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Ubiquitin-Proteasome System in Neurodegenerative Disorders

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Abstract

Cellular proteostasis is a highly dynamic process and is primarily carried out by the degradation tools of ubiquitin-proteasome system (UPS). Abnormalities in UPS function result in the accumulation of damaged or misfolded proteins which can form intra- and extracellular aggregated proteinaceous deposits leading to cellular dysfunction and/or death. Deposition of abnormal protein aggregates and the cellular inability to clear them have been implicated in the pathogenesis of a number of neurodegenerative disorders such as Alzheimer's and Parkinson's. Contrary to the upregulation of proteasome function in oncogenesis and the use of proteasome inhibition as a therapeutic strategy, activation of proteasome function would serve therapeutic objectives of treatment of neurodegenerative diseases. This review describes the current understanding of the role of the proteasome in neurodegenerative disorders and potential utility of proteasomal modulation therein.

Keywords: Ubiquitin-proteasome system; Neurodegenerative disorders; Proteasome modulators; Brain pathologies; Proteostasis

Introduction

The Ubiquitin-proteasome system (UPS) is the key intracellular molecular machinery for protein degradation and maintenance of protein homeostasis in eukaryotic cells. Although originally dismissed as a "garbage disposal" system, in the last two decades, UPS has been recognized as a central player in the regulation of essential cellular functions including cell cycle, cell differentiation, antigen processing, stress signaling, inflammatory responses, and apoptosis. UPS also exhibits important functions in normal brain development by controlling cell fate and specification [1]. Apparently, the presence of functional UPS components in both pre- and postsynaptic compartments of neurons is required for their proper function [2]. Alterations in UPS activity have been shown to induce pathological changes and abnormal brain function. Many brain pathologies, especially neurodegenerative diseases, are characterized by the accumulation of toxic levels of protein aggregates which challenges the proteostatic mechanisms to the point of collapse. Modulating UPS mechanisms has therefore emerged as a promising adjunct treatment strategy for diverse brain pathologies including brain cancer, neurodegeneration, brain-associated autoimmune disorders and inherited brain disorders associated with protein misfolding and toxic gain of functions [3-5]. During the last two decades many mechanisms that regulate the UPS have been unraveled, and depending on the disorder in question, both proteasome inhibition and activation present significant potential in pharmacotherapeutic development. As the general nature of UPS [6-8] and its participation in aging and cancer [9-13] have been widely reviewed in the published literature, this short review primarily covers the role of proteasome and investigational use of proteasome modulation in the therapy of neurodegenerative disorders.

The Ubiquitin-Proteasome System (UPS)

UPS is the primary degradation system in eukaryotic cells, which mediates the degradation of short-lived regulatory proteins and the removal of damaged soluble proteins [3]. It involves the implementation of two sequential steps: ubiquitination and proteolytic degradation of ubiquitinated proteins (Figure 1). The ubiquitination step covalently attaches an ubiquitin chain to the lysine residues in substrate proteins, which serves as a recognition signal for further processing of proteins by proteasome. The formation of an isopeptide bond between the ε-amino group of lysine residues and the carboxyl group of the C-terminal glycine of ubiquitin is an ATP-dependent process. It is achieved via a cascade involving three distinct classes of enzymes: ubiquitin-activating enzymes (E1), ubiquitin-conjugating enzymes (E2) and ubiquitin ligases (E3) [14]. An E1 enzyme mediates the ATP-dependent activation of ubiquitin. The activated ubiquitin is translocated to an E2-conjugating enzyme, followed by E3 ligase-mediated facilitation of ubiquitin transfer to a specific lysine residue to the target substrate [15]. In this process, the substrate specificity is achieved through the availability of a large number of different E3s that interact with specific target substrates [16]. To date, at least 35 E2s and over 600 E3s have been discovered to exist in mammalian cells, which suggests a system with a high degree of substrate specificity [17]. When a proper ubiquitin chain consisting of at least four ubiquitin moieties is assembled on a substrate protein, it becomes a subject for the proteasome wherein it is degraded into short peptides and amino acids which are recycled for new protein synthesis.

The Proteasome Assemblies

In its constitutive presentation, the proteasome is a mono-capped or bi-capped cylindrical structure housing the proteolytic active sites. The cylindrical core (also known as core particle 20S or CP) is formed by two different types of protein subunits, α and β, which are arranged in four stacked heptameric rings enclosing a central cavity. In eukaryotes, seven distinct α subunits are located in the two outer rings of the barrel, and seven distinct β subunits form the two inner rings

[18]. The β subunits face the interior cavity of the cylinder and house the active sites for proteolytic activity: β1 cleaves after acidic residues (caspase-like activity), β2 cleaves after basic residues (trypsin-like activity), and β5 cleaves after hydrophobic residues (chymotrypsin-like activity). Access to the active sites is regulated by a gate consisting of N-terminal protrusions of the α subunits [19,20].

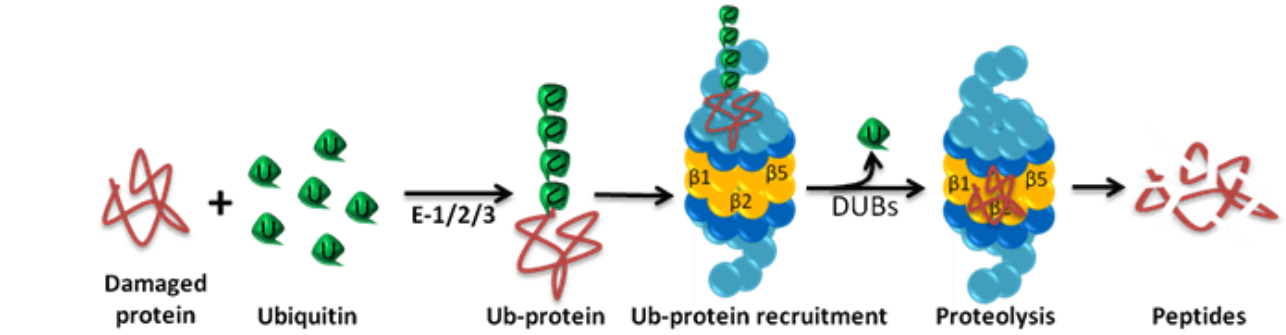

Figure 1: Ubiquitin-proteasome system (UPS). UPS involves ubiquitination and proteolytic degradation of ubiquitinated proteins. Ubiquitin is first attached to the target protein via a cascade involving three distinct enzymes: ubiquitin-activating enzymes (E1), ubiquitin-conjugating enzymes (E2), and ubiquitin ligases (E3). The ubiquitinated substrate is recognized, unfolded, and deubiquitinated by the 19S regulatory particle. The unfolded protein enters the 20S catalytic particle where it is degraded by the β1 (trypsin-like activity), β2 (caspase-like activity) and β5 (chymotrypsin-like activity) subunits.

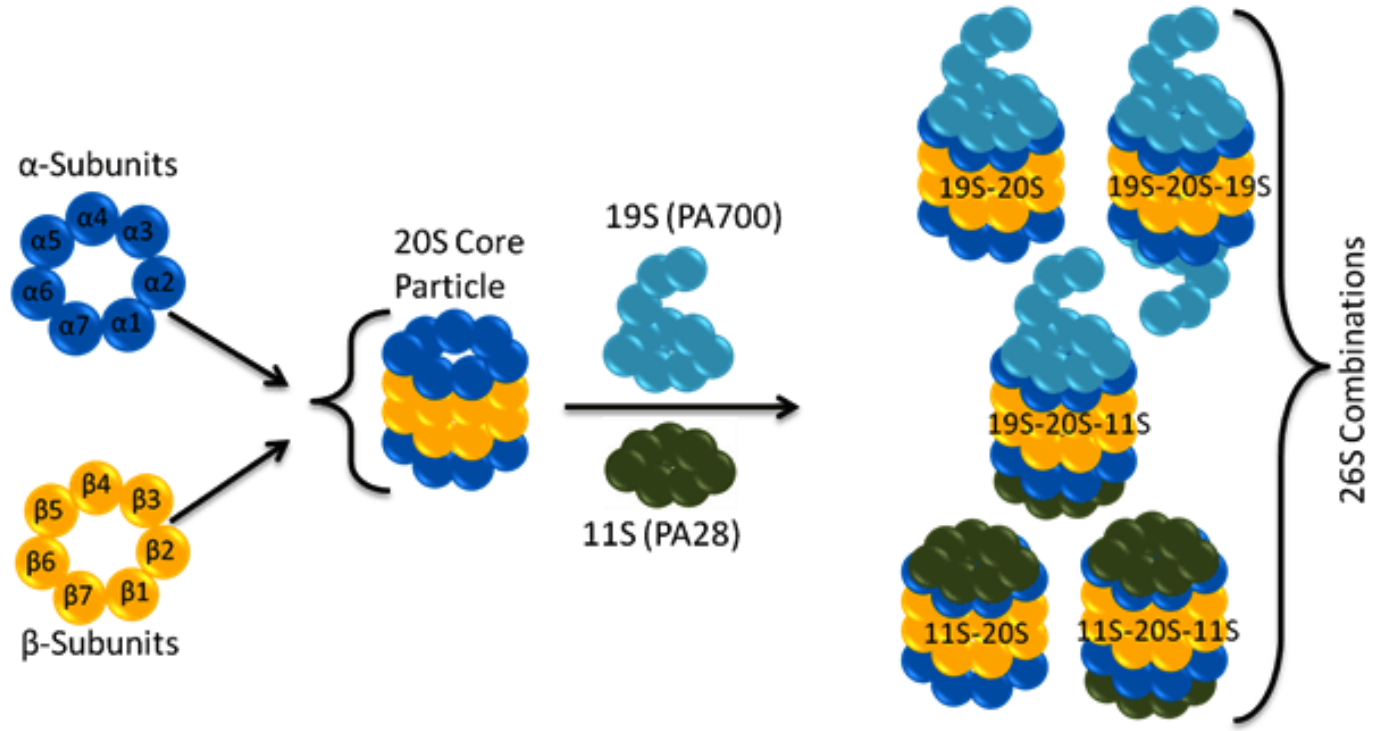

Figure 2: Various assemblies of proteasome. The proteasome is a mono-capped or bi-capped cylindrical structure. The cylindrical core (20S or CP) is formed by two different types of protein subunits, α and β, which are arranged in four stacked heptameric rings enclosing a central cavity. The proteasome core particle can be capped with 19S or 11S activator complexes (a third activator complex Blm10/PA200 is not shown).

The default status of the CP gate is closed. Thus, for substrate access and proteasomal degradation to occur, the N-termini need to be displaced from their axial position to reveal a continuous channel leading into the catalytic cavity. Modulation of the gate is a prerequisite for substrate entry into the proteolytic chamber and is mediated by proteasome activators. Several endogenous modulators have been described, including the regulatory particle (RP/19S/PA700), activator of the PA28 protein family (11S) and Blm10/PA200

activator [21]. As shown in Figure 2, these regulator assemblies cap the two ends of CP and modify the function of constitutively active 20S CP.

The dominant partner of 20S CP in the assembly of 26S proteasome is RP/19S/PA700, which can connect to one or both ends of the core by binding to the terminal α-rings of the 20S cylinder. It is composed of 19 integral subunits that form two biochemically separable sub-complexes, the lid and base [22]. The base subcomplex is situated proximal to the CP gate region. It contains six homologous ATPases (Regulatory particle triphosphatase proteins (Rpt) 1–6), which form a hexameric ring. They belong to the family of ATPases associated with diverse cellular activities (AAA). The lid, on the other hand, consists of nine non-ATPase subunits [3]. When the 20S core is bound by two 19S modules (19S–20S–19S proteasome complex), the assembly is categorized as the classic 26S proteasome. The 19S ATP-dependent proteasome activator (PA700) recognizes the ubiquitinated protein substrates for deubiquitination, unfolding, and threading them into the catalytic chamber of the proteasome in an ATP- and ubiquitin-dependent manner [23].

Like the 19S regulator, the 11S regulator (PA28 complex) also activates the 20S proteasome by binding to the α-rings of the 20S proteasome, but its function is ATP-independent [24]. PA28 responds to stress by increased expression [25]. It is expressed as PA28α, PA28β, and PA28γ isoforms, the exact functions of which are not clearly understood [25]. PA28α and PA28β have been shown to form hetero-heptameric rings in cytosol [26,27], while PA28γ forms homo-heptameric rings and is found in the nuclei of vertebrates as well as invertebrates [26,27].

Both PA28α and PA28β units are inducible by interferon-γ, which suggests a potential role of PA28α/β in major histocompatibility complex (MHC) Class I-mediated antigen presentation [28]. They are also expressed in organs involved in non-immune functions. In eukaryotic cells, PA28α/β can generate hybrid 26S proteasomes with enhanced proteolytic efficiency [29]. It can also facilitate heat shock protein (HSP) 90-mediated protein refolding [30]. The role of PA28γ is not entirely clear, but the mice deficient in PA28γ exhibit reduced body-size, and embryonic fibroblasts derived from these mice shows cell cycle defects [31]. It is thought that 11S–20S–11S complex can only degrade simple unstructured proteins, whereas 19S–20S–11S and 19S–20S–19S complexes can hydrolyze large complex proteins [29].

The Blm10/PA200 family can also form pure or hybrid complexes in which Blm10/PA200 binds to one end and the 19S to the other end of the CP cylinder [32,33]. It is conserved from yeast to humans and is populated by monomeric proteins of ~ 250 kDa. Blm10 binds to the proteasome during the late phases of CP assembly and contributes to the final maturation of CP complexes [34,35]. One physiological target for Blm10–proteasome complexes is the transcription factor split finger protein 1 (Sfp1), which regulates ribosomal protein genes [36]. Additional studies suggest a potential role for Blm10 in mitochondrial homeostasis [37,38]. Furthermore, it may be an important participant in DNA or oxidative damage repair processes and chromosome stability [32,39,40], most likely through ATP- and ubiquitin-independent degradation of acetylated histones in somatic cells [41].

Immunoproteasome and thymoproteasome

In addition to the constitutive proteasome assemblies discussed above, adaptive processes can induce the cells to express alternative proteasomal phenotypes. The immunoproteasome and thymoproteasome are the two known alternative proteasome forms. Their expression is primarily regulated by the prevailing cytokine environment [42-45]. In the immunoproteasome, β1, β2, and β5 subunits are replaced by LMP2 (low-molecular mass polypeptide 2, also known as β1i), MECL-1 (multicatalytic endopeptidase complex-like-1, β2i), and LMP7 (β5i). LMP7 and MECL-1 immuno-subunits display essentially the same cleavage specificity as their constitutive counterparts, but LMP2 shows more chymotrypsin-like activity than the caspase-like activity of β1 [46]. Recent studies have suggested a role of the immunoproteasome in inflammation [47], tumor development [48], lipid metabolism [49] and NF-κB signaling [50]. Constitutive proteasome and immunoproteasome usually coexist in cells, but the ratio between the two isoforms varies on the basis of cell type and environment [51]. The reports suggest that the triggering factor for the conversion of constitutive proteasome into immunoproteasome is interferon-γ [52-54], and the immunoproteasome is assembled four times faster than the constitutive proteasome, but exhibits greatly reduced stability [55,56]. Unlike the ubiquitous expression of immunoproteasome, thymoproteasome is exclusively present in the thymus [57]. Thymoproteasome contains the β1i and β2i immune-subunits as well as a thymic proteasome subunit β5t (also known as proteasome subunit beta type-11 or PSMB11). The incorporation of β5t results in the reduction of the chymotrypsin-like activity of the proteasome [57], and its expression is essential for positive selection of T cells in the thymus [58].

UPS dysfunction in Neurodegenerative disorders

The high metabolic activity in the brain makes intracellular neuronal content particularly vulnerable to oxidative damage. Apart from the recently discovered glymphatic system [59], the brain's only known method for disposal is to break down and recycle the proteins within individual cells. The glymphatic system is a paravascular transport system that allows for cerebrospinal fluid (CSF) and interstitial fluid (ISF) exchange, facilitating the efficient clearance of solutes and waste from the brain [60]. On the other hand, as the primary proteolytic complex responsible for the elimination of damaged and misfolded intracellular proteins, UPS plays an important role in preventing accumulation of proteinaceous trash in brain cells. Given the importance of housekeeping function delivered by UPS, its potential impact on several neuronal dysfunctions is significant. Both the constitutive and immunoproteasome participate in normal neuronal physiology [61-63], and their aberration is linked to various brain pathologies (Figure 3). Evidence suggests that a unifying characteristic of several neurodegenerative disorders is the inability of cells to dispose of aggregated and misfolded proteins. In the text below, we briefly discuss the identified role of UPS in various neurodegenerative disorders.

Alzheimer's disease (AD): AD is characterized by dementia and loss of cognitive function, resulting in memory impairment, personality changes, psychosis, and language disturbances [3]. The progressive intellectual decline in AD patients is accompanied by an increase in the deposition of protein aggregates that eventually form intracellular neurofibrillary tangles (NFT) and extracellular senile/amyloid plaques [64]. The chronic neuroinflammation observed in the brain samples from AD patients has been found to be associated with increased immunoproteasome (LMP2) expression [63].

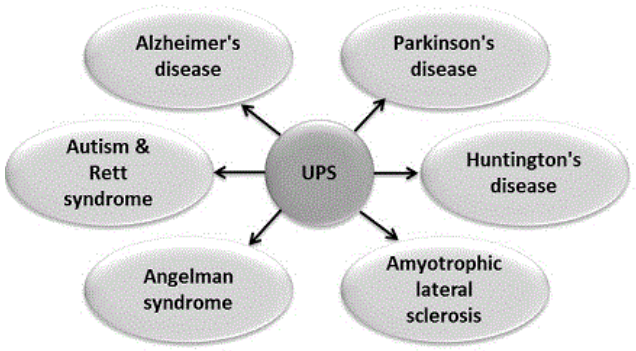

Figure 3: UPS dysregulation in neurodegenerative disorders. Almost all neurodisorders of contemporary interest are characterized by imbalanced UPS function, indicating the possible role of modulators of UPS as adjunct therapy.

Reports suggest that UPS may be involved in the degradation of amyloid precursor protein (APP) via the endoplasmic reticulum-associated degradation (ERAD) arm of the UPS [65]. Amyloid-β also interacts with the molecular pathways that regulate the phosphorylation of microtubule-associated tau protein which is the second major protein associated with AD plaques [66]. It increases the expression of the regulator for the calcineurin gene (RCAN1), which inhibits tau dephosphorylation by a serine-threonine phosphatase calcineurin [67]. Hyperphosphorylation of tau disrupts its normal function and results in the accumulation of neurofibrillary tangles. The fibrillar tau co-precipitates with the proteasome, and proteasome activity is significantly reduced in AD patients, as compared to age-matched controls [68]. Amyloid-β aggregates have also been shown to block the UPS function [69]. The degradation of tau can be accelerated by proteasome activator Blm10 [37], as well as by inhibiting the proteasome-associated deubiquitinating enzyme Usp14 [70].

Parkinson's disease (PD): Parkinson's disease is a chronic progressive neurodegenerative disorder, clinically characterized by resting tremor, rigidity, and bradykinesia, as well as cognitive deficit and autonomic dysfunction [71]. The role of UPS in PD was first revealed by the discovery of E3 ligase activity of parkin and mutation in parkin gene [72,73]. Parkin mutations account for up to 77% of the familial cases with an age of onset <30 yr [74], and for 10%–20% of early-onset PD (EOPD) patients [75]. Parkin, a 53 kDa protein, is normally expressed diffusely in neurons throughout the brain [76], but is absent in the brain of patients with autosomal recessive juvenile parkinsonism [77]. Mutant parkin fails to effectively function as a ligase, resulting in toxic accumulation of its substrates, such as cell division control-related protein (CDCrel-1) and parkin-associated endothelial-like receptor (Pael-R). CDCrel-1 is a septin protein that regulates synaptic vesicle release and is found to be toxic to dopaminergic neurons [78]. Pael-R, on other hand, accumulates in Lewy bodies [79] which are eosinophilic intracytoplasmic inclusions present in dopaminergic neurons of the substantia nigra in the brains of PD patients.

Parkin itself has been found to be a component of Lewy bodies [80], but the major structural protein associated with Lewy bodies is a 14.5 kDa protein called α-synuclein,. Based on the reports that depletion of the proteasome subunit Rpt2 results in accumulation of α-synuclein and the development of Lewy body-like inclusions in mice [81-83], α-synuclein is identified as a substrate for the 26S proteasome. However, α-synuclein monomers could also be degraded by 20S core particle without prior ubiquitination and in the absence of 19S RP [84]. The aggregates of misfolded α-synuclein perpetuate the UPS defect by interacting with the regulatory 19S unit and inhibiting the function of the 26S proteasome [85]. More evidence supporting the role of UPS-mediated α-synuclein degradation in the genesis of PD comes from a recent mice study where proteasomal inhibition in the nigrostriatal pathway by lactacystin resulted in partial dopaminergic cell loss and concurrent striatal dopamine depletion, accompanied by increased expression of Ser129-phosphorylated α-synuclein [86]. It is important to note that α-synuclein is also affected at the genetic level in PD, characterized by mutations, as well as duplication or triplication of the synuclein gene [87,88]. Furthermore, the role of chaperone-mediated autophagy (CMA) and macroautophagy in the degradation of α-synuclein is also critical [89] and two familial mutations (A30P and A53T) of α-synuclein have been found to impair CMA degradation [90]. Another implication of the UPS in PD comes from the observation associating PD with a mis-sense mutation (I93M) in a deubiquitinase enzyme, ubiquitin carboxyl-terminal hydrolase L1 (UCHL1), which decreases its deubiquitinating activity [91,92]. Several other instances of familial PD being associated with genetic defects in UPS have been discussed elsewhere in greater detail [6,93-95].

Huntington's disease (HD): HD is an autosomal dominant disease, which is characterized by motor dysfunction, cognitive decline, and psychosis. The disease is caused by an expansion of a CAG (cytosine-adenine-guanine) triplet repeat region in huntingtin (Htt) gene through out-of-register recombination between repeat elements. The result is an expansion of a poly-glutamine (poly Q) stretch in the N-terminal domain of the Htt protein [96]. At the structural level, such an expansion (more than 40 glutamines repeats) results in fibril formation and aggregation [97,98].

Although proteasome activity is reduced in HD brains [99], the origin of proteasome dysfunction remains unclear. Studies have shown that proteasomes are sequestered in Htt inclusion bodies, which results in an overall reduction in UPS function [100]. In a striatal cell culture model of HD, the chymotrypsin-like and caspase-like activity were found to be reduced, while the trypsin-like activity was markedly enhanced [101]. These changes in enzyme activities were associated with reduction in the ability to recognize and degrade ubiquitinated substrates [101]. In HD94 conditional mouse model of HD as well as in the post-mortem brain of HD patients, Díaz-Hernández et al observed an induction of immunoproteasome subunits (LMP2 and LMP7) [61]. Despite an incomplete understanding of the role of proteasome in HD, evidence is accumulating to suggest that enhancement of proteasome activity may be beneficial in cells challenged by polyQ-Htt, since upregulation of PA28γ transcription improved cell survival in a cellular HD model [102].

Amyotrophic lateral sclerosis (ALS): ALS is a progressive neurodegenerative disorder affecting motor neurons. Ubiquitinated inclusion bodies are found within the motor-neurons in both familial and sporadic forms of the disease, suggesting that UPS dysfunction is a possible contributor to the genesis of ALS [3]. Accordingly, mice with a conditional knockout of proteasome subunit Rpt3 in motor neurons exhibited ALS-like pathology, particularly the accumulation of protein aggregates with signature components of ALS inclusion bodies, such as the transactive response (TAR)DNA-binding protein 43 (TDP-43) and fused in sarcoma (FUS) RNA-binding protein [103]. Induction of

immunoproteasome subunits (LMP2, MECL-1, and LMP7) has been observed in ALS [104], and pyrrolidine dithiocarbamate treatment, which completely blocked the induction of immunoproteasome expression, led to decreased survival in the mutant superoxide dismutase 1 (SOD1-G93A) rat model of ALS [105]. These results suggest that induction of immunoproteasome may help the nervous system to cope with ALS caused by SOD1 mutation.

Disorders associated with mutation or loss of function of proteasomal gene

Angelman syndrome (AS), Rett syndrome (RS), and autism are neurodegenerative disorders, where UPS dysfunction has been implicated. AS is a neurodevelopmental disorder whose main features are intellectual disability, lack of speech, seizures, and a behavioral profile characterized by a happy demeanor, easily provoked laughter, short attention span, hypermotoric behavior, mouthing of objects, sleep disturbance, and an affinity for water [107]. RS is an X-linked dominant disorder predominantly affecting females, which is classified as an autism spectrum disorder (ASD). Clinically, it is characterized by psychomotor regression with loss of volitional hand use and spoken language, the development of repetitive hand stereotypes, and gait impairment. Classical autism, on the other hand, is marked by distinct impaired social interaction. It is suggested that these diseases are associated with loss of function of the ubiquitin protein ligase UBE3A, also known as E6AP ubiquitin-protein ligase (E6AP) [106, 107], and the disease manifestation appears to be associated with the severity of UBE3A loss [108]. For instance, the occurrence of autism has been correlated with significantly dysregulated ubiquitin protein ligase E3A gene in the isodicentric chromosome 15 (Idic15) of autistic subjects [109-111]. The UBE3A gene product, E6-AP, has been shown to function both as an E3 ligase in the ubiquitin proteasome pathway and as a transcriptional co-activator. Thus, induction of UBE3A may provide a therapeutic means to treat autism and similar disorders. The proteasome system also plays a role in controlling mutated neuroligins and cholinesterases in ASD [112,113].

Recently, the potential role of γ -aminobutyric acid (GABAA) receptors in the development of autism has been suggested [114], mostly because of the co-morbid association between autism and epilepsy and GABAergic mechanisms responsible for epilepsy [115,116]. GABAA-mediated neurotransmission is known to play a crucial role in synaptic tuning and neuronal wiring in pre and early postnatal days [117]. In a recent study on postmortem middle frontal gyrus tissues from ASD patients, Crider et al. found a significant decrease in GABAAα1 protein accompanied by an increased expression of synovial apoptosis inhibitor 1 (SYVN1), an endoplasmic reticulum (ER)-associated degradation (ERAD) E3 ubiquitin ligase [118]. In a simulated in vitro cortical neuron culture model, the authors collected evidence of polyubiquitination and proteasomal degradation of GABAAα1, a phenomenon which was inhbited by proteasome inhibitor MG132 and SYVN1 siRNA [118].

Drug	Classification	Target pathology
PSI (Z-Ile-Glu(OtBu)-Ala-Leu-al)	Reversible β5 inhibitor	PD [**132**] AD [**133**]
Epoxomicin	Irreversible β5=β2> β1 inhibitor	PD [**134**]
		HD [**135**]
Lactacystin/Clasto-lactacystin β-lactone	Irreversible β5=β2= β1 inhibitor	PD [**2**] AD [**136**] HD [**137**], ALS [**138-141**] Autism [**109**, **118**]
MG101 or ALLN (N-acetyl-Leu-Leu-Norleu-al)	Reversible β5 inhibitor	PD [**142**] AD [**143**]
MG115 (Z-Leu-Leu-Nva-al)	Reversible β5 and β1 inhibitor	PD and AD [**144**]
MG132 (Z-Leu-Leu-Leu-al)	Covalently binds to the active site of the β subunits	PD [**142**] ALS [**145**] Autism [**109**, **118**] AD [**133**, **136**]
MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine hydrochloride)	Mitochondrial Complex I inhibitor	PD [**144**, **146**]
PDTC (Pyrrolidine dithiocarbamate)	NF-κB inhibitor, antioxidant, immunoproteasome inhibitor	ALS [**105**]
Clioquinol	20S inhibitor (Cu-mediated interaction)	HD [**147**]
Cyclosporin A	Non-competitive β5 inhibitor	PD [**148**, **149**]

Paraquat (pesticide)	20S inhibitor	PD [**124**, **150**, **151**]
Betulinic acid	β5 activator	Autism [**118**]
Benzamil	Inhibition of acid-sensing ion channels (ASIC1a)	HD [**126**]

Table 1: Proteasome modulators in neurodegenerative disorders. Proteasome inhibitors (unshaded rows) have been mostly employed to create models of neurodegenerative diseases, whereas proteasome activators (shaded rows) have been tested for therapeutic application in neurodegeneration.

UPS as a Target in Neurodegenerative Diseases

The prevailing views on proteasome function have changed radically over the last two decades. It appears that the regulation of proteasomal levels and activity at various steps including its assembly, localization, and function is highly complex, which might serve to fine-tune proteasome function to specific cellular environments and demands. Although we still do not know whether the proteasomal defects in brain pathologies are the primary cause or are secondary to an alternate etiology such as mitochondrial damage, ER stress or oxidative stress [119-125], modulation of proteasome function as a therapeutic strategy in neurodegenerative disorders is beginning to gain momentum. Some of the investigational drugs in this respect are listed in Table 1.

It must be noted, however, that neurodegenerative disorders are caused by UPS downregulation, and only few instances appear in the literature where the therapeutic induction of UPS has been tested. For example, betulinic acid, a proteasome activator, may have therapeutic implications in ASD which has been found to be associated with enhanced GABAergic activity. Betulinic acid has been shown to significantly suppress the induction of GABAAα1 protein levels in an ASD model of cortical neurons [118]. Benzamil is another example of a proteasome activator with the potential to act against neurodegenerative diseases (Table 1) [126]. Most of the examples of UPS modulators enlisted in Table 1 are proteasome inhibitors which have been employed to create in vivo and in vitro models of neurodegenerative disorders. Regardless, as our understanding of the various players involved in the UPS, in particular, the ligases and deubiquitinases which are known to be directly involved in various brain pathologies, becomes clearer, therapeutic strategies to upregulate UPS function will evolve. Nevertheless, it is well recognized that maintaining steady-state levels of proteasome composition and function is important for the maintenance of proteostasis in neuronal cells which depend heavily on balanced UPS functioning. As discussed above, proteostatic imbalances are common among neurodegenerative diseases leading to increased damage to the cellular protein pool, intracellular protein aggregation, and reduced proteasome activity. Therefore, pharmacotherapeutic strategies aimed at modulating the proteasome system might prove beneficial for neurodegenerative disease treatment. The discovery of small molecule inhibitors of deubiquitinating ubiquitin-specific proteases (USP) and other deubiquitinating enzymes will provide more specific targets than the 20S inhibitors presently available. Moreover, many neurodegenerative cytoplasmic inclusions can also be cleared by autophagy, and upregulation of autophagy has also been proposed as a general treatment for Parkinson's disease, polyglutamine repeat disorders, and tauopathies [127]. It is noteworthy that impairment of the UPS results in upregulation of autophagy [128,129] and in some cases, this upregulation can compensate for diminished UPS function [128,130].

In pathologies where the UPS components are mutated, as in autosomal recessive forms of Parkinson's and Angelman disease, gene therapy to replace the loss of E3 ligase activity may be possible in the future. Furthermore, it has been demonstrated that overexpression of UBE3A protects against the toxicity of polyglutamine repeat proteins in models of Huntington's disease and spinocerebellar ataxia [131]. In another interesting study, anti-acidosis drug benzamil was found to enhance UPS activity and decrease mutant huntingtin aggregation in the brains of a mouse model of Huntington's disease [126].

Conclusion

Although the interest in investigating the potential utility of proteasome modulation is increasing, current applications are limited by an incomplete understanding of the various players involved in the UPS, in particular the ligases and deubiquitinases which have been directly implicated in various brain pathologies. The future research will allow revelation of more specific targets and may provide potential insight for the treatment of neurodegenerative disorders. However, the eventual therapeutic targeting of UPS in neurodegenerative diseases will solely depend on the discovery and development of specific activators of the proteasome system.

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