



The relationship between parkin and protein aggregation in neurodegenerative diseases

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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, A β , 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 (Petrucci 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 $\alpha\beta$ 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 (Petrucci 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 (A β) 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; A β , β -amyloid; β APP, 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 A β 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 A β , 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 cooperation 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 palsy (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, A β and Tau are found in neurodegenerative diseases with secondary LBs (Popescu et al., 2004; Lippa et al., 2005). A β deposition is associated with increased cortical α -Synuclein regions in PD and DLB (Pletnikova et al., 2005). These data suggest that α -Synuclein and A β 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 (Baner 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 β_{42} is believed to be the initiating molecular mechanism for the disease process (Younkin, 1995). Over-expression of/or mutations, outside the A β 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 β_{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 A β plaques as well as astrocytes associated with plaques and A β -containing vascular lesions and enhanced astrocytic parkin immunoreactivity is observed in inflammatory lesions in Multiple 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 β_{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 β_{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 β_{42}

The pathology of AD is characterized by intraneuronal deposition of hyperphosphorylated Tau as well as extracellular A β plaques (Hardy and Selkoe, 2002). A β 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 β_{1-40} and A β_{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 A β 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 A β 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 A β (Cataldo et al., 2000), suggesting a crucial role for intracellular A β 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 A β (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). A β immunoreactivity is observed within neuronal

projections and synapses, presumably transported from the soma of A β -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 A β 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 A β is a strategic step in the prevention of A β accumulation in AD pathology and other diseases that implicate A β pathogenesis. Clearance or degradation of extracellular and intracellular A β -amyloid is exploited therapeutically to lessen amyloid burden. Insulin degrading Enzyme (IDE) appears to engage extracellular secreted monomeric A β , plaque A β 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 A β . Both IDE and a proteasome-dependent pathway degrade ER-localized A β in transfected HeLa cells. However, only 30% of A β 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 A β inhibits proteasomal activity and parkin reserves these effects, suggesting that parkin can alleviate intracellular A β 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 A β degradation via ubiquitination 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 A β and α -Synuclein in LBs, suggest that parkin may ubiquitinate and degrade intraneuronal A β .

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 frontotemporal 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 A β , Tau, TDP-43 and α -Synuclein-based diseases. Parkin can protect against proteasome inhibition and over-expression of α -Synuclein, Tau, A β 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 β 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 (Petrucci 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 A β 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 β 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 A β deposits were observed in the brain (Rodriguez-Navarro et al., 2008), suggesting that lack of parkin may result in accumulation of A β deposits. We also showed that parkin can at least mono-ubiquitinate intracellular A β 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 these 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 ubiquitination 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.

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