frontiers in
PSYCHIATRY

REVIEW ARTICLE
published: 03 June 2010
doi: 10.3389/fpsyt.2010.00015

The relationship between parkin and protein aggregation in neurodegenerative diseases

Preeti J. Khandelwal[1] and Charbel E-H Moussa[1,2]*

[1] *Department of Neuroscience, Georgetown University Medical Center, Washington, DC, USA*
[2] *Department of Biochemistry, Molecular and Cell Biology, Georgetown University Medical Center, Washington, DC, USA*

Edited by:
Mark R. Cookson,
National Institutes of Health, USA

Reviewed by:
Patrick A. Lewis,
University College London, UK
Mark R. Cookson,
National Institutes of Health, USA

***Correspondence:**
Charbel E-H Moussa,
Department of Neuroscience,
Department of Biochemistry,
Molecular and Cell Biology,
Georgetown University School of
Medicine, 3970 Reservoir Rd, NW,
TRB, Room WP26B, Washington,
DC 20057, USA.
e-mail: cem46@georgetown.edu

The most prominent changes in neurodegenerative diseases are protein accumulation and inclusion formation. Several neurodegenerative diseases, including Alzheimer's, the Synucleinopathies and Tauopathies share several overlapping clinical symptoms manifest in Parkinsonism, cognitive decline and dementia. As degeneration progresses in the disease process, clinical symptoms suggest convergent pathological pathways. Biochemically, protein cleavage, ubiquitination and phosphorylation seem to play fundamental roles in protein aggregation, inclusion formation and inflammatory responses. In the following we provide a synopsis of the current knowledge about protein accumulation and astrogliosis as a common denominator in neurodegenerative diseases, and we propose insights into protein degradation and anti-inflammation. We review the E3-ubiquitin ligase and other possible functions of parkin as a suppressant of inflammatory signs and a strategy to clear amyloid proteins in neurodegenerative diseases.

Keywords: parkin, Aβ, α-Synuclein, Tau, TDP-43, dementia, Tauopathies, Synucleinopathies

PARKIN AS AN E3-UBIQUITIN LIGASE

Parkin is an E3 ubiquitin-protein ligase, which facilitates proteasomal degradation of misfolded proteins (Shimura et al., 2000). Mutations in the parkin gene are linked to autosomal-recessive juvenile onset Parkinson disease (ARJPD) (Kitada et al., 1998; Lucking et al., 2000). Parkin is a 465-amino acid protein containing an N-terminal ubiquitin-like (Ubl) domain linked to a C-terminal RING box (Shimura et al., 2000). The latter is divided into two RING-finger domains and a third RING-finger motif referred to as "in-between-RING" (IBR) (Morett and Bork, 1999; Ardley et al., 2001). Over a hundred parkin mutations have been identified and one of the earliest familial PD-causing mutations in parkin is T240R, a Threonine to Arginine substitution in the RING1 domain (Hattori et al., 1998). Parkin E3 ubiquitin-ligase activity targets a number of substrates, which have intrinsic toxic and aggregative properties *in vivo*, including an O-glycosylated form of α-Synuclein and α-SynucleinP22 (Shimura et al., 2001). Parkin suppresses the toxicity of parkin-associated endothelin-like receptor Pael-R (Imai et al., 2000, 2001), mutated α-Synuclein A53T (Petrucelli et al., 2002; Lo Bianco et al., 2004) and a poly (Q)-expanded mutant of ataxin-3 (Tsai et al., 2003). In cell culture systems, parkin fusion proteins interact with the synaptic vesicle protein, CDC-rel-1 (Zhang et al., 2000), the α-Synuclein-binding protein, synphilin-1 (Chung et al., 2001), actin filaments (Huynh et al., 2000) and αβ tubulin (Ren et al., 2003). Parkin is up-regulated during the integrated cellular response to misfolded protein-induced endoplasmic reticulum stress (Imai et al., 2000). Deletions in the parkin gene result in the accumulation of non-ubiquitinated forms of α-Synuclein and Pael-R in the brain (Imai et al., 2000; Shimura et al., 2001).

Parkin may reduce the levels of intracellular proteins by ubiquitination and proteasomal degradation in cell culture and animal models. Parkin rescues the toxic effects of mutant α-Synuclein or proteasome inhibition in catecholaminergic neurons in primary midbrain cultures in a manner dependent on its E3 ubiquitin-ligase activity (Shimura et al., 2001). Knockdown of parkin increases sensitivity to proteasome inhibitors (Petrucelli et al., 2002). Several pieces of evidence suggest that α-Synuclein and proteasome function may be related. Whether α-Synuclein turnover is regulated by the proteasome is still controversial, with both positive (Bennett et al., 1999; Tofaris et al., 2001) and negative (Ancolio et al., 2000; Paxinou et al., 2001) results reported. However, over-expression of α-Synuclein, especially the mutant forms, sensitize PC12 (Stefanis et al., 2001; Tanaka et al., 2001), NT2 and SK-NMC (Lee et al., 2001a) neuroblastoma cells to toxicity induced by the proteasome inhibitor lactacystin. Over-expression of α-Synuclein mutants produces an inhibition of proteasome-associated proteolytic activities (Stefanis et al., 2001) and proteasome function is impaired in sporadic PD (McNaught and Jenner, 2001). Taken together, these studies suggest that proteasome function and protein accumulation maybe a common link in neurodegenerative diseases, including PD and other Synucleinopathies. The association of β-amyloid (Aβ) with ubiquitin in Alzheimer's disease (AD) (He et al., 1993) and

Abbreviations: AD, Alzheimer's disease; ALS, amyotrophic lateral sclerosis; APP, amyloid precursor protein; ARJPD, autosomal-recessive juvenile Parkinson's disease; Aβ,β-amyloid; βAPP, β-amyloid precursor protein; CBD, corticobasal degeneration; DLB, Dementia with Lewy bodies, TDP-43, TAR-DNA-binding protein-43, UPS, ubiquitin proteasome system; FTDP, frontotemporal dementia with Parkinsonism; FTLD-U, Frontotemporal lobar degeneration with ubiquitin-positive inclusions; LBs, Lewy bodies; MND, motor neuron disease; NTF, neurofibrillary tangle formation; PD, Parkinson's disease; PHFs, paired helical filaments; PSP, progressive supranuclear palsy.

the co-occurrence of diffuse amyloid deposits with α-Synuclein and ubiquitin-positive Lewy bodies (LBs), which are intracellular inclusions, in Dementia with LB (DLB) (Harrington et al., 1994), suggest that parkin may participate in the ubiquitination of intracellularly expressed Aβ and stimulate its removal. The ability of parkin to function as an E3 ubiquitin-protein ligase and its relationship with proteasomal function suggest that parkin may contribute to proteasomal clearance of α-Synuclein and Aβ, thus attenuating the toxicity of these amyloids. However, because of the selective vulnerability of various groups of neurons in different diseases, implicating proteasome dysfunction as an explanation for neurodegenerative diseases remains conjecture.

PARKIN, THE MITOCHONDRIA AND AUTOPHAGY

Parkin is a broad neuro-protective agent against a wide range of toxic insults including those that are not even part of the ubiquitin-proteasome system (UPS) (Hyun et al., 2002, 2005; Darios et al., 2003; Staropoli et al., 2003; Manfredsson et al., 2007). Increasing parkin expression reduces oxidative stress (Hyun et al., 2002), while blocking parkin expression increases oxidative damage (Palacino et al., 2004; Greene et al., 2005). Loss of function mutations of parkin result in degeneration of dopaminergic neurons which could be rescued by increased glutathione *S*-transferase expression in transgenic flies (Whitworth et al., 2005). The effects of parkin on markers of oxidative stress may be a result of parkin's role in mitochondria function as parkin knockout transgenic mice (Palacino et al., 2004) and flies (Greene et al., 2003) have deficient mitochondria. The oxidative damage that can be prevented with parkin expression is a likely mechanism that could be targeted for therapeutic intervention. Parkin has mitochondrial trophic properties *in vivo*, where in *Drosophila*, the mutation of parkin increases sensitivity to free oxy-radical stress (Pesah et al., 2004) and mitochondrial dysfunction and build-up of peroxidized protein and lipid products is shown in parkin deficient mice (Palacino et al., 2004). We previously showed that wild type and mutant α-Synuclein differentially cause leakage of mitochondrial cytochrome c in human SH-SY5Y neuroblastoma cells (Moussa et al., 2004), and parkin is shown to prevent cytochrome c release in mitochondria-dependent cell death (Darios et al., 2003). Therefore, parkin's protective effect against mitochondrial toxicity is expected to restore ATP levels, on which both ubiquitination and the proteasome heavily depend, thus, enhancing the ubiquitin-proteasome activity to clear toxic proteins.

Parkin also associates with mitochondrial membranes (Darios et al., 2003) and interacts with PTEN-induced putative kinase (PINK1) gene, to protect mitochondrial function (Winklhofer and Haass, 2010). The relationship between parkin, ubiquitination and mitochondrial function emerged as an interesting area of investigation of protein aggregation and defected organelles in neurodegenerative diseases. Several findings demonstrated that parkin is associated with enhanced activity of the autophagy-lysosome system, by promoting the autophagy of dysfunctional mitochondria following loss of mitochondrial membrane potential (Matsuda and Tanaka, 2009; Chin et al., 2010). These new findings challenged the exclusive role of the proteasome as parkin's sole medium to clear ubiquitinated proteins, and raised more questions about the relationship between parkin, the proteasome and mitochondrial autophagy. Recently, the ubiquitin-ligase parkin and the protein kinase PINK1 were shown to function in a pathway that links ubiquitination with selective autophagy of damaged mitochondria (Wild and Dikic, 2010). The interaction between PINK1 and parkin appears to be pivotal in cellular coping mechanisms with mitochondrial damage. Silencing PINK1 leads to neuronal death accompanied by mitochondrial dysfunction and compensatory responses that facilitate clearance of defective mitochondria by co-operation with parkin (Cherra et al., 2009; Narendra et al., 2010; Vives-Bauza et al., 2010). Therefore, PINK1 and parkin collaborate to maintain mitochondrial homeostasis (Dagda and Chu, 2009; Geisler et al., 2010), but when mitochondria become defective, PINK1 interacts with parkin to promote mitophagy (Kanki and Klionsky, 2010; Michiorri et al., 2010; Vives-Bauza et al., 2010). The relationship between parkin, ubiquitination and the mitochondria is a triad that deserves more research. Further studies of the biochemical interactions between parkin and PINK1 and the identification of the components that underlie the parkin-PINK1 pathway (Kawajiri et al., 2010; Tanaka, 2010; Zhang and Ney, 2010; Ziviani et al., 2010) are likely to provide insights into PD pathogenesis and cellular post-ubiquitination strategies to cope with aggregated proteins and mitochondrial stress, including autophagy (Dodson and Guo, 2007).

α-SYNUCLEIN AND NEURODEGENERATIVE DISEASES

α-Synuclein is localized primarily to synaptic terminals (Jakes et al., 1994). Duplication or triplication of α-Synuclein gene is the cause of familial PD, which is clinically characterized by bradykinesia, tremor and rigidity (Chartier-Harlin et al., 2004; Ibanez et al., 2004). Mutations in α-Synuclein, including A30P, A53T and E46K, are reported in autosomal dominant PD (Polymeropoulos et al., 1997; Kruger et al., 1998; Spira et al., 2001; Zarranz et al., 2004) and Parkinson and DLB (Spillantini et al., 1997). α-Synuclein is the major component of LB inclusions, the pathological hallmarks of a group of diseases collectively known as Synucleinopathies, including PD, DLB and multiple system atrophy (MSA) (Spillantini et al., 1997; Jellinger, 2004). The A30P mutation, a substitution of alanine with proline at amino acid 30, presents clinically, as typical PD (Kruger et al., 1998, 2001), whereas affected members of PD families with the A53T mutation, a substitution of alanine with threonine at amino acid 53, have early dementia as a common feature (Polymeropoulos et al., 1997; Spira et al., 2001). Therefore, mutations in the α-Synuclein gene can cause a spectrum of clinical phenotypes ranging from pure Parkinsonism to Parkinsonism with dementia and DLB. LBs and immunoreactivity to α-Synuclein are also present in the brains of AD patients (Hamilton, 2000) and in cases of progressive supranuclear plasy (PSP) (Mori et al., 2002; Jellinger, 2004), amyotrophic lateral sclerosis (ALS) and frontotemporal dementia-linked to chromosome-17 (FTDP-17) (Wilhelmsen et al., 2004). A diffuse distribution of α-Synuclein staining is reported in 50% of brains from patients with a pathological diagnosis of AD (Jellinger, 2004).

Several studies show a relationship between parkin, ubiquitin and Tau as well as α-Synuclein and Tau. α-Synuclein and Tau self-aggregate (Dickson, 1999; Dawson and Dawson, 2003), and the respective pathologies for Tau or α-Synuclein, are frequently found

co-expressed in several neurodegenerative diseases (Dickson, 1999; Giasson et al., 2003; Galpern and Lang, 2006). Tau expression and neurofibrillary tangle (NFT) formation are evident in studies using viral vector gene transfer targeted to either the rat cholinergic basal forebrain (Klein et al., 2006) or the dopaminergic substantia nigra (SN) (Klein et al., 2005), where parkin is protective against Tau toxicity *in vivo*. Cross-linking ubiquitin, parkin and α-Synuclein by gamma-glutamyl-epsilon-lysine bonds is reported in NFT in AD (Nemes et al., 2004). Intraneuronal inclusions containing ubiquitinated filamentous protein aggregates are a common feature of AD and PD (Layfield et al., 2003) and ubiquitin immunoreactivity is observed in Tauopathies (Paviour et al., 2004). Furthermore, Tau and α-Synuclein co-aggregate in LBs in PD (Ishizawa et al., 2003; Yancopoulou et al., 2005). Abnormal aggregates of α-Synuclein, Aβ and Tau are found in neurodegenerative diseases with secondary LBs (Popescu et al., 2004; Lippa et al., 2005). Aβ deposition is associated with increased cortical α-Synuclein regions in PD and DLB (Pletnikova et al., 2005). These data suggest that α-Synuclein and Aβ may provide an amyloid scaffold that trigger Tau modification in certain neurodegenerative diseases, suggesting a convergent point in amyloid pathology. Furthermore, parkin multifunctional role may serve as a mitigating factor that attenuates amyloid effects on Tau pathology.

THE MICROTUBULE-ASSOCIATED PROTEIN TAU

Changes in Tau metabolism are common to primary Tauopathies, including AD, FTDP-17, CBD, Pick's Disease and PSP (Dickson, 1999; Buee et al., 2000; Di Maria et al., 2000; Dawson and Dawson, 2003; Popescu et al., 2004; Lippa et al., 2005; Pletnikova et al., 2005; Yancopoulou et al., 2005). Tau is a causal factor for neurodegeneration in primary Tauopathies. Tau comprises a family of six proteins from a single gene by alternative mRNA splicing (Goedert et al., 1989; Himmler et al., 1989). In AD, all six isoforms are present in a hyperphosphorylated state in paired helical filaments (PHFs), which form NTFs (Grundke-Iqbal et al., 1986, 1989). In AD, hyperphosphorylation of Tau appears to precede the appearance of NTFs (Bancher et al., 1989; Kopke et al., 1993). Mutations in the Tau gene causes FTDP-17 (Hutton et al., 1998), and particular variants are associated with increased risk for other Parkinsonian disorders including PSP (Baker et al., 1999) and CBD (Di Maria et al., 2000). The P301L FTDP-17-related form of Tau is particularly pathogenic as it exhibits accelerated filament formation *in vitro* (Nacharaju et al., 1999) and transgenic mice expressing P301L Tau develop NTFs (Lewis et al., 2000). Genetic variants of Tau may also be risk factors for PD (Martin et al., 2001; Healy et al., 2004). While idiopathic PD is not associated with NTFs, Tau has been demonstrated in a sub-population of LBs (Ishizawa et al., 2003). Using a viral vector for P301L Tau, targeted to the SN in rats, dopamine neuron function was affected by Tau gene transfer and these neurons were more susceptible to Tau rather than α-Synuclein in this animal model, but both Tau and α-Synuclein induced degeneration in SN (Klein et al., 2004, 2005, 2006). Taken together, these data indicate the importance of Tau protein in the group of diseases with dementia and Parkinsonism and, are suggestive of the potential to target Tau cytopathy for therapeutic strategies in neurodegenerative diseases. Changes in Tau phosphorylation and conformation are also present in AD, where deposition of $A\beta_{42}$ is believed to be the initiating molecular mechanism for the disease process (Younkin, 1995). Over-expression of/or mutations, outside the Aβ region affecting the amyloid precursor protein (APP) gene, are sufficient to cause early onset AD in Down's syndrome (DS) and rare families. Whereas, the primary Tauopathies and PD have distinctive clinical features, significant overlap exists, particularly manifest in *the variable appearances of dementia and Parkinsonism* (Klein et al., 2006). $A\beta_{42}$ and/or α-Synuclein depositions to varying degrees or ratios may share a property to incite Tau aggregation. However, it is not known how either of them interacts with Tau to provoke NFT formation across the Tauopathies. Because of the clinical and pathological overlap across the *Tauopathies and PD*, abnormalities in neurofilament and Tau protein aggregation seem to constitute a fairly common denominator among degenerative disorders with Parkinsonism and dementia.

NEUROINFLAMMATION IS A COMMON FEATURE OF NEURODEGENERATION

Glial pathology and inflammation are a common secondary denominator in neurodegenerative diseases. Particular variants in the Tau gene are associated with increased risk for Parkinsonian disorders including PSP (Baker et al., 1999) and CBD (Di Maria et al., 2000). Mutations in the parkin gene which result in ARJPD (Kitada et al., 1998) have notable formation of NFTs in the cortex and brainstem (Mori et al., 1998). Pathologically, NFTs are detected in the spinocerebellar system, along with selective loss of dopaminergic neurons in the SN, in a Dutch family with ARJPD and heterozygous missense mutation in combination with a heterozygous exon deletion in the parkin gene (van de Warrenburg et al., 2001). Neuronal loss with gliosis and NFTs in the brainstem, basal ganglia, entorhinal and premotor cortices are prominent pathological findings in PSP (Hof et al., 1992; Hanihara et al., 1995; Ito et al., 2008). Other studies point to a single heterozygous C212Y parkin mutation in the brain of a patient with a clinical and pathological phenotype of PSP, and with Tau pathology and high levels of phosphorylated Tau (Morales et al., 2002; Sanchez et al., 2002). An association between the V380L polymorphism of parkin and Tau pathology in PSP (Ros et al., 2008), suggests an intimate link between the genetic variants of parkin and risk of Tau pathology in PSP and, perhaps, other Tauopathies. The changes in Tau and parkin observed in PSP may be coincidental, but more studies are needed to better understand the relationship between these two major genes in the pathogenesis of PSP and development of new therapeutic interventions. Filamentous Tau inclusions, which are accompanied by extensive neuronal loss and gliosis, are the neuropathological hallmarks of neurodegenerative diseases (Lee et al., 2001b). In some primary Tauopathies, NFTs are not restricted to neurons, but they also are abundant, mainly in PSP and CBD, in glia as astrocytic plaques, tufted astrocytes or coiled bodies in astrocytes (Nishimura et al., 1992; Yamazaki et al., 1994; Feany and Dickson, 1995; Dickson et al., 1996). Gliosis is also well established in AD, even in the absence of NTFs in glial cells (Iwatsubo et al., 1994; Nishimura et al., 1995). Oligodendrocytic inclusions formed by α-Synuclein in MSA can also occur with Tau pathology (Tu et al., 1995; Chin and Goldman, 1996). Transgenic mouse models overexpressing three-repeat Tau isoforms display

degeneration and glial pathology similar to human Tauopathies (Higuchi et al., 2002). The development of α-Synuclein immunoreactive astrocytes parallels the stages of intraneuronal pathology in PD (Braak et al., 2007). In AD brains, parkin colocalizes with Aβ plaques as well as astrocytes associated with plaques and Aβ-containing vascular lesions and enhanced astrocytic parkin immunoreactivity is observed in inflammatory lesions in Mulitple Sclerosis (MS) (Witte et al., 2009). Parkin mRNA expression increases in an astrocytoma cell line after free radical exposure, indicating that parkin is upregulated in AD and MS brain tissue and might represent a defense mechanism to counteract stress-induced damage in pathogenesis (Witte et al., 2009). Recently, we found that intracellular $A\beta_{1-42}$ or α-Synuclein expression in lentiviral gene transfer animal models induce gliosis, and parkin reverses these effects when it is co-expressed with $A\beta_{1-42}$ or α-Synuclein (Rebeck et al., 2010). Parkin deficiency increases the risk of inflammation in SN neurons in an animal model of PD (Frank-Cannon et al., 2008). These findings suggest that parkin has an anti-inflammatory function in neurodegenerative diseases. This hypothesis needs further examination to better understand the mechanisms by which parkin exerts its protection against neuro-inflammation. Parkin protects against mitochondrial dysfunction and oxidative damage, which may induce inflammation in mitochondria based diseases. Alternatively, parkin ability to target some amyloid proteins for proteasomal degradation and decrease inclusion formation may also indirectly contribute to anti-inflammation.

INTRACELLULAR $A\beta_{42}$

The pathology of AD is characterized by intraneuronal deposition of hyperphosphorylated Tau as well as extracellular Aβ plaques (Hardy and Selkoe, 2002). Aβ is produced intracellularly via the endosomal system and secretory pathways that mediate the processing of APP (Haass et al., 1992; Koo and Squazzo, 1994). $A\beta_{1-40}$ and $A\beta_{1-42}$ are produced intracellularly (Cook et al., 1997; Xu et al., 1997; Lee et al., 1998; Skovronsky et al., 1998; Greenfield et al., 1999), and accumulate in the brain of individuals with AD (Wilson et al., 1999; Gouras et al., 2000). Both intracellular and extracellular oligomeric Aβ have been implicated in AD pathology, but intracellular oligomeric species may be formed first and thus act in the earlier stages of disease (Oddo et al., 2003; Li et al., 2007). In primary cultures of neurons over-expressing APP, accumulation of intraneuronal Aβ induces neuronal apoptotic cell death (Octave, 2005). In AD, endosomes in the pyramidal neurons are significantly bigger than control (Cataldo et al., 1997), and endocytic alterations can even happen before clinical symptoms and accumulation of Aβ (Cataldo et al., 2000), suggesting a crucial role for intracellular Aβ production in the early stages of AD. The brain of AD patients also has a high level of LBs, which amounts to 13% of cognitively normal aged individuals (Knopman et al., 2003) compared to ~60% of sporadic AD patients (Hamilton, 2000).

Immunocytochemical studies on AD, DS and APP transgenic mouse brains reveal abundant intraneuronal Aβ (LaFerla et al., 1995; D'Andrea et al., 2001; Gyure et al., 2001; Wirths et al., 2001, 2004; Echeverria and Cuello, 2002; Mori et al., 2002; Tabira et al., 2002). Aβ immunoreactivity is observed within neuronal projections and synapses, presumably transported from the soma of Aβ-bearing neurons, involving the perforant path originating from layer II entorhinal cortex (Gouras et al., 2000). Accumulation of intracellular β-amyloid appears to be critical in AD pathogenesis, leading to build-up of extracellular Aβ and plaques derived from degenerated neuronal cell bodies (Gouras et al., 2000; D'Andrea et al., 2001). Therapeutic intervention that decreases the level of intracellular Aβ is a strategic step in the prevention of Aβ accumulation in AD pathology and other diseases that implicate Aβ pathogenesis. Clearance or degradation of extracellular and intracellular Aβ-amyloid is exploited therapeutically to lessen amyloid burden. Insulin degrading Enzyme (IDE) appears to engage extracellular secreted monomeric Aβ, plaque Aβ and the amyloid intracellular domain (AICD), the latter through the cytosolic pool of enzyme (Qiu et al., 1998; Edbauer et al., 2002; Farris et al., 2003; Leissring et al., 2003). Less is known about the clearance of intracellularly generated Aβ. Both IDE and a proteasome-dependent pathway degrade ER-localized Aβ in transfected Hela cells. However, only 30% of Aβ is sensitive to the proteasome inhibitor MG132, suggesting an inefficient process (Schmitz et al., 2004). The details behind the proteasome effects are not further explored, nor were any role of ubiquitin demonstrated. We have shown that Aβ inhibits proteasomal activity and parkin reserves these effects, suggesting that parkin can alleviate intracellular Aβ burden (Rosen et al., 2010). The effects of parkin on amyloid seem to play a role in cell survival (Burns et al., 2009; Perucho et al., 2010) and parkin deficiency can result in behavioral changes and amyloid processing in APP transgenic mice (Perucho et al., 2010). Parkin can promote intraneuronal Aβ degradation via ubiqutination and proteasomal degradation (Burns et al., 2009; Rosen et al., 2010). Although parkin is not associated with AD, but immunoreactivity to parkin in LBD, along with Aβ and α-Synuclein in LBs, suggest that parkin may ubiquitinate and degrade intraneuronal Aβ.

TDP-43 IN NEURODEGENERATIVE DISEASES

The number of neurodegenerative diseases associated with pathological aggregates of transactivation response element (TAR)-DNA-binding protein 43 (TDP-43) has increased in the last decade. Full-length TDP-43 has been localized predominantly to the nucleus, with small amounts of cytosolic presence under normal conditions (Wang et al., 2004; Buratti et al., 2005; Buratti and Baralle, 2008; Winton et al., 2008). TDP-43 pathology both in the brain and spinal cord is characterized by decreased solubility, ubiquitination, hyperphosphorylation and cleavage of TDP-43 into 25- and 35-kDa fragments, as well as cellular translocation from the nuclear to cytosolic compartments (Neumann et al., 2006, 2007a,b; Amador-Ortiz et al., 2007; Hasegawa et al., 2007; Mackenzie et al., 2007; Tan et al., 2007; Zhang et al., 2007; Geser et al., 2008). Neumann and colleagues identified TDP-43 in the inclusions of frontotemoral lobar degeneration with ubiquitin-positive inclusions (FTLD-U) and ALS (Neumann et al., 2006). FTLD is one of the major causes of dementia in young adults (Ratnavalli et al., 2002; Snowden et al., 2002) and comprises a group of heterogeneous neurodegenerative disorders that are occasionally associated with motor neuron disease (MND) (Neary et al., 1990, 2000). FTLD associated with MND is a non-Tauopathy in which neuronal and glial inclusions are positive for

ubiquitin and negative for Tau and α-Synuclein (Forman et al., 2006; Neumann et al., 2007a). TDP-43 is a major constituent of inclusions in motor and non-motor neurons in ALS and FTLD-MND (Arai et al., 2006; Neumann et al., 2007a; Tan et al., 2007). Some inclusions in familial ALS have no TDP-43 immunoreactivity. ALS is a neurodegenerative disorder that affects both upper and lower motor neurons, leading to progressive paralysis and death (Pasinelli and Brown, 2006). Only ~20% of ALS cases are familial associated with missense mutation in Cu/Zn superoxide dismutase gene (SOD1) (Rosen, 1993; Gros-Louis et al., 2006). Most ALS cases are sporadic with 50% of patients display coincident deterioration of both motor and cognitive function (Morita et al., 2006; Talbot and Ansorge, 2006) and 20% develop clinical features suggestive of FTLD (Lomen-Hoerth et al., 2002, 2003). Pathologically, ALS patients have TDP-43 accumulation in motor neurons (Ayala et al., 2005; Neumann et al., 2006) and Tau-negative ubiquitin inclusions identical to those of FTLD-U patients (Forman et al., 2006). Although no TDP-43 mutations have been associated with FTLD-U, several mutations (Q331K, M337V, G294A, A90V) have been identified in MND/ALS (Gitcho et al., 2008; Sreedharan et al., 2008). TDP-43 pathology has not been identified in primary Tauopathies, including FTD, PSP and CBD (Davidson et al., 2007) but Tau pathology associated with AD co-exists with TDP-43 pathology (Amador-Ortiz et al., 2007). A large number (75%) of AD cases, which are characterized by neuronal loss and gliosis in the hippocampus, show TDP-43 pathology (Amador-Ortiz et al., 2007). Lewy body disorders also demonstrate TDP-43 pathology in AD with LBD (30%), PD (7%) and PD with dementia (19%) (Nakashima-Yasuda et al., 2007). Colocalization between TDP-43 and NFTs and TDP-43 and α-Synuclein in dystrophic neurites were also identified, despite studies showing lack of co-existence between TDP-43 and Tau pathologies (Arai et al., 2006; Nakashima-Yasuda et al., 2007; Neumann et al., 2007b). The aggregative nature of TDP-43 inclusions is similar to amyloid protein aggregation. Therefore, increased or facilitated clearance of the protein via stimulation of the UPS or increased autophagy may lead to decreased level of protein aggregation and attenuation of associated gliosis. A well known function of ubiquitination is to target substrates for degradation by the proteasome, so the dual role of parkin as an E3-ubiquitin ligase and a suppressant of inflammation could be exploited to lessen TDP-43 burden in neurodegenerative diseases, including MND-FTLD and AD.

CONVERGENT CELLULAR AND MOLECULAR PATHWAYS AND THE ROLE OF PARKIN IN NEURODEGENERATIVE DISEASES

The most reproducible function of parkin is its pan-protective activity as an E3-ubiquitin ligase involved in proteasomal degradation of proteins, defense against mitochondrial insults, and potential suppressant of inflammatory signs either directly or indirectly via its effects on oxidative stress. Inhibition of the proteasome could be a common link in neurodegenerative diseases marked by accumulation of intracellular proteins, providing a mechanistic link between Aβ, Tau, TDP-43 and α-Synuclein-based diseases. Parkin can protect against proteasome inhibition and over-expression of α-Synuclein, Tau, Aβ peptide and polyglutamine fragments (Rosen, 1993; Moore, 2006; Burns et al., 2009; Moussa, 2009; Rebeck et al., 2010; Rosen et al., 2010; Winklhofer and Haass, 2010). At least in cell culture studies, inhibition of proteasomal activity causes formation of nontoxic inclusions in cells over-expressing parkin, suggesting that parkin requires proteasome activity (Ardley et al., 2001; Hyun et al., 2002). Parkin reverses proteasomal inhibition by β-amyloid by decreasing the level of intracellular $A\beta_{1-42}$ (Rosen et al., 2006; Burns et al., 2009), which was shown to directly bind to the proteasome (Serpell et al., 2000; Lopez Salon et al., 2003). Inhibition of the proteasome in the presence of wild type parkin, or the use of parkin (T240R) mutation, leads to proteasomal inability to reduce β-amyloid levels (Rosen et al., 2006, 2010; Burns et al., 2009). Parkin over-expression significantly increases the activity of the 20S proteasome (Rosen et al., 2006, 2010; Burns et al., 2009), demonstrating that parkin is involved in mechanisms that enhance proteasome activity and degradation of proteins (Petrucelli et al., 2002; Dawson and Dawson, 2003; Lo Bianco et al., 2004), while inhibition of the 20S proteasome indicates that parkin function depends on proteasomal integrity. The ability of parkin to promote proteasomal activity is very useful to degrade or clear proteins to prevent accumulation and inclusion formation. Clearance of intracellular Aβ may be a strategic step to prevent accumulation of amyloids in certain neurodegenerative diseases. We have shown that parkin knockout muscle cells are sensitive to $A\beta_{1-42}$ toxicity, while cells virally over-expressing parkin have increased resistance (Rosen et al., 2006). In a parkin-null mouse model, over-expressing human mutated Tau, accumulation of extracellular Aβ deposits were observed in the brain (Rodriguez-Navarro et al., 2008), suggesting that lack of parkin may result in accumulation of Aβ deposits. We also showed that parkin can at least mono-ubiquitinate intracellular $A\beta_{1-42}$ and significantly reduce its level (Burns et al., 2009; Rosen et al., 2010), indicating that parkin can decrease amyloid levels in AD, adding β-amyloid to the list of parkin substrates. The clinical and pathological overlap across neurodegenerative diseases, *including* abnormalities in neurofilament formation, protein aggregation, inflammation and cell death suggest convergent molecular and cellular pathways at least at later stages of theses diseases. This review explains some overlapping pathologies that lead to similar phenotypes in certain neurodegenerative diseases. Parkin is a protective gene that may be exploited as a therapeutic agent to counteract multiple pathologies in neurodegenerative diseases.

We hypothesize that parkin reduces aggregated protein burden in neurodegenerative diseases by ubiqutination of aggregated proteins and clearance either via the proteasome or autophagy. Although parkin is not directly associated with diseases other than PD, the multiple functions of this protein make it a very interesting molecule to study in neurodegenerative diseases. Protein degradation and autophagy of aggregated molecules and malfunctioning organelles are an important aspect of parkin function in cellular processes. The role of parkin in reducing oxidative stress should be tested in association with its role in mitophagy and interaction with kinases, including tau kinases. Parkin can induce post-translational modification of substrate proteins, and the potential for parkin to ubiquitinate non-PD related proteins, such as β-amyloid and TDP-43 should be further explored. The dual function of parkin as an E3-ubiquitin ligase and anti-oxidative stress may play a role in its emerging role in suppressing inflammatory reactions in animal models of neurodegeneration.

REFERENCES

Amador-Ortiz, C., Lin, W. L., Ahmed, Z., Personett, D., Davies, P., Duara, R., Graff-Radford, N. R., Hutton, M. L., and Dickson, D. W. (2007). TDP-43 immunoreactivity in hippocampal sclerosis and Alzheimer's disease. *Ann. Neurol.* 61, 435–445.

Ancolio, K., Alves da Costa, C., Ueda, K., and Checler, F. (2000). Alpha-synuclein and the Parkinson's disease-related mutant Ala53Thr-alpha-synuclein do not undergo proteasomal degradation in HEK293 and neuronal cells. *Neurosci. Lett.* 285, 79–82.

Arai, T., Hasegawa, M., Akiyama, H., Ikeda, K., Nonaka, T., Mori, H., Mann, D., Tsuchiya, K., Yoshida, M., Hashizume, Y., and Oda, T. (2006). TDP-43 is a component of ubiquitin-positive tau-negative inclusions in frontotemporal lobar degeneration and amyotrophic lateral sclerosis. *Biochem. Biophys. Res. Commun.* 351, 602–611.

Ardley, H. C., Tan, N. G., Rose, S. A., Markham, A. F., and Robinson, P. A. (2001). Features of the parkin/ariadne-like ubiquitin ligase, HHARI, that regulate its interaction with the ubiquitin-conjugating enzyme, Ubch7. *J. Biol. Chem.* 276, 19640–19647.

Ayala, Y. M., Pantano, S., D'Ambrogio, A., Buratti, E., Brindisi, A., Marchetti, C., Romano, M., and Baralle, F. E. (2005). Human, *Drosophila*, and C.elegans TDP43: nucleic acid binding properties and splicing regulatory function. *J. Mol. Biol.* 348, 575–588.

Baker, M., Litvan, I., Houlden, H., Adamson, J., Dickson, D., Perez-Tur, J., Hardy, J., Lynch, T., Bigio, E., and Hutton, M. (1999). Association of an extended haplotype in the tau gene with progressive supranuclear palsy. *Hum. Mol. Genet.* 8, 711–715.

Bancher, C., Brunner, C., Lassmann, H., Budka, H., Jellinger, K., Wiche, G., Seitelberger, F., Grundke-Iqbal, I., Iqbal, K., and Wisniewski, H. M. (1989). Accumulation of abnormally phosphorylated tau precedes the formation of neurofibrillary tangles in Alzheimer's disease. *Brain Res.* 477, 90–99.

Bennett, M. C., Bishop, J. F., Leng, Y., Chock, P. B., Chase, T. N., and Mouradian, M. M. (1999). Degradation of alpha-synuclein by proteasome. *J. Biol. Chem.* 274, 33855–33858.

Braak, H., Sastre, M., and Del Tredici, K. (2007). Development of alpha-synuclein immunoreactive astrocytes in the forebrain parallels stages of intraneuronal pathology in sporadic Parkinson's disease. *Acta Neuropathol.* 114, 231–241.

Buee, L., Bussiere, T., Buee-Scherrer, V., Delacourte, A., and Hof, P. R. (2000). Tau protein isoforms, phosphorylation and role in neurodegenerative disorders. *Brain Res. Brain Res. Rev.* 33, 95–130.

Buratti, E., and Baralle, F. E. (2008). Multiple roles of TDP-43 in gene expression, splicing regulation, and human disease. *Front. Biosci.* 13, 867–878.

Buratti, E., Brindisi, A., Giombi, M., Tisminetzky, S., Ayala, Y. M., and Baralle, F. E. (2005). TDP-43 binds heterogeneous nuclear ribonucleoprotein A/B through its C-terminal tail: an important region for the inhibition of cystic fibrosis transmembrane conductance regulator exon 9 splicing. *J. Biol. Chem.* 280, 37572–37584.

Burns, M. P., Zhang, L., Rebeck, G. W., Querfurth, H. W., and Moussa, C. E. (2009). Parkin promotes intracellular Abeta1-42 clearance. *Hum. Mol. Genet.* 18, 3206–3216.

Cataldo, A. M., Barnett, J. L., Pieroni, C., and Nixon, R. A. (1997). Increased neuronal endocytosis and protease delivery to early endosomes in sporadic Alzheimer's disease: neuropathologic evidence for a mechanism of increased beta-amyloidogenesis. *J. Neurosci.* 17, 6142–6151.

Cataldo, A. M., Peterhoff, C. M., Troncoso, J. C., Gomez-Isla, T., Hyman, B. T., and Nixon, R. A. (2000). Endocytic pathway abnormalities precede amyloid beta deposition in sporadic Alzheimer's disease and Down syndrome: differential effects of APOE genotype and presenilin mutations. *Am. J. Pathol.* 157, 277–286.

Chartier-Harlin, M. C., Kachergus, J., Roumier, C., Mouroux, V., Douay, X., Lincoln, S., Levecque, C., Larvor, L., Andrieux, J., Hulihan, M., Waucquier, N., Defebvre, L., Amouyel, P., Farrer, M., and Destee, A. (2004). Alpha-synuclein locus duplication as a cause of familial Parkinson's disease. *Lancet* 364, 1167–1169.

Cherra, S. J. III, Dagda, R. K., Tandon, A., and Chu, C. T. (2009). Mitochondrial autophagy as a compensatory response to PINK1 deficiency. *Autophagy* 5, 1213–1214.

Chin, L. S., Olzmann, J. A., and Li, L. (2010). Parkin-mediated ubiquitin signalling in aggresome formation and autophagy. *Biochem. Soc. Trans.* 38, 144–149.

Chin, S. S., and Goldman, J. E. (1996). Glial inclusions in CNS degenerative diseases. *J. Neuropathol. Exp. Neurol.* 55, 499–508.

Chung, K. K., Zhang, Y., Lim, K. L., Tanaka, Y., Huang, H., Gao, J., Ross, C. A., Dawson, V. L., and Dawson, T. M. (2001). Parkin ubiquitinates the alpha-synuclein-interacting protein, synphilin-1: implications for Lewy-body formation in Parkinson disease. *Nat. Med.* 7, 1144–1150.

Cook, D. G., Forman, M. S., Sung, J. C., Leight, S., Kolson, D. L., Iwatsubo, T., Lee, V. M., and Doms, R. W. (1997). Alzheimer's A beta(1-42) is generated in the endoplasmic reticulum/intermediate compartment of NT2N cells. *Nat. Med.* 3, 1021–1023.

Dagda, R. K., and Chu, C. T. (2009). Mitochondrial quality control: insights on how Parkinson's disease related genes PINK1, parkin, and Omi/HtrA2 interact to maintain mitochondrial homeostasis. *J. Bioenerg. Biomembr.* 41, 473–479.

D'Andrea, M. R., Nagele, R. G., Wang, H. Y., Peterson, P. A., and Lee, D. H. (2001). Evidence that neurones accumulating amyloid can undergo lysis to form amyloid plaques in Alzheimer's disease. *Histopathology* 38, 120–134.

Darios, F., Corti, O., Lucking, C. B., Hampe, C., Muriel, M. P., Abbas, N., Gu, W. J., Hirsch, E. C., Rooney, T., Ruberg, M., and Brice, A. (2003). Parkin prevents mitochondrial swelling and cytochrome c release in mitochondria-dependent cell death. *Hum. Mol. Genet.* 12, 517–526.

Davidson, Y., Kelley, T., Mackenzie, I. R., Pickering-Brown, S., Du Plessis, D., Neary, D., Snowden, J. S., and Mann, D. M. (2007). Ubiquitinated pathological lesions in frontotemporal lobar degeneration contain the TAR DNA-binding protein, TDP-43. *Acta Neuropathol.* 113, 521–533.

Dawson, T. M., and Dawson, V. L. (2003). Molecular pathways of neurodegeneration in Parkinson's disease. *Science* 302, 819–822.

Dickson, D. W. (1999). Tau and synuclein and their role in neuropathology. *Brain Pathol.* 9, 657–661.

Dickson, D. W., Feany, M. B., Yen, S. H., Mattiace, L. A., and Davies, P. (1996). Cytoskeletal pathology in non-Alzheimer degenerative dementia: new lesions in diffuse Lewy body disease, Pick's disease, and corticobasal degeneration. *J. Neural Transm. Suppl.* 47, 31–46.

Di Maria, E., Tabaton, M., Vigo, T., Abbruzzese, G., Bellone, E., Donati, C., Frasson, E., Marchese, R., Montagna, P., Munoz, D. G., Pramstaller, P. P., Zanusso, G., Ajmar, F., and Mandich, P. (2000). Corticobasal degeneration shares a common genetic background with progressive supranuclear palsy. *Ann. Neurol.* 47, 374–377.

Dodson, M. W., and Guo, M. (2007). Pink1, Parkin, DJ-1 and mitochondrial dysfunction in Parkinson's disease. *Curr. Opin. Neurobiol.* 17, 331–337.

Echeverria, V., and Cuello, A. C. (2002). Intracellular A-beta amyloid, a sign for worse things to come? *Mol. Neurobiol.* 26, 299–316.

Edbauer, D., Willem, M., Lammich, S., Steiner, H., and Haass, C. (2002). Insulin-degrading enzyme rapidly removes the beta-amyloid precursor protein intracellular domain (AICD). *J. Biol. Chem.* 277, 13389–13393.

Farris, W., Mansourian, S., Chang, Y., Lindsley, L., Eckman, E. A., Frosch, M. P., Eckman, C. B., Tanzi, R. E., Selkoe, D. J., and Guenette, S. (2003). Insulin-degrading enzyme regulates the levels of insulin, amyloid beta-protein, and the beta-amyloid precursor protein intracellular domain *in vivo*. *Proc. Natl. Acad. Sci. U.S.A.* 100, 4162–4167.

Feany, M. B., and Dickson, D. W. (1995). Widespread cytoskeletal pathology characterizes corticobasal degeneration. *Am. J. Pathol.* 146, 1388–1396.

Forman, M. S., Farmer, J., Johnson, J. K., Clark, C. M., Arnold, S. E., Coslett, H. B., Chatterjee, A., Hurtig, H. I., Karlawish, J. H., Rosen, H. J., Van Deerlin, V., Lee, V. M., Miller, B. L., Trojanowski, J. Q., and Grossman, M. (2006). Frontotemporal dementia: clinicopathological correlations. *Ann. Neurol.* 59, 952–962.

Frank-Cannon, T. C., Tran, T., Ruhn, K. A., Martinez, T. N., Hong, J., Marvin, M., Hartley, M., Trevino, I., O'Brien, D. E., Casey, B., Goldberg, M. S., and Tansey, M. G. (2008). Parkin deficiency increases vulnerability to inflammation-related nigral degeneration. *J. Neurosci.* 28, 10825–10834.

Galpern, W. R., and Lang, A. E. (2006). Interface between tauopathies and synucleinopathies: a tale of two proteins. *Ann. Neurol.* 59, 449–458.

Geisler, S., Holmstrom, K. M., Skujat, D., Fiesel, F. C., Rothfuss, O. C., Kahle, P. J., and Springer, W. (2010). PINK1/Parkin-mediated mitophagy is dependent on VDAC1 and p62/SQSTM1. *Nat. Cell Biol.* 12, 119–131.

Geser, F., Winton, M. J., Kwong, L. K., Xu, Y., Xie, S. X., Igaz, L. M., Garruto, R. M., Perl, D. P., Galasko, D., Lee, V. M., and Trojanowski, J. Q. (2008). Pathological TDP-43 in parkinsonism-dementia complex and amyotrophic lateral sclerosis of Guam. *Acta Neuropathol.* 115, 133–145.

Giasson, B. I., Lee, V. M., and Trojanowski, J. Q. (2003). Interactions of amyloidogenic proteins. *Neuromolecular Med.* 4, 49–58.

Gitcho, M. A., Baloh, R. H., Chakraverty, S., Mayo, K., Norton, J. B., Levitch, D., Hatanpaa, K. J., White, C. L. III, Bigio, E. H., Caselli, R., Baker, M., Al-Lozi, M. T., Morris, J. C., Pestronk, A., Rademakers, R., Goate, A. M., and Cairns, N. J. (2008). TDP-43 A315T mutation in familial motor neuron disease. *Ann. Neurol.* 63, 535–538.

Goedert, M., Spillantini, M. G., Jakes, R., Rutherford, D., and Crowther, R. A.

(1989). Multiple isoforms of human microtubule-associated protein tau: sequences and localization in neurofibrillary tangles of Alzheimer's disease. *Neuron* 3, 519–526.

Gouras, G. K., Tsai, J., Naslund, J., Vincent, B., Edgar, M., Checler, F., Greenfield, J. P., Haroutunian, V., Buxbaum, J. D., Xu, H., Greengard, P., and Relkin, N. R. (2000). Intraneuronal Abeta42 accumulation in human brain. *Am. J. Pathol.* 156, 15–20.

Greene, J. C., Whitworth, A. J., Andrews, L. A., Parker, T. J., and Pallanck, L. J. (2005). Genetic and genomic studies of *Drosophila* parkin mutants implicate oxidative stress and innate immune responses in pathogenesis. *Hum. Mol. Genet.* 14, 799–811.

Greene, J. C., Whitworth, A. J., Kuo, I., Andrews, L. A., Feany, M. B., and Pallanck, L. J. (2003). Mitochondrial pathology and apoptotic muscle degeneration in *Drosophila* parkin mutants. *Proc. Natl. Acad. Sci. U.S.A.* 100, 4078–4083.

Greenfield, J. P., Tsai, J., Gouras, G. K., Hai, B., Thinakaran, G., Checler, F., Sisodia, S. S., Greengard, P., and Xu, H. (1999). Endoplasmic reticulum and trans-Golgi network generate distinct populations of Alzheimer beta-amyloid peptides. *Proc. Natl. Acad. Sci. U.S.A.* 96, 742–747.

Gros-Louis, F., Gaspar, C., and Rouleau, G. A. (2006). Genetics of familial and sporadic amyotrophic lateral sclerosis. *Biochim. Biophys. Acta* 1762, 956–972.

Grundke-Iqbal, I., Iqbal, K., George, L., Tung, Y. C., Kim, K. S., and Wisniewski, H. M. (1989). Amyloid protein and neurofibrillary tangles coexist in the same neuron in Alzheimer disease. *Proc. Natl. Acad. Sci. U.S.A.* 86, 2853–2857.

Grundke-Iqbal, I., Iqbal, K., Tung, Y. C., Quinlan, M., Wisniewski, H. M., and Binder, L. I. (1986). Abnormal phosphorylation of the microtubule-associated protein tau (tau) in Alzheimer cytoskeletal pathology. *Proc. Natl. Acad. Sci. U.S.A.* 83, 4913–4917.

Gyure, K. A., Durham, R., Stewart, W. F., Smialek, J. E., and Troncoso, J. C. (2001). Intraneuronal abeta-amyloid precedes development of amyloid plaques in Down syndrome. *Arch. Pathol. Lab. Med.* 125, 489–492.

Haass, C., Schlossmacher, M. G., Hung, A. Y., Vigo-Pelfrey, C., Mellon, A., Ostaszewski, B. L., Lieberburg, I., Koo, E. H., Schenk, D., Teplow, D. B., and Selkoe, D. J. (1992). Amyloid beta-peptide is produced by cultured cells during normal metabolism. *Nature* 359, 322–325.

Hamilton, R. L. (2000). Lewy bodies in Alzheimer's disease: a neuropathological review of 145 cases using alpha-synuclein immunohistochemistry. *Brain Pathol.* 10, 378–384.

Hanihara, T., Amano, N., Takahashi, T., Nagatomo, H., and Yagashita, S. (1995). Distribution of tangles and threads in the cerebral cortex in progressive supranuclear palsy. *Neuropathol. Appl. Neurobiol.* 21, 319–326.

Hardy, J., and Selkoe, D. J. (2002). The amyloid hypothesis of Alzheimer's disease: progress and problems on the road to therapeutics. *Science* 297, 353–356.

Harrington, C. R., Perry, R. H., Perry, E. K., Hurt, J., McKeith, I. G., Roth, M., and Wischik, C. M. (1994). Senile dementia of Lewy body type and Alzheimer type are biochemically distinct in terms of paired helical filaments and hyperphosphorylated tau protein. *Dementia* 5, 215–228.

Hasegawa, M., Arai, T., Akiyama, H., Nonaka, T., Mori, H., Hashimoto, T., Yamazaki, M., and Oyanagi, K. (2007). TDP-43 is deposited in the Guam parkinsonism-dementia complex brains. *Brain* 130, 1386–1394.

Hattori, N., Matsumine, H., Asakawa, S., Kitada, T., Yoshino, H., Elibol, B., Brookes, A. J., Yamamura, Y., Kobayashi, T., Wang, M., Yoritaka, A., Minoshima, S., Shimizu, N., and Mizuno, Y. (1998). Point mutations (Thr240Arg and Gln311Stop) [correction of Thr240Arg and Ala311Stop] in the Parkin gene. *Biochem. Biophys. Res. Commun.* 249, 754–758.

He, Y., Duyckaerts, C., Delaere, P., Piette, F., and Hauw, J. J. (1993). Alzheimer's lesions labelled by anti-ubiquitin antibodies: comparison with other staining techniques. A study of 15 cases with graded intellectual status in ageing and Alzheimer's disease. *Neuropathol. Appl. Neurobiol.* 19, 364–371.

Healy, D. G., Abou-Sleiman, P. M., Lees, A. J., Casas, J. P., Quinn, N., Bhatia, K., Hingorani, A. D., and Wood, N. W. (2004). Tau gene and Parkinson's disease: a case-control study and meta-analysis. *J. Neurol. Neurosurg. Psychiatr.* 75, 962–965.

Higuchi, M., Ishihara, T., Zhang, B., Hong, M., Andreadis, A., Trojanowski, J., and Lee, V. M. (2002). Transgenic mouse model of tauopathies with glial pathology and nervous system degeneration. *Neuron* 35, 433–446.

Himmler, A., Drechsel, D., Kirschner, M. W., and Martin, D. W. Jr. (1989). Tau consists of a set of proteins with repeated C-terminal microtubule-binding domains and variable N-terminal domains. *Mol. Cell. Biol.* 9, 1381–1388.

Hof, P. R., Delacourte, A., and Bouras, C. (1992). Distribution of cortical neurofibrillary tangles in progressive supranuclear palsy: a quantitative analysis of six cases. *Acta Neuropathol.* 84, 45–51.

Hutton, M., Lendon, C. L., Rizzu, P., Baker, M., Froelich, S., Houlden, H., Pickering-Brown, S., Chakraverty, S., Isaacs, A., Grover, A., Hackett, J., Adamson, J., Lincoln, S., Dickson, D., Davies, P., Petersen, R. C., Stevens, M., de Graaff, E., Wauters, W., van Baren, J., Hillebrand, M., Joosse, M., Kwon, J. M., Nowotny, P., Che, L. K., Norton, J., Morris, J. C., Reed, L. A., Trojanowski, J., Basun, H., Lannfelt, L., Neystat, M., Fahn, S., Dark, F., Tannenberg, T., Dodd, P. R., Hayward, N., Kwok, J. B. J., Schofield, P. R., Andreadis, A., Snowden, J., Craufurd, D., Neary, D., Owen, F., Oostra, B. A., Hardy, J., Goate, A., van Swieten, J., Mann, D., Lynch, T., and Heutink, P. (1998). Association of missense and 5'-splice-site mutations in tau with the inherited dementia FTDP-17. *Nature* 393, 702–705.

Huynh, D. P., Scoles, D. R., Ho, T. H., Del Bigio, M. R., and Pulst, S. M. (2000). Parkin is associated with actin filaments in neuronal and nonneural cells. *Ann. Neurol.* 48, 737–744.

Hyun, D. H., Lee, M., Halliwell, B., and Jenner, P. (2005). Effect of overexpression of wild-type or mutant parkin on the cellular response induced by toxic insults. *J. Neurosci. Res.* 82, 232–244.

Hyun, D. H., Lee, M., Hattori, N., Kubo, S., Mizuno, Y., Halliwell, B., and Jenner, P. (2002). Effect of wild-type or mutant Parkin on oxidative damage, nitric oxide, antioxidant defenses, and the proteasome. *J. Biol. Chem.* 277, 28572–28577.

Ibanez, P., Bonnet, A. M., Debarges, B., Lohmann, E., Tison, F., Pollak, P., Agid, Y., Durr, A., and Brice, A. (2004). Causal relation between alpha-synuclein gene duplication and familial Parkinson's disease. *Lancet* 364, 1169–1171.

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

Imai, Y., Soda, M., and Takahashi, R. (2000). Parkin suppresses unfolded protein stress-induced cell death through its E3 ubiquitin-protein ligase activity. *J. Biol. Chem.* 275, 35661–35664.

Ishizawa, T., Mattila, P., Davies, P., Wang, D., and Dickson, D. W. (2003). Colocalization of tau and alpha-synuclein epitopes in Lewy bodies. *J. Neuropathol. Exp. Neurol.* 62, 389–397.

Ito, K., Arai, K., Yoshiyama, Y., Kashiwado, K., Sakakibara, Y., and Hattori, T. (2008). Astrocytic tau pathology positively correlates with neurofibrillary tangle density in progressive supranuclear palsy. *Acta Neuropathol.* 115, 623–628.

Iwatsubo, T., Hasegawa, M., and Ihara, Y. (1994). Neuronal and glial tau-positive inclusions in diverse neurologic diseases share common phosphorylation characteristics. *Acta Neuropathol.* 88, 129–136.

Jakes, R., Spillantini, M. G., and Goedert, M. (1994). Identification of two distinct synucleins from human brain. *FEBS Lett.* 345, 27–32.

Jellinger, K. A. (2004). Lewy body-related alpha-synucleinopathy in the aged human brain. *J. Neural Transm.* 111, 1219–1235.

Kanki, T., and Klionsky, D. J. (2010). The molecular mechanism of mitochondria autophagy in yeast. *Mol. Microbiol.* 75, 795–800.

Kawajiri, S., Saiki, S., Sato, S., Sato, F., Hatano, T., Eguchi, H., and Hattori, N. (2010). PINK1 is recruited to mitochondria with parkin and associates with LC3 in mitophagy. *FEBS Lett.* 584, 1073–1079.

Kitada, T., Asakawa, S., Hattori, N., Matsumine, H., Yamamura, Y., Minoshima, S., Yokochi, M., Mizuno, Y., and Shimizu, N. (1998). Mutations in the parkin gene cause autosomal recessive juvenile parkinsonism. *Nature* 392, 605–608.

Klein, R. L., Dayton, R. D., Henderson, K. M., and Petrucelli, L. (2006). Parkin is protective for substantia nigra dopamine neurons in a tau gene transfer neurodegeneration model. *Neurosci. Lett.* 401, 130–135.

Klein, R. L., Dayton, R. D., Lin, W. L., and Dickson, D. W. (2005). Tau gene transfer, but not alpha-synuclein, induces both progressive dopamine neuron degeneration and rotational behavior in the rat. *Neurobiol. Dis.* 20, 64–73.

Klein, R. L., Lin, W. L., Dickson, D. W., Lewis, J., Hutton, M., Duff, K., Meyer, E. M., and King, M. A. (2004). Rapid neurofibrillary tangle formation after localized gene transfer of mutated tau. *Am. J. Pathol.* 164, 347–353.

Knopman, D. S., Parisi, J. E., Salviati, A., Floriach-Robert, M., Boeve, B. F., Ivnik, R. J., Smith, G. E., Dickson, D. W., Johnson, K. A., Petersen, L. E., McDonald, W. C., Braak, H., and Petersen, R. C. (2003). Neuropathology of cognitively normal elderly. *J. Neuropathol. Exp. Neurol.* 62, 1087–1095.

Koo, E. H., and Squazzo, S. L. (1994). Evidence that production and release of amyloid beta-protein involves the endocytic pathway. *J. Biol. Chem.* 269, 17386–17389.

Kopke, E., Tung, Y. C., Shaikh, S., Alonso, A. C., Iqbal, K., and Grundke-Iqbal, I.

(1993). Microtubule-associated protein tau. Abnormal phosphorylation of a non-paired helical filament pool in Alzheimer disease. *J. Biol. Chem.*268, 24374–24384.

Kruger, R., Kuhn, W., Leenders, K. L., Sprengelmeyer, R., Muller, T., Woitalla, D., Portman, A. T., Maguire, R. P., Veenma, L., Schroder, U., Schols, L., Epplen, J. T., Riess, O., and Przuntek, H. (2001). Familial parkinsonism with synuclein pathology: clinical and PET studies of A30P mutation carriers. *Neurology* 56, 1355–1362.

Kruger, R., Kuhn, W., Muller, T., Woitalla, D., Graeber, M., Kosel, S., Przuntek, H., Epplen, J. T., Schols, L., and Riess, O. (1998). Ala30Pro mutation in the gene encoding alpha-synuclein in Parkinson's disease. *Nat. Genet.* 18, 106–108.

LaFerla, F. M., Tinkle, B. T., Bieberich, C. J., Haudenschild, C. C., and Jay, G. (1995). The Alzheimer's A beta peptide induces neurodegeneration and apoptotic cell death in transgenic mice. *Nat. Genet.* 9, 21–30.

Layfield, R., Cavey, J. R., and Lowe, J. (2003). Role of ubiquitin-mediated proteolysis in the pathogenesis of neurodegenerative disorders. *Ageing Res. Rev.* 2, 343–356.

Lee, M., Hyun, D., Halliwell, B., and Jenner, P. (2001a). Effect of the overexpression of wild-type or mutant alpha-synuclein on cell susceptibility to insult. *J. Neurochem.* 76, 998–1009.

Lee, S. J., Liyanage, U., Bickel, P. E., Xia, W., Lansbury, P. T. Jr., and Kosik, K. S. (1998). A detergent-insoluble membrane compartment contains A beta *in vivo*. *Nat. Med.* 4, 730–734.

Lee, V. M., Goedert, M., and Trojanowski, J. Q. (2001b). Neurodegenerative tauopathies. *Annu. Rev. Neurosci.* 24, 1121–1159.

Leissring, M. A., Farris, W., Chang, A. Y., Walsh, D. M., Wu, X., Sun, X., Frosch, M. P., and Selkoe, D. J. (2003). Enhanced proteolysis of beta-amyloid in APP transgenic mice prevents plaque formation, secondary pathology, and premature death. *Neuron* 40, 1087–1093.

Lewis, J., McGowan, E., Rockwood, J., Melrose, H., Nacharaju, P., Van Slegtenhorst, M., Gwinn-Hardy, K., Paul Murphy, M., Baker, M., Yu, X., Duff, K., Hardy, J., Corral, A., Lin, W. L., Yen, S. H., Dickson, D. W., Davies, P., and Hutton, M. (2000). Neurofibrillary tangles, amyotrophy and progressive motor disturbance in mice expressing mutant (P301L) tau protein. *Nat. Genet.* 25, 402–405.

Li, M., Chen, L., Lee, D. H., Yu, L. C., and Zhang, Y. (2007). The role of intracellular amyloid beta in Alzheimer's disease. *Prog. Neurobiol.* 83, 131–139.

Lippa, S. M., Lippa, C. F., and Mori, H. (2005). Alpha-Synuclein aggregation in pathological aging and Alzheimer's disease: the impact of beta-amyloid plaque level. *Am. J. Alzheimers Dis. Other Demen.* 20, 315–318.

Lo Bianco, C., Schneider, B. L., Bauer, M., Sajadi, A., Brice, A., Iwatsubo, T., and Aebischer, P. (2004). 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.* 101, 17510–17515.

Lomen-Hoerth, C., Anderson, T., and Miller, B. (2002). The overlap of amyotrophic lateral sclerosis and frontotemporal dementia. *Neurology* 59, 1077–1079.

Lomen-Hoerth, C., Murphy, J., Langmore, S., Kramer, J. H., Olney, R. K., and Miller, B. (2003). Are amyotrophic lateral sclerosis patients cognitively normal? *Neurology* 60, 1094–1097.

Lopez Salon, M., Pasquini, L., Besio Moreno, M., Pasquini, J. M., and Soto, E. (2003). Relationship between beta-amyloid degradation and the 26S proteasome in neural cells. *Exp. Neurol.* 180, 131–143.

Lucking, C. B., Durr, A., Bonifati, V., Vaughan, J., De Michele, G., Gasser, T., Harhangi, B. S., Meco, G., Denefle, P., Wood, N. W., Agid, Y., and Brice, A. (2000). Association between early-onset Parkinson's disease and mutations in the parkin gene. *N. Engl. J. Med.* 342, 1560–1567.

Mackenzie, I. R., Bigio, E. H., Ince, P. G., Geser, F., Neumann, M., Cairns, N. J., Kwong, L. K., Forman, M. S., Ravits, J., Stewart, H., Eisen, A., McClusky, L., Kretzschmar, H. A., Monoranu, C. M., Highley, J. R., Kirby, J., Siddique, T., Shaw, P. J., Lee, V. M., and Trojanowski, J. Q. (2007). Pathological TDP-43 distinguishes sporadic amyotrophic lateral sclerosis from amyotrophic lateral sclerosis with SOD1 mutations. *Ann. Neurol.* 61, 427–434.

Manfredsson, F. P., Burger, C., Sullivan, L. F., Muzyczka, N., Lewin, A. S., and Mandel, R. J. (2007). rAAV-mediated nigral human parkin over-expression partially ameliorates motor deficits via enhanced dopamine neurotransmission in a rat model of Parkinson's disease. *Exp. Neurol.* 207, 289–301.

Martin, E. R., Scott, W. K., Nance, M. A., Watts, R. L., Hubble, J. P., Koller, W.C., Lyons, K., Pahwa, R. B., Stern, M. B., Colcher, A., Hiner, B. C., Jankovic, J., Ondo, W. G., Allen, F. H., Jr., Goetz, C. G., Small, G. W., Masterman, D., Mastaglia, F., Laing, N. G., Stajich, J. M., Ribble, R. C., Booze, M. W., Rogala, A., Hauser, M. A., Zhang, F., Gibson, R. A., Middleton, L. T., Roses, A. D., Haines, J. L., Scott, B. L., Pericak-Vance, M. A., and Vance, J. M. (2001). Association of single-nucleotide polymorphisms of the tau gene with late-onset Parkinson disease. *JAMA* 286, 2245–2250.

McNaught, K. S., and Jenner, P. (2001). Proteasomal function is impaired in substantia nigra in Parkinson's disease. *Neurosci. Lett.* 297, 191–194.

Michiorri, S., Gelmetti, V., Giarda, E., Lombardi, F., Romano, F., Marongiu, R., Nerini-Molteni, S., Sale, P., Vago, R., Arena, G., Torosantucci, L., Cassina, L., Russo, M. A., Dallapiccola, B., Valente, E. M., and Casari, G. (2010). The Parkinson-associated protein PINK1 interacts with Beclin1 and promotes autophagy. *Cell Death Differ.* 17, 962–974.

Moore, D. J. (2006). Parkin: a multifaceted ubiquitin ligase. *Biochem. Soc. Trans.* 34, 749–753.

Morales, B., Martinez, A., Gonzalo, I., Vidal, L., Ros, R., Gomez-Tortosa, E., Rabano, A., Ampuero, I., Sanchez, M., Hoenicka, J., and Garcia De Yebenes, J. (2002). Steele-Richardson-Olszewski syndrome in a patient with a single C212Y mutation in the parkin protein. *Mov. Disord.* 17, 1374–1380.

Morett, E., and Bork, P. (1999). A novel transactivation domain in parkin. *Trends Biochem. Sci.* 24, 229–231.

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

Mori, H., Oda, M., Komori, T., Arai, N., Takanashi, M., Mizutani, T., Hirai, S., and Mizuno, Y. (2002). Lewy bodies in progressive supranuclear palsy. *Acta Neuropathol.* 104, 273–278.

Morita, M., Al-Chalabi, A., Andersen, P. M., Hosler, B., Sapp, P., Englund, E., Mitchell, J. E., Habgood, J. J., de Belleroche, J., Xi, J., Jongjaroenprasert, W., Horvitz, H. R., Gunnarsson, L. G., and Brown, R. H. Jr. (2006). A locus on chromosome 9p confers susceptibility to ALS and frontotemporal dementia. *Neurology* 66, 839–844.

Moussa, C. E. (2009). Parkin attenuates wild-type tau modification in the presence of beta-amyloid and alpha-synuclein. *J. Mol. Neurosci.* 37, 25–36.

Moussa, C. E., Wersinger, C., Tomita, Y., and Sidhu, A. (2004). Differential cytotoxicity of human wild type and mutant alpha-synuclein in human neuroblastoma SH-SY5Y cells in the presence of dopamine. *Biochemistry* 43, 5539–5550.

Nacharaju, P., Lewis, J., Easson, C., Yen, S., Hackett, J., Hutton, M., and Yen, S. H. (1999). Accelerated filament formation from tau protein with specific FTDP-17 missense mutations. *FEBS Lett.* 447, 195–199.

Nakashima-Yasuda, H., Uryu, K., Robinson, J., Xie, S. X., Hurtig, H., Duda, J. E., Arnold, S. E., Siderowf, A., Grossman, M., Leverenz, J. B., Woltjer, R., Lopez, O. L., Hamilton, R., Tsuang, D. W., Galasko, D., Masliah, E., Kaye, J., Clark, C. M., Montine, T. J., Lee, M. -Y., and Trojanowski, J. Q. (2007). Co-morbidity of TDP-43 proteinopathy in Lewy body related diseases. *Acta Neuropathol.* 114, 221–229.

Narendra, D. P., Jin, S. M., Tanaka, A., Suen, D. F., Gautier, C. A., Shen, J., Cookson, M. R., and Youle, R. J. (2010). PINK1 is selectively stabilized on impaired mitochondria to activate Parkin. *PLoS Biol.* 8, e1000298. doi:10.1371/journal.pbio.1000298.

Neary, D., Snowden, J. S., and Mann, D. M. (2000). Classification and description of frontotemporal dementias. *Ann. N. Y. Acad. Sci.* 920, 46–51.

Neary, D., Snowden, J. S., Mann, D. M., Northen, B., Goulding, P. J., and Macdermott, N. (1990). Frontal lobe dementia and motor neuron disease. *J. Neurol. Neurosurg. Psychiatr.* 53, 23–32.

Nemes, Z., Devreese, B., Steinert, P. M., Van Beeumen, J., and Fesus, L. (2004). Cross-linking of ubiquitin, HSP27, parkin, and alpha-synuclein by gamma-glutamyl-epsilon-lysine bonds in Alzheimer's neurofibrillary tangles. *FASEB J.* 18, 1135–1137.

Neumann, M., Kwong, L. K., Sampathu, D. M., Trojanowski, J. Q., and Lee, V. M. (2007a). TDP-43 proteinopathy in frontotemporal lobar degeneration and amyotrophic lateral sclerosis: protein misfolding diseases without amyloidosis. *Arch. Neurol.* 64, 1388–1394.

Neumann, M., Mackenzie, I. R., Cairns, N. J., Boyer, P. J., Markesbery, W. R., Smith, C. D., Taylor, J. P., Kretzschmar, H. A., Kimonis, V. E., and Forman, M. S. (2007b). TDP-43 in the ubiquitin pathology of frontotemporal dementia with VCP gene mutations. *J. Neuropathol. Exp. Neurol.* 66, 152–157.

Neumann, M., Sampathu, D. M., Kwong, L. K., Truax, A. C., Micsenyi, M. C., Chou, T. T., Bruce, J., Schuck, T., Grossman, M., Clark, C. M., McCluskey, L. F., Miller, B. L., Masliah, E., Mackenzie, I. R., Feldman, H., Feiden, W., Kretzschmar, H. A., Trojanowski, J. Q., and Lee, V. M. (2006). Ubiquitinated TDP-43 in frontotemporal lobar degeneration and amyotrophic lateral sclerosis. *Science* 314, 130–133.

Nishimura, M., Namba, Y., Ikeda, K., and Oda, M. (1992). Glial fibrillary tangles with straight tubules in the brains of patients with progressive

supranuclear palsy. *Neurosci. Lett.* 143, 35–38.

Nishimura, M., Tomimoto, H., Suenaga, T., Namba, Y., Ikeda, K., Akiguchi, I., and Kimura, J. (1995). Immunocytochemical characterization of glial fibrillary tangles in Alzheimer's disease brain. *Am. J. Pathol.* 146, 1052–1058.

Octave, J. N. (2005). Alzheimer disease: cellular and molecular aspects. *Bull. Mem. Acad. R. Med. Belg.* 160, 445–449; discussion 450–441.

Oddo, S., Caccamo, A., Kitazawa, M., Tseng, B. P., and LaFerla, F. M. (2003). Amyloid deposition precedes tangle formation in a triple transgenic model of Alzheimer's disease. *Neurobiol. Aging* 24, 1063–1070.

Palacino, J. J., Sagi, D., Goldberg, M. S., Krauss, S., Motz, C., Wacker, M., Klose, J., and Shen, J. (2004). Mitochondrial dysfunction and oxidative damage in parkin-deficient mice. *J. Biol. Chem.* 279, 18614–18622.

Pasinelli, P., and Brown, R. H. (2006). Molecular biology of amyotrophic lateral sclerosis: insights from genetics. *Nat. Rev. Neurosci.* 7, 710–723.

Paviour, D. C., Lees, A. J., Josephs, K. A., Ozawa, T., Ganguly, M., Strand, C., Godbolt, A., Howard, R. S., Revesz, T., and Holton, J. L. (2004). Frontotemporal lobar degeneration with ubiquitin-only-immunoreactive neuronal changes: broadening the clinical picture to include progressive supranuclear palsy. *Brain* 127, 2441–2451.

Paxinou, E., Chen, Q., Weisse, M., Giasson, B. I., Norris, E. H., Rueter, S. M., Trojanowski, J. Q., Lee, V. M., and Ischiropoulos, H. (2001). Induction of alpha-synuclein aggregation by intracellular nitrative insult. *J. Neurosci.* 21, 8053–8061.

Perucho, J., Casarejos, M. J., Rubio, I., Rodriguez-Navarro, J. A., Gomez, A., Ampuero, I., Rodal, I., Solano, R. M., Carro, E., Garcia de Yebenes, J., and Mena, M. A. (2010). The effects of parkin suppression on the behaviour, amyloid processing, and cell survival in APP mutant transgenic mice. *Exp. Neurol.* 221, 54–67.

Pesah, Y., Pham, T., Burgess, H., Middlebrooks, B., Verstreken, P., Zhou, Y., Harding, M., Bellen, H., and Mardon, G. (2004). Drosophila parkin mutants have decreased mass and cell size and increased sensitivity to oxygen radical stress. *Development* 131, 2183–2194.

Petrucelli, L., O'Farrell, C., Lockhart, P. J., Baptista, M., Kehoe, K., Vink, L., Choi, P., Wolozin, B., Farrer, M., Hardy, J., and Cookson, M. R. (2002). Parkin protects against the toxicity associated with mutant alpha-synuclein: proteasome dysfunction selectively affects catecholaminergic neurons. *Neuron* 36, 1007–1019.

Pletnikova, O., West, N., Lee, M. K., Rudow, G. L., Skolasky, R. L., Dawson, T. M., Marsh, L., and Troncoso, J. C. (2005). Abeta deposition is associated with enhanced cortical alpha-synuclein lesions in Lewy body diseases. *Neurobiol. Aging* 26, 1183–1192.

Polymeropoulos, M. H., Lavedan, C., Leroy, E., Ide, S. E., Dehejia, A., Dutra, A., Pike, B., Root, H., Rubenstein, J., Boyer, R., Stenroos, E. S., Chandrasekharappa, S., Athanassiadou, A., Papapetropoulos, T., Johnson, W. G., Lazzarini, A. M., Duvoisin, R. C., Di Iorio, G., Golbe, L. I., and Nussbaum, R. L. (1997). Mutation in the alpha-synuclein gene identified in families with Parkinson's disease. *Science* 276, 2045–2047.

Popescu, A., Lippa, C. F., Lee, V. M., and Trojanowski, J. Q. (2004). Lewy bodies in the amygdala: increase of alpha-synuclein aggregates in neurodegenerative diseases with tau-based inclusions. *Arch. Neurol.* 61, 1915–1919.

Qiu, W. Q., Walsh, D. M., Ye, Z., Vekrellis, K., Zhang, J., Podlisny, M. B., Rosner, M. R., Safavi, A., Hersh, L. B., and Selkoe, D. J. (1998). Insulin-degrading enzyme regulates extracellular levels of amyloid beta-protein by degradation. *J. Biol. Chem.* 273, 32730–32738.

Ratnavalli, E., Brayne, C., Dawson, K., and Hodges, J. R. (2002). The prevalence of frontotemporal dementia. *Neurology* 58, 1615–1621.

Rebeck, G. W., Hoe, H. S., and Moussa, C. E. (2010). [beta]-Amyloid1-42 gene transfer model exhibits intraneuronal amyloid, gliosis, tau phosphorylation, and neuronal loss. *J. Biol. Chem.* 285, 7440–7446.

Ren, Y., Zhao, J., and Feng, J. (2003). Parkin binds to alpha/beta tubulin and increases their ubiquitination and degradation. *J. Neurosci.* 23, 3316–3324.

Rodriguez-Navarro, J. A., Gomez, A., Rodal, I., Perucho, J., Martinez, A., Furio, V., Ampuero, I., Casarejos, M. J., Solano, R. M., de Yebenes, J. G., and Mena, M. A. (2008). Parkin deletion causes cerebral and systemic amyloidosis in human mutated tau overexpressing mice. *Hum. Mol. Genet.* 17, 3128–3143.

Ros, R., Ampuero, I., and Garcia de Yebenes, J. (2008). Parkin polymorphisms in progressive supranuclear palsy. *J. Neurol. Sci.* 268, 176–178.

Rosen, D. R. (1993). Mutations in Cu/Zn superoxide dismutase gene are associated with familial amyotrophic lateral sclerosis. *Nature* 364, 362.

Rosen, K. M., Moussa, C. E., Lee, H. K., Kumar, P., Kitada, T., Qin, G., Fu, Q., and Querfurth, H. W. (2010). Parkin reverses intracellular beta-amyloid accumulation and its negative effects on proteasome function. *J. Neurosci. Res.* 88, 167–178.

Rosen, K. M., Veereshwarayya, V., Moussa, C. E., Fu, Q., Goldberg, M. S., Schlossmacher, M. G., Shen, J., and Querfurth, H. W. (2006). Parkin protects against mitochondrial toxins and beta-amyloid accumulation in skeletal muscle cells. *J. Biol. Chem.* 281, 12809–12816.

Sanchez, M. P., Gonzalo, I., Avila, J., and De Yebenes, J. G. (2002). Progressive supranuclear palsy and tau hyperphosphorylation in a patient with a C212Y parkin mutation. *J. Alzheimers Dis.* 4, 399–404.

Schmitz, A., Schneider, A., Kummer, M. P., and Herzog, V. (2004). Endoplasmic reticulum-localized amyloid beta-peptide is degraded in the cytosol by two distinct degradation pathways. *Traffic* 5, 89–101.

Serpell, L. C., Berriman, J., Jakes, R., Goedert, M., and Crowther, R. A. (2000). Fiber diffraction of synthetic alpha-synuclein filaments shows amyloid-like cross-beta conformation. *Proc. Natl. Acad. Sci. U.S.A.* 97, 4897–4902.

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

Shimura, H., Schlossmacher, M. G., Hattori, N., Frosch, M. P., Trockenbacher, A., Schneider, R., Mizuno, Y., Kosik, K. S., and Selkoe, D. J. (2001). Ubiquitination of a new form of alpha-synuclein by parkin from human brain: implications for Parkinson's disease. *Science* 293, 263–269.

Skovronsky, D. M., Doms, R. W., and Lee, V. M. (1998). Detection of a novel intraneuronal pool of insoluble amyloid beta protein that accumulates with time in culture. *J. Cell Biol.* 141, 1031–1039.

Snowden, J. S., Neary, D., and Mann, D. M. (2002). Frontotemporal dementia. *Br. J. Psychiatry* 180, 140–143.

Spillantini, M. G., Schmidt, M. L., Lee, V. M., Trojanowski, J. Q., Jakes, R., and Goedert, M. (1997). Alpha-synuclein in Lewy bodies. *Nature* 388, 839–840.

Spira, P. J., Sharpe, D. M., Halliday, G., Cavanagh, J., and Nicholson, G. A. (2001). Clinical and pathological features of a Parkinsonian syndrome in a family with an Ala53Thr alpha-synuclein mutation. *Ann. Neurol.* 49, 313–319.

Sreedharan, J., Blair, I. P., Tripathi, V. B., Hu, X., Vance, C., Rogelj, B., Ackerley, S., Durnall, J. C., Williams, K. L., Buratti, E., Baralle, F., de Belleroche, J., Mitchell, J. D., Leigh, P. N., Al-Chalabi, A., Miller, C. C., Nicholson, G., and Shaw, C. E. (2008). TDP-43 mutations in familial and sporadic amyotrophic lateral sclerosis. *Science* 319, 1668–1672.

Staropoli, J. F., McDermott, C., Martinat, C., Schulman, B., Demireva, E., and Abeliovich, A. (2003). Parkin is a component of an SCF-like ubiquitin ligase complex and protects postmitotic neurons from kainate excitotoxicity. *Neuron* 37, 735–749.

Stefanis, L., Larsen, K. E., Rideout, H. J., Sulzer, D., and Greene, L. A. (2001). Expression of A53T mutant but not wild-type alpha-synuclein in PC12 cells induces alterations of the ubiquitin-dependent degradation system, loss of dopamine release, and autophagic cell death. *J. Neurosci.* 21, 9549–9560.

Tabira, T., Chui, D. H., and Kuroda, S. (2002). Significance of intracellular Abeta42 accumulation in Alzheimer's disease. *Front. Biosci.* 7, a44–a49.

Talbot, K., and Ansorge, O. (2006). Recent advances in the genetics of amyotrophic lateral sclerosis and frontotemporal dementia: common pathways in neurodegenerative disease. *Hum. Mol. Genet.* 15, R182–R187.

Tan, C. F., Eguchi, H., Tagawa, A., Onodera, O., Iwasaki, T., Tsujino, A., Nishizawa, M., Kakita, A., and Takahashi, H. (2007). TDP-43 immunoreactivity in neuronal inclusions in familial amyotrophic lateral sclerosis with or without SOD1 gene mutation. *Acta Neuropathol.* 113, 535–542.

Tanaka, A. (2010). Parkin-mediated selective mitochondrial autophagy, mitophagy: Parkin purges damaged organelles from the vital mitochondrial network. *FEBS Lett.* 584, 1386–1392.

Tanaka, Y., Engelender, S., Igarashi, S., Rao, R. K., Wanner, T., Tanzi, R. E., Sawa, A., V, L. D., Dawson, T. M., and Ross, C. A. (2001). Inducible expression of mutant alpha-synuclein decreases proteasome activity and increases sensitivity to mitochondria-dependent apoptosis. *Hum. Mol. Genet.* 10, 919–926.

Tofaris, G. K., Layfield, R., and Spillantini, M. G. (2001). alpha-synuclein metabolism and aggregation is linked to ubiquitin-independent degradation by the proteasome. *FEBS Lett.* 509, 22–26.

Tsai, Y. C., Fishman, P. S., Thakor, N. V., and Oyler, G. A. (2003). Parkin facilitates the elimination of expanded polyglutamine proteins and leads to

preservation of proteasome function. *J. Biol. Chem.* 278, 22044–22055.

Tu, P. H., Elder, G., Lazzarini, R. A., Nelson, D., Trojanowski, J. Q., and Lee, V. M. (1995). Overexpression of the human NFM subunit in transgenic mice modifies the level of endogenous NFL and the phosphorylation state of NFH subunits. *J. Cell Biol.* 129, 1629–1640.

van de Warrenburg, B. P., Lammens, M., Lucking, C. B., Denefle, P., Wesseling, P., Booij, J., Praamstra, P., Quinn, N., Brice, A., and Horstink, M. W. (2001). Clinical and pathologic abnormalities in a family with parkinsonism and parkin gene mutations. *Neurology* 56, 555–557.

Vives-Bauza, C., Zhou, C., Huang, Y., Cui, M., de Vries, R. L., Kim, J., May, J., Tocilescu, M. A., Liu, W., Ko, H. S., Magrane, J., Moore, D. J., Dawson, V. L., Grailhe, R., Dawson, T. M., Li, C., Tieu, K., and Przedborski, S. (2010). PINK1-dependent recruitment of Parkin to mitochondria in mitophagy. *Proc. Natl. Acad. Sci. U.S.A.* 107, 378–383.

Wang, H. Y., Wang, I. F., Bose, J., and Shen, C. K. (2004). Structural diversity and functional implications of the eukaryotic TDP gene family. *Genomics* 83, 130–139.

Whitworth, A. J., Theodore, D. A., Greene, J. C., Benes, H., Wes, P. D., and Pallanck, L. J. (2005). Increased glutathione S-transferase activity rescues dopaminergic neuron loss in a *Drosophila* model of Parkinson's disease. *Proc. Natl. Acad. Sci. U.S.A.* 102, 8024–8029.

Wild, P., and Dikic, I. (2010). Mitochondria get a Parkin' ticket. *Nat. Cell Biol.* 12, 104–106.

Wilhelmsen, K. C., Forman, M. S., Rosen, H. J., Alving, L. I., Goldman, J., Feiger, J., Lee, J. V., Segall, S. K., Kramer, J. H., Lomen-Hoerth, C., Rankin, K. P., Johnson, J., Feiler, H. S., Weiner, M. W., Lee, V. M., Trojanowski, J. Q., and Miller, B. L. (2004). 17q-linked frontotemporal dementia-amyotrophic lateral sclerosis without tau mutations with tau and alpha-synuclein inclusions. *Arch. Neurol.* 61, 398–406.

Wilson, C. A., Doms, R. W., and Lee, V. M. (1999). Intracellular APP processing and A beta production in Alzheimer disease. *J. Neuropathol. Exp. Neurol.* 58, 787–794.

Winklhofer, K. F., and Haass, C. (2010). Mitochondrial dysfunction in Parkinson's disease. *Biochim. Biophys. Acta* 1802, 29–44.

Winton, M. J., Igaz, L. M., Wong, M. M., Kwong, L. K., Trojanowski, J. Q., and Lee, V. M. (2008). Disturbance of nuclear and cytoplasmic TAR DNA-binding protein (TDP-43) induces disease-like redistribution, sequestration, and aggregate formation. *J. Biol. Chem.* 283, 13302–13309.

Wirths, O., Multhaup, G., and Bayer, T. A. (2004). A modified beta-amyloid hypothesis: intraneuronal accumulation of the beta-amyloid peptide--the first step of a fatal cascade. *J. Neurochem.* 91, 513–520.

Wirths, O., Multhaup, G., Czech, C., Blanchard, V., Moussaoui, S., Tremp, G., Pradier, L., Beyreuther, K., and Bayer, T. A. (2001). Intraneuronal Abeta accumulation precedes plaque formation in beta-amyloid precursor protein and presenilin-1 double-transgenic mice. *Neurosci. Lett.* 306, 116–120.

Witte, M. E., Bol, J. G., Gerritsen, W. H., van der Valk, P., Drukarch, B., van Horssen, J., and Wilhelmus, M. M. (2009). Parkinson's disease-associated parkin colocalizes with Alzheimer's disease and multiple sclerosis brain lesions. *Neurobiol. Dis.* 36, 445–452.

Xu, H., Sweeney, D., Wang, R., Thinakaran, G., Lo, A. C., Sisodia, S. S., Greengard, P., and Gandy, S. (1997). Generation of Alzheimer beta-amyloid protein in the trans-Golgi network in the apparent absence of vesicle formation. *Proc. Natl. Acad. Sci. U.S.A.* 94, 3748–3752.

Yamazaki, M., Nakano, I., Imazu, O., Kaieda, R., and Terashi, A. (1994). Astrocytic straight tubules in the brain of a patient with Pick's disease. *Acta Neuropathol.* 88, 587–591.

Yancopoulou, D., Xuereb, J. H., Crowther, R. A., Hodges, J. R., and Spillantini, M. G. (2005). Tau and alpha-synuclein inclusions in a case of familial frontotemporal dementia and progressive aphasia. *J. Neuropathol. Exp. Neurol.* 64, 245–253.

Younkin, S. G. (1995). Evidence that A beta 42 is the real culprit in Alzheimer's disease. *Ann. Neurol.* 37, 287–288.

Zarranz, J. J., Alegre, J., Gomez-Esteban, J. C., Lezcano, E., Ros, R., Ampuero, I., Vidal, L., Hoenicka, J., Rodriguez, O., Atares, B., Llorens, V., Gomez Tortosa, E., del Ser, T., Munoz, D. G., and de Yebenes, J. G. (2004). The new mutation, E46K, of alpha-synuclein causes Parkinson and Lewy body dementia. *Ann. Neurol.* 55, 164–173.

Zhang, J., and Ney, P. A. (2010). Reticulocyte mitophagy: monitoring mitochondrial clearance in a mammalian model. *Autophagy* 6, 405–408.

Zhang, Y., Gao, J., Chung, K. K., Huang, H., Dawson, V. L., and Dawson, T. M. (2000). 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.* 97, 13354–13359.

Zhang, Y. J., Xu, Y. F., Dickey, C. A., Buratti, E., Baralle, F., Bailey, R., Pickering-Brown, S., Dickson, D., and Petrucelli, L. (2007). Progranulin mediates caspase-dependent cleavage of TAR DNA binding protein-43. *J. Neurosci.* 27, 10530–10534.

Ziviani, E., Tao, R. N., and Whitworth, A. J. (2010). *Drosophila* Parkin requires PINK1 for mitochondrial translocation and ubiquitinates Mitofusin. *Proc. Natl. Acad. Sci. U.S.A.* 107, 5018–5023.

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Received: 12 March 2010; paper pending published: 08 April 2010; accepted: 10 May 2010; published online: 03 June 2010.
*Citation: Khandelwal PJ and Moussa CE-H (2010) The relationship between parkin and protein aggregation in neurodegenerative diseases. Front. Psychiatry **1**:15. doi: 10.3389/fpsyt.2010.00015*
This article was submitted to Frontiers in Neurodegeneration, a specialty of Frontiers in Psychiatry.