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The role of the ubiquitin proteasome system in synapse remodeling and neurodegenerative diseases

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Summary

The ubiquitin proteasome system is a potent regulatory mechanism used to control protein stability in numerous cellular processes, including neural development. Many neurodegenerative diseases are featured by the accumulation of UPS-associated proteins, suggesting the UPS dysfunction may be crucial for pathogenesis. Recent experiments have highlighted the UPS as a key player during synaptic development. Here we summarize recent discoveries centered on the role of the UPS in synapse remodeling and draw attention to the potential link between the synaptic UPS dysfunction and the pathology of neurodegenerative diseases.

Introduction

Ubiquitin-mediated protein degradation, also known as the ubiquitin proteasome system (UPS), is an evolutionally conserved and tightly regulated biochemical pathway. It participates in essentially every cellular process. Recent work has begun to elucidate the role of the UPS in the development of the nervous system.(1) Neurons are polarized cells that transmit electric signals from one cell to another with high spatial precision and speed. Synapses are specialized intercellular junctions between neurons or between neurons and non-neuronal target cells where signals are propagated. Mounting data demonstrates that the UPS functions locally at neuronal synapses and serves as a potent regulatory element that shapes synapse structure and function.(2-4)

Aberrations in the UPS have been implicated, either as a primary cause or secondary consequences in the pathological conditions of the nervous system. Examples include neurodegenerative diseases, such as Parkinson's, Alzheimer's, Huntington's and Prion diseases as well as amyotrophic lateral sclerosis.(5) The early symptoms of some of these neuronal disorders are characterized by synaptic dysfunction.(6) Here we summarize recent studies that have defined the important roles of ubiquitination in synapse remodeling and observations that link the synaptic UPS to neuropathology.

The ubiquitin proteasome system

Numerous proteins are targeted for degradation through the UPS pathway. It can be divided into two successive steps: (1) a chain of a highly conserved 76-residue molecule, ubiquitin,

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is covalently attached to the target protein and (2) the polyubiquitin-tagged protein is degraded by a large protease complex, the 26S proteasome. While the polyubiquitinated substrate is cleaved to short peptides, the free and reusable ubiquitin is released via the activity of deubiquitination enzymes.

Conjugating of ubiquitin to the protein substrate is composed of three steps. The first step is activation of ubiquitin: the ubiquitin-activating enzyme, E1, utilizes the energy of ATP hydrolysis to activate ubiquitin during which the C-terminal glycine residue of ubiquitin binds to the active-site cystine of an E1 with a thioester covalent bond. In mammals, there are only two E1 enzymes, which are created from alternative translational sites encoded by a single gene.[7-9] Next, the activated ubiquitin is transferred to the E2 ubiquitin-conjugating enzyme via formation of another thioester bond with G76 of ubiquitin. Over 30 E2 enzymes have been found in mammals and they are characterized by a conserved ubiquitin-conjugating (UBC) domain and a conserved catalytic cysteine residue.[10] In the third step, E3 ubiquitin ligases accept ubiquitin molecules from E2 enzymes and catalyze their addition to lysine residues of target proteins. It appears that ubiquitination specificity is determined mainly by the large variety of E3 ligases.

Two major classes of E3 ubiquitin ligases are recognized: HECT (homologous to E6-AP carboxyl terminus) domain and RING (really interesting new gene) domain. Approximately 50 different HECT E3s exist in humans.[11,12] There are hundreds of RING-domain E3s, making it the largest family of ubiquitin ligases. The RING class is further subdivided into those that function as single proteins, such as Parkin, and those that function in multisubunits complexes. One well-known example of a multisubunit RING E3 ligase is the SCF (Skp1–Cullin–F-box) complex, which is composed of the Skp1 linker, the Cullin scaffold, the RING domain containing molecule, and one of a suite of F-box proteins that serve as substrate recognition components.[13,14]

Degradation of polyubiquitinated proteins is carried out by the 26S proteasome. It is noteworthy that ubiquitination is highly dynamic and reversible: polyubiquitin chain can be removed or its length can be modulated by deubiquitinating enzymes (DUBs).[15] Recent studies also indicate that modification of receptors and transporters by ubiquitin conjugating can function as a recognition signal for the endocytosis and intracellular trafficking of various membrane proteins. Several recent reviews have focused on the proteasome-independent functions of ubiquitin.[16-18]

UPS regulates synapse development and remodeling

Synapse formation

The first causal links between UPS and synapse formation came from the genetic studies in *C. elegans* and *Drosophila. rpm-1*, a mutant compromised in the function of a RING domain ubiquitin ligase, causes disorganized presynaptic cytoarchitecture and axonal morphology.[19-21] The F-box protein, FSN-1, physically interacts with RPM-1 and functions in an SCF complex, which is composed of *C. elegans* homologues of SKP1 and Cullin at presynaptic region.[22] Liao and colleagues also showed that ALK is a direct binding partner of FSN-1. The expanded protein distribution and increased protein levels of ALK in both *fsn-1* and *rpm-1* mutants are consistent with the hypothesis that ALK is the FSN-1 target.[22] Subsequent studies in *C. elegans* showed that RPM-1 functioned through another route: negative regulation of the P38 MAPK (mitogen-activated protein kinase) signaling pathway.[23,24] Mutation on DLK-1, the closest homolog of MAPKKK, strongly suppresses *rpm-1* phenotype. In addition, overexpression of MAPKK, MKK-4 or other downstream components creates synaptic phenotype identical to *rpm-1*. However, since the

loss-of-function mutations of these kinases have very subtle effect on synaptic development, it is likely that other redundant pathways also exist.[23,24]

highwire (*hiw*), a mutant of the RPM-1 homologue, was isolated based on its morphological and signaling defects at neuromuscular junction (NMJ) synapses in *Drosophila*. Disruption of *hiw* locus, particularly the loss of the Highwire RING domain, causes synaptic overgrowth with extensive branching and an expanded number of presynaptic boutons.[20,24,25] Recently, a forward genetic screen identified Wallenda, a MAPKKK homologous to the *C. elegans* DLK, as a target for Highwire, suggesting that the UPS regulation of a MAPK pathway on synaptic growth is highly conserved.[24] Furthermore, Wu and colleagues recently demonstrated that the *Drosophila* homolog of FSN-1, DFsn, collaborates with Highwire to restrain synaptic terminal growth by down-regulating the same target, the Wallenda/DLK kinase.[26] Interestingly, the gain of function of *fat facets* (*faf*), a deubiquitinating enzyme, imitates *hiw* mutants and the loss-of-function *faf* genetically suppresses the overgrowth pheno-type in the *hiw* mutants. These data support the notion that a proper balance of ubiquitination and deubiquitination is critical for appropriate synapse formation.[27-29] In zebrafish and mice, mutations in the orthologue of RPM-1/ Highwire, lead to defects on other aspects of neuronal development, including fasciculation, axonal growth and path finding, demonstrating that the E3 ubiquitin ligase RPM-1/Highwire could also control the long-range guidance of axons to reach synaptic targets.[30-32] Interestingly, the study by Lewcock and colleagues shows that Phr1 negatively regulates the same MAP kinase signaling by defining a DLK-deficient zone to promote the stability of microtubules during neurite polarity maintenance.[32] How this elegant apparatus relates to synapse formation has yet to be elucidated.

Another multimeric E3 ubiquitin ligase, APC (Anaphase Promoting Complex), has also been implicated to modulate synapse formation.[33] At the *Drosophila* NMJ, APC localizes to presynaptic terminals and the loss of function of the APC subunit in motor neurons results in overgrowth of synaptic boutons. This overgrowth phenotype requires Liprin-α,[33] the presynaptic scaffold protein.[34-36] Furthermore, Liprin-α contains multiple conserved APC destruction box motifs and immunoprecipitation experiments show that Liprin-α is ubiquitinated in vivo.[33] Taken together, these findings support the hypothesis that the APC may regulate synapse development by degrading Liprin-α.

At the mammalian NMJ, the formation of synapses require a complex signaling cascades, including agrin, a proteoglycan derived from presynaptic terminal, and MuSK (MUscle-Specific receptor tyrosine Kinase), a key organizer of post-synaptic components.[37-39] Lu and colleagues recently identified PDZRN3, a PDZ domain containing Ring ubiquitin ligase, as a MuSK-binding partner. PDZRN3 proteins are concentrated at postsynapses and able to promote MuSK ubiquitination in transfected COS-7 cells. Furthermore, over-expressing PDZRN3 suppresses the agrin-induced AChRs clustering and the lack of Ring domain abolishes this suppression effect, suggesting that the E3 ligase activity of PDZRN3 is important for postsynaptic development.[40]

Synapse elimination

The overall architecture of the nervous system is shaped by the formation of synapse at appropriate sites as well as by the removal of excess connections from inappropriate sites. Recent studies revealed that specific synapse elimination can be achieved through local control of protein degradation.[41] In *C. elegans*, an egg-laying motor neuron, HSNL, connects to its targets via a cluster of synapses localized exclusively near the vulval region, the primary synapse region (PSR). At early stages of development, synapses also form in the region adjacent to vulval area, the secondary synapse region (SSR), but these synapses are eliminated before adulthood. However, in *syg-1* mutant animals, synapses at the SSR fail to

be removed. *syg-1* has been shown to encode a immunoglobulin protein and is localized to the PSR specifically.[41,42] Through a yeast two-hybrid screen, we have identified SKR-1 (Skp1 homologue in *C. elegans*) as an SYG-1-binding partner. RNAi knockdown of either SKR-1, Cullin or a mutation in the F-box protein, SEL-10, causes synapse elimination defect for the SSR synapses. Furthermore, inhibition of proteasome activity results in the failure of synapse removal, suggesting that the SCF-complex-mediated protein degradation is required for synapse elimination. SYG-1 inhibits the binding of SEL-10 with SKR-1 in vitro; therefore SYG-1 protects synapses at the PSR through its inhibition on the SCF complex assembly. This inhibition by SYG-1 ensures that synapses are stabilized at appropriate sites and removed from inappropriate sites. This model is consistent with genetics data showing that primary synapses are unstable in animals lacking SYG-1 and that the SCF complex also functions in synapse elimination at the PSR.[41] Although additional information about the mechanism is needed to build a detailed biochemical model, these data support an intriguing hypothesis that synapse-specific stabilization and elimination can be achieved through tight spatial and temporal regulation of E3 ligase activity.

While HSN synapses are eliminated without changes in axon morphology, synapse elimination often involves the pruning of axons and dendrites in other systems. In *Drosophila*, axon pruning in the mushroom body requires the activity of the UPS.[43] While developmental axon pruning in normal animals differs from the injury-induced Wallerian degeneration in their dependence on Wlds, recent studies have shown that the UPS plays a critical role in both processes.[43-45] Through a candidate screen in *Drosophila*, Kuo and colleagues uncovered a mutation in the E2 ubiquitin-conjugating enzyme mutation in *ubcD1* that causes dendritic pruning defects.[46,47] Additional experiments reveal that UbcD1 is likely to degrade the ubiquitin ligase DIAP1 (*Drosophila* inhibitor of apoptosis protein 1). Degradation of DIAP1 leads to local activation of Dronc caspases, thus allowing the cleavage of larval dendrites while preserving neurons.[46,47] This work not only identifies a set of E2/E3 enzymes that regulate neuronal process remodeling, it also provides a mechanistic link between the UPS and the apoptotic machinery.

UPS regulates synaptic function

Presynaptic function

Synaptic transmission is initiated when an action potential induces the opening of the Ca^{2+} channel, and the Ca^{2+} flow triggers synaptic vesicle exocytosis. During exocytosis, neurotransmitter-filled vesicles dock with the plasma membrane, where they undergo a priming process. A calcium signal then triggers vesicle fusion with the plasma membrane and neurotransmitters are released into the synaptic cleft. Discharged neurotransmitters activate postsynaptic receptors, thus signaling can be transmitted to downstream target cells.[48] In the last few years, the emerging role of UPS in the regulation of synaptic transmission has been revealed.[49] In biochemically isolated synaptosomes, acute depolarization causes a global decrease in ubiquitin-conjugated proteins, suggestive of a rapid turnover rate protein ubiquitination at the presynaptic terminal.[50]

How does the ubiquitination of individual proteins affect presynaptic function? Interestingly, several studies show that proteins that are involved in the synaptic vesicle cycle are modified by the UPS system. Inhibition of the proteasome activity increases the abundance of the synaptic vesicle-priming protein DUNC-13[51] and leads to a strengthening of neurotransmission. UNC-13 is ubiquitinated and accumulates at the presynaptic terminal after proteasome inhibition, suggesting that UNC-13 may serve as one of the primary targets for this UPS-mediated regulation.[49,52] The t-SNARE in the synaptic vesicle cycle, Syntaxin-1 can be ubiquitinated by the Ring-finger E3 ligases Staring.[53] Siah-1 and Siah-2 are both Ring-finger ligases that bind to a synaptic vesicle protein, synaptophysin and

promote its ubiquitination and degradation.[54] However, how regulation of these synaptic vesicle proteins by UPS affects synaptic transmission has not been determined.

In a more-recent study, Yao and colleagues provided compelling arguments that the active zone component RIM1 was regulated by ubiquitination and this regulation can be utilized to modulate synaptic transmission.[55] RIM1 binds to multiple presynaptic components, including UNC-13 and Liprin-α, and regulates synaptic transmission.[56] Yao et al. showed that the amount of RIM1 is tightly controlled by a new E3 ligase F-box protein, SCRAPPER, which is localized on the presynaptic membrane and binds to and ubiquitinates RIM1. In a SCRAPPER knockout mouse, RIM1 expression level is increased and the frequency of miniature EPSC shows a three-fold increase, suggesting that SCRAPPER regulated synaptic transmitter release. Noticeably, in addition to its effect on RIM1, an increased level of SCRAPPER results in a reduction in several other presynaptic molecules, including synaptophysin and synapsin, suggesting that SCAPPER might regulate presynaptic function via other targets.[55]

In cultured hippocampal neurons, acute proteasome inhibition leads to an increased size of the recycling pool of synaptic vesicles.[57] However, the transmitter release probability is unchanged when UPS function is blocked, suggesting that the proteasome may function to maintain vesicle homeostasis. Interestingly, it has been shown previously that the recycling pool can be refilled from the reserve pool through the PKA (Protein Kinase A) pathway.[58] The studies of Willeumier et al. show that, in the presence of proteasome inhibitor, PKA activation does not further enhance the vesicle recycling pool, suggesting that these two processes may share common or intersecting pathways. As phosphorylation can trigger subsequent ubiquitination[59,60] and the UPS has been demonstrated to activate PKA during long-term facilitation,[61] it is tempting to hypothesize that protein phosphorylation and ubiquitination may provide a temporal link between presynaptic function and protein degradation.

Postsynaptic transmission

The postsynaptic apparatus, characterized by the postsynaptic density structure under electron microscopy, is a dynamic structure whose molecular composition is modulated by neuronal activity.[62] A systematic survey of the ubiquitin level of postsynaptic proteins revealed that many PSD components are ubiquitinated and their ubiquitination level is differentially regulated by neuronal activity. Certain PSD components become more abundant in the presence of UPS blockade while others become less abundant.[62] Recently, direct visualization of the proteasome complex showed that synaptic stimulation drives the proteasome into dendritic spines.[63] These studies present compelling arguments that the UPS is present at PSD and regulates the half-life of proteins there. More importantly, these data suggest that UPS-mediated mechanisms might participate in activity-induced modulation of synaptic strength. Therefore, a critical question is to understand what the effects of postsynaptic UPS inhibition are on synaptic transmission. Such an experiment was performed in the *Drosophila* neuromuscular junction. Hass and colleagues showed that constitutive postsynaptic proteasome inhibition alters synaptic function and molecular composition of the postsynaptic apparatus. Inhibition of proteasome activity in muscle cells leads to dramatic increase in the level of DLG (Disc Large) and B-class glutamate receptor. Further proteomic analysis identifies several proteins with marked changes in proteasome mutants. However, the precise roles of those proteins in synapse formation or function remain to be determined.[64]

If the proteasome activity is essential to achieve the appropriate level of synaptic proteins, how are individual proteins regulated? Accumulating evidence suggests that diverse ubiquitin ligase complexes regulated various proteins in the postsynaptic density. Burbea

and colleagues first reported that the ubiquitination of GLR-1 (Glutamate Receptor) induces its removal from the postsynaptic membrane in *C. elegans* and this process requires clathrin-mediated endocytosis.[65] The Kaplan laboratory further identified the E3 ubiquitin ligases, APC and LIN-23, that control synaptic GLR-1 abundance through the targeting of non-receptor substrates.[66,67] Similar to the observations made in worms, van Roessel and colleagues found that APC mutant flies have enlarged synapses, elevated levels of postsynaptic glutamate receptors and defects in synaptic transmission.[33] More recently, *kel-8* (BTB-Kelch protein) mutant worms were identified for their effect on glutamate receptor accumulation. KEL-8 is a substrate of cullin 3 ligase, suggesting that GLR-1 degradation may be mediated by a CUL-3-containing SCF complex.[68]

At mammalian excitatory synapses, changes of postsynaptic composition, such as the number of surface AMPA receptor, are regulated by synaptic activity and require the UPS.[62] Several studies show that protein degradation is needed for AMPA receptor endocytosis and this ubiquitin regulation is achieved indirectly through the degradation of the postsynaptic PSD-95 scaffolding protein.[69,70] In addition to AMPA receptors, the UPS also regulates NMDA-type glutamate receptor turnover. F-box protein, Fbx2, binds to NMDA receptor NR1 subunit and ubiquitination of NR1 is increased by Fbx2. The expression of a dominant-negative Fbx2 increases NR1 levels in an activity-dependent manner, suggesting that activity may release synaptic NR1, which relocates to the dendrites and soma for retranslocation and degradation.[71]

Actinfilin, an actin-associating protein, is localized to the dendritic spines[72,73] and recent studies show that actinfilin can act as a substrate adaptor and links GluR6 to the E3 ubiquitin ligase complex.[74] In addition, a postsynaptic actin regulatory protein, SPAR, has been shown to undergo activity and phosphorylation-dependent degradation through the UPS.[75] This result further confirms the complex interactions between neuronal activity, protein degradation and cellular architecture.

Another recent study reports that proteasome inhibition causes translocation of the proteasome from the nucleus to dendritic spines and this translocation is dependent on the transcriptional protein NAC1, which forms complex with the UPS components, including cullins.[76] These results suggest a potential link between the recruitment of protein degradation machinery and synaptic remodeling. However, the upstream signaling pathway that modulates NAC1 function remains to be identified. Scaffolding protein liprin-α is present at both presynaptic and postsynaptic sites.[77,78] In cultured hippocampal neurons, liprin-α is co-localized with CaMKII and PSD-95 in dendritic spines.[79] Recent studies show that synaptic activity can suppress liprin-α protein level and this process is mediated by both CaMKII and the UPS pathways.[79] Although the UPS has long-lasting effects at the PSD, few PSD proteins have been shown to be ubiquitinated. Among them are Shank, GKAP, PSD-95, and AKAP79/ 150.[62,69] These proteins all contain multiple protein–protein interacting domains and function as scaffolding molecules, suggesting that the UPS may regulate PSD dynamics through targeting a subset of distinct master proteins.

At mammalian inhibitory synapses, the stability of the ionotropic GABA receptor subunit is also sensitive to proteasome inhibition and is regulated by Plic-1. Plic-1 is an adaptor protein, which contains an N-terminal UBL domain and a C-terminal UBA domain that is essential for binding to GABA receptors. From these data, Bedford and colleagues propose a model that Plic-1 may bind to monoubiquitinated GABA receptors and prevent its polyubiquitination, thus reducing the targeting of receptors to the proteasome.[80]

Modification of synaptic strength has been thought to be the basis of synaptic plasticity, learning and memory. It has been shown that long-term potentiation (LTP) and long-term

depression (LTD) are both blocked in the presence of proteasome inhibitors.[69,81-83] Furthermore, modification of synaptic strength likely involves an intricate balance between protein synthesis and protein degradation.[82] An intriguing observation made by Lee and colleagues illustrates the role of synaptic protein degradation in retrieved fear memory.[84] After retrieval polyubiquitinated postsynaptic proteins, Shank and GKAP (Guanylate Kinase Associated Protein), but not PSD-95, are significantly increased. Infusion of proteasome inhibitor with protein synthesis blocker, anisomycin, prevents the memory impairment caused by the single infusion of anisomycin, suggesting that protein degradation after memory retrieval is important for the destabilization of preexisting memory. Moreover, proteasome inhibitor infusion into area CA1 suppresses the extinction of contextual fear memory, supporting the idea that the UPS is also required for the memory extinction.[84] Together, Lee et al. propose that memory reorganization after retrieval requires both degradation of preexisting synapses and synthesis of updated synapses.

The synaptic UPS dysfunction in neurodegenerative diseases

A common feature of many neurodegenerative diseases is the accumulation of UPS-associated proteins. It is not always clear whether impairment in proteolysis is a direct cause of neuronal dysfunction or a reflection of failed attempts by the UPS to remove the damaged protein. However, given the broad and essential roles of UPS on nearly all aspects of neuronal development, it is plausible that the UPS directly or indirectly participates in the pathogenesis of some neuronal disorders. As previously mentioned, the UPS is critical for synaptic remodeling. In this section, we will discuss recent studies centered on the synaptic UPS function in neurodegenerative diseases with an emphasis on Parkinson's disease (PD), Alzheimer's disease (AD) and Huntington's disease (HD).

PD is a movement disorder with a selective degeneration of dopaminergic neurons in the substantia nigra. Six genetic loci are linked to the rare, inheritable forms of PD. Among them, UCH-L1 is a ubiquitin carboxyl-terminal hydrolase and the disease-linked mutation is thought to drastically reduce its deubiquitinating activity.[85] Mice deficient in UCH-L1 are progressively ataxic with decreased monoubiquitin pools in their brains,[86,87] suggesting that UCH-L1 may function in maintaining the proper monoubiquitin level within cells. This notion is consistent with the enzymatic activity of UCH-L1 in recycling the ubiquitin from ubiquitinated proteins. In addition, UCH-L1 has been proposed to undergo homodimerization and thus act as a ubiquitin ligase to ubiquitinate synuclein.[88,89]

Parkin, another PD locus, encodes a Ring E3 ligase with an N-terminal UBL domain and a C-terminal PDZ domain.[89] Individuals carrying the mutant forms of Parkin display the characteristic loss of dopaminergic neurons, but lack the accumulation of Lewy bodies.[90] Parkin is widely expressed in the nervous system and localizes to both pre- and postsynaptic sites. Putative Parkin substrates include presynaptic proteins, such as α-synuclein, synphillin and synaptotagmin XI, suggesting that Parkin may function at synapses.[1] Recently, another Parkin substrate, GPR37 (orphan G protein-coupled receptor 37),[91] was shown to localize at mouse striatal presynaptic membranes and are associated with dopamine transport. In the GPR37 null mouse, the dopamine transport activity and expression level are enhanced. These data indicate that the interaction between GPR37 and dopamine transport can regulate DAT-mediated dopaminergic signaling.[92]

AD is characterized by progressive loss of memory and other cognitive skills. The early cognitive impairment in AD correlates well with the dysfunction of synapses, such as a decreased synaptic number and density in cortical neurons.[93] In addition, subtle alterations in synaptic efficacy occur prior to neuronal degeneration.[6] AD is featured by the accumulation of the toxic Aβ peptide. Recently, UCH-L1 was found to rescue the synaptic

dysfunction caused by either treatment of oligomeric Aβ or an absence of APP/PSEN1,[94] suggesting that perturbations in the UPS could be an important causative factor in AD. Aβ treatment of primary cortical neurons decreases the expression level of PtdIns (4,5)P(2) phosphatase. The destabilizing effect of Ab on PtdIns(4,5)P(2) metabolism is mediated by synaptojanin (Synj). Berman and colleagues also found that the inhibitory effect of Aβ on hippocampal long-term potentiation is suppressed in slices from $Synj1^{+/-}$ mice. Synaptojanin can be ubiquitinated,[95] but how this observation is applied to the pathogenesis of AD remains to be determined.

HD is one of the polyglutamine (polyQ) repeat disorders, which results from the expansion of CAG triplet repeats in the Huntington (HTT) gene. Abnormal accumulation of HTT results in the deposition of ubiquitin-positive protein inclusions in the brain, suggesting that dysfunction of the UPS may contribute to the pathogenesis of this disease.[96,97] It is well accepted that the UPS is impaired in cell-culture models of HD, but in vivo studies of UPS function in transgenic mouse systems have not yielded consistent results.[98,99] Bennett and colleagues attempted to evaluate the function of the UPS in vivo. They used the ubiquitin-association domain of human P2UBA to capture polyubiquitin chains and the captured polypeptides are analyzed with mass spectrometer. In both R6/2 and $Hdh^{Q150/Q150}$ mice, the HD animal models, the temporal profiles of UPS impairment correlate with the progressively deteriorated phenotypes of HD animals.[100] In addition, the polyubiquitin chain level is elevated in the striatum and the cortex of human HD patients, supporting the idea that the UPS impairment is a consistent feature of HD pathology in both humans and animal models.[100] Recently, Wang et al. created synaptic reporters for UPS activity by fusing GFP with a CL-1 degron sequence specific for ubiquitination and proteasome degradation to synaptic proteins PSD95 or SNAP25. With these reporters, they found that synaptic UPS activity is decreased in synapses of HD neurons and HD knock-in mice, offering an important link between synaptic dysfunction and selective neuropathology of HD.[101]

Conclusions

Dynamic control of protein stability is crucial for synaptic development and function. Mounting data from different experimental systems started to build a convincing argument that the UPS is an essential component for regulation of synaptic proteins (Table 1). However, many questions remain. The UPS is composed of a large number of components, but only a few of them have been studied. What are the roles of other UPS components in the formation of neural circuits? What are their prospective protein targets? Most synapses in CNS are formed in an en passant manner. How are those UPS components positioned at various regions of a polarized neuron corresponding to the specificity of synapse formation? It is clear that the UPS controls the abundance of synaptic proteins, thus regulating the synaptic activity. How are individual synaptic proteins accessed by the UPS? Alteration of synaptic strength or activity affects the distribution of UPS, but how is this achieved molecularly? Future studies on these issues are required for both elucidating the role of UPS in neuronal development and identifying potential UPS components as therapeutic targets in neurodegenerative diseases.

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Abbreviations

UPS	ubiquitin proteasome system
SCF	Skp1/Cullin/ F-box complex
APC	Anaphase Promoting Complex
PSR	Primary Synapse Region
SSR	Secondary Synapse Region
PSD	Post-Synaptic Density
PD	Parkinson disease
AD	Alzheimer’s disease
HD	Huntington’s disease

Table 1

UPS molecules implicated in synaptic function

Protein	Synaptic function	References
E2 enzymes		
UbcDl	Dendritic pruning	(47)
E3 enzymes		
RPM-1/Highwire	Regulation of synapse number and presynaptic development	(19,20,21)
FSN-1/DFsn	F-box component of SCF^{FSN-L} complex; synapse formation	(22,26)
APC	Regulation of Synaptic size and function by degrading liprin-α; glutamate receptor clustering	(33,66)
PDZRN3	Postsynaptic function; AchRs clustering	(40)
SEL-10	F-box component of SCF^{SEL-10} complex; synapse elimination	(41)
DIAP1	Dendritic pruning	(47)
Staring	Regulating syntaxin-1; synaptic transmission	(53)
Siah-1	Regulating synaptophysin; synaptic transmission	(54)
Siah-2	Regulating synaptophysin; synaptic transmission	(54)
SCRAPPER	Regulating RIM; synaptic vesicle release	(55)
LIN-23	F-box component of SCF^{LIN-23} complex; glutamate receptor abundance	(67)
Fbx2	NMDA-type glutamate receptor degradation	(71)
Parkin	Targets multiple presynaptic components; synaptic function	(1,91,92)
Deubiquitinating enzymes		
UCH-L1	Alleviates the synaptic dysfunction associated with Alzheimer's disease in mouse	(94)
Fat faces	Synapse formation in *Drosophila*	(29)
Ubiquitin-like		
Plic-1	Protects GABA receptor from degradation	(80)