Proteins associated with neurodegenerative diseases

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Quality control of the proteins associated with neurodegenerative diseases

Most neurodegenerative diseases including Alzheimer’s disease, Parkinson’s disease, Huntington’s disease and other polyglutamine diseases are associated with degeneration and death of specific neuronal populations due to misfolding or aggregation of certain proteins. These aggregates often contain ubiquitin that is the signal for proteolysis by the ubiquitin-proteasome system, and chaperone proteins that are involved in the assistance of protein folding. Here we review the role of protein quality control systems in the pathogenesis of neurodegenerative diseases, and aim to learn more from the cooperation between molecular chaperones and ubiquitin-proteasome system responding to cellular protein aggregates, in order to find molecular targets for therapeutic intervention.

Keywords quality control; protein misfolding; molecular chaperones; ubiquitin-proteasome system; neurodegenerative disease

Protein folding is a very important post-translational process in cells. Newly synthesized proteins must fold into their correct three-dimensional structures and maintain these native states throughout their lifetime with the help of molecular chaperones and other cofactors. However, many cellular events such as genetic mutation, biosynthetic errors, or the absence of a necessary post-translational binding partner can result in protein misfolding. Cellular stresses such as chemical or temperature perturbation can also unfold or misfold proteins. Misfolding of a protein leads to the exposure of hydrophobic patches, which may cause protein aggregation in the aqueous cellular environment. This may result in the formation of toxic protein precipitates, inactivation of functional proteins, and ultimately cause cell death.

Neurodegenerative diseases are the nerve disorders caused by gradual loss of neurons in patient brains. Changes in these neurons result in abnormal cellular function, and eventually bringing about cell death. These diseases are now known to result, directly or indirectly, from aberrant protein folding and aggregation (Table 1). Classic examples include Alzheimer’s disease (AD), Parkinson’s disease (PD), Huntington’s disease (HD) and other polyglutamine (polyQ)-expanded diseases. The hallmark of a large group of neurodegenerative diseases is the presence of cytosolic, nuclear or extracellular protein aggregates, which are often ubiquitinilated and may be associated with chaperones [1]. The misfolded proteins or aggregates are apparently tagged for refolding by molecular chaperones or degradation by ubiquitin-proteasome system (UPS). In a normal cell, this protein quality control system is well organized and self-regulated for the whole life; however, these protein aggregates in an abnormal cell fail to be targeted to or degraded by the proteasome. Here we review the protein quality control components in the pathology of neurodegenerative diseases, and the molecular mechanisms underlying how the chaperones cooperate with the UPS in safeguarding cellular proteins and eliminating the degenerated proteins.

Molecular Chaperones: the First Line of Defense against Protein Misfolding and Aggregation

Molecular chaperones, most of which belong to heat shock proteins (HSP), are the first line of defense against protein misfolding and aggregation. Chaperones bind to unfolded stretches in proteins and keep them in a folding-competent state while preventing aggregation. In addition, they can help dissolve aggregates and target misfolded proteins for degradation. Recent research also indicates that molecular
Proteins associated with neurodegenerative diseases

Chaperones can assist correct folding not only of wild-type proteins but also of some mutant proteins [2,3]. Of particular interest for the formation of aggregates in eukaryotes is the 70 kDa heat shock protein (Hsp70) class of chaperones. Hsp70 binds to small hydrophobic stretches in proteins, in cooperation with a cochaperone of the Hsp40 family. Binding to the substrate requires ATP hydrolysis and with the help of a nucleotide-exchange factor (NEF) or/and other specific regulators. The ADP molecule is exchanged for a new ATP, which will be hydrolyzed in order to release the substrate [4]. Additional Hsp70 cochaperones have been identified that modulate the various activities of Hsp70s during specialized cellular functions in eukaryotes [5]. Members of the 90 kDa heat shock protein (Hsp90) family act downstream of the Hsp70/Hsp40-chaperone system and play an important role in conformational protein regulation and cell signaling [4]. The small heat shock proteins (sHsps) are a ubiquitous class of ATP-independent chaperones. They have subunit molecular masses ranging from ~15 to ~40 kDa and share a C-terminal core domain of about 100 residues, thought to be involved in the formation of dynamic higher order oligomers of up to 50 subunits. These large structures were suggested to reorganize into smaller, active complexes when a cell is exposed to stress [6].

Many studies have shown that misfolded proteins or their aggregates are associated with molecular chaperones, most prominently those of the Hsp70 family. For instance, Hsp70 and Hsp40 chaperones were shown to colocalize with the aggregates formed by polyQ-expanded proteins, such as huntingtin (Htt) and ataxin-3, in cellular models and in disease tissue [7,8], as well as with Lewy bodies in the affected brain tissue of PD patients [9]. Additionally, Hsp70 and Hsp16 chaperones may interact with intracellular amyloid β peptide (Aβ) [10]. The association of misfolded protein or aggregates with chaperones implies that the cellular quality control machinery is activated in an attempt to prevent the accumulation of misfolded proteins. Consistent with this notion, the presence of aggregates in cells is known to trigger the heat-shock response, which induces the expression of Hsps [11].

More than co-localization, a growing body of evidence suggests that molecular chaperones modulate the aggregation of a variety of neurodegenerative disease-associated proteins, including polyQ-containing proteins, Aβ peptide, α-synuclein (α-Syn), and prion protein (PrP) [12]. In the case of polyQ proteins, the expression of chaperones Hsp70 and Hsp40 diverts the polyQ aggregation pathway from formation of sodium dodecyl sulfate (SDS)-insoluble fibrils to formation of amorphous and less stable (SDS-soluble) aggregates. Fluorescence resonance energy transfer (FRET) experiments suggest that toxic oligomerization of mutant Htt begins with an intra-molecular structural rearrangement of monomeric Htt. Hsp70 and Hsp40 inhibit this intra-molecular rearrangement, presumably preventing monomeric Htt from achieving the β-sheet conformation necessary for the formation of mature fibrils. Under these conditions, the formation of soluble, amorphous aggregates would instead be favored for the cell survival. Co-transfection of mutant ataxin-1 with human DnaJ 2 (Hdj2) results in a significant reduction in aggregate formation. On the other hand, when the mutant ataxin-3, a causal protein of spinocerebellar ataxia type 3 (SCA3)/Machado-Joseph disease (MJD), is transfected into COS7 or PC12 cells, it forms large nuclear aggregates. In this case, both Hdj1/Hsp40 and Hdj2 could suppress the aggregate formation [13]. Hsp70 could also inhibit α-Syn fibril formation through preferential binding to prefibrillar species

<table>
<thead>
<tr>
<th>Disease</th>
<th>Pathological protein aggregates</th>
<th>Misfolded protein</th>
<th>Quality control factors</th>
<th>Reference</th>
</tr>
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<tbody>
<tr>
<td>AD</td>
<td>Extra cellular plaques</td>
<td>Aβ</td>
<td>+</td>
<td>[10,12,17,37]</td>
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<tr>
<td>PD</td>
<td>Intranuclear inclusions</td>
<td>α-Syn</td>
<td>+</td>
<td>[9,12,17,25,27]</td>
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<tr>
<td>HD</td>
<td>Intranuclear inclusions</td>
<td>Htt/polyQ</td>
<td>+</td>
<td>[8,11,17,26,35]</td>
</tr>
<tr>
<td>SCAs</td>
<td>Intranuclear inclusions</td>
<td>Ataxins/polyQ</td>
<td>+</td>
<td>[18,26,35]</td>
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AD, Alzheimer’s disease; CHIP, carboxyl terminus of Hsp70 interacting protein; HD, Huntington’s disease; PD, Parkinson’s disease; SCAs, spinocerebellar ataxias; Ub, ubiquitin.

Table 1 Protein aggregates and quality control in neurodegenerative diseases

to change the characteristics of toxic α-Syn aggregates [14]. These studies suggest that molecular chaperones are capable of modulating the conformation of the disease-related proteins, which in some circumstances may prevent the toxic accumulation of misfolded species.

In agreement with the chaperone mechanism described above, several studies have reported a reduction in cellular toxicity upon expression of chaperones (Hsp70, Hsp40) in aggregation-associated disease models [2,15]. For example, in a Drosophila melanogaster model of PD, directed expression of the molecular chaperone Hsp70 prevents the neuronal loss caused by α-Syn [15]. Likewise, in a yeast model of HD, expression of Hsp70 and Hsp40 reduces the toxicity associated with expression of mutant Htt, by preventing its aberrant interaction with an essential polyQ-containing transcription factor [2]. Moreover, the mutant ataxin-3-mediated neurodegeneration is suppressed by Hsp70 in a transgenic fruit fly model [13]. These findings support a general concept that chaperone action is a crucial aspect in protecting against the otherwise damaging consequences of protein misfolding and aggregation.

**Ubiquitin-proteasome System: the Second Line of Defense against Protein Misfolding and Aggregation**

The ubiquitin-proteasome system (UPS) is now believed to be the principal system for turnover of short-lived, misfolded or truncated proteins in eukaryotic cells. Targeted proteins must become conjugated to a poly-ubiquitin chain to be recognized by the proteasome, including a battery of enzymes orchestrated by many enzymes and protein factors. Ubiquitin conjugation or ubiquitination is a highly ordered process, in which an ubiquitin-activating enzyme (E1) first activates and transfers ubiquitin to an ubiquitin-conjugating enzyme (E2) that then acts in concert with an E3 ligase to transfer ubiquitin to a lysine residue on the target substrate. A chain of at least four ubiquitin moieties is required for substrate recognition by the 26S proteasome complex [16].

Cellular ubiquitin-containing inclusions are a characteristic feature of major neurodegenerative diseases, suggesting an involvement of the ubiquitin-proteasome system. The first indication that ubiquitin-mediated proteolysis may play a role in the pathogenesis of neurodegenerative disorders came in the late 1980s, with the finding that ubiquitin immunoreactivity is detected in the cellular inclusions, which characterize a number of the major human degenerative diseases, such as neurofibrillary tangle in AD, Lewy bodies in PD and nuclear inclusions in HD [17].

There is growing evidence for proteasome involvement in neurodegenerative diseases. In both diseased tissue and in vitro model, the 26S proteasome complex redistributes into the cellular aggregates. In the neurons from SCA3/MJD brain, the proteasome localizes in the intranuclear inclusions that contain the mutant ataxin-3 [18]. While in transfected cells, the proteasome redistributes into the inclusions formed by expanded polyQ proteins. On the other hand, inhibition of proteasome causes an increase in aggregate formation with a repeat length-dependent manner, implying that the proteasome plays a direct role in suppressing polyQ aggregation in disease [18]. Moreover, the proteasomal 20S subunit is redistributed to the polyQ aggregates in HD 60Q and HD 150Q cell lines and in the brain of HD exon 1 transgenic mouse models. Proteasome inhibitor dramatically increases the rate of aggregate formation caused by N-terminal Htt protein with 60Q repeats, but not by the protein with 150Q [19]. Interestingly, a massive accumulation of ubiquitinated derivatives was observed in Htt protein containing 150Q but not 60Q or 16Q [19]. These results strongly suggest that the expanded polyQ proteins are degraded by proteasome, but the rate of degradation is inversely proportional to the repeat length. Overexpression of a number of neurodegenerative disease-associated proteins including presenilin-1, parkin and Htt that are associated with AD, PD and HD, respectively, in proteasome-inhibited mammalian cells leads to inclusion formation [5,10,12,15]. Moreover, the disease-associated mutant proteins readily form aggregates without the need for proteasome inhibition [20], and a systemic administration of a proteasome inhibitor can induce a Parkinson-like phenotype in rats, developing a progressive parkinsonism with bradykinesia, rigidity, tremor, and an abnormal posture, which improved with apomorphine treatment [21].

How are misfolded proteins recognized by the ubiquitin-proteasome system in neurodegenerative diseases? Up to now, many E2 conjugation enzymes and E3 ligases have been identified as proteins that are either directly responsible for, or associated with specific neurodegenerative diseases. Ubiquitin conjugating enzymes (Ubc) have been identified that affect polyQ aggregates in Caenorhabditis elegans. Specifically, RNA interference (RNAi) knockdown of ubc-2 or ubc-22 causes a significant increase in the size of aggregates as well as a reduction in aggregate number. In contrast, RNAi of ubc-1, ubc-13, or uev-1 leads to a reduction of aggregate size and eliminates ubiquitin and proteasome localization to aggregates. In cultured human cells, knockdown of human homologs of these Ubcs (Ube2A, UbcH5b, and E2-25K) causes similar...
effects, indicating a conserved role for ubiquitination in polyQ protein aggregation [22]. Mutant product of presenilin can increase Aβ deposits and subsequent plaque formation, is also degraded via the UPS by an E3 SKP1-CUL1-F-box protein (SCF) complex containing the F-box and WD repeat domain containing 7 (FBXW7) [23]. Co-expression of FBXW7 and amyloid precursor protein (APP) can increase presenilin ubiquitination and elevate Aβ production.

Parkin is a PD-related E3 ligase; it contains both a really interested new gene (RING) domain with E3 ligase activity and an ubiquitin-like (UbL) domain [24]. Parkin can promote ubiquitination of three PD-associated proteins, α-Syn, parkin-associated endothelin-receptor-like receptor (Pael-R) and synphilin-1 (Sph1) both in vitro and in vivo [25], and ubiquitination and degradation of an expanded polyQ protein [26]. Overexpression of parkin reduces aggregation and cytotoxicity of an expanded polyQ ataxin-3 fragment [26]. Parkin forms a complex with the expanded polyQ protein, Hsp70 and the proteasome, which may be important for the elimination of the expanded polyQ protein. Hsp70 enhances parkin binding and ubiquitination of the expanded polyQ protein in vitro, suggesting that Hsp70 may help to recruit misfolded proteins as substrates for the ubiquitin E3 ligase activity of parkin. Parkin may function to relieve endoplasmic reticulum stress by preserving proteasome activity in the presence of misfolded proteins. Loss of parkin function and the resulting proteasomal impairment may contribute to the accumulation of toxic aberrant proteins in neurodegenerative diseases including PD.

Other E3 ligases may have a significant role in PD pathology. For example, the U-box E4 ligase carboxyl terminus of Hsp70 interacting protein (CHIP) interacts with Pael-R and enhances ubiquitination of Pael-R by parkin [27]. Additionally, the RING E3 ligases dorfin and Siah-1 are both capable of targeting an α-Syn partner Sph1 for degradation [28,29]. Dorfin is another mammalian E3 ligase implicated in quality control of protein misfolding. Like parkin containing two RING domains, dorfin associates with and selectively ubiquitinates mutant but not wild-type superoxide dismutase 1 (SOD1) [30]. It colocalizes with SOD1 inclusions in transgenic mice expressing an aggregation-prone SOD1 mutant and with Lewy bodies in PD brains. Overexpression of dorfin increases the viability of cells that express aggregation-prone SOD1; it also promotes ubiquitination of the parkin substrate Sph1 in cultured cells [29]. However, contrary to parkin, dorfin can associate with its known substrates without an obvious link to Hsp70 or other chaperones.

It is unclear whether proteins with an expanded polyQ tract are good proteasome substrates. Htt interacts with the human ubiquitin-conjugating enzyme E2-25K, which requires the polyQ domain. As previously described, parkin also colocalizes with mutant Htt aggregates in HD mice and human brains, and overexpression of parkin enhances the clearance of the mutant proteins. These results suggest that Htt may be a proteasome substrate. Consistent with this, proteasome inhibitors such as lactacystin and epoxomycin prevent clearance of mutant Htt in a conditional HD mouse model or cell models after its expression is stopped [31].

Other studies by confocal and immunoelectron microscopies find that ubiquitin-associating protein sequestosome-1/p62 colocalizes to Tau aggregates isolated from AD brain, along with an E3 ubiquitin ligase TNF receptor-associated factor 6 (TRAF6). Tau is a substrate of TRAF6, and p62 interacts with K63-polyubiquitinated tau through its ubiquitin-associated (UBA) domain and shuttles poly-ubiquitinated tau for proteasomal degradation [32].

Cooperation between Molecular Chaperones and the Ubiquitin-proteasome System in Neurodegenerative Diseases

Protein quality control is an integral process in eukaryotic cells. Molecular chaperones and UPS may not work alone all of the time; instead, they work cooperatively. For instance, molecular mechanisms underlying the sorting process rely on a cooperation of chaperone machineries and ubiquitin-chain recognition factors [33].

A function for chaperones in targeting misfolded proteins for degradation has been established in various ways. For example, overexpression of Hsp70 and Hsp40 increases the proteasome-mediated degradation of α-Syn and polyQ-expanded proteins [34]. The identification of E3 ligases and cochaperones that physically link chaperones to the UPS further supports the idea of direct communication between the folding and degradation machineries. A hallmark of these emerging families of modular proteins is the presence of a combination of chaperone-interacting domains and the domains that function in the UPS (Fig. 1).

Among the cofactors, CHIP is a well defined linker between chaperones and UPS. CHIP contains three chaperone-interacting tetratricopeptide repeat (TPR) domains at its N-terminus that confer binding to Hsp70 and Hsp90, and a U-box domain with E3/E4 ligase activity at the C-terminus [35]. The emerging role of CHIP in
Proteins associated with neurodegenerative diseases

Protein triage decision-making would imply that this unique ubiquitin ligase is intimately involved in the mechanism of Hsp-mediated degradation of mutant Htt and ataxins. CHIP associates with and ubiquitinates mutated forms of both Htt and ataxin-3 to prevent cytotoxicity [35]. When CHIP overexpression is accompanied by Hsp70 overexpression, removal of these mutants is further enhanced. In addition, CHIP is a component of Lewy bodies in human brains, where it colocalizes with α-Syn and Hsp70 [36]. In a cell culture model, endogenous CHIP colocalizes with α-Syn and Hsp70 in intracellular inclusions, and overexpression of CHIP inhibits α-Syn inclusion formation and reduces α-Syn level by its TPR domain [36]. Furthermore, α-Syn, Sph1 and Hsp70 all co-immunoprecipitate with CHIP, raising the possibility of a direct α-Syn-CHIP interaction.

Together with Hsp70, CHIP not only has a unique binding affinity for aberrant tau species, but is also responsible for its ubiquitination [37]. The isolated Tau protein from AD brain is poly-ubiquitinated at lysine residues within the microtubule-binding domain, the same region as the CHIP-binding region. The study from CHIP-knockout mice also indicates that CHIP is required to ubiquitinate aberrant phospho-tau species specifically and to target them for proteasomal degradation [38]. The fact that the TPR domain of CHIP is required for the effects on the morphology and number of inclusions, proteasomal degradation as well as direct interaction of CHIP with Hsp70 implicates a cooperation of CHIP and Hsp70 in the processes of disease development.

As an E3 ligase, parkin can also bind to and cooperate with CHIP and Hsp70, for overexpression of CHIP enhances the ubiquitin ligase activity of parkin towards the PD-associated receptor Pael-R [27]. As with CHIP, parkin also binds to polyQ-expanded Htt in vitro and localizes to Htt inclusions in the brains of HD patients [26]. Furthermore, overexpression of parkin in cultured cells increases the survival rate of these cells [26]. Conversely, BAG5 (Bcl-2-associated athanogene 5), an inhibitor of both parkin and Hsp70, accelerates neuronal degeneration in rat brains [39]. Parkin may also shuttle certain aggregation-prone substrates to the proteasome, because it interacts with the 26S proteasome, presumably via its UbL domain [26]. Thus, similar to CHIP, parkin may link Hsp70-bound substrates and the proteasome while it also acts as an E3 ligase.

The exact mechanism of the delivery of poly-ubiquitinated cargo to the 26S proteasome is not fully elucidated yet, but it is clear that proteins like Rad23, Dsk2 and P97/CDC48 are involved in escorting the poly-ubiquitinated proteins to the proteasome [40]. BAG1 is the first identified member of the BAG protein family, which consists of at least six different members in mammals to date [41]. The BAG domain of BAG1 isoforms can modulate the chaperone activity of Hsc70 and Hsp70 in the mammalian cytosol and nucleus. Remarkably, the BAG1 isoforms resemble the Rad23 protein, which possesses a similar UbL domain at its N-terminus and uses this domain to bind to the proteasome in a stable manner [42]. Following immunoprecipitation of BAG1 isoforms from HeLa cells, the C-8 subunit, a component of the 20S catalytic core of the proteolytic complex, and the S-1 subunit of the regulatory particle of the proteasome were found in association with the chaperone cofactor. The present research reveals a role of BAG1 as a physical link between the Hsc70/Hsp70 chaperone and the proteasome. In fact, targeting of BAG1 to the proteasome promotes an association of the chaperones with the proteolytic complex both in vitro and in vivo [43].

*Homo sapiens* DnaJ1 (HSJ1) protein, another cochaperone, has been identified as a neuronal shuttling factor for ubiquitinated proteins [44]. HSJ1 combines a J-domain that stimulates substrate loading onto the Hsp70 chaperone with ubiquitin-interacting motifs (UIMs)
involved in binding ubiquitinated chaperone clients. Additionally, HSJ1 prevents client aggregation, shields clients against chain trimming by ubiquitin hydrolase, and stimulates their sorting to the proteasome. In this way, HSJ1 isoforms participate in endoplasmic reticulum-associated degradation (ERAD) and protect neurons against cytotoxic protein aggregation. Overexpression of Hsp70, Hsp40, HSJ1a and HSJ1b significantly reduce protein inclusion formation in a model of X-linked spinal and bulbar muscular atrophy (SBMA) [45]. HSJ1a can also mediate a significant decrease in the number of inclusions formed in a primary neuronal model of protein aggregation. Studies on the mechanism underlying the reduction of these inclusions suggest that Hsp70 and Hsp40 increase chaperone-mediated refolding [46]. In contrast, expression of HSJ1 does not promote chaperone activity but cause an increase in ubiquitination. These findings clearly demonstrate that HSJ1 proteins mediate an increase in targeting protein degradation via the UPS.

**Perspectives**

The strong links between protein misfolding/aggregation and neurodegenerative diseases require a better understanding of the factors and mechanisms involved in protein quality control systems (Fig. 2). The chaperones promote folding/refolding of the misfolded proteins (such as Aβ, α-Syn and polyQ-expanded proteins) and reduce the aggregates formed by misfolded proteins, while the UPS components assist degradation of the misfolded proteins and eliminate the aggregates. Cooperation of chaperone machineries and UPS is accomplished by some special cofactors (such as CHIP, BAG1 and HSJ1). It is apparent that the molecular chaperones and the UPS components work coordinately to keep the cell in a stable and well-operated state. Identifying new factors linking chaperone bound substrates to proteasome degradation will help us understand more about the mechanism of molecular cooperation. Advances in the research of protein folding/misfolding and degradation in eukaryotic cells will shed light on the feasibility of clinical application of chaperones and UPS components in neurodegenerative diseases.

**Fig. 2 A sketch map of protein quality control in neurodegenerative diseases**  

Protein misfolding and aggregation are the major cause of some neurodegenerative diseases. A, Chaperones (such as Hsp70, Hsp40) promote folding/refolding of the misfolded proteins and reduce the aggregates formed by misfolded proteins. B, Ubiquitin proteasome system (UPS) components assist degradation of the misfolded proteins and reduces the aggregates. C, Cooperation of chaperone machineries and UPS is accomplished by some special cofactors [such as carboxyl terminus of Hsp70 interacting protein (CHIP), Bel-2-associated anathogenone 1 (BAG1) and Homo sapiens DnaJ1 (HSJ1)].

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Proteins associated with neurodegenerative diseases

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