts to stimulate parkin biology and tap into a potential endogenous reservoir of neuroprotection in the human brain.

Bibliography

Alcalay RN, Clark LN, Marder KS, Bradley WE. Lack of association between cancer history and PARKIN genotype: a family based study in PARKIN/Parkinson's families. Genes Chromosomes Cancer. 2012; 51(12):1109–1113. [PubMed: 22927236]

Alves da Costa C, Checler F. Parkin: much more than a simple ubiquitin ligase. Neurodegener Dis. 2012; 10(1-4):49–51. [PubMed: 22204976]

Amadoro G, Corsetti V, Florenzano F, Atlante A, Bobba A, Nicolin V, Nori SL, Calissano P. Morphological and bioenergetic demands underlying the mitophagy in post-mitotic neurons: the pink-parkin pathway. Front Aging Neurosci. 2014; 6:18. [PubMed: 24600391]

Ashrafi G, Schlehe JS, LaVoie MJ, Schwarz TL. Mitophagy of damaged mitochondria occurs locally in distal neuronal axons and requires PINK1 and Parkin. J Cell Biol. 2014; 206(5):655–670. [PubMed: 25154397]

Askwith T, Zeng W, Eggo MC, Stevens MJ. Taurine reduces nitrosative stress and nitric oxide synthase expression in high glucose-exposed human Schwann cells. Exp Neurol. 2012; 233(1):154–162. [PubMed: 21952043]

Bartek J, Hodny Z. PARK2 orchestrates cyclins to avoid cancer. Nat Genet. 2014; 46(6):527–528. [PubMed: 24866187]

Berger AK, Cortese GP, Amodeo KD, Weihofen A, Letai A, LaVoie MJ. Parkin selectively alters the intrinsic threshold for mitochondrial cytochrome c release. Hum Mol Genet. 2009; 18(22):4317–4328. [PubMed: 19679562]

Bhowmick P, Pancsa R, Guharoy M, Tompa P. Functional diversity and structural disorder in the human ubiquitination pathway. PLoS One. 2013; 8(5):e65443. [PubMed: 23734257]

Bingol B, Tea JS, Phu L, Reichelt M, Bakalarski CE, Song Q, Foreman O, Kirkpatrick DS, Sheng M. The mitochondrial deubiquitinase USP30 opposes parkin-mediated mitophagy. Nature. 2014; 510(7505):370–375. [PubMed: 24896179]

Bosco DA, LaVoie MJ, Petsko GA, Ringe D. Proteostasis and movement disorders: Parkinson's disease and amyotrophic lateral sclerosis. Cold Spring Harb Perspect Biol. 2011; 3(10):a007500. [PubMed: 21844169]

Bossy-Wetzel E, Schwarzenbacher R, Lipton SA. Molecular pathways to neurodegeneration. Nat Med. 2004; 10(Suppl):S2–9. [PubMed: 15272266]

Bouman L, Schlierf A, Lutz AK, Shan J, Deinlein A, Kast J, Galehdar Z, Palmisano V, Patenge N, Berg D, Gasser T, Augustin R, Trumbach D, Irrcher I, Park DS, Wurst W, Kilberg MS, Tatzelt J, Winklhofer KF. Parkin is transcriptionally regulated by ATF4: evidence for an interconnection between mitochondrial stress and ER stress. Cell Death Differ. 2011; 18(5):769–782. [PubMed: 21113145]

Braak H, Ghebremedhin E, Rub U, Bratzke H, Del Tredici K. Stages in the development of Parkinson's disease-related pathology. Cell Tissue Res. 2004; 318(1):121–134. [PubMed: 15338272]

Burns MP, Zhang L, Rebeck GW, Querfurth HW, Moussa CE. Parkin promotes intracellular Abeta1-42 clearance. Hum Mol Genet. 2009; 18(17):3206–3216. [PubMed: 19483198]

Cesari R, Martin ES, Calin GA, Pentimalli F, Bichi R, McAdams H, Trapasso F, Drusco A, Shimizu M, Masciullo V, D'Andrilli G, Scambia G, Picchio MC, Alder H, Godwin AK, Croce CM. Parkin, a gene implicated in autosomal recessive juvenile parkinsonism, is a candidate tumor suppressor gene on chromosome 6q25-q27. Proc Natl Acad Sci U S A. 2003; 100(10):5956–5961. [PubMed: 12719539]

Chan NC, Salazar AM, Pham AH, Sweredoski MJ, Kolawa NJ, Graham RL, Hess S, Chan DC. Broad activation of the ubiquitin-proteasome system by Parkin is critical for mitophagy. Hum Mol Genet. 2011; 20(9):1726–1737. [PubMed: 21296869]

Charan RA, Johnson BN, Zaganelli S, Nardozzi JD, LaVoie MJ. Inhibition of apoptotic Bax translocation to the mitochondria is a central function of parkin. Cell Death Dis. 2014; 5:e1313. [PubMed: 24991765]

Chaturvedi RK, Beal MF. Mitochondria targeted therapeutic approaches in Parkinson's and Huntington's diseases. Mol Cell Neurosci. 2013; 55:101–114. [PubMed: 23220289]

Chaturvedi RK, Flint Beal M. Mitochondrial diseases of the brain. Free Radic Biol Med. 2013; 63:1–29. [PubMed: 23567191]

Checler F, Alves da Costa C. Interplay between parkin and p53 governs a physiological homeostasis that is disrupted in Parkinson's disease and cerebral cancer. Neurodegener Dis. 2014; 13(2-3):118–121. [PubMed: 24008413]

Chen D, Gao F, Li B, Wang H, Xu Y, Zhu C, Wang G. Parkin mono-ubiquitinates Bcl-2 and regulates autophagy. J Biol Chem. 2010; 285(49):38214–38223. [PubMed: 20889974]

Chen H, Chan DC. Mitochondrial dynamics--fusion, fission, movement, and mitophagy--in neurodegenerative diseases. Hum Mol Genet. 2009; 18(R2):R169–176. [PubMed: 19808793]

Chen H, Detmer SA, Ewald AJ, Griffin EE, Fraser SE, Chan DC. Mitofusins Mfn1 and Mfn2 coordinately regulate mitochondrial fusion and are essential for embryonic development. J Cell Biol. 2003; 160(2):189–200. [PubMed: 12527753]

Chen X, Burdett TC, Desjardins CA, Logan R, Cipriani S, Xu Y, Schwarzschild MA. Disrupted and transgenic urate oxidase alter urate and dopaminergic neurodegeneration. Proc Natl Acad Sci U S A. 2013; 110(1):300–305. [PubMed: 23248282]

Chen Y, Dorn GW 2nd. PINK1-phosphorylated mitofusin 2 is a Parkin receptor for culling damaged mitochondria. Science. 2013; 340(6131):471–475. [PubMed: 23620051]

Chung KK, Thomas B, Li X, Pletnikova O, Troncoso JC, Marsh L, Dawson VL, Dawson TM. S-nitrosylation of parkin regulates ubiquitination and compromises parkin's protective function. Science. 2004; 304(5675):1328–1331. [PubMed: 15105460]

Cipolat S, Martins de Brito O, Dal Zilio B, Scorrano L. OPA1 requires mitofusin 1 to promote mitochondrial fusion. Proc Natl Acad Sci U S A. 2004; 101(45):15927–15932. [PubMed: 15509649]

Cipriani S, Chen X, Schwarzschild MA. Urate: a novel biomarker of Parkinson's disease risk, diagnosis and prognosis. Biomark Med. 2010; 4(5):701–712. [PubMed: 20945982]

Clark IE, Dodson MW, Jiang C, Cao JH, Huh JR, Seol JH, Yoo SJ, Hay BA, Guo M. Drosophila pink1 is required for mitochondrial function and interacts genetically with parkin. Nature. 2006; 441(7097):1162–1166. [PubMed: 16672981]

Cornelissen T, Haddad D, Wauters F, Van Humbeeck C, Mandemakers W, Koentjoro B, Sue C, Gevaert K, De Strooper B, Verstreken P, Vandenberghe W. The deubiquitinase USP15 antagonizes Parkin-mediated mitochondrial ubiquitination and mitophagy. Hum Mol Genet. 2014; 23(19):5227–5242. [PubMed: 24852371]

Corti O, Lesage S, Brice A. What genetics tells us about the causes and mechanisms of Parkinson's disease. Physiol Rev. 2011; 91(4):1161–1218. [PubMed: 22013209]

Cunningham CN, Baughman JM, Phu L, Tea JS, Yu C, Coons M, Kirkpatrick DS, Bingol B, Corn JE. USP30 and parkin homeostatically regulate atypical ubiquitin chains on mitochondria. Nat Cell Biol. 2015; 17(2):160–169. [PubMed: 25621951]

da Costa CA, Sunyach C, Giaime E, West A, Corti O, Brice A, Safe S, Abou-Sleiman PM, Wood NW, Takahashi H, Goldberg MS, Shen J, Checler F. Transcriptional repression of p53 by parkin and impairment by mutations associated with autosomal recessive juvenile Parkinson's disease. Nat Cell Biol. 2009; 11(11):1370–1375. [PubMed: 19801972]

Darios F, Corti O, Lucking CB, Hampe C, Muriel MP, Abbas N, Gu WJ, Hirsch EC, Rooney T, Ruberg M, Brice A. Parkin prevents mitochondrial swelling and cytochrome c release in mitochondria-dependent cell death. Hum Mol Genet. 2003; 12(5):517–526. [PubMed: 12588799]

Dauer W, Przedborski S. Parkinson's disease: mechanisms and models. Neuron. 2003; 39(6):889–909. [PubMed: 12971891]

Davis JW, Grandinetti A, Waslien CI, Ross GW, White LR, Morens DM. Observations on serum uric acid levels and the risk of idiopathic Parkinson's disease. Am J Epidemiol. 1996; 144(5):480–484. [PubMed: 8781463]

Dawson TM, Dawson VL. Rare genetic mutations shed light on the pathogenesis of Parkinson disease. J Clin Invest. 2003; 111(2):145–151. [PubMed: 12531866]

Deng H, Dodson MW, Huang H, Guo M. The Parkinson's disease genes pink1 and parkin promote mitochondrial fission and/or inhibit fusion in Drosophila. Proc Natl Acad Sci U S A. 2008; 105(38):14503–14508. [PubMed: 18799731]

Detmer SA, Chan DC. Functions and dysfunctions of mitochondrial dynamics. Nat Rev Mol Cell Biol. 2007; 8(11):870–879. [PubMed: 17928812]

Ding WX, Ni HM, Li M, Liao Y, Chen X, Stolz DB, Dorn GW 2nd, Yin XM. Nix is critical to two distinct phases of mitophagy, reactive oxygen species-mediated autophagy induction and Parkin-ubiquitin-p62-mediated mitochondrial priming. J Biol Chem. 2010; 285(36):27879–27890. [PubMed: 20573959]

Dorn GW 2nd. Mitochondrial pruning by Nix and BNip3: an essential function for cardiac-expressed death factors. J Cardiovasc Transl Res. 2010; 3(4):374–383. [PubMed: 20559783]

Dorsey ER, Constantinescu R, Thompson JP, Biglan KM, Holloway RG, Kieburtz K, Marshall FJ, Ravina BM, Schifitto G, Siderowf A, Tanner CM. Projected number of people with Parkinson disease in the most populous nations, 2005 through 2030. Neurology. 2007; 68(5):384–386. [PubMed: 17082464]

Dove KK, Klevit RE. Structural Biology: Parkin's Serpentine Shape Revealed in the Year of the Snake. Curr Biol. 2013; 23(16):R691–693. [PubMed: 23968926]

Duplan E, Sevalle J, Viotti J, Goiran T, Bauer C, Renbaum P, Levy-Lahad E, Gautier CA, Corti O, Leroudier N, Checler F, da Costa CA. Parkin differently regulates presenilin-1 and presenilin-2 functions by direct control of their promoter transcription. J Mol Cell Biol. 2013; 5(2):132–142. [PubMed: 23359614]

Durcan TM, Tang MY, Perusse JR, Dashti EA, Aguileta MA, McLelland GL, Gros P, Shaler TA, Faubert D, Coulombe B, Fon EA. USP8 regulates mitophagy by removing K6-linked ubiquitin conjugates from parkin. EMBO J. 2014

Exner N, Lutz AK, Haass C, Winklhofer KF. Mitochondrial dysfunction in Parkinson's disease: molecular mechanisms and pathophysiological consequences. EMBO J. 2012; 31(14):3038–3062. [PubMed: 22735187]

Fallon L, Belanger CM, Corera AT, Kontogiannea M, Regan-Klapisz E, Moreau F, Voortman J, Haber M, Rouleau G, Thorarinsdottir T, Brice A, van Bergen En Henegouwen PM, Fon EA. A regulated interaction with the UIM protein Eps15 implicates parkin in EGF receptor trafficking and PI(3)K-Akt signalling. Nat Cell Biol. 2006; 8(8):834–842. [PubMed: 16862145]

Farrer M, Chan P, Chen R, Tan L, Lincoln S, Hernandez D, Forno L, Gwinn-Hardy K, Petrucelli L, Hussey J, Singleton A, Tanner C, Hardy J, Langston JW. Lewy bodies and parkinsonism in families with parkin mutations. Ann Neurol. 2001; 50(3):293–300. [PubMed: 11558785]

Ferretta A, Gaballo A, Tanzarella P, Piccoli C, Capitanio N, Nico B, Annese T, Di Paola M, Dell'aquila C, De Mari M, Ferranini E, Bonifati V, Pacelli C, Cocco T. Effect of resveratrol on mitochondrial function: implications in parkin-associated familiar Parkinson's disease. Biochim Biophys Acta. 2014; 1842(7):902–915. [PubMed: 24582596]

Forno LS. Neuropathology of Parkinson's disease. J Neuropathol Exp Neurol. 1996; 55(3):259–272. [PubMed: 8786384]

Frank-Cannon TC, Tran T, Ruhn KA, Martinez TN, Hong J, Marvin M, Hartley M, Trevino I, O'Brien DE, Casey B, Goldberg MS, Tansey MG. Parkin deficiency increases vulnerability to inflammation-related nigral degeneration. J Neurosci. 2008; 28(43):10825–10834. [PubMed: 18945890]

Gao F, Chen D, Si J, Hu Q, Qin Z, Fang M, Wang G. The mitochondrial protein BNIP3L is the substrate of PARK2 and mediates mitophagy in PINK1/PARK2 pathway. Hum Mol Genet. 2015 in press.

Garber K. Parkinson's disease and cancer: the unexplored connection. J Natl Cancer Inst. 2010; 102(6): 371–374. [PubMed: 20215596]

Glessner JT, Wang K, Cai G, Korvatska O, Kim CE, Wood S, Zhang H, Estes A, Brune CW, Bradfield JP, Imielinski M, Frackelton EC, Reichert J, Crawford EL, Munson J, Sleiman PM, Chiavacci R, Annaiah K, Thomas K, Hou C, Glaberson W, Flory J, Otieno F, Garris M, Soorya L, Klei L, Piven J, Meyer KJ, Anagnostou E, Sakurai T, Game RM, Rudd DS, Zurawiecki D, McDougle CJ, Davis LK, Miller J, Posey DJ, Michaels S, Kolevzon A, Silverman JM, Bernier R, Levy SE, Schultz RT, Dawson G, Owley T, McMahon WM, Wassink TH, Sweeney JA, Nurnberger JI, Coon H, Sutcliffe JS, Minshew NJ, Grant SF, Bucan M, Cook EH, Buxbaum JD, Devlin B, Schellenberg GD, Hakonarson H. Autism genome-wide copy number variation reveals ubiquitin and neuronal genes. Nature. 2009; 459(7246):569–573. [PubMed: 19404257]

Goldberg MS, Fleming SM, Palacino JJ, Cepeda C, Lam HA, Bhatnagar A, Meloni EG, Wu N, Ackerson LC, Klapstein GJ, Gajendiran M, Roth BL, Chesselet MF, Maidment NT, Levine MS, Shen J. Parkin-deficient mice exhibit nigrostriatal deficits but not loss of dopaminergic neurons. J Biol Chem. 2003; 278(44):43628–43635. [PubMed: 12930822]

Gong Y, Zack TI, Morris LG, Lin K, Hukkelhoven E, Raheja R, Tan IL, Turcan S, Veeriah S, Meng S, Viale A, Schumacher SE, Palmedo P, Beroukhim R, Chan TA. Pan-cancer genetic analysis identifies PARK2 as a master regulator of G1/S cyclins. Nat Genet. 2014; 46(6):588–594. [PubMed: 24793136]

Greene JC, Whitworth AJ, Kuo I, Andrews LA, Feany MB, Pallanck LJ. Mitochondrial pathology and apoptotic muscle degeneration in Drosophila parkin mutants. Proc Natl Acad Sci U S A. 2003; 100(7):4078–4083. [PubMed: 12642658]

Grenier K, McLelland GL, Fon EA. Parkin- and PINK1-Dependent Mitophagy in Neurons: Will the Real Pathway Please Stand Up? Front Neurol. 2013; 4:100. [PubMed: 23882257]

Henn IH, Bouman L, Schlehe JS, Schlierf A, Schramm JE, Wegener E, Nakaso K, Culmsee C, Berninger B, Krappmann D, Tatzelt J, Winklhofer KF. Parkin mediates neuroprotection through activation of IkappaB kinase/nuclear factor-kappaB signaling. J Neurosci. 2007; 27(8):1868–1878. [PubMed: 17314283]

Henn IH, Gostner JM, Lackner P, Tatzelt J, Winklhofer KF. Pathogenic mutations inactivate parkin by distinct mechanisms. J Neurochem. 2005; 92(1):114–122. [PubMed: 15606901]

Hertz NT, Berthet A, Sos ML, Thorn KS, Burlingame AL, Nakamura K, Shokat KM. A neo-substrate that amplifies catalytic activity of parkinson's-disease-related kinase PINK1. Cell. 2013; 154(4): 737–747. [PubMed: 23953109]

Hirtz D, Thurman DJ, Gwinn-Hardy K, Mohamed M, Chaudhuri AR, Zalutsky R. How common are the “common” neurologic disorders? Neurology. 2007; 68(5):326–337. [PubMed: 17261678]

Hornykiewicz O, Kish SJ. Biochemical pathophysiology of Parkinson's disease. Adv Neurol. 1987; 45:19–34. [PubMed: 2881444]

Hristova VA, Beasley SA, Rylett RJ, Shaw GS. Identification of a novel Zn2+-binding domain in the autosomal recessive juvenile Parkinson-related E3 ligase parkin. J Biol Chem. 2009; 284(22): 14978–14986. [PubMed: 19339245]

Huynh DP, Dy M, Nguyen D, Kiehl TR, Pulst SM. Differential expression and tissue distribution of parkin isoforms during mouse development. Brain Res Dev Brain Res. 2001; 130(2):173–181.

Iguchi M, Kujuro Y, Okatsu K, Koyano F, Kosako H, Kimura M, Suzuki N, Uchiyama S, Tanaka K, Matsuda N. Parkin-catalyzed ubiquitin-ester transfer is triggered by PINK1-dependent phosphorylation. J Biol Chem. 2013; 288(30):22019–22032. [PubMed: 23754282]

Imai Y, Soda M, Inoue H, Hattori N, Mizuno Y, Takahashi R. An unfolded putative transmembrane polypeptide, which can lead to endoplasmic reticulum stress, is a substrate of Parkin. Cell. 2001; 105(7):891–902. [PubMed: 11439185]

Imai Y, Soda M, Takahashi R. Parkin suppresses unfolded protein stress-induced cell death through its E3 ubiquitin-protein ligase activity. J Biol Chem. 2000; 275(46):35661–35664. [PubMed: 10973942]

Imaizumi Y, Okada Y, Akamatsu W, Koike M, Kuzumaki N, Hayakawa H, Nihira T, Kobayashi T, Ohyama M, Sato S, Takanashi M, Funayama M, Hirayama A, Soga T, Hishiki T, Suematsu M, Yagi T, Ito D, Kosakai A, Hayashi K, Shouji M, Nakanishi A, Suzuki N, Mizuno Y, Mizushima N, Amagai M, Uchiyama Y, Mochizuki H, Hattori N, Okano H. Mitochondrial dysfunction associated with increased oxidative stress and alpha-synuclein accumulation in PARK2 iPSC-derived neurons and postmortem brain tissue. Mol Brain. 2012; 5:35. [PubMed: 23039195]

Jain S. Multi-organ autonomic dysfunction in Parkinson disease. Parkinsonism Relat Disord. 2011; 17(2):77–83. [PubMed: 20851033]

James DI, Parone PA, Mattenberger Y, Martinou JC. hFis1, a novel component of the mammalian mitochondrial fission machinery. J Biol Chem. 2003; 278(38):36373–36379. [PubMed: 12783892]

Jiang H, Ren Y, Zhao J, Feng J. Parkin protects human dopaminergic neuroblastoma cells against dopamine-induced apoptosis. Hum Mol Genet. 2004; 13(16):1745–1754. [PubMed: 15198987]

Jin H, Kanthasamy A, Ghosh A, Anantharam V, Kalyanaraman B, Kanthasamy AG. Mitochondria-targeted antioxidants for treatment of Parkinson's disease: preclinical and clinical outcomes. Biochim Biophys Acta. 2014; 1842(8):1282–1294. [PubMed: 24060637]

Jin HS, Kim J, Lee SJ, Kim K, Go MJ, Lee JY, Lee HJ, Song J, Jeon BT, Roh GS, Kim SJ, Kim BY, Hong KW, Yoo YH, Oh B, Kang Y, Jeong SY. The PARK2 gene is involved in the maintenance of pancreatic beta-cell functions related to insulin production and secretion. Mol Cell Endocrinol. 2014; 382(1):178–189. [PubMed: 24096089]

Johnson BN, Berger AK, Cortese GP, Lavoie MJ. The ubiquitin E3 ligase parkin regulates the proapoptotic function of Bax. Proc Natl Acad Sci U S A. 2012; 109(16):6283–6288. [PubMed: 22460798]

Johnson BN, Charan RA, LaVoie MJ. Recognizing the cooperative and independent mitochondrial functions of Parkin and PINK1. Cell Cycle. 2012; 11(15):2775–2776. [PubMed: 22801534]

Kahle PJ, Leimer U, Haass C. Does failure of parkin-mediated ubiquitination cause juvenile parkinsonism? Trends Biochem Sci. 2000; 25(11):524–527. [PubMed: 11084358]

Kaidery NA, Banerjee R, Yang L, Smirnova NA, Hushpulian DM, Liby KT, Williams CR, Yamamoto M, Kensler TW, Ratan RR, Sporn MB, Beal MF, Gazaryan IG, Thomas B. Targeting Nrf2-mediated gene transcription by extremely potent synthetic triterpenoids attenuate dopaminergic neurotoxicity in the MPTP mouse model of Parkinson's disease. Antioxid Redox Signal. 2013; 18(2):139–157. [PubMed: 22746536]

Kane LA, Lazarou M, Fogel AI, Li Y, Yamano K, Sarraf SA, Banerjee S, Youle RJ. PINK1 phosphorylates ubiquitin to activate Parkin E3 ubiquitin ligase activity. J Cell Biol. 2014; 205(2): 143–153. [PubMed: 24751536]

Karbowski M, Lee YJ, Gaume B, Jeong SY, Frank S, Nechushtan A, Santel A, Fuller M, Smith CL, Youle RJ. Spatial and temporal association of Bax with mitochondrial fission sites, Drp1, and Mfn2 during apoptosis. J Cell Biol. 2002; 159(6):931–938. [PubMed: 12499352]

Kawahara K, Hashimoto M, Bar-On P, Ho GJ, Crews L, Mizuno H, Rockenstein E, Imam SZ, Masliah E. alpha-Synuclein aggregates interfere with Parkin solubility and distribution: role in the pathogenesis of Parkinson disease. J Biol Chem. 2008; 283(11):6979–6987. [PubMed: 18195004]

Kazlauskaite A, Kondapalli C, Gourlay R, Campbell DG, Ritorto MS, Hofmann K, Alessi DR, Knebel A, Trost M, Muqit MM. Parkin is activated by PINK1-dependent phosphorylation of ubiquitin at Ser65. Biochem J. 2014; 460(1):127–139. [PubMed: 24660806]

Kim SJ, Syed GH, Khan M, Chiu WW, Sohail MA, Gish RG, Siddiqui A. Hepatitis C virus triggers mitochondrial fission and attenuates apoptosis to promote viral persistence. Proc Natl Acad Sci U S A. 2014; 111(17):6413–6418. [PubMed: 24733894]

Kitada T, Asakawa S, Hattori N, Matsumine H, Yamamura Y, Minoshima S, Yokochi M, Mizuno Y, Shimizu N. Mutations in the parkin gene cause autosomal recessive juvenile parkinsonism. Nature. 1998; 392(6676):605–608. [PubMed: 9560156]

Kondapalli C, Kazlauskaite A, Zhang N, Woodroof HI, Campbell DG, Gourlay R, Burchell L, Walden H, Macartney TJ, Deak M, Knebel A, Alessi DR, Muqit MM. PINK1 is activated by mitochondrial membrane potential depolarization and stimulates Parkin E3 ligase activity by phosphorylating Serine 65. Open Biol. 2012; 2(5):120080. [PubMed: 22724072]

Koyano F, Okatsu K, Kosako H, Tamura Y, Go E, Kimura M, Kimura Y, Tsuchiya H, Yoshihara H, Hirokawa T, Endo T, Fon EA, Trempe JF, Saeki Y, Tanaka K, Matsuda N. Ubiquitin is phosphorylated by PINK1 to activate parkin. Nature. 2014; 510(7503):162–166. [PubMed: 24784582]

Kubli DA, Quinsay MN, Gustafsson AB. Parkin deficiency results in accumulation of abnormal mitochondria in aging myocytes. Commun Integr Biol. 2013; 6(4):e24511. [PubMed: 23986804]

Kubli DA, Zhang X, Lee Y, Hanna RA, Quinsay MN, Nguyen CK, Jimenez R, Petrosyan S, Murphy AN, Gustafsson AB. Parkin protein deficiency exacerbates cardiac injury and reduces survival following myocardial infarction. J Biol Chem. 2013; 288(2):915–926. [PubMed: 23152496]

Kupsky WJ, Grimes MM, Sweeting J, Bertsch R, Cote LJ. Parkinson's disease and megacolon: concentric hyaline inclusions (Lewy bodies) in enteric ganglion cells. Neurology. 1987; 37(7): 1253–1255. [PubMed: 3037441]

Langston JW. The Parkinson's complex: parkinsonism is just the tip of the iceberg. Ann Neurol. 2006; 59(4):591–596. [PubMed: 16566021]

LaVoie MJ, Ostaszewski BL, Weihofen A, Schlossmacher MG, Selkoe DJ. Dopamine covalently modifies and functionally inactivates parkin. Nat Med. 2005; 11(11):1214–1221. [PubMed: 16227987]

Lee BH, Lee MJ, Park S, Oh DC, Elsasser S, Chen PC, Gartner C, Dimova N, Hanna J, Gygi SP, Wilson SM, King RW, Finley D. Enhancement of proteasome activity by a small-molecule inhibitor of USP14. Nature. 2010; 467(7312):179–184. [PubMed: 20829789]

Lee JM, Shih AY, Murphy TH, Johnson JA. NF-E2-related factor-2 mediates neuroprotection against mitochondrial complex I inhibitors and increased concentrations of intracellular calcium in primary cortical neurons. J Biol Chem. 2003; 278(39):37948–37956. [PubMed: 12842875]

Lee Y, Lee HY, Hanna RA, Gustafsson AB. Mitochondrial autophagy by Bnip3 involves Drp1-mediated mitochondrial fission and recruitment of Parkin in cardiac myocytes. Am J Physiol Heart Circ Physiol. 2011; 301(5):H1924–1931. [PubMed: 21890690]

Liesa M, Shirihai OS. Mitochondrial dynamics in the regulation of nutrient utilization and energy expenditure. Cell Metab. 2013; 17(4):491–506. [PubMed: 23562075]

Lo Bianco C, Schneider BL, Bauer M, Sajadi A, Brice A, Iwatsubo T, Aebischer P. Lentiviral vector delivery of parkin prevents dopaminergic degeneration in an alpha-synuclein rat model of Parkinson's disease. Proc Natl Acad Sci U S A. 2004; 101(50):17510–17515. [PubMed: 15576511]

Lonskaya I, Desforges NM, Hebron ML, Moussa CE. Ubiquitination increases parkin activity to promote autophagic alpha-synuclein clearance. PLoS One. 2013; 8(12):e83914. [PubMed: 24386307]

Lonskaya I, Shekoyan AR, Hebron ML, Desforges N, Algarzae NK, Moussa CE. Diminished parkin solubility and co-localization with intraneuronal amyloid-beta are associated with autophagic defects in Alzheimer's disease. J Alzheimers Dis. 2013; 33(1):231–247. [PubMed: 22954671]

Loson OC, Song Z, Chen H, Chan DC. Fis1, Mff, MiD49, and MiD51 mediate Drp1 recruitment in mitochondrial fission. Mol Biol Cell. 2013; 24(5):659–667. [PubMed: 23283981]

Lu B. Neuronal Mitophagy: Long-Distance Delivery or Eating Locally? Current Biology. 2014; 24(20):R1006–R1008. [PubMed: 25442848]

Lucking CB, Durr A, Bonifati V, Vaughan J, De Michele G, Gasser T, Harhangi BS, Meco G, Denefle P, Wood NW, Agid Y, Brice A. Association between early-onset Parkinson's disease and mutations in the parkin gene. N Engl J Med. 2000; 342(21):1560–1567. [PubMed: 10824074]

Lutz AK, Exner N, Fett ME, Schlehe JS, Kloos K, Lammermann K, Brunner B, Kurz-Drexler A, Vogel F, Reichert AS, Bouman L, Vogt-Weisenhorn D, Wurst W, Tatzelt J, Haass C, Winklhofer KF. Loss of parkin or PINK1 function increases Drp1-dependent mitochondrial fragmentation. J Biol Chem. 2009; 284(34):22938–22951. [PubMed: 19546216]

Mata IF, Lockhart PJ, Farrer MJ. Parkin genetics: one model for Parkinson's disease. Hum Mol Genet. 2004; 13:R127–133. Spec No 1. [PubMed: 14976155]

Matsumine H, Saito M, Shimoda-Matsubayashi S, Tanaka H, Ishikawa A, Nakagawa-Hattori Y, Yokochi M, Kobayashi T, Igarashi S, Takano H, Sanpei K, Koike R, Mori H, Kondo T, Mizutani Y, Schaffer AA, Yamamura Y, Nakamura S, Kuzuhara S, Tsuji S, Mizuno Y. Localization of a gene for an autosomal recessive form of juvenile Parkinsonism to chromosome 6q25.2-27. Am J Hum Genet. 1997; 60(3):588–596. [PubMed: 9042918]

Meng F, Yao D, Shi Y, Kabakoff J, Wu W, Reicher J, Ma Y, Moosmann B, Masliah E, Lipton SA, Gu Z. Oxidation of the cysteine-rich regions of parkin perturbs its E3 ligase activity and contributes to protein aggregation. Mol Neurodegener. 2011; 6:34. [PubMed: 21595948]

Mira MT, Alcais A, Nguyen VT, Moraes MO, Di Flumeri C, Vu HT, Mai CP, Nguyen TH, Nguyen NB, Pham XK, Sarno EN, Alter A, Montpetit A, Moraes ME, Moraes JR, Dore C, Gallant CJ, Lepage P, Verner A, Van De Vosse E, Hudson TJ, Abel L, Schurr E. Susceptibility to leprosy is associated with PARK2 and PACRG. Nature. 2004; 427(6975):636–640. [PubMed: 14737177]

Mizushima N. Autophagy: process and function. Genes Dev. 2007; 21(22):2861–2873. [PubMed: 18006683]

Molina AJ, Wikstrom JD, Stiles L, Las G, Mohamed H, Elorza A, Walzer G, Twig G, Katz S, Corkey BE, Shirihai OS. Mitochondrial networking protects beta-cells from nutrient-induced apoptosis. Diabetes. 2009; 58(10):2303–2315. [PubMed: 19581419]

Mori H, Kondo T, Yokochi M, Matsumine H, Nakagawa-Hattori Y, Miyake T, Suda K, Mizuno Y. Pathologic and biochemical studies of juvenile parkinsonism linked to chromosome 6q. Neurology. 1998; 51(3):890–892. [PubMed: 9748052]

Moszczynska A, Yamamoto BK. Methamphetamine oxidatively damages parkin and decreases the activity of 26S proteasome in vivo. J Neurochem. 2011; 116(6):1005–1017. [PubMed: 21166679]

Muller-Rischart AK, Pilsl A, Beaudette P, Patra M, Hadian K, Funke M, Peis R, Deinlein A, Schweimer C, Kuhn PH, Lichtenthaler SF, Motori E, Hrelia S, Wurst W, Trumbach D, Langer T, Krappmann D, Dittmar G, Tatzelt J, Winklhofer KF. The E3 ligase parkin maintains mitochondrial integrity by increasing linear ubiquitination of NEMO. Mol Cell. 2013; 49(5):908–921. [PubMed: 23453807]

Narendra D, Tanaka A, Suen DF, Youle RJ. Parkin is recruited selectively to impaired mitochondria and promotes their autophagy. J Cell Biol. 2008; 183(5):795–803. [PubMed: 19029340]

Narendra DP, Jin SM, Tanaka A, Suen DF, Gautier CA, Shen J, Cookson MR, Youle RJ. PINK1 is selectively stabilized on impaired mitochondria to activate Parkin. PLoS Biol. 2010; 8(1):e1000298. [PubMed: 20126261]

Narendra DP, Youle RJ. Targeting mitochondrial dysfunction: role for PINK1 and Parkin in mitochondrial quality control. Antioxid Redox Signal. 2011; 14(10):1929–1938. [PubMed: 21194381]

Oliveira SA, Scott WK, Martin ER, Nance MA, Watts RL, Hubble JP, Koller WC, Pahwa R, Stern MB, Hiner BC, Ondo WG, Allen FH Jr. Scott BL, Goetz CG, Small GW, Mastaglia F, Stajich JM, Zhang F, Booze MW, Winn MP, Middleton LT, Haines JL, Pericak-Vance MA, Vance JM. Parkin mutations and susceptibility alleles in late-onset Parkinson's disease. Ann Neurol. 2003; 53(5):624–629. [PubMed: 12730996]

Ong SB, Subrayan S, Lim SY, Yellon DM, Davidson SM, Hausenloy DJ. Inhibiting mitochondrial fission protects the heart against ischemia/reperfusion injury. Circulation. 2010; 121(18):2012–2022. [PubMed: 20421521]

Ordureau A, Sarraf SA, Duda DM, Heo JM, Jedrychowski MP, Sviderskiy VO, Olszewski JL, Koerber JT, Xie T, Beausoleil SA, Wells JA, Gygi SP, Schulman BA, Harper JW. Quantitative Proteomics Reveal a Feedforward Mechanism for Mitochondrial PARKIN Translocation and Ubiquitin Chain Synthesis. Mol Cell. 2014

Park J, Lee G, Chung J. The PINK1-Parkin pathway is involved in the regulation of mitochondrial remodeling process. Biochem Biophys Res Commun. 2009; 378(3):518–523. [PubMed: 19056353]

Park J, Lee SB, Lee S, Kim Y, Song S, Kim S, Bae E, Kim J, Shong M, Kim JM, Chung J. Mitochondrial dysfunction in Drosophila PINK1 mutants is complemented by parkin. Nature. 2006; 441(7097):1157–1161. [PubMed: 16672980]

Pawlyk AC, Giasson BI, Sampathu DM, Perez FA, Lim KL, Dawson VL, Dawson TM, Palmiter RD, Trojanowski JQ, Lee VM. Novel monoclonal antibodies demonstrate biochemical variation of brain parkin with age. J Biol Chem. 2003; 278(48):48120–48128. [PubMed: 12972409]

Perez FA, Palmiter RD. Parkin-deficient mice are not a robust model of parkinsonism. Proc Natl Acad Sci U S A. 2005; 102(6):2174–2179. [PubMed: 15684050]

Petrucelli L, O'Farrell C, Lockhart PJ, Baptista M, Kehoe K, Vink L, Choi P, Wolozin B, Farrer M, Hardy J, Cookson MR. Parkin protects against the toxicity associated with mutant alpha-

synuclein: proteasome dysfunction selectively affects catecholaminergic neurons. Neuron. 2002; 36(6):1007–1019. [PubMed: 12495618]

Pilsl A, Winklhofer KF. Parkin, PINK1 and mitochondrial integrity: emerging concepts of mitochondrial dysfunction in Parkinson's disease. Acta Neuropathol. 2012; 123(2):173–188. [PubMed: 22057787]

Piquereau J, Godin R, Deschenes S, Bessi VL, Mofarrahi M, Hussain SN, Burelle Y. Protective role of PARK2/Parkin in sepsis-induced cardiac contractile and mitochondrial dysfunction. Autophagy. 2013; 9(11):1837–1851. [PubMed: 24121678]

Poole AC, Thomas RE, Yu S, Vincow ES, Pallanck L. The mitochondrial fusion-promoting factor mitofusin is a substrate of the PINK1/parkin pathway. PLoS One. 2010; 5(4):e10054. [PubMed: 20383334]

Pramstaller PP, Schlossmacher MG, Jacques TS, Scaravilli F, Eskelson C, Pepivani I, Hedrich K, Adel S, Gonzales-McNeal M, Hilker R, Kramer PL, Klein C. Lewy body Parkinson's disease in a large pedigree with 77 Parkin mutation carriers. Ann Neurol. 2005; 58(3):411–422. [PubMed: 16130111]

Rana A, Rera M, Walker DW. Parkin overexpression during aging reduces proteotoxicity, alters mitochondrial dynamics, and extends lifespan. Proc Natl Acad Sci U S A. 2013; 110(21):8638–8643. [PubMed: 23650379]

Rawal N, Corti O, Sacchetti P, Ardilla-Osorio H, Sehat B, Brice A, Arenas E. Parkin protects dopaminergic neurons from excessive Wnt/beta-catenin signaling. Biochem Biophys Res Commun. 2009; 388(3):473–478. [PubMed: 19591802]

Reiter RJ, Korkmaz A, Paredes SD, Manchester LC, Tan DX. Melatonin reduces oxidative/nitrosative stress due to drugs, toxins, metals, and herbicides. Neuro Endocrinol Lett. 2008; 29(5):609–613. [PubMed: 18987585]

Riley BE, Lougheed JC, Callaway K, Velasquez M, Brecht E, Nguyen L, Shaler T, Walker D, Yang Y, Regnstrom K, Diep L, Zhang Z, Chiou S, Bova M, Artis DR, Yao N, Baker J, Yednock T, Johnston JA. Structure and function of Parkin E3 ubiquitin ligase reveals aspects of RING and HECT ligases. Nat Commun. 2013; 4:1982. [PubMed: 23770887]

Rosen KM, Veereshwarayya V, Moussa CE, Fu Q, Goldberg MS, Schlossmacher MG, Shen J, Querfurth HW. Parkin protects against mitochondrial toxins and beta-amyloid accumulation in skeletal muscle cells. J Biol Chem. 2006; 281(18):12809–12816. [PubMed: 16517603]

Ross CA, Poirier MA. Protein aggregation and neurodegenerative disease. Nat Med. 2004; 10(Suppl):S10–17. [PubMed: 15272267]

Rubio de la Torre E, Luzon-Toro B, Forte-Lago I, Minguez-Castellanos A, Ferrer I, Hilfiker S. Combined kinase inhibition modulates parkin inactivation. Hum Mol Genet. 2009; 18(5):809–823. [PubMed: 19050041]

Sakata E, Yamaguchi Y, Kurimoto E, Kikuchi J, Yokoyama S, Yamada S, Kawahara H, Yokosawa H, Hattori N, Mizuno Y, Tanaka K, Kato K. Parkin binds the Rpn10 subunit of 26S proteasomes through its ubiquitin-like domain. EMBO Rep. 2003; 4(3):301–306. [PubMed: 12634850]

Santos D, Cardoso SM. Mitochondrial dynamics and neuronal fate in Parkinson's disease. Mitochondrion. 2012; 12(4):428–437. [PubMed: 22609323]

Sarraf SA, Raman M, Guarani-Pereira V, Sowa ME, Huttlin EL, Gygi SP, Harper JW. Landscape of the PARKIN-dependent ubiquitylome in response to mitochondrial depolarization. Nature. 2013; 496(7445):372–376. [PubMed: 23503661]

Schlehe JS, Lutz AK, Pilsl A, Lammermann K, Grgur K, Henn IH, Tatzelt J, Winklhofer KF. Aberrant folding of pathogenic Parkin mutants: aggregation versus degradation. J Biol Chem. 2008; 283(20):13771–13779. [PubMed: 18362144]

Sharp ME, Marder KS, Cote L, Clark LN, Nichols WC, Vonsattel JP, Alcalay RN. Parkinson's disease with Lewy bodies associated with a heterozygous PARKIN dosage mutation. Mov Disord. 2014; 29(4):566–568. [PubMed: 24375549]

Shiba-Fukushima K, Imai Y, Yoshida S, Ishihama Y, Kanao T, Sato S, Hattori N. PINK1-mediated phosphorylation of the Parkin ubiquitin-like domain primes mitochondrial translocation of Parkin and regulates mitophagy. Sci Rep. 2012; 2:1002. [PubMed: 23256036]

Shimura H, Hattori N, Kubo S, Mizuno Y, Asakawa S, Minoshima S, Shimizu N, Iwai K, Chiba T, Tanaka K, Suzuki T. Familial Parkinson disease gene product, parkin, is a ubiquitin-protein ligase. Nat Genet. 2000; 25(3):302–305. [PubMed: 10888878]

Shimura H, Schlossmacher MG, Hattori N, Frosch MP, Trockenbacher A, Schneider R, Mizuno Y, Kosik KS, Selkoe DJ. Ubiquitination of a new form of alpha-synuclein by parkin from human brain: implications for Parkinson's disease. Science. 2001; 293(5528):263–269. [PubMed: 11431533]

Shin JH, Ko HS, Kang H, Lee Y, Lee YI, Pletinkova O, Troconso JC, Dawson VL, Dawson TM. PARIS (ZNF746) repression of PGC-1alpha contributes to neurodegeneration in Parkinson's disease. Cell. 2011; 144(5):689–702. [PubMed: 21376232]

Smirnova E, Griparic L, Shurland DL, van der Bliek AM. Dynamin-related protein Drp1 is required for mitochondrial division in mammalian cells. Mol Biol Cell. 2001; 12(8):2245–2256. [PubMed: 11514614]

Sriram SR, Li X, Ko HS, Chung KK, Wong E, Lim KL, Dawson VL, Dawson TM. Familial-associated mutations differentially disrupt the solubility, localization, binding and ubiquitination properties of parkin. Hum Mol Genet. 2005; 14(17):2571–2586. [PubMed: 16049031]

Staropoli JF, McDermott C, Martinat C, Schulman B, Demireva E, Abeliovich A. Parkin is a component of an SCF-like ubiquitin ligase complex and protects postmitotic neurons from kainate excitotoxicity. Neuron. 2003; 37(5):735–749. [PubMed: 12628165]

Suen DF, Norris KL, Youle RJ. Mitochondrial dynamics and apoptosis. Genes Dev. 2008; 22(12): 1577–1590. [PubMed: 18559474]

Takahashi H, Ohama E, Suzuki S, Horikawa Y, Ishikawa A, Morita T, Tsuji S, Ikuta F. Familial juvenile parkinsonism: clinical and pathologic study in a family. Neurology. 1994; 44(3 Pt 1): 437–441. [PubMed: 8145912]

Tanaka K, Suzuki T, Chiba T, Shimura H, Hattori N, Mizuno Y. Parkin is linked to the ubiquitin pathway. J Mol Med (Berl). 2001; 79(9):482–494. [PubMed: 11692161]

Tran TA, Nguyen AD, Chang J, Goldberg MS, Lee JK, Tansey MG. Lipopolysaccharide and tumor necrosis factor regulate Parkin expression via nuclear factor-kappa B. PLoS One. 2011; 6(8):e23660. [PubMed: 21858193]

Trempe JF, Sauve V, Grenier K, Seirafi M, Tang MY, Menade M, Al-Abdul-Wahid S, Krett J, Wong K, Kozlov G, Nagar B, Fon EA, Gehring K. Structure of parkin reveals mechanisms for ubiquitin ligase activation. Science. 2013; 340(6139):1451–1455. [PubMed: 23661642]

Van Humbeeck C, Cornelissen T, Hofkens H, Mandemakers W, Gevaert K, De Strooper B, Vandenberghe W. Parkin interacts with Ambra1 to induce mitophagy. J Neurosci. 2011; 31(28): 10249–10261. [PubMed: 21753002]

Van Laar VS, Arnold B, Cassady SJ, Chu CT, Burton EA, Berman SB. Bioenergetics of neurons inhibit the translocation response of Parkin following rapid mitochondrial depolarization. Hum Mol Genet. 2011; 20(5):927–940. [PubMed: 21147754]

Van Laar VS, Berman SB. The interplay of neuronal mitochondrial dynamics and bioenergetics: implications for Parkinson's disease. Neurobiol Dis. 2013; 51:43–55. [PubMed: 22668779]

Ved R, Saha S, Westlund B, Perier C, Burnam L, Sluder A, Hoener M, Rodrigues CM, Alfonso A, Steer C, Liu L, Przedborski S, Wolozin B. Similar patterns of mitochondrial vulnerability and rescue induced by genetic modification of alpha-synuclein, parkin, and DJ-1 in Caenorhabditis elegans. J Biol Chem. 2005; 280(52):42655–42668. [PubMed: 16239214]

Veeriah S, Morris L, Solit D, Chan TA. The familial Parkinson disease gene PARK2 is a multisite tumor suppressor on chromosome 6q25.2-27 that regulates cyclin E. Cell Cycle. 2010; 9(8): 1451–1452. [PubMed: 20372088]

Veeriah S, Taylor BS, Meng S, Fang F, Yilmaz E, Vivanco I, Janakiraman M, Schultz N, Hanrahan AJ, Pao W, Ladanyi M, Sander C, Heguy A, Holland EC, Paty PB, Mischel PS, Liau L, Cloughesy TF, Mellinghoff IK, Solit DB, Chan TA. Somatic mutations of the Parkinson's disease-associated gene PARK2 in glioblastoma and other human malignancies. Nat Genet. 2010; 42(1):77–82. [PubMed: 19946270]

Vinish M, Prabhakar S, Khullar M, Verma I, Anand A. Genetic screening reveals high frequency of PARK2 mutations and reduced Parkin expression conferring risk for Parkinsonism in North West India. J Neurol Neurosurg Psychiatry. 2010; 81(2):166–170. [PubMed: 19734163]

Wang C, Ko HS, Thomas B, Tsang F, Chew KC, Tay SP, Ho MW, Lim TM, Soong TW, Pletnikova O, Troncoso J, Dawson VL, Dawson TM, Lim KL. Stress-induced alterations in parkin solubility promote parkin aggregation and compromise parkin's protective function. Hum Mol Genet. 2005; 14(24):3885–3897. [PubMed: 16278233]

Wang C, Tan JM, Ho MW, Zaiden N, Wong SH, Chew CL, Eng PW, Lim TM, Dawson TM, Lim KL. Alterations in the solubility and intracellular localization of parkin by several familial Parkinson's disease-linked point mutations. J Neurochem. 2005; 93(2):422–431. [PubMed: 15816865]

Wang H, Song P, Du L, Tian W, Yue W, Liu M, Li D, Wang B, Zhu Y, Cao C, Zhou J, Chen Q. Parkin ubiquitinates Drp1 for proteasome-dependent degradation: implication of dysregulated mitochondrial dynamics in Parkinson disease. J Biol Chem. 2011; 286(13):11649–11658. [PubMed: 21292769]

Wauer T, Komander D. Structure of the human Parkin ligase domain in an autoinhibited state. EMBO J. 2013; 32(15):2099–2112. [PubMed: 23727886]

Whelan RS, Konstantinidis K, Wei AC, Chen Y, Reyna DE, Jha S, Yang Y, Calvert JW, Lindsten T, Thompson CB, Crow MT, Gavathiotis E, Dorn GW 2nd, O'Rourke B, Kitsis RN. Bax regulates primary necrosis through mitochondrial dynamics. Proc Natl Acad Sci U S A. 2012; 109(17): 6566–6571. [PubMed: 22493254]

Winklhofer KF, Henn IH, Kay-Jackson PC, Heller U, Tatzelt J. Inactivation of parkin by oxidative stress and C-terminal truncations: a protective role of molecular chaperones. J Biol Chem. 2003; 278(47):47199–47208. [PubMed: 12972428]

Wirdefeldt K, Adami HO, Cole P, Trichopoulos D, Mandel J. Epidemiology and etiology of Parkinson's disease: a review of the evidence. Eur J Epidemiol. 2011; 26(Suppl 1):S1–58. [PubMed: 21626386]

Witte ME, Bol JG, Gerritsen WH, van der Valk P, Drukarch B, van Horssen J, Wilhelmus MM. Parkinson's disease-associated parkin colocalizes with Alzheimer's disease and multiple sclerosis brain lesions. Neurobiol Dis. 2009; 36(3):445–452. [PubMed: 19716418]

Xu L, Lin DC, Yin D, Koeffler HP. An emerging role of PARK2 in cancer. J Mol Med (Berl). 2014; 92(1):31–42. [PubMed: 24297497]

Yamamoto A, Friedlein A, Imai Y, Takahashi R, Kahle PJ, Haass C. Parkin phosphorylation and modulation of its E3 ubiquitin ligase activity. J Biol Chem. 2005; 280(5):3390–3399. [PubMed: 15557340]

Yang JY, Yang WY. Bit-by-bit autophagic removal of parkin-labelled mitochondria. Nat Commun. 2013; 4:2428. [PubMed: 24013556]

Yao D, Gu Z, Nakamura T, Shi ZQ, Ma Y, Gaston B, Palmer LA, Rockenstein EM, Zhang Z, Masliah E, Uehara T, Lipton SA. Nitrosative stress linked to sporadic Parkinson's disease: S-nitrosylation of parkin regulates its E3 ubiquitin ligase activity. Proc Natl Acad Sci U S A. 2004; 101(29): 10810–10814. [PubMed: 15252205]

Yao Z, Gandhi S, Burchell VS, Plun-Favreau H, Wood NW, Abramov AY. Cell metabolism affects selective vulnerability in PINK1-associated Parkinson's disease. J Cell Sci. 2011; 124(Pt 24): 4194–4202. [PubMed: 22223879]

Yokochi M. Development of the nosological analysis of juvenile parkinsonism. Brain Dev. 2000; 22(Suppl 1):S81–86. [PubMed: 10984665]

Yoshii SR, Kishi C, Ishihara N, Mizushima N. Parkin mediates proteasome-dependent protein degradation and rupture of the outer mitochondrial membrane. J Biol Chem. 2011; 286(22): 19630–19640. [PubMed: 21454557]

Zesiewicz TA, Strom JA, Borenstein AR, Hauser RA, Cimino CR, Fontanet HL, Cintron GB, Staffetti JF, Dunne PB, Sullivan KL. Heart failure in Parkinson's disease: analysis of the United States medicare current beneficiary survey. Parkinsonism Relat Disord. 2004; 10(7):417–420. [PubMed: 15465398]

Zhan M, Usman IM, Sun L, Kanwar YS. Disruption of Renal Tubular Mitochondrial Quality Control by Myo-Inositol Oxygenase in Diabetic Kidney Disease. J Am Soc Nephrol. 2014

Zhang C, Lin M, Wu R, Wang X, Yang B, Levine AJ, Hu W, Feng Z. Parkin, a p53 target gene, mediates the role of p53 in glucose metabolism and the Warburg effect. Proc Natl Acad Sci U S A. 2011; 108(39):16259–16264. [PubMed: 21930938]

Zhang Y, Gao J, Chung KK, Huang H, Dawson VL, Dawson TM. Parkin functions as an E2-dependent ubiquitin- protein ligase and promotes the degradation of the synaptic vesicle-associated protein, CDCrel-1. Proc Natl Acad Sci U S A. 2000; 97(24):13354–13359. [PubMed: 11078524]

Highlights

- Parkin biology is relevant to the etiology of familial and idiopathic PD
- There is a critical need to understand the full consequences of parkin deficiency
- Parkin regulates complex pathways of mitochondrial quality control and cell death
- Players in parkin biology may evolve to novel targets for therapeutic intervention