OPINION

Failure of the ubiquitin–proteasome system in Parkinson's disease

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Parkinson's disease (PD) is a neurodegenerative movement disorder characterized by degeneration of dopamine-containing neurons in the midbrain. In cases of familial PD, mutations that lead to failure of the ubiquitin–proteasome system (UPS) have been identified. These genetic abnormalities do not occur in sporadic PD, but we propose that impairment of the UPS could also contribute to neurodegeneration in this disorder. We discuss evidence that failure of the UPS is a common aetiopathogenic factor that underlies the development of familial and sporadic PD, an idea that might help to explain clinical and pathological differences and similarities in these disorders.

Parkinson's disease (PD) is an age-dependent neurological disorder that is characterized clinically by resting tremor, rigidity, bradykinesia, gait dysfunction and postural instability. The disorder is defined pathologically by the preferential degeneration of dopamine neurons in the substantia nigra pars compacta (SNc), and by the intracytoplasmic accumulation of proteinaceous inclusions — Lewy bodies[1]. Mutations in the genes that encode α-synuclein, parkin and ubiquitin carboxy-terminal hydrolase L1 (UCHL1) have been identified as the cause of a small number of familial cases of PD, and it is likely that there are several other gene defects underlying this disorder[2]. However, genetic causes of PD are relatively rare and do not account for most cases, which seem to be sporadic. In sporadic PD, the specific aetiology is unknown, but neuronal death is associated with several biochemical defects in the SNc, including mitochondrial dysfunction secondary to complex I inhibition[3], and oxidative stress reflected in the depletion of reduced glutathione (GSH) content[4] and increased iron levels[5]. So, there could be many different causes of PD, and it is not yet clear how they relate to one another. Recently, interest has begun to focus on the possibility that dysfunctions of protein degradation might be an important factor in the degenerative processes that occur in the various aetiological forms of PD[6,7]. Indeed, the different gene mutations in familial PD point to the possibility that an alteration in protein conformation and/or degradation is a key factor in the origin of the degenerative process[2]. In addition, the occurrence of elevated levels of oxidatively damaged proteins[8], increased protein aggregation[9] and impaired proteolysis[10] in the SNc of patients with the sporadic disorder are consistent with the idea that impaired protein clearance is a crucial factor in the pathogenesis of cell death in PD[7]. Current evidence has, therefore, converged on the idea that the accumulation of intracellular proteins due to alterations in their folding or degradation leads to neurodegeneration in both familial and sporadic cases of PD. We postulate that this mechanism also accounts for the age-related nature of sporadic PD, for the early age of onset in the familial disorders, for the relatively selective involvement of the SNc, and for the differential formation of Lewy bodies in these disorders. Here we review the processes by which abnormal proteins are usually degraded by the ubiquitin–proteasome system (UPS), the mechanisms by which the accumulation and aggregation of proteins might cause neurotoxicity when the UPS fails, and the evidence that defects in protein degradation might be a common aetiopathogenic factor that links and unifies the different causes of PD.

The ubiquitin–proteasome system

The UPS is essential for the non-lysosomal degradation and clearance of short-lived, mislocated, misfolded, mutant and damaged (for example, by oxidative injury) proteins in eukaryotic cells[11]. This is accomplished through a series of enzyme-mediated reactions that first identify and covalently link abnormal proteins with multiple ubiquitin molecules as a signal for degradation (FIG. 1). Activated ubiquitin is generated by a ubiquitin-activating enzyme (E1) through an ATP-dependent mechanism. It is then transferred to ubiquitin-conjugating enzymes (E2) and ligated to lysine residues of protein substrates in a reaction catalysed by many different ubiquitin protein ligases (E3) that, together with specific E2s, ensure selective protein targeting[12] (FIG. 1). Ubiquitin–protein conjugates are subsequently recognized and degraded by 26S proteasomes, which are multisubunit proteases found in the cytosol, perinuclear regions and nucleus of eukaryotic cells[13] (BOX 1). The degradation products of 26S proteasomal catalysis are short peptide fragments and amino acids that can be recycled to produce new proteins. Simultaneously, polyubiquitin chains are released from targeted proteins, and are then disassembled by ubiquitin carboxy-terminal hydrolases to produce monomeric ubiquitin molecules that re-enter the UPS at E1, from which point they can contribute to the clearance of other abnormal proteins[12] (FIG. 1).

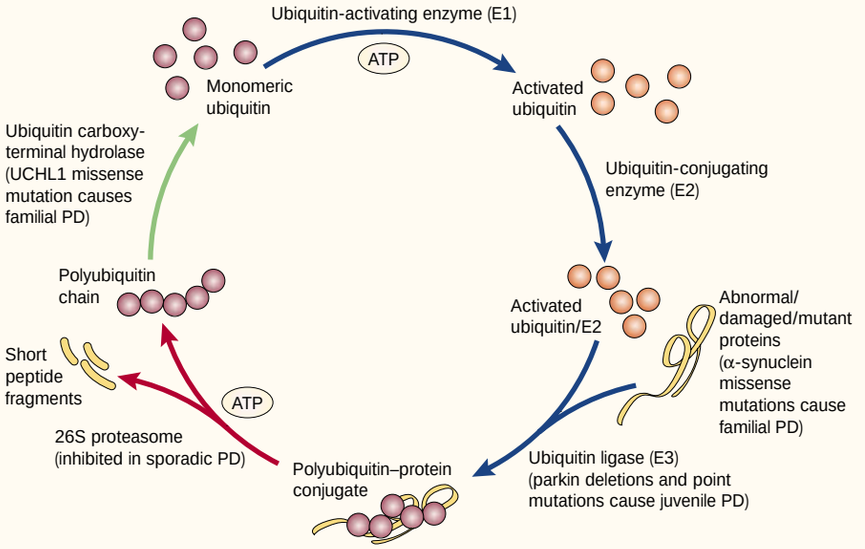


Figure 1 | **Degradation of abnormal proteins by the ubiquitin–proteasome system and impairments that lead to the development of Parkinson's disease.** The section of the cycle represented in blue shows the ATP-dependent identification and labelling of abnormal proteins with multiple ubiquitin molecules (ubiquitination) as a signal for ATP-dependent degradation by the 26S proteasome complex (proteolysis), which is depicted by the red component of the cycle. The final part of the cycle (green) shows the recovery (de-ubiquitination) and subsequent recycling of ubiquitin molecules from polyubiquitin chains that are released from proteins immediately before their translocation into the proteasome. We and others have revealed defects in several components of the ubiquitin–proteasome system in sporadic Parkinson's disease (PD) and the various forms of familial PD, as detailed in the figure. These alterations could be significant in the initiation, development and/or progression of the neurodegenerative process in PD, and indicate that impaired protein clearance due to misfolding or proteasomal defects might be a common theme underlying the different aetiologies of PD.

Protein deposition in Lewy bodies in PD

The first indication that altered protein handling could be a crucial factor in the pathogenesis of PD is the presence of proteinaceous, eosinophilic cytoplasmic inclusions, known as Lewy bodies, within the remaining dopamine cells in the SNc[1,14]. These inclusions were initially described in sporadic PD, but have now been found in α-synuclein-linked familial disease[15,16]. Lewy bodies accumulate a wide range of free and ubiquitinated proteins, which might be normal or abnormal[14]. These include ubiquitin[1], neurofilaments[1], torsin-A[17], parkin[18,19], UCHL1[20], proteasomal elements[21], protein adducts of 3-nitrotyrosine[22] and α-synuclein, which can be extensively nitrated[23,24]. It is not known whether these proteins are partially or completely degraded, or whether they are unprocessed.

Although Lewy bodies have been recognized for many decades to be a characteristic feature of PD neuropathology, the mechanism by which these protein aggregates are formed is unclear. Normal, mutated, misfolded, denatured and oxidatively damaged proteins that accumulate tend to aggregate and form insoluble inclusions[25–27]. Indeed, the oxidative modification of proteins leads to the exposure of hydrophobic regions, which crosslink extensively with normal and damaged proteins to form insoluble aggregates[28]. Such aggregated proteins are relatively refractory to degradation by normal proteolytic mechanisms, and are therefore transported to perinuclear microtubule-organizing centres (centrosomes). Here they become associated with components of the UPS, and are encapsulated by intermediate filaments to form large structures called aggresomes[11,25–27]. Aggresomes seem to be sites of enhanced proteolysis, and their formation might serve to protect the nucleus and other organelles from exposure to the cytotoxic effects of abnormal proteins[27]. The presence of ubiquitinating and proteolytic enzymes, as well as tubulin and other cytoskeletal elements, in Lewy bodies indicates that these inclusions could be specialized aggresome-related structures that are formed in dopamine neurons as a means of controlling excessive levels of abnormal proteins. However, defects in the 26/20S proteasome or the relentless production of abnormal proteins (see below) could exceed the degradation capacity of the UPS aggresome and cause poorly degraded proteins to aggregate extensively, promoting the formation of insoluble Lewy body inclusions in the dopamine neurons of PD patients. In support of these ideas, impairment of the UPS or overexpression of proteins is associated with neurodegeneration and the formation of inclusion bodies in cultured dopamine neurons or Lewy-body-like inclusions in animal models of parkinsonism[29,30].

Together, these observations raise the possibility that Lewy body formation might be a cytoprotective event in which dopamine neurons attempt to sequester and compartmentalize poorly degraded proteins into insoluble aggregates and thereby protect against protein-mediated neurotoxicity. Lewy bodies have not yet been reported in the brains of patients with autosomal-recessive juvenile parkinsonism (AR–JP) caused by mutations in the parkin gene (see below)[31]. This might relate to a failure of protein ubiquitination necessary for crosslinking and polymerization of proteins, and the formation of insoluble aggregates or inclusion bodies[19,25,32].

Mutant proteins in familial PD

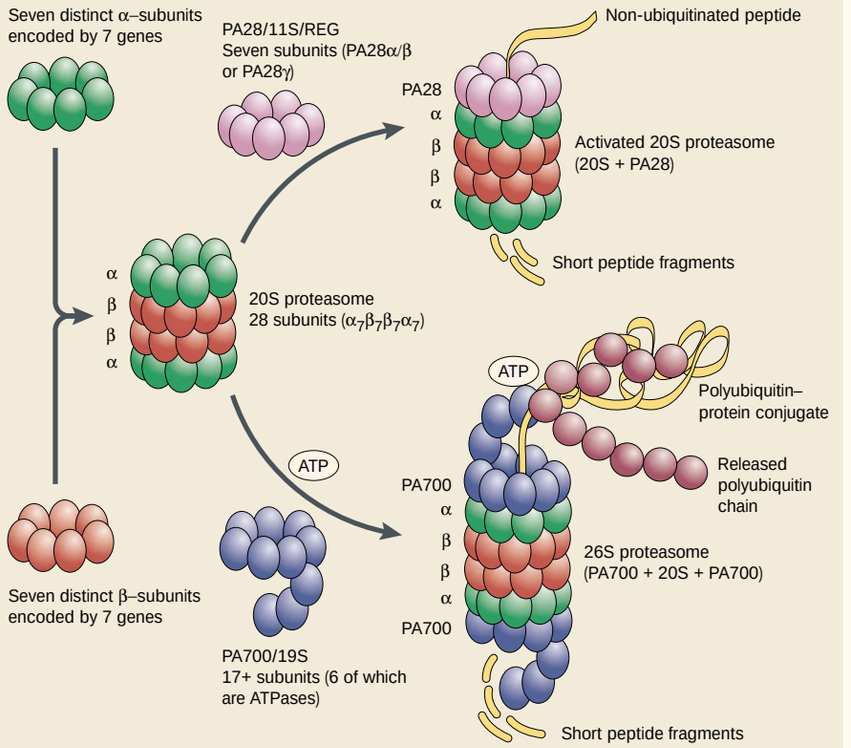
About 10% of PD cases have an inheritance pattern consistent with an autosomal-dominant form of transmission[33]. In recent years, several gene mutations associated with familial PD have been identified[2] (TABLE 1). Each of these defects seems to have the capacity to interfere with protein clearance in nigral dopamine neurons, leading to their subsequent degeneration.

α-Synuclein mutations. Studies of familial parkinsonism in a large Italian–American family known as the Contursi kindred demonstrated linkage to a specific gene[34]. These patients had a relatively early age of onset, but otherwise showed clinical and pathological features (including Lewy bodies) that are typical of PD[15,16]. A similar syndrome was identified in several apparently unrelated families of Greek and German origin[16,35,36]. Sequence analysis in these families demonstrated mutations in the gene that encodes the 140-amino-acid protein α-synuclein (TABLE 1). So far, gene screening has failed to detect the presence of these mutations in other familial cases of PD, or in patients with the sporadic disorder, with Parkinson-plus syndromes or with dementia with Lewy bodies, indicating that mutations in α-synuclein are a specific but rare cause of PD[34–37].

An understanding of the mechanisms by which mutations in α-synuclein induce dopamine cell death in familial PD might help to explain the neurodegenerative process in most forms of PD[2]. Wild-type α-synuclein

is abundant in the brain, and expressed at high levels in presynaptic nerve terminals, but its physiological functions are poorly understood[2,38]. The expression of mutant α-synuclein in a variety of cell lines and primary neuronal cultures leads to apoptotic cell death and increased susceptibility to various toxic insults, including serum withdrawal, dopamine, 1-methyl-4-phenylpyridinium, 6-hydroxydopamine and hydrogen peroxide[39–41]. Expression of human α-synuclein mutants in transgenic mice results in the appearance of inclusions that are immunoreactive for α-synuclein and ubiquitin in SNc dopamine neurons, but without cell loss[29]. However, the expression of either wild-type or mutant α-synuclein in *Drosophila* leads to the degeneration of dopamine-containing neurons in the brain and retina, to the appearance of inclusion bodies, and to locomotor abnormalities[30]. These findings indicate that neuropathology is unlikely to result from a loss of physiological processes, but, rather, occurs from a toxic gain of function when α-synuclein is mutated. At present, the evidence indicates that this might be related to the tendency of mutant α-synuclein to misfold, aggregate, and thereby resist degradation by the UPS[2]. Stably folded proteins typically have a regular secondary structure and a hydrophobic core with tightly packed non-polar amino acids that are free from contact with aqueous solutions[42]. Near-ultraviolet circular dichroism studies indicate that α-synuclein does not have a hydrophobic core, and might, therefore, be prone to misfolding. Far-ultraviolet circular dichroism studies and Fourier transform infrared spectroscopy indicate that α-synuclein exists primarily as a random coil, but becomes more helical on exposure to solvents, indicating that it is able to undergo conformational transitions. Furthermore, wild-type α-synuclein has exposed hydrophobic residues that can aggregate with each other to form insoluble intermolecular aggregates. These observations indicate that α-synuclein has a high capacity to aggregate and form insoluble amyloid fibrils[43,44]. The PD-related mutations in α-synuclein occur in the amphipathic region, which might cause the protein to become less soluble and further promote its aggregation. Impaired degradation of mutant α-synuclein might exacerbate its accumulation within dopamine neurons. Indeed, the colocalization of ubiquitin with α-synuclein in Lewy bodies indicates that the protein could have been prepared for degradation[16]. However, α-synuclein mutants can adopt an unusual folding pattern that does not permit it to undergo proteasomal degradation even when it is polyubiquitinated[43,45]. α-Synuclein has been shown to interact with the regulatory cap of 26S proteasomes[46], and the expression of mutant α-synuclein in dopamine cell lines causes impairments of proteasomal function with increased sensitivity of the cells to pro-apoptotic toxins[47]. These observations led us to speculate that mutations in α-synuclein in familial PD might cause dopamine cell death with Lewy body formation as a result of failure of the UPS. It is possible that the relentless production of mutant α-synuclein could saturate the UPS, leading to impaired degradation and clearance of a wide range of proteins within dopamine neurons in α-synucelin-linked familial PD. Consistent with this suggestion, Lewy bodies in this disorder accumu-

Box 1 | Composition and organization of the proteasome and their intracellular activators



The 26S proteasome is a multicatalytic protease that is found in the cytosol, perinuclear regions and nucleus of eukaryotic cells. It consists of a 28-subunit catalytic core — 20S proteasome (2,100 kDa) — which is an assembly of two outer and two inner heptameric rings stacked axially to form a hollow cylindrical structure in which proteolysis occurs[13]. Each of the two inner rings of the 20S proteasome is composed of seven different β-subunits, which host the three different catalytic sites on the inner surface of the 20S proteasome complex, preventing the indiscriminate degradation of intracellular proteins. These proteolytically active sites mediate the hydrolysis of proteins at the carboxyl terminus of hydrophobic, basic and acidic residues, and are referred to, respectively, as the chymotrypsin-like, trypsin-like and peptidylglutamyl-peptide hydrolytic activities. The β-subunits of 20S proteasome might be constitutively or inducibly expressed, and assembled in a selective manner to form complexes with distinct proteolytic characteristics, adapting to altered physiological conditions[13]. The outer rings comprise seven different α-subunits, none of which has catalytic activity, but which serve as an anchor for the multisubunit ATPase-containing PA700 (19S) regulator (700 kDa) that binds to form a complex referred to as the 26S proteasome. Linking of the 19S regulatory complex serves two functions: it opens the channel through the 20S proteasome, which is normally gated by the amino termini of the α-subunits, and it unfolds ubiquitinated proteins to allow entry to the catalytic core; both processes require ATP[66]. The PA28 (11S) regulatory (REG) complex (180 kDa) can also bind to the 20S proteasome and open the channel through the complex, but this process is ATP-independent, and mediates the degradation of non-ubiquitinated short peptides[66]. Indeed, recent studies indicate that, in addition to or instead of the 26S proteasome, the 20S proteasome could be responsible for the degradation of oxidatively damaged proteins, which occurs in an ATP- and ubiquitin-independent manner[28]. Several poorly characterized endogenous proteins are thought to inhibit 26/20S proteasomal activity by competing with PA700 and PA28 for binding, thereby serving to control proteolysis[66].

Table 1 | Gene mutations in familial Parkinson's disease

Gene	Locus	Mutation	Inheritance pattern	Age of onset (yr)	Phenotype
α-Synuclein	4q21-23	Missense mutations (A30P and A53T)	Dominant	Mean: 46	Levodopa-responsive; rapid progression; sporadic PD-like neurodegeneration; Lewy-body/neurite-positive
UCHL1	4p14	Missense mutation (I93M)	Dominant	49 and 50	Levodopa-responsive; neuropathology not yet determined
Parkin	6q15.2-27	Various deletions and point mutations	Recessive	Mean: 38 (range: 7–58)	Levodopa-responsive; slow progression; selective and severe destruction of the SNc and locus ceruleus; Lewy-body-negative

PD, Parkinson's disease; UCHL1, ubiquitin carboxy-terminal hydrolase L1; SNc, substantia nigra pars compacta.

late other proteins in addition to α-synuclein[16]. α-Synuclein is also abundant in the Lewy bodies of patients with sporadic PD, who do not have mutations in the α-synuclein gene[23]. This observation strengthens our suggestion that a more general defect in the control of mutant or wild-type α-synuclein by the UPS could underlie neurodegeneration in familial and sporadic PD. Moreover, failure of the UPS to control α-synuclein seems to occur in several neurodegenerative disorders in which α-synuclein-positive inclusions are found in neuronal and glial cells[2].

Ubiquitin carboxy-terminal hydrolase L1. A missense mutation in UCHL1 has been identified in two siblings of a German family with autosomal-dominant familial PD that is characterized by typical levodopa-responsive motor symptoms[48] (TABLE 1). The failure to detect similar mutations in hundreds of other patients with familial and sporadic PD indicates that this gene mutation is responsible for only a few rare cases of PD[49]. UCHL1 is a widely distributed protein, making up about 2% of all proteins in the brain. It belongs to a family of de-ubiquitinating enzymes that are responsible for the hydrolysis of bonds between ubiquitin molecules and small adducts[12,38] (FIG. 1). UCHL1 is therefore important for the provision of monomeric ubiquitin molecules necessary to label abnormal proteins for 26S proteasomal degradation (BOX 1). Expression of mutant UCHL1 in *Escherichia coli* causes a 50% reduction in the ability of the enzyme to cleave ubiquitin adducts[48]. So, a loss of UCHL1 activity in PD might lead to reduced labelling and impaired clearance of abnormal proteins, and consequent neurodegeneration. Post-mortem brain tissue from PD patients with this mutation is not yet available, so it is not known whether Lewy body formation occurs in this illness. However, in the gracile axonal dystrophic mouse — an autosomal-recessive mutant — mutations in UCHL1 cause sensory and motor neuron degeneration with the presence of inclusion bodies that are immunoreactive for ubiquitin and other proteins[50]

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Parkin. AR–JP has been described in a series of Japanese kindreds[51]. Patients show a very early onset of typical levodopa-responsive motor disability. Pathologically, the disease is characterized by degeneration of dopamine neurons in the SNc and locus ceruleus, but Lewy bodies have not yet been reported in this disorder[51]. Various deletions and point mutations have been detected in the gene that encodes the 465-amino-acid protein parkin[31,52] (TABLE 1). Mutations in parkin are now thought to represent the cause of about 50% of early-onset PD cases[53]. Parkin mRNA and protein are normally expressed diffusely in neurons throughout the brain[38], but both wild-type and mutant forms of parkin are absent from the brain of patients with AR–JP[18,19].

It is now known that parkin is a ubiquitin ligase (E3)[19,54] (FIG. 1), and that ubiquitin ligase enzymatic activity is markedly decreased in the SNc and striatum of patients with AR–JP[19,54]. So far, three cellular proteins have been reported to act as normal substrates for wild-type parkin. These are the putative G-protein-coupled transmembrane polypeptide named the Pael receptor (parkin-associated endothelin-receptor-like receptor)[55], a synaptic vesicle-associated protein called CDCrel-1 (cell-division-control-related protein 1)[56], and a 22-kDa glycosylated form of α-synuclein referred to as αSp22[19]. It seems that the familial PD-related mutations in parkin reduce the polyubiquitination of these proteins, as αSp22 has been shown to accumulate in a non-ubiquitinated form in dopamine neurons in the SNc of AR–JP patients[19,55,56]. These observations raise the possibility that the ability of the UPS to clear abnormal proteins is impaired in patients with AR–JP. So, toxicity that is secondary to the accumulation of poorly degraded proteins could be responsible for the death of dopamine neurons that occurs in the SNc in AR–JP. A reduction in parkin activity might also explain why there is a failure to form Lewy bodies in AR–JP, as protein ubiquitination might be required for crosslinking and polymerization of proteins to form insoluble aggregates and inclusion bodies[19,25,32]. One can also speculate that the absence of Lewy bodies and their putative protective role could underlie the rapid neuronal degeneration and early onset that occur in AR–JP. These concepts are supported by recent observations in an animal model of the neurodegenerative disorder known as spinocerebellar ataxia (SCA). Transgenic mice that express polyglutamine-containing forms of the ataxin-1 gene develop polyubiquitinated inclusions in the nucleus of cerebellar Purkinje cells before their degeneration and the onset of

motor dysfunction[32]. When SCA mice are crossed with another transgenic mice that lacks the gene for a ubiquitin ligase, there is a marked reduction in the formation of intranuclear inclusions coupled with earlier and more severe neurodegeneration[32].

Protein accumulation in sporadic PD

There is increasing evidence that failure of the UPS contributes to the development of sporadic PD. As discussed previously, Lewy bodies in sporadic PD accumulate various proteins that seem to have been prepared for degradation, but remain inadequately processed. The brains, particularly the SNc, of PD patients also contain markedly increased levels of oxidized, nitrated and 4-hydroxynonenal-modified proteins that could be misfolded and resistant to 26/20S proteasomal degradation[7,57]. Indeed, the substantia nigra normally has a high basal rate of protein oxidation, and there is substantial evidence of oxidative stress in the SNc in PD[58]. Increased levels of 3-nitrotyrosine in the SNc indicate that excitotoxicity might also contribute to protein damage in PD[22]. A recent study reported a significant reduction in each of the three enzymatic activities of 26/20S proteasomes in the SNc in sporadic PD[10]. These changes do not occur in the frontal cortex, striatum, hippocampus, pons or cerebellum (K.S.P.M., unpublished observation). The precise cause of 26/20S proteasome defects in sporadic PD is unclear at present, but could relate to as yet undetermined genetic abnormalities or oxidative damage. Sporadic PD is also associated with a reduction in mitochondrial complex I activity in the SNc[3]. As protein ubiquitination, degradation, de-ubiquitination and the regulation of these processes require ATP, the inhibition of complex I activity might lead to impairment of the UPS and protein degradation[13]. In support of this idea, the chronic, systemic administration of the specific complex I inhibitor rotenone to rats resulted in the accumulation of α-synuclein/ubiquitin-positive inclusion bodies in nigrostriatal dopamine neurons before their degeneration[59]. Complex I defects can also induce oxidative stress, and this could damage components of the UPS.

Conclusion

We propose that the accumulation of intracellular proteins due to failure of the UPS is common to both familial and sporadic PD, and could cause or contribute to the initiation and/or progression of nigrostriatal degeneration in these disorders. In familial PD, the expression of mutant proteins that misfold, and therefore resist, inhibit or overwhelm proteolysis (for example, α-synuclein), or mutations that impair normal ubiquitination (for example, parkin) or de-ubiquitination (for example, UCHL1) mechanisms, could account for the accumulation of poorly degraded proteins. In sporadic PD, impaired protein clearance could result from protein damage, misfolding or inhibition of 26/20S proteasomal function, due to as yet undiscovered genetic alterations, oxidative damage, mitochondrial dysfunction or environmental factors[60]. Indeed, we believe that other factors that interfere with the normal function of the UPS could be associated with the development of PD. Precisely how failure of the UPS and the intracellular accumulation of proteins might lead to neurodegeneration is not yet known. Damage to the proteasomal system could, indirectly, result in mitochondrial dysfunction[47] and the enhancement of oxidative stress[61]. In addition, protein accumulation is thought to induce apoptotic cell death through a mechanism involving the upregulation of Jun kinase, a pro-apoptotic signal. In this regard, it is noteworthy that neuronal death in the SNc in PD has been associated with an apoptotic process[62].

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The association of Lewy bodies with late-onset sporadic PD, and their relative absence in patients with young-onset familial PD, leads us to speculate that the formation of Lewy bodies could serve as a protective event that delays the onset of neuronal degeneration. The relative paucity or absence of Lewy bodies in patients with parkin mutations might deprive them of a natural defence mechanism that segregates abnormal proteins, and protects other cellular structures from their cytotoxic effects. This might account for the relatively severe neurodegeneration and early age of disease onset that characterize these cases. There is normally an age-related decline in mitochondrial function and activity of the UPS that might promote the accumulation of poorly degraded proteins[63,64]. As differentiated neurons have a long lifespan, it is possible that these proteins might continue to accumulate within cells, and render them more sensitive to toxic insults. This could explain why the frequency of sporadic PD increases with age. Furthermore, the progressive accumulation of intracellular proteins might account for the presence of incidental Lewy bodies in the brains of 5–10% of individuals over the age of 60, who appear to be normal but are thought to be in the preclinical stages of PD[65]. This idea is supported by the reduced levels of GSH and complex I activity that are found in these people[58]. So, the sequestration and compartmentalization of poorly degraded and cytotoxic proteins as insoluble aggregates in Lewy bodies could serve as defence mechanism that reduces pathological neurodegeneration and prevents the onset of clinical symptoms in patients with incidental Lewy bodies.

It is unclear why the SNc preferentially degenerates in PD. The oxidative metabolism of dopamine, and its propensity to yield oxidative species, could cause local damage to intracellular proteins and components of the UPS over time. We have found that, in the aged human brain, 26/20S proteasomal function is lower in the SNc compared with other brain regions, and that dopamine cells are more vulnerable than GABA (γ-aminobutyric acid)-releasing neurons to proteasome inhibition in culture (K.S.P.M *et al.*, unpublished observations). This could explain the unique vulnerability of the SNc in PD, and its preferential degeneration in α-synuclein/parkin-linked familial PD, even though the expression of these proteins is altered throughout the brain in these illnesses.

We conclude that failure of the UPS system could cause or contribute to the development of both familial and sporadic PD, and might help to explain clinical and neuropathological differences and similarities in these disorders. Determination of the relationship between altered protein handling and other biochemical changes found in PD should provide a clearer understanding of the neurodegenerative processes that occur in these disorders. These insights should lead to more focused efforts in the quest to develop therapeutics agents and strategies that could slow, halt or prevent the onset of neurodegeneration in PD.

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Links

DATABASE LINKS Parkinson's disease | α-synuclein | parkin | ubiquitin | UCHL1 | 26S proteasomes | neurofilaments | torsin-A | AR–JP | dementia with Lewy bodies | Pael receptor | CDCrel-1 | spinocerebellar ataxia | Jun kinase | PA700 | PA28

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