

The role of the ubiquitin-proteasomal pathway in Parkinson's disease and other neurodegenerative disorders

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A unifying feature of neurodegenerative diseases is the abnormal accumulation and processing of mutant or damaged intra- and extracellular proteins; this leads to selective neuronal vulnerability and dysfunction. The ubiquitin-proteasomal pathway (UPP) is poised to play a central role in the processing of damaged and toxic proteins by ubiquitin-dependent proteolysis. The UPP can be overwhelmed in several neurodegenerative diseases. This results in the accumulation of toxic proteins and the formation of inclusions, and ultimately to neuronal dysfunction and cell death. Further analysis of the cellular and molecular mechanisms by which the UPP influences the detoxification of damaged and toxic proteins in neurodegenerative diseases could provide novel concepts and targets for the treatment and understanding of the pathogenesis of these devastating disorders.

Most, if not all, neurodegenerative diseases are marked by the presence of protein aggregates or inclusion bodies¹. These include the prion protein (PrP) plaques in Prion disease, amyloid plaques and neurofibrillary tangles in Alzheimer's disease (AD), Lewy bodies in Parkinson's disease (PD) and dementia with Lewy bodies (DLB), nuclear inclusions in the poly-glutamine repeat diseases such as Huntington's disease (HD), spinocerebellar ataxias (SCA), dentatorubral and pallidolusian atrophy (DRPLA), as well as other neurodegenerative diseases (Table 1). The linkage of two genes within the ubiquitin-proteasomal pathway (UPP) in hereditary PD (Refs 2,3), and recent advances in other neurological disorders, clearly indicate that the UPP plays a crucial role in the pathogenesis of neurodegenerative diseases, and has elevated the importance of the UPP in these disorders.

The close relationship between neurodegeneration and the ubiquitin system has long been implicated through the consistent findings of ubiquitin-positive protein aggregates in various neuropathological studies. In fact, the observation of ubiquitinated-protein inclusion bodies is one of the hallmarks of neurodegeneration. One

general idea is that, under certain adverse conditions [including oxidative stress, protein misfolding during endoplasmic reticulum (ER) stress and aging], damaged proteins can accumulate in the cell. In addition, abnormal accumulation of proteins could occur owing to altered post-translational modification of newly synthesized proteins, abnormal proteolytic cleavage, diminished clearance of degraded protein and/or improper expression or altered gene splicing. The UPP might play a prominent role in the detoxification and targeting of damaged proteins for degradation. Under some conditions, the protein damage could be so severe that the clearance of damaged protein by the UPP and other degradative pathways might not be able to cope with the demand, resulting in the accumulation of damaged ubiquitin-tagged proteins and ultimately neuronal dysfunction and/or death.

Neurodegeneration and the UPP

There is increasing interest in the UPP in relation to the control of various important cellular processes. The system was first studied in reticulocyte lysates, which later resulted in the discovery of a pathway that provides

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Table 1. Representative neurodegenerative diseases that have ubiquitin-positive protein aggregates or inclusion bodies^{a,b}

Disease	Gene	Mutations	Pathology	Ubiquitin-positive inclusion?
AD	<i>APP</i> <i>PS1</i> <i>PS2</i>	Missense	Amyloid plaques, neurofibrillary tangles	Yes
FTDP	<i>Tau</i>	Missense	Tau inclusions	Yes
Pick's	<i>Tau</i>		Pick bodies	Yes
ALS	<i>SOD</i>	Missense	Lewy-body-like inclusions	Yes
PD	<i>α-Synuclein</i> <i>UchL1</i> <i>Parkin</i>	Missense	Lewy bodies	Yes
DLB	<i>α-Synuclein</i>		Lewy bodies	Yes
MSA	<i>α-Synuclein</i>		Glial cytoplasmic inclusions (GCIs)	Yes
Prion	<i>Prion</i>	Missense	Prion protein (PrP) plaques	Yes ⁵⁸
DRPLA	<i>Atrophin 1</i>	Polyglutamine	Nuclear inclusions	Yes
HD	<i>Huntingtin</i>	Polyglutamine	Nuclear inclusions	Yes
SCA1	<i>Ataxin1</i>	Polyglutamine	Nuclear inclusions	Yes
SCA3/MJD	<i>Ataxin3</i>	Polyglutamine	Nuclear inclusions	Yes
SCA7	<i>Ataxin7</i>	Polyglutamine	Nuclear inclusions	Yes

^aAbbreviations: AD, Alzheimer's disease; ALS, amyotrophic lateral sclerosis; APP, amyloid precursor protein; DLB, dementia with Lewy bodies; DRPLA, dentatorubral and pallidoluysian atrophy; FTDP, frontotemporal dementia with parkinsonism; HD Huntington's disease; MJD, Machado Joseph disease; MSA, multiple system atrophy; PD, Parkinson's disease; PS, presenilin; SCA, spinocerebellar ataxis; SOD, superoxide dismutase.

^bTable adapted from Refs 1 and 44 (with the information regarding Prion taken from Ref. 58, as indicated).

controlled protein degradation in eukaryotes⁴. The basic biochemical steps of the pathway have been reviewed in detail (Fig. 1)⁵⁻⁷. Interestingly, some proteins that are linked to neurodegenerative diseases might also be connected to the ubiquitin system (Table 2). For instance, genomic studies in familial PD have discovered mutations in two ubiquitin-related proteins – the ubiquitin-like domain containing protein parkin, and the ubiquitin C-terminal hydrolase L1 (UchL1), which might cause PD (Refs 2,3 and discussed later in this review). In addition, different ubiquitin-like proteins have been found to interact with proteins that cause neurodegenerative diseases (Table 2); thus, the UPP might play secondary roles in these disorders.

Parkinson's disease and the UPP

PD is a prototypical neurodegenerative disease with prominent intracytoplasmic inclusions of proteinaceous material called Lewy bodies. Lewy bodies are one of the defining pathological hallmarks of PD and DLB, and are composed of eosinophilic intracellular neuronal proteinaceous inclusions that mainly contain lipids, neurofilament and related proteins, α -synuclein, synphilin-1, ubiquitin and the ubiquitin-pathway-related enzymes⁸⁻¹².

PD is currently the only neurodegenerative disease that is caused by mutations in proteins within the UPP. Thus, understanding how these mutations cause PD could lead to greater insight into other neurodegenerative disorders.

Great advances in our understanding of the etiology of PD have occurred over the past few years^{13,14}. Genetic linkage studies have identified several mutations that cause familial PD. Two familial-associated PD genes are part of the UPP: UchL1 (Ref. 3) and parkin, which has a ubiquitin-like domain². Mutations in α -synuclein, one of the major components of the Lewy bodies¹⁵, is also linked to familial PD (Ref. 16). Other families with hereditary PD have been reported but the genes associated with these families are not known¹⁷.

A mutation in UchL1 (Ile93Met) was identified in a small German pedigree composed of two affected family members³. UchL1 is one of the most abundant proteins in the brain and belongs to a family of enzymes that is responsible for degrading polyubiquitin chains back to the ubiquitin monomer^{18,19}. UchL1 is present in Lewy bodies²⁰. The mutation (Ile93Met) was found to decrease the enzymatic activity of UchL1, but how this is linked to PD is not known³. Mutations in UchL1 are rare in PD – only two affected

family members in one family have been identified in a large, genome-wide search²¹. The rarity of the mutation suggests that it is either a very rare cause of PD or it is a chance occurrence that is unrelated to the cause of PD in this family.

However, polymorphisms in UchL1 might protect against PD, providing potential support for the importance of UchL1 in the pathogenesis of PD (Ref. 22). A malfunction of UchL1 in degrading the polyubiquitin chain could impair the overall efficiency of the ubiquitin system and ultimately increase the accumulation of damaged protein, thus threatening the survival of neurons under any additional unfavorable conditions. An in-frame deletion including exons 7 and 8 of UchL1 in mice causes gracile axonal dystrophy (Gad)²³. Gad mice have sensory ataxia at an early age, followed by motor ataxia as they age. There is also an accumulation of β -amyloid (A β) and ubiquitin deposits, suggesting that the altered function of the de-ubiquitinating system is directly responsible for neurodegeneration.

Parkin belongs to a family of proteins with conserved ubiquitin-like and RING finger motifs^{2,24}. Mutations in parkin cause autosomal recessive PD (AR-PD). In the limited neuropathological studies of patients with parkin mutations, there is a selective loss of dopaminergic neurons without the presence of Lewy bodies. *In situ* hybridization studies show that parkin, UchL1 and α -synuclein mRNA have similar expression patterns²⁵. Parkin can interact with actin filaments, but how this is related to the pathogenesis of AR-PD is not known²⁶. Recently, parkin was reported to function as a ubiquitin E3 protein ligase (Fig 2)^{27–29}. It appears to use both Ubch7 and Ubch8 as its E2 and also utilizes the ER-associated E2s, Ubc6 and Ubc7 (Ref. 30). Familial-associated mutations in parkin have impaired binding to either Ubch7 or Ubch8 and are defective in E3 ubiquitin–protein-ligase activity, which suggests that the disruption of the E3 ubiquitin–protein-ligase activity of parkin is probably the cause of AR-PD (Refs 27–29). Several potential substrates for parkin have recently been identified, one of which is cell division control-related protein 1 (CDCrel-1) (mutations in parkin impair its ability to regulate the turnover of CDCrel-1)²⁹. CDCrel-1 belongs to a family of septin GTPases; it has been suggested that it regulates synaptic vesicle release in the nervous system³¹. Whether CDCrel-1 is involved in the release of dopamine (DA) is not yet known but it is possible that mutations in parkin affect CDCrel-1-mediated dopamine release, which ultimately contributes to the Parkinsonian state of AR-PD patients²⁹. Because septins are highly conserved proteins³², it is conceivable that parkin could interact with other septins to regulate their levels as well. Whether CDCrel-1 or a closely related septin accumulates in PD and/or contributes to the pathogenesis of AR-PD, awaits further study.

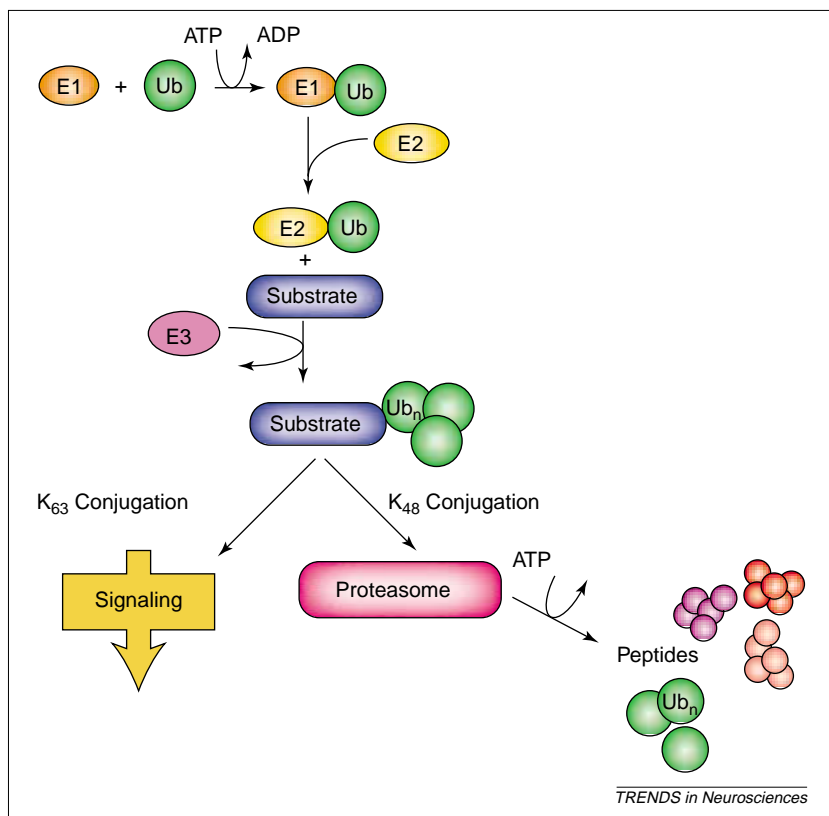


Figure 1. The steps and components in the ubiquitination of substrate proteins in the ubiquitin-proteasomal pathway

Ubiquitin (Ub) is first activated by ubiquitin-activating enzyme (E1) in the presence of ATP. Next, the activated ubiquitin is transferred to ubiquitin-conjugating enzyme (E2). The E2 in conjunction with ubiquitin-protein ligase (E3) recognizes the substrate and mediates the attachment of polyubiquitin chains to the substrate. The polyubiquitin chain is then recognized by the proteasome and degraded in an ATP-dependent manner. E3 is therefore one of the most important factors in the regulation and selectivity of substrates targeted for degradation. There are several established families of E3 enzymes. One of the best known is the HECT domain E3 family, which was first characterized by its representative member, the E6 associated protein (E6-AP)⁵. Another emerging major class of E3 ligases are proteins that contain a RING finger domain⁶⁶. Proteins that are polyubiquitinated by the ubiquitin system are typically targets for degradation by the proteasome^{5,6}. However, ubiquitination of protein substrates without proteolysis has recently been described in several systems, thus unveiling potential new regulatory functions for ubiquitin^{67–70}. Interestingly, RING-finger E3 ligases seem to play a prominent role in the functional modification of target proteins through ubiquitination in a protein-degradation-independent fashion^{67–70}. Some of these functional alterations in target proteins occur through alternative types of ubiquitination, such as lysine (K)₆₃ chains^{69,70} rather than the more common lysine (K)₄₈ ubiquitin chain, which is well known to promote the corresponding proteasomal dependent protein degradation^{69,71}. Thus, derangements in the ubiquitin system could potentially lead to alterations in processes that are unrelated to protein degradation. These non-degradative pathways might be attractive drug targets. Abbreviation: Ub_n, polyubiquitin chain.

Parkin is upregulated by unfolded protein stress and has been found to suppress unfolded protein-stress-induced toxicity²⁸. The unfolded protein response regulates a variety of proteins, including multiple ER and secretory pathway genes [including proteins involved with ER-associated protein degradation (ERAD)]. Many of the ERAD proteins are components of the UPP. Misfolded proteins are retrotranslocated across the ER membrane into the cytosol, where they are degraded through the ERAD system^{33,34}. Because parkin is localized to the microsomal fractions, as well as to the cytosol and Golgi fractions³⁵, it is conceivable that it is involved in ERAD. Thus, mutations

Table 2. Proteins in the ubiquitin pathway that are connected to neurodegenerative diseases^a

Disease	UPP proteins potentially linked to neurodegenerative diseases	Function in the ubiquitin pathway	Mutations cause disease?	Disease-related interactors	Refs
AD	Ubiquilin	Linker for E3 ligase and proteasome?	No	PS1, PS2	59
DRPLA	AIP2, AIP4, AIP5	E3 ligase?	No	Atrophin-1	60
HD	hE2-25K	E2	No	Huntingtin	61
PD	Parkin	E3 ligase	Yes	CDCrel-1 Synphilin-1 Pael-R α -Sp22	2,27, 28,30, 37,38
	UchL1	De-ubiquitination enzyme	?	?	3
SCA1	A1Up	Linker for E3 ligase and proteasome?	No	Ataxin 1	62
SCA3/MJD	HHR23A, HHR23B	Inhibits multi-ubiquitin chain formation	No	Ataxin 3	63,64

^aParkin functions as an E3 ligase and has four potential substrates: CDCrel-1, synphilin-1, Pael-R and α -Sp22 (see text for full discussion). Atrophin-1, the DRPLA gene product, interacts with a family of WW and HECT domain-containing proteins (AIP2, AIP4, AIP5), which are highly homologous to the HECT domain E3 ligase⁶⁰. HD interacts with the E2 conjugating enzyme hE2-25K (Ref. 61). In SCA1, ataxin-1 interacts with a novel protein, A1Up, which contains both ubiquitin-like (UBL) or ubiquitin associated (UBA) domains⁶². Ataxin-3, the Machado Joseph Disease gene product, interacts with HHR23A and HHR23B, which are homologous to the yeast protein, RAD23 (Ref. 63). Ubiquilin (hPLIC-1), which also has a UBL and UBA domain, interacts with presenilin 1 and 2 (Ref. 59). Mutations in presenilins (PS) 1 and 2 are linked to early-onset familial AD (Ref. 65). Interestingly, A1Up and ubiquilin belong to a highly conserved family of proteins containing UBL and UBA domains. UBL- and UBA-containing proteins are thought to have important functions in protein degradation and possibly link the ubiquitin tagging system with the proteasome. Whether various disease-causing mutations in these neurodegenerative-disease-associated proteins could interfere with the processing of proteins via the UPP (owing to alterations in their binding or disruption of the function of these UBL- and UBA-domain-containing proteins) awaits further study. Abbreviations: A1Up, ataxin-1 interacting protein; AIP, atrophin-1 interacting protein; AD, Alzheimer's disease; CDCrel-1, cell division control-related protein1; DRPLA, dentatorubral and pallidolusian atrophy; PD, Parkinson's disease.

or deletions of the *parkin* gene could result in accumulation of misfolded substrate proteins in the ER, leading to dopamine cell death in AR-PD (Ref. 28).

Recently, an unfolded putative G-protein-coupled transmembrane receptor – the parkin-associated endothelin-receptor-like receptor (Pael-R) – was found to be a parkin substrate³⁰. When overexpressed, Pael-R tends to become unfolded, insoluble and ubiquitinated, and causes unfolded protein-induced cell death³⁰. Co-expression of parkin results in protection against Pael-R-induced cell toxicity³⁰. Insoluble forms of Pael-R accumulate in the brains of AR-PD patients³⁰. Thus, accumulation of Pael-R caused by parkin mutations could result in the selective neurodegeneration of AR-PD. Although Pael-R is a potentially important disease-causing substrate of parkin, its localization in oligodendrocytes and its enrichment both in DA neurons and in other neurons does not entirely explain the selective loss of DA neurons in AR-PD patients³⁰.

UPP and Lewy bodies

The prominence of ubiquitinated protein species within the Lewy body, and the observation that parkin functions as an E3 ligase, make it conceivable that proteins con-

tained within Lewy bodies are targets of parkin-mediated ubiquitination. Furthermore, the absence of Lewy bodies in patients with parkin mutations suggests that parkin might be involved in the formation of Lewy bodies²⁹. Two mutations in α -synuclein – A53T and A30P – cause an early-onset, autosomal dominant form of familial PD (Refs 16,36). In addition, α -synuclein is a major component of Lewy bodies, suggesting that it might play a prominent role in sporadic PD (Ref. 15).

It has been suggested that the ubiquitin system tags α -synuclein for proteasomal degradation. Under adverse conditions, the ubiquitin system might not be able to cope with the rate of formation of damaged and/or mutant α -synuclein, and, thus, ubiquitin- and α -synuclein-positive protein inclusions (i.e. Lewy bodies) would be formed. Using immunological methods in normal human brain, Shimura and colleagues identified a protein complex containing parkin, UbcH7 and a novel glycosylated form of α -synuclein (α -Sp22)³⁷. Familial-associated parkin mutants failed to bind α -Sp22 and, in an *in vitro* ubiquitination assay, α -Sp22 was ubiquitinated by normal but not mutant parkin. Interestingly, α -Sp22 accumulated as a non-ubiquitinated form in AR-PD brains. Non-glycosylated

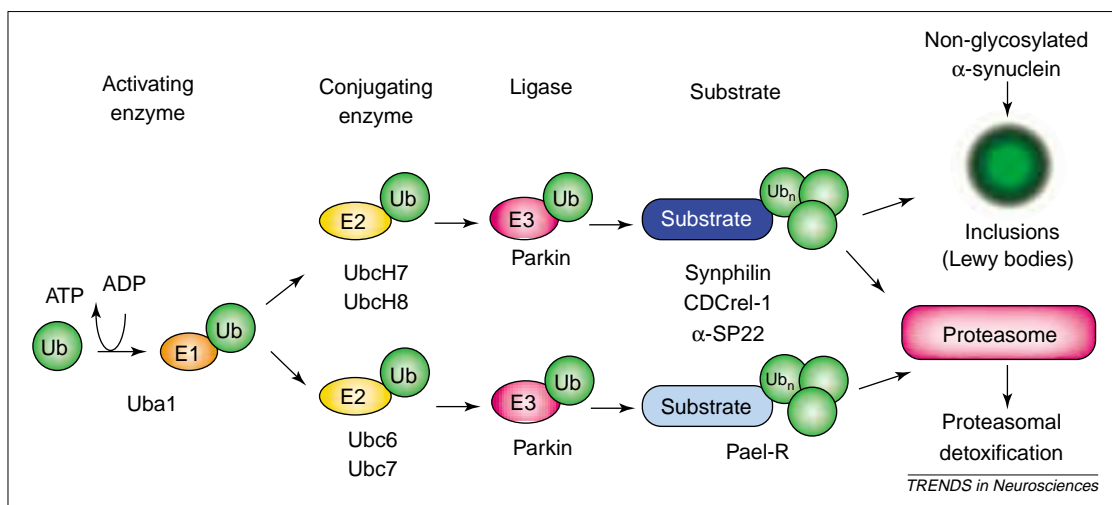


Figure 2. Parkin functions in the ubiquitin-proteasomal pathway as an E3 ubiquitin–protein-ligase

Parkin appears to work in conjunction with the E1 ubiquitin-activating (Uba) 1 and the E2 ubiquitin-conjugating (Ubc) enzymes UbcH7 or UbcH8 to ubiquitinate the target proteins CDCrel-1, α -Sp22 or the α -synuclein interacting protein, synphilin-1. Ubiquitination of CDCrel-1 by parkin enhances its degradation via the proteasomal degradation system²⁹. Ubiquitination of synphilin-1 in the presence of non-glycosylated α -synuclein by parkin leads to ubiquitinated cytoplasmic Lewy-body-like inclusions. α -Sp22 accumulates in the brains of patients with Parkinson's disease (PD) owing to familial associated parkin mutations. Whether α -Sp22 accumulates in Lewy bodies is not known. Parkin also appears to participate in endoplasmic-reticulum-associated protein degradation (ERAD) (see text for discussion) and utilizes the ER-associated E2s, Ubc6 and Ubc7 to degrade toxic unfolded proteins such as the parkin-associated endothelin-receptor-like receptor (Pael-R). Pael-R accumulates in autosomal recessive PD (AR-PD) brains and cell death induced by Pael-R overexpression is rescued by parkin. Abbreviations: CDCrel-1, cell division control-related protein 1; Ub_n, polyubiquitin chain.

α -synuclein, the major species in brain, does not appear to be a parkin substrate: both *in vitro* (in heterologous transfection assays in cell lines) and in brain^{30,37,38}, parkin fails to interact with non-glycosylated α -synuclein, and fails to ubiquitinate non-glycosylated α -synuclein³⁸. Thus, parkin and α -synuclein might be linked in a common pathogenic mechanism through glycosylation of α -synuclein, and this interaction could result in ubiquitinated α -synuclein in PD.

Although α -Sp22 appears to be ubiquitinated by parkin *in vitro*, as yet no ubiquitin-positive α -synuclein species have been definitively isolated *in vivo*. Immunohistochemical studies show that Lewy bodies have a distinct central ubiquitin-positive domain, whereas α -synuclein-positive staining primarily occurs in the peripheral and outer domain of the Lewy body^{8,10}, suggesting that these two proteins might not be in the same compartment. In addition, pale bodies (or diffuse 'cloud-like' inclusions) are found in PD and DLB that are only α -synuclein positive⁸, suggesting that non-ubiquitinated α -synuclein protein inclusions do exist. Thus, the issues of whether α -synuclein is being ubiquitinated *in vivo*, and how proteins contained within Lewy bodies are ubiquitinated, remain to be resolved. A potential clue to this process comes from recent studies in which parkin was shown to interact with, and ubiquitinate, the α -synuclein-interacting protein, synphilin-1^{38–41}. *In vitro* reconstitution assays indicate that synphilin-1 is a direct protein target of parkin³⁸ and is enriched in Lewy bodies¹². Interestingly, co-transfection of parkin, α -synuclein and synphilin-1 results in the formation

of ubiquitin-positive protein inclusion bodies³⁸, and familial-associated mutations in parkin disrupt the formation of ubiquitin-positive protein inclusions. Thus, parkin and the major non-glycosylated form of α -synuclein might also be linked in a common pathogenic pathway through their interaction with synphilin-1³⁸, in addition to the direct interaction with glycosylated α -synuclein. Furthermore, parkin and synphilin-1 appear to be required for the formation of ubiquitinated α -synuclein inclusions³⁸.

Inclusion body: friend or foe?

The UPP appears to be at the intersection of whether a toxic protein is degraded or whether it is packaged into an inclusion. Molecular chaperones also participate in attempts by the cells to suppress aggregate formation. One general hypothesis is that ubiquitinated protein aggregates provide a nucleation center for the formation of inclusion bodies. Aggresomes appear to be part of the general cellular response to the formation of aggregated proteins and it appears that aggregated proteins are delivered specifically to inclusion bodies by dynein-dependent retrograde transport on microtubules⁴². The accumulation of these inclusion bodies might subsequently induce neuronal dysfunction and/or cell death leading to neurodegeneration^{43–46}. Neurodegeneration could be induced by the intracellular aggregates overwhelming the capacity of the protein-folding chaperones and/or the UPP to degrade important cellular regulatory factors, leading to a positive feedback

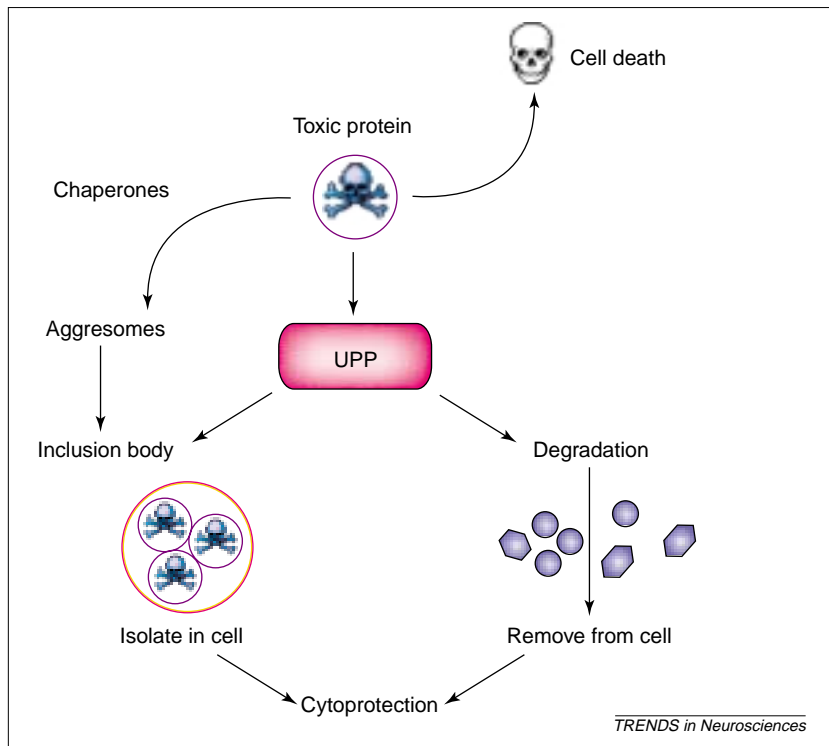


Figure 3. A toxic or damaged protein can be detoxified via at least two pathways

The first involves the ubiquitin-proteasomal pathway (UPP) where the protein is tagged for degradation by the proteasome. If the toxic or damaged protein exceeds the capacity of the proteasome the ubiquitinated protein might serve as a nucleation center for aggregates and inclusion bodies. Aggresomes might be intermediates in the formation of inclusion bodies. Inclusion bodies and the UPP appear to work in a coordinated fashion to protect the cell from toxic or damaged proteins. The capacity of both of these systems might be overwhelmed, leading to further compromise in a feed-forward pathway that ultimately results in the demise of the neuron.

mechanism in which increased aggregation leads to a further decline in the UPP and disruption of fundamental cellular events, and ultimately to neuronal cell death⁴⁶.

Although intracellular aggregates might eventually be toxic to cells⁴⁶, accumulating evidence suggests that the presence of inclusion bodies is not necessarily deleterious and that, in fact, they might be protective. Thus, the question arises: are inclusion bodies toxic or are they protective agents against some of the more toxic intermediate protein-aggregate species? In PD, for instance, the prefibrillar α -synuclein intermediate might be more toxic than the fibrillized α -synuclein protein aggregates^{47,48}.

Together with various chaperones, the ubiquitin system might promote the formation of inclusion bodies to render the damaged or mutant protein less toxic than its soluble form. It has been proposed that Lewy bodies are protective in PD (Refs 47,49). As discussed earlier, parkin belongs to a family of proteins with ubiquitin-like domains; this class of proteins might be important in protein folding and degradation, linking the ubiquitin tagging system to the proteasomal apparatus. The finding that parkin is an E3 ligase, and that it can protect cells from unfolded protein

stress, further supports this idea. Based on the hypothesis that inclusion bodies might be protective, it is tempting to speculate that parkin could be responsible for detoxifying damaged proteins. One potential pathway for this is through the formation of protein inclusions like Lewy bodies, which could render damaged proteins less toxic. In addition, parkin might tag proteins with polyubiquitin chains for degradation through the proteasome. Both pathways could work together to protect the cell from toxic mutant and/or damaged proteins (Fig 3). The observations that AR-PD patients develop PD symptoms at an earlier age than other patients, that they accumulate the parkin substrates Pael-R and α -SP22, and that they demonstrate an absence of Lewy bodies appears to support this scenario.

Other studies have suggested that the formation of inclusion bodies is one of the strategies of the cell to process damaged and/or mutated potentially toxic proteins and that, given a chance, the cell will recover from such stress (Fig 3). In the mouse model of HD, nuclear inclusions (NI) are present in surviving neurons, suggesting that the inclusion body might itself be protective⁵⁰. In the mouse model of SCA1, mutant ataxin-1 that cannot self-aggregate is still toxic to neurons⁵¹. In the fly model of polyglutamine disease, overexpression of protein chaperones, such as HSP40 or HSP70, protects against polyglutamine-induced toxicity without a visible effect on NI formation⁵²⁻⁵⁴. In another interesting study, mice with a pathogenic ataxin-1 transgene crossed with mice with a defective ubiquitin system (mutation in E6AP) resulted in enhanced ataxin-1-mediated toxicity, despite decreased formation of ubiquitinated NI (Ref. 55). In an *in vitro* model, conditions that prevent the formation of NI and ubiquitination in neuronal culture were found to enhance mutant huntingtin-induced cell death⁵⁶.

In a recent exciting report, lowering the expression of the toxic HD transgene expressing pathogenic expanded polyglutamines in symptomatic mice reversed the neuropathological and behavioral abnormalities, clearly indicating that neurons with inclusion bodies are not those that are dying and that, in fact, inclusion bodies could be reversible protein reservoirs⁵⁷. Despite the notion that inclusions might, in part, be protective, neurons ultimately fail to compensate for the abnormal and/or toxic protein accumulations and die. However, the possibility that inclusions are, in part, protective and reversible means that it could be possible in the future to improve or even reverse neurodegenerative disease before significant neuronal cell death has occurred.

Concluding remarks

It is clear that the UPP is emerging as a major player in neurodegenerative diseases and a full understanding of this intricate system must be achieved to better understand the

pathogenesis of these devastating disorders. Most studies have focused on the biosynthetic anabolic pathways of proteins involved in neurodegenerative diseases. Very little attention has been given to the degradative and catabolic pathways. Greater understanding of these pathways will be required to understand fully the pathogenesis of neurodegenerative disorders. The challenge in the future will be to identify ways to harness the UPP for treatment of neurodegenerative disorders. Inhibition of the UPP might be expected to worsen most neurodegenerative disease. Augmentation of the UPP possesses unique challenges, such as delivery of UPP components to the nervous system or identification of drugs that enhance the degradation of damaged and toxic proteins without compromising normal UPP functions.

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