Critical Roles of Deubiquitinating Enzymes in the Nervous System and Neurodegenerative Disorders

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https://doi.org/10.14348/molcells.2020.2289
www.molcells.org

Post-translational modifications play major roles in the stability, function, and localization of target proteins involved in the nervous system. The ubiquitin-proteasome pathway uses small ubiquitin molecules to degrade neuronal proteins. Deubiquitinating enzymes (DUBs) reverse this degradation and thereby control neuronal cell fate, synaptic plasticity, axonal growth, and proper function of the nervous system. Moreover, mutations or downregulation of certain DUBs have been found in several neurodegenerative diseases, as well as gliomas and neuroblastomas. Based on emerging findings, DUBs represent an important target for therapeutic intervention in various neurological disorders. Here, we summarize advances in our understanding of the roles of DUBs related to neurobiology.

Keywords: Alzheimer's disease, deubiquitinating enzyme inhibitors, epilepsy, neural stem cells, Parkinson's disease

INTRODUCTION

Post-translational modifications (PTMs) play key regulatory roles in development and function of the nervous system. Ubiquitination is one of the most important PTMs mediated by specific ligases for proteasomal degradation of target proteins. Expression of intercellular proteins is tightly regulated by a process of synthesis and degradation mediated directly or indirectly by the proteasomal pathway. The small regulatory protein ubiquitin (Ub) targets specific proteins for degradation by the ubiquitin proteasome system (UPS) or the lysosomal system. Conjugation of Ub to proteins, or ubiquitination, occurs through a series of events mediated by three enzymes: E1 (Ub activating enzyme), E2 (Ub conjugating enzyme), and E3 (Ub ligase) (Fig. 1A). Covalent attachment of one ubiquitin molecule to the lysine site of the target protein residue (monoubiquitination) can regulate its subcellular localization, activity, and interacting affinity. Similarly, ubiquitin molecules can bind to each other, forming an Ub-chain to a substrate protein and leading to its degradation by polyubiquitination. Ubiquitin has seven lysine residues (K6, K11, K27, K29, K33, K48, and K63), which together form numerous branched or linear chains that are involved in determination of the fate of target proteins (Kulathu and Komander, 2012; Ye and Rape, 2009). Erroneous ubiquitination of a protein could be detrimental for cells, as proteins may degrade prematurely, leading to autophagy and unintended cell death. Ubiquitin molecules are abundantly expressed in neurodegenerative disorders: as neurofibrillary tangles in Alzheimer’s disease (AD), Lewy bodies in Parkinson’s disease (PD), and intranuclear inclusions in hereditary polyglutamine diseases (Lennox et al., 1988; Mori et al., 1987; Paulson et al., 1997). Moreover, ubiquitin controls diverse neuronal processes including cell survival, cell fate determination, neurite outgrowth, morphogenesis, synapse development, and synaptic functions (DiAntonio et al., 2001; Ding and Shen, 2008; Jason and Ehlers, 2007; Tai and Schuman, 2008). Ubiquitina-
tion of synaptic proteins can be controlled by acute or chronic changes in synaptic activity (Chen et al., 2003; Ehlers, 2003). Ubiquitination is antagonized by ubiquitin proteases, referred to as deubiquitinating enzymes (DUBs), which counteract the action of ligases by removing ubiquitin chains or maintaining the cellular pool of free ubiquitin monomer (Fig. 1B). DUBs are categorized into seven subfamilies: ubiquitin-specific proteases/ubiquitin-specific processing proteases (USPs/UBPs), ubiquitin C-terminal hydrolases (UCHs), ovarian tumor proteases, Josephin or Machado–Joseph disease protein domain proteases, Jab1/MPN domain-associated metalloisopeptidase (JAMM) domain proteins, motif interacting with Ub-containing novel DUB family (MINDY), and ZUFSP/C6orf113 (Abdul Rehman et al., 2016; Kwasna et al., 2018; Nishi et al., 2014) (Fig. 1B). The role of DUBs in the nervous system can be estimated by growing evidence on mouse (Sagiho et al., 1999; Wilson et al., 2002) and human (Kawaguchi et al., 1994) neurological disorders associated with mutations in certain DUBs. Several DUBs are involved in regulation of proteins involved in nervous system functions, neurodegenerative diseases, and brain cancers. In this review, we focus on DUBs that regulate intra-cellular processes for proper function of the nervous system and are implicated in several neurological disorders and brain tumors.

**UBIQUITIN SPECIFIC PROTEASES**

**USP4**

Ubiquitin-specific protease 4 (USP4) directly interacts with and deubiquitinates a specific G-protein coupled receptor, adenosine A2 (A2A), regulating the level of A2A receptors through the endoplasmic reticulum-associated protein degradation (ERAD) pathway. Overexpression of USP4 depletes ubiquitinylated A2A and increases the number of functional receptors in hippocampal neurons (Milojević et al., 2006). Adenosine receptors mediate neuroprotection in the brain and are important targets for treatment of chronic neurodegenerative diseases (Abbracchio and Cattabeni, 1999). USP4, a deubiquitinase of A2AR, plays an important role in regulating its subcellular localization for ligand binding and signal generation (Toews, 2006). Therefore, pharmacological manipulation of USPs (like USP4) to regulate the expression of GPCRs could be a novel therapeutic strategy for various ailments including neurological disorders (Toews, 2006) (Fig. 2F).

Neurological inflammation can be induced by the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) pathway upon activation of microglia, an active inductor of secondary spinal cord injury. The level of microglia is tightly maintained in the central nervous system (CNS); however, during traumatic conditions, microglia are excessively activated, inducing inflammatory cytokines and thereby aggravating secondary neuronal injury and inflammation. Tumor necrosis factor receptor associated factor 6 (TRAF6) is an essential adaptor protein for NF-κB signaling and has a major role in inflammation and immune response. In the microglial cells of rats, the expression of USP4 decreases after spinal cord injury (SCI). USP4 deubiquitinates TRAF6 and inhibits the TRAF6-stimulated NF-κB reporter gene and regulates the activation of NF-κB (Xiao et al., 2012) (Fig. 2F). USP4 might participate in promoting the activation of microglial-mediated neuronal inflammation by deubiquitinating TRAF6 via regulating the NF-κB signaling pathway (Jiang et al., 2017). Additionally, USP4 is frequently expressed in glioblastoma tissues and cell lines (Fig. 2E). Upon treatment with the anti-glioblastoma drug Temozolomide, USP4 knockdown cells undergo apoptosis in a p53 dependent manner (Qin et al., 2019). Taken together, these reports highlight the dynamic conversion of ubiquitin proteases to regulatory enzymes.
role of USP4 and likely other DUBs in regulation of diverse neurological pathways and disease pathologies.

**USP7**

USP7, or herpesvirus-associated ubiquitin-specific protease (HAUSP), regulates various brain functions and neurodegenerative disorders. USP7 interacts with Ataxin-1, which is associated with the spinocerebellar ataxia type 1 (SCA1), an autosomal-dominant neurodegenerative disorder characterized by several neurological defects and symptoms (Hong et al., 2002). Another important role of USP7 is maintenance of the level of repressor element 1-silencing transcription factor (REST), which is involved in inhibition of neuronal cell differentiation (Huang et al., 2011). During protemporal degradation of REST, multiple E3 ligases are actively involved in maintaining REST expression. γ-TrCP, an E3 ligase of REST, is abundantly expressed during neuronal differentiation, while the levels of USP7 and REST are low, suggesting a critical role for USP7 in neuronal differentiation and cell proliferation (Huang et al., 2011). Deletion of USP7 in neural cells causes neonatal lethality, hypoplasia, and deficiencies in development, primarily due to USP7-p53-mediated apoptosis (Kon et al., 2011). USP7-mediated p53 stability is highly crucial for brain development, while p53 dependent or independent functions of USP7 contribute largely to mice lethality (Kon et al., 2011).

USP7 also deubiquitinates N-MYC proto-oncogene, which is amplified in numerous advanced stage tumors such as neuroblastomas. Knockdown of USP7 in neuroblastoma cancer cells and genetic manipulation of USP7 expression in mouse brain inhibit the stability and activity of N-MYC, suggesting USP7 as a potential therapeutic target for N-MYC-amplified tumors (Tavana et al., 2016). Lysinespecific demethylase 1 (LSD1) and USP7 are frequently overexpressed in aggressive brain tumors such as gliomas (Fig. 2E). USP7 inhibits the ubiquitination of LSD1 and regulates its protein turnover in A172 and T98G cells leading to rapid proliferation and inva-
sion of glioblastoma cells (Yi et al., 2016). Thus, it could be estimated that USP7 demonstrates a crucial prognostic marker and potential therapeutic target for neuroblastomas and gliomas (Tavana et al., 2016; Yi et al., 2016).

**USP8**

PD is pathologically characterized by neuronal death and formation of inclusions known as Lewy bodies (LBs). Misfolding of a-synuclein is a common feature of PD (Spillantini et al., 1997) which leads to cognitive dysfunction (Schneider et al., 2012) as well as risk of dementia at an early age (Ross et al., 2008). Recently, a-synuclein inclusion was found to contain K63-linked ubiquitin chains, and USP8 present in Lewy bodies controls the K63-linked ubiquitination of a-synuclein in dopaminergic neurons to regulate PD state (Alexopoulou et al., 2016). USP8 also deubiquitinates LepRb, a receptor of leptin that has been implicated in regulation of synapses, neuronal plasticity, cognition, cortical volume, memory function, and depression-related phenomena. Additionally, the abundance of USP8 increases glutamatergic synapse formation in hippocampal structures (Bland et al., 2019).

Regulation of SHANK3 protein level is important to maintain synaptic density and levels of multiple synaptic proteins. SHANK3 mutations or any alterations in its expression often lead to neurodevelopmental disorders such as Phelan-McDermid syndrome, autism spectrum disorders, and schizophrenia. USP8/UBP9 enhances the protein levels of SHANK3 and SHANK1 and subsequently enhances dendritic spine density in primary rat neurons (Kerrisk Campbell and Sheng, 2018) (Fig. 2C). USP8 also plays a key role in trafficking and stabilization of ß-site amyloid precursor protein-cleaving (BACE1) enzyme, which is involved in the production of amyloid-ß that accumulates in the brains of Alzheimer’s patients (Yeates and Tesco, 2016).

The tropomyosin-related kinase (Trk) family of receptor tyrosine kinases control synaptic plasticity, morphology, functions, and neuronal cell survival. USP8 interacts with TrkA receptor in a nerve growth factor (NGF)-dependent manner and inhibits neuronal differentiation in PC12 cells. Additionally, overexpression of USP8 blocks neurite outgrowth, which highlights the importance of USP8 in brain development (Ceriani et al., 2015). Considering the diverse role of USP8 in synaptic development and neurological disorders, USP8 could be a key target for future research on neurobiology.

**USP9X**

Faf (fat facets) play a major role in maintaining synaptic span, synaptic branching, and boutons in Drosophila (DiAntonio et al., 2001) and deubiquitinates liquid facets (Lqf) that are implicated in endocytosis (Cadavid et al., 2000: Chen et al., 2002). USP9X is the mammalian ortholog of Faf and binds to the Lqf ortholog epsin-1 and regulates its function and protein stability (Chen et al., 2003). USP9X is often overexpressed in glioblastomas, the most common primary brain tumours (Fig. 2E). A recent study showed that inhibition of USP9X by small-molecule inhibitor WP1130 decreases stem-cell-like glioblastoma cells, patient-derived xenografts, and cell viability of glioblastomas (Karpel-Massler et al., 2016), suggesting that USP9X could be a potential therapeutic target for glioblastomas.

USP9X is also correlated to lissencephaly, epilepsy (Friocourt et al., 2005) (Fig. 2B), and Alzheimer’s disease (Chastagner et al., 2008; Overstreet et al., 2004: Qiu et al., 2000), Wnt (Taya et al., 1999), and transforming growth factor beta (TGF-ß) (Dupont et al., 2009). USP9X regulates the stability of ubiquitin ligases Mind Bomb1 (Choe et al., 2007: Yoon and Gaiano, 2005) and intracellular domain E3 ligase, Itch in the Notch pathway (Mouchantaf et al., 2006), which plays a major role in early neurodevelopment, learning, memory, and certain neurological diseases in adults (Lasky and Wu, 2005). USP9X also interacts with acute lymphoblastic leukemia-1 fusion partner chromosome 6 (AF-6), which is involved in establishment of adherens junctions and polarity in neural progenitor cells (Ike-da et al., 1999; Zhadanov et al., 1999).

USP9X is very important for development of the human CNS due to its association with the microtubule-associated protein doublecortin (DCX) (Friocourt et al., 2005) (Fig. 2A), which is implicated in neuronal migration, protein sorting, and trafficking of vesicles (Francis et al., 1999). Mutations in PRICKLE genes often cause epilepsy-related seizures. USP9X deubiquitinates PRICKLE and regulates PRICKLE-mediated seizures (Paerinka et al., 2015), delineating the significance of USP9X in epilepsy. During the development of PD, USP9X regulates the level of a-synuclein and activates SMAD4 by stabilizing it at K519 and subsequently promoting the TGF-ß pathway (often correlated with several neurodegenerative diseases) (Valderrama-Carvajal et al., 2002). Additionally, the Huntington’s disease protein has also been associated with USP9X in mouse brain (Kaltenbach et al., 2007). Recently, the expression of USP9X or Mcl-1 (an anti-apoptotic member of the Bcl-2 family and a substrate of USP9X) has been shown to cause rapid death in malignant peripheral nerve sheath tumors (MPNSTs) (Bianchetti et al., 2018). Considering the diverse role of USP9X in nervous system, it could be a promising therapeutic target in neurogenerative disorders and malignancies (Li et al., 2017).

**USP13**

Glioblastoma harbors glial stem cells (GSCs) are key players in tumor propagation and maintained by core transcriptional factors such as SOX2 and C-MYC. USP13 stabilizes C-Myc by inhibiting the E3 ligase and FBXL14-mediated ubiquitinatation and thereby maintains GSC self-renewal and tumorigenic potential (Fang et al., 2017) (Fig. 2E). Moreover, MYC proteins, which include L-MYC, C-MYC, and N-MYC, are also involved in development of the mid-, fore-, and hind-brain (Wey and Knoepfler, 2010). USP13 is abundantly expressed in the brain of PD patients (Fig. 2B), and deubiquitinates Parkin (an E3 ligase that targets certain neurological protein for degradation) and a-synuclein to regulate their metabolism in a-synucleinopathies (Liu et al., 2018). Missense mutations in the a-synuclein gene are common in PD, Lewy body dementia, and multiple system atrophy (Spillantini and Goedert, 2000). Thus, being a regulator of parkin and a-synuclein, USP13 could be a novel therapeutic target in
α-synucleinopathies (Liu et al., 2018) (Fig. 2B).

**USP14**

USP14 is a key DUB involved in maintaining monoubiquitin level at developing synapses and is indispensable for development of synapses and proper regulation of neuromuscular junctions (NMJs). Loss of USP14 causes developmental defects at motor neurons. In axia (ax) mice, the Purkinje cells in the cerebellum highly express GABA<sub>A</sub> receptors (GABA<sub>A</sub>Rs), which undergo proteasomal degradation (Saliba et al., 2007). GABA<sub>A</sub>Rs are one of the most studied neurotransmitter receptors and contribute to regulation of various brain functions and brain-related disorders (Everington et al., 2018). USP14 interacts with GABA<sub>A</sub>Rs and regulates their stability and cell surface distribution (Lappe-Siefke et al., 2009) (Fig. 2C). Moreover, depletion of USP14 in (ax) mice not only results in perinatal lethality, reduced muscle development, structural and functional defects at the NMJ; but also leads to depletion of free ubiquitin in the brain and spinal cord (Anderson et al., 2005; Chen et al., 2009). The dominantly-negative, catalytically mutant USP14 in the murine nervous system mimics many defective phenotypes such as NMJ structure defects, reduced muscle development, and reduced motor performance (Vaden et al., 2015). However, restoring free ubiquitin level in the USP14 catalytically-inactive mice causes improvements in NMJ structure and reduction in pJNK accumulation in the motor neurons as well as negatively affects muscle development and motor functions (Vaden et al., 2015), indicating a crucial role for USP14 in synaptic development and functions.

**USP46**

USP46 was identified as the first DUB regulating glutamate receptors (GLuRs) by an RNAi-based screen in Caenorhabditis elegans. USP46 inhibits proteasomal degradation of glutamate receptor 1 (GLR-1) at synapses by deubiquitinating the receptor and stabilizing it in the lysosome (Kowalski et al., 2011). GLR-1 encodes a receptor subunit of a non-NMDA excitatory ionotropic glutamate receptor subtype and has 40% homology with mammalian (α-aminooxyacetic acid)-AMP deaminase (GLU2), which controls the majority of excitatory transmissions in the brain, as well as synaptic development and functions (Anggono and Huganir, 2012). Mammalian USP46 is expressed throughout the brain, including the hippocampus, amygdala, cerebellum, and prefrontal cortex, and stabilizes AMPARs (GlutA1 and GluA2) (Huo et al., 2015) (Fig. 2C). Thus, it could be predicted that USP46 might be involved in regulation of synaptic plasticity, brain functions, and synaptic transmission by stabilizing glutamatergic AMPARs (Huo et al., 2015). USP46 has also been associated with regulation of the GABAergic system in mice, which maintains fast-inhibitory transmission in the brain (Tomiida et al., 2009). Loss of USP46 results in depression-like behaviors in mice (Imai et al., 2012) as well as reduction in expression of GABA synthesis enzyme glutamic acid decarboxylase (GAD67) (Tomiida et al., 2009). Taken together, the involvement of USP46 in regulation of diverse synaptic receptors, underscores the importance of USP46 in synaptic formation and neuronal morphogenesis (Huo et al., 2015).

**CYLD**

CYLD negatively regulates NF-κB (Fig. 2F), which is involved in neuroinflammation, by reducing NF-κB activity in ischemic stroke (Kovalenko et al., 2003). NF-κB transcription factors are abundantly expressed in glial cells and cerebral blood vessels and protect neurons against different injuries or neuronal inflammatory reactions (Shih et al., 2015).

**Other USPs**

USP12 is a potent inducer of neuronal autophagy and regulates neuronal proteostasis and mutant huntingtin (mHTT), one of the main causes of the neurodegenerative disorder Huntington’s disease (Aron et al., 2018) (Fig. 2B). USP17 is downregulated in glioma tissues (Fig. 2E), but overexpression of USP17 reduces tumorigenesis and cell proliferation in gliomas by reducing Ras and MYC protein levels (Hu et al., 2016).

Tissue homeostasis in the CNS is usually controlled by microglia, and dysregulation of microglia often leads to neuropsychiatric, neurodegenerative, and neuroinflammatory diseases known as microgliopathies. USP18 in the white matter of microglia contributes to microglial quiescence (Fig. 2D), and activates Stat 1 or other interferon genes, controlling IFN signaling (Goldmann et al., 2015). Moreover, USP18-deleted mouse brains exhibit microglial clusters in white matter, similar to the state in several human microgliopathies (Schwabland et al., 2019).

USP22 gene is highly expressed in human brain glioma cells (Fig. 2E) and is associated with several neurological disorders (Li et al., 2013; Melo-Cardenas et al., 2016). Knockdown of USP22 effectively inhibits the cell viability of brain glioma cells, resulting in apoptosis and cell cycle arrest (Li et al., 2013).

USP33 is associated with the axonal guidance receptor Roundabout (Robo) 1 (Fig. 2A), which plays a major role in controlling axon crossing across the midline between brain hemispheres and neuronal dendrites (Yuasa-Kawada et al., 2009). USP33 protects the signal-competent Robo1 receptor complex from degradation and promotes the Slit signaling pathway (Yuasa-Kawada et al., 2009), which is essential for axon pathfinding in the CNS (Guan and Rao, 2003; Tessier-Lavigne and Goodman, 1996).

USP36 binds to one of the E3 ligases of TrkA neurotrophin receptor Nedd 4-2 and thereby regulates the association of Nedd 4-2 and TrkA (Anta et al., 2016). Nedd 4-2 has been directly implicated in the growth of peripheral neuropathic pain (Laedermann et al., 2013).

In addition to its role on neuronal differentiation (Tang, 2009), REST also controls proliferation of medulloblastoma cells (Das et al., 2013). REST expression downregulates CD-KNIB/p27 (a cyclin-dependent kinase inhibitor) and promotes the proliferation of medulloblastomas. REST transcriptionally represses USP37 expression, whereas USP37 stabilizes p27 protein and block cell proliferation. Thus, REST and USP37 play an important role in regulating the stability of p27 and thereby controlling the proliferation of medulloblastomas (Das et al., 2013). Recently, USP37 has been reported to have tumor-suppressive properties in neural cancers: the level of USP37 was found to be downregulated in human medul-
loblastoma specimens (Dobson et al., 2017). Moreover, G9a (a histone methyltransferase) promotes USP37 depletion in a REST-dependent manner and causes growth and proliferation of medulloblastoma cells (Dobson et al., 2017).

USP39 has been implicated in human glioma by regulating the TAZ proteins in orthotopic xenografts (Fig. 2E). Knockdown of USP39 causes downregulation of TAZ pre-mRNA splicing efficiency in glioma cells, leading to depletion of TAZ protein (Ding et al., 2019).

Gli1 is an important downstream target of the Hedgehog (Hh) signaling pathway implicated in cell proliferation and tumorigenesis. USP48 has been shown to stabilize Gli1, whereas the Hh pathway has been shown to induce USP48 expression by transactivating Gli1, forming a reciprocal feedback loop. Depletion of USP48 inhibits glioma cell viability and tumor generation by partially stabilizing Gli1, which incites a critical role of the USP48-Gli1 axis in glioblastoma tumorigenesis (Zhou et al., 2017) (Fig. 2E).

**UCH family**

The carboxyl-terminal hydrolase UCH-L1 is highly expressed in the brain and is often implicated in neurodegenerative disorders in both mice and humans. UCH-L1 is abundantly found in the protein aggregates and inclusion bodies associated with PD and AD (Lowe et al., 1990; Setsuie and Wada, 2007; Wilkinson et al., 1992) (Fig. 2B). UCH-L1 plays a significant role in synaptic remodeling by maintaining synaptic structure in hippocampal neurons and modulating level of free monoubiquitin pools in an activity-dependent manner (Cartier et al., 2009). Downregulation of UCH-L1 causes synaptic defects such as decreased spine density, accumulation of pre- and post-synaptic proteins, and increased spine size (Cartier et al., 2009). Interestingly, pharmacological inhibition of UCH-L1 increases spine size and pre-synaptic and post-synaptic protein clusters and decreases spine density, implying an important role of UCH-L1 in regulation of brain functions (Setsuie and Wada, 2007). Moreover, UCH-L1 is correlated with decrease in synaptic vesicle number, increases in tubulovesicular structures in axons, and denervation of muscles (Chen et al., 2010) (Fig. 2C). In a mouse model of AD, reductions of monomeric ubiquitin and long-term potentiation (LTP) were observed due to loss of UCH-L1 in the brain (Gong et al., 2006).

Ap-UCH removes ubiquitin from polyubiquitinated substrates during proteasomal degradation and thereby maintains synaptic activity in Aplysia (Hegde et al., 1997). Similarly, in mammals, UCH-L3, an orthologue of AP-UCH, plays a major role in maintaining synaptic plasticity. Deficiency of UCH-L3 causes significant deficits in learning and memory in homoygous mice without any developmental, histological, or fertile abnormalities (Wood et al., 2005). Considering the importance of UCH sub-family of DUBs in synaptic development and regulation, further investigation is required to understand their role in synaptic defects related neurodegenerative disorders.

**Ataxin-3**

Ataxin-3, a member of the MJD sub-family of DUBs, was first implicated in the neurodegenerative disorder spinocerebellar ataxia type 3 (SCA3), also known as Machado-Joseph Disease (Fig. 2B). SCA3 is the most aggressive inherited ataxic age-related disorder and often leads to difficulties in speech and swallowing, impaired eye movements, neuropathy, and sometimes dystonia or parkinsonism (Todi et al., 2007; Williams and Paulson, 2008). Several studies have associated Ataxin-3 with several E3 ligases such as the carboxy-terminal of HSC70-interacting protein (CHIP) (Jana et al., 2005), ubiquitination factor E4B (E4B/Ufd2) (Matsumoto et al., 2004), and parkin (Duncan et al., 2010). Parkin is a multifunctional ubiquitin ligase associated with maintenance of neuronal survival. Loss of Parkin increases risks of certain neurodegenerative diseases such as PD, AD, and amyotrophic lateral sclerosis (ALS) (Zhang et al., 2016).

The development and integrity of the nervous system are dependent on the balance between various components of Ub-dependent pathways, particularly DUBs. The tight regulation of ubiquitination and deubiquitination and the availability of mono-ubiquitins are critical for synapse structure and function. Several studies have explored the importance of DUBs in neurodevelopmental disorders and brain tumors. However, the search for DUB-based therapies is still in its infancy, and structural studies, enzymatic assays, and extensive research into the DUBs involved in diverse neurological ailments are needed to support drug development.

**DUBs AS THERAPEUTIC TARGETS FOR NEURODEGENERATIVE DISEASES**

Over the past decade, therapies focusing on the proteasomal pathway have shown huge promise due to their critical roles in protein regulation and several signaling pathways. Among post-translational regulators, DUBs offer several advantages as therapeutic targets due to their cell-type or substrate specificity. Although DUBs exhibit strong similarities between the active-enzyme site cysteine and histidine boxes, several DUBs demonstrate critical differences in accessibility to the catalytic pocket (Colland, 2010). Thus, developing DUB-specific inhibitors may be an attractive alternative for design of novel therapeutics to treat malignancies and neurodegenerative disorders. Several specific-DUB inhibitors, including USP7 and UCH-L1, have been developed to date (Colland, 2010; Todi and Das, 2012). Moreover, inhibition of USP14 by 1-[1-(4-fluoroaryl)-2,5-dimethylpyrrol-3-yl]-2-pyrrolidin-1-ylethyl (IU1) has been found to enhance the degradation of several proteins related to neurodegenerative diseases (Lee et al., 2010). A small-molecule inhibitor of USP9X, WP1130, demonstrated anti-proliferative properties by attenuating the growth of glioblastoma cells (Karpel-Massler et al., 2016). Although DUBs are a promising target in neurobiology, pharmacological inhibition of DUBs provides several challenges for the scientific community.

**CURRENT CHALLENGES IN DUB-BASED THERAPEUTICS FOR NEUROBIOLOGY**

DUB activity in cells is specific to the target substrates undergoing mono-ubiquitination or poly-ubiquitination, which comprise ubiquitin-chains bearing linkages or mixed chains
containing ubiquitin and UBLs (Hospenthal et al., 2015; Komander and Rape, 2012). Although proteasomal inhibition is an important therapeutic strategy for various disorders related to neurobiology, indiscriminate inhibition of DUB activity might affect other cellular processes that rely on the 26S proteasomal system. Several DUBs are involved in the regulation of normal brain function as well as neurodegenerative disorders. For instance, USP14 inhibitor has a significant effect in regulating the level of proteins involved in neurodegeneration (Lee et al., 2010), but also functions in synaptic development and plasticity (Vaden et al., 2015; Wilson et al., 2002).

Similarly, USP8 regulates the synapses by deubiquitinating LepRb and SHANK3 (Kerrisk Campbell and Sheng, 2018), but also stabilizes the BACE1 enzyme involved in AD (Yeates and Tesco, 2016). Thus, full or near-complete pharmacological inhibition of DUBs to control a neurological condition may have adverse effects.

Despite having druggable catalytic pockets, there are several challenges to developing potent compounds for inhibiting DUB expression. First, several DUBs share similar structure and properties and there are several limitations to developing classical small-molecule chemical inhibitors specifically tar-

**Table 1. List of DUBs and their functions in neurobiology**

| DUBs  | Functions | Reference |
|-------|-----------|-----------|
| USPs  | Biological functions | Clinical significance |
| USP4  | Regulates the stability of G-protein coupled receptor, adenosine A2 (A2A) | Abundantly expressed in glioblastoma |
|       | Regulates functional receptors in neurons | Regulates cell viability in glioblastomas |
|       | | Involved in neuro-inflammation by deubiquitinating TRAF6 |
| USP7  | Involved in transcription of Ataxin-1 | Deubiquinates N-MYC and regulates neuroblastomas |
|       | Regulates neuronal differentiation by stabilizing REST | Abundantly expressed in gliomas |
|       | Regulates neonatal lethality, hypoplasia, and developmental defects | Inhibits LSD1 to regulate glioblastomas |
| USP8  | Controls ubiquitination of α-synuclein | Regulates the stability of SHANK3, involved in several neurodegenerative disorders |
|       | Deubiquitinates LepRb receptor | Stabilizes the BACE1 enzyme involved in production of amyloid-β in the AD-affected brain |
|       | Regulates glutamatergic synapse formation in the hippocampus | |
|       | Inhibits neuronal differentiation by interacting with TrkA | |
|       | Blocks neurite outgrowth | |
| USP9X | Regulates the stability of substrates involved in neurodevelopment signaling pathways (Notch, Wnt, TGF-β, and Itch) | Highly expressed in glioblastomas |
|       | Interacts with AF-6, involved in development of neural progenitor cells | Involved in lissencephaly, epilepsy and X-linked intellectual disability |
|       | Associated with neuronal protein DCX | Regulates cell death and apoptosis in glioblastomas |
|       | | Regulates seizures by deubiquitinating PRICKLE |
|       | | Regulates α-synuclein, SMAD4 and TGF-β pathway (involved in neurodegenerative disorders) |
| USP13 | Stabilizes C-MYC and maintains glioma stem cells | Overexpressed in the brain of PD patients |
|       | | Stabilizes Parkin and α-synuclein (involved in PD, dementia and neurological disorders) |
| USP14 | Maintains the synaptic structure and function | Inhibition of USP14 leads to degradation of several proteins involved in neurodegenerative disorders |
|       | Interacts with neurotransmitter receptor, GABA_A Rs | |
|       | | Mutations in USP14 lead to defects in NMJ structure and reduction in motor performance |
| USP46 | Deubiquitinates GLR-1 at synapses | Highly expressed throughout the brain |
|       | Stabilizes AMPARs (GLuA1 and GLuA2) | Depletion of USP46 leads to depression-like behaviors |
|       | Involved in mice GABAergic system | Negatively regulates NF-κB (involved in neuroinflammation) |
| CYLD  | Negatively regulates NF-κB (involved in neuroinflammation) | |

**Table 1. List of DUBs and their functions in neurobiology**

- USP4
  - Regulates the stability of G-protein coupled receptor, adenosine A2 (A2A)
  - Regulates functional receptors in neurons

- USP7
  - Involved in transcription of Ataxin-1
  - Regulates neuronal differentiation by stabilizing REST
  - Regulates neonatal lethality, hypoplasia, and developmental defects

- USP8
  - Controls ubiquitination of α-synuclein
  - Deubiquitinates LepRb receptor
  - Regulates glutamatergic synapse formation in the hippocampus
  - Inhibits neuronal differentiation by interacting with TrkA
  - Blocks neurite outgrowth

- USP9X
  - Regulates the stability of substrates involved in neurodevelopment signaling pathways (Notch, Wnt, TGF-β, and Itch)
  - Interacts with AF-6, involved in development of neural progenitor cells
  - Associated with neuronal protein DCX

- USP13
  - Stabilizes C-MYC and maintains glioma stem cells

- USP14
  - Maintains the synaptic structure and function
  - Interacts with neurotransmitter receptor, GABA_A Rs
  - Mutations in USP14 lead to defects in NMJ structure and reduction in motor performance

- USP46
  - Deubiquitinates GLR-1 at synapses
  - Stabilizes AMPARs (GLuA1 and GLuA2)
  - Involved in mice GABAergic system

- CYLD
  - Negatively regulates NF-κB (involved in neuroinflammation)
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Table 1. Continued

| DUBs           | Functions                                                                                           | Reference                      |
|---------------|-----------------------------------------------------------------------------------------------------|--------------------------------|
| Other USPs    |                                                                                                      |                                |
| USP12         | Regulates neuronal autophagy and neuronal proteostasis                                               | (Aron et al., 2018)            |
| USP17         | Regulates the expression of mHTT (involved in Huntington’s disease)                                  | (Hu et al., 2016)              |
| USP18         | Causes microglial quiescence                                                                       | (Goldmann et al., 2015:        |
|               | Activates Stat 1 or other interferons and controls IFN signaling                                    | Schwabenland et al., 2019)    |
| USP22         | Overexpressed in brain gliomas and regulates proliferation of gliomas                              | (Li et al., 2013; Melo-Cardenas et al., 2016) |
| USP33         | Associated with axonal guidance receptor Robo1                                                     | (Yuasa-Kawada et al., 2009)    |
| USP36         | Interacts with E3 ligases of TrkA neurotrophin receptor, Nedd 4-2                                   | (Anta et al., 2016)            |
| USP37         | Associated with the stabilization of p27                                                            | (Das et al., 2013; Dobson et al., 2017) |
| USP39         | Associated with the suppression of growth and proliferation of medulloblastomas                    | (Ding et al., 2019)            |
| USP48         | Stabilizes Gli1 (a downstream target of Hedgehog signaling pathway)                                 | (Zhou et al., 2017)            |
| USP33         | Associated with axonal guidance receptor Robo1                                                     | (Yuasa-Kawada et al., 2009)    |
| USP36         | Interacts with E3 ligases of TrkA neurotrophin receptor, Nedd 4-2                                   | (Anta et al., 2016)            |
| USP37         | Associated with the stabilization of p27                                                            | (Das et al., 2013; Dobson et al., 2017) |
| USP39         | Associated with the suppression of growth and proliferation of medulloblastomas                    | (Ding et al., 2019)            |
| USP48         | Stabilizes Gli1 (a downstream target of Hedgehog signaling pathway)                                 | (Zhou et al., 2017)            |
| UCH family    |                                                                                                      |                                |
| UCH-L1        | Regulates synaptic mono-ubiquitination                                                               | Highly expressed in protein aggregates and inclusion bodies associated with PD and AD |
|               | Maintains synaptic structure                                                                       | (Cartier et al., 2009; Gong et al., 2006; Lowe et al., 1988) |
|               | Maintains spine density and size                                                                    |                                |
|               | Regulates pre- and postsynaptic protein levels                                                       |                                |
|               | Regulates monomeric Ub an LTP                                                                      |                                |
| UCH-L3        | Regulates memory and conditions related to memory defects in mice                                   | (Wood et al., 2005)            |
| Ataxin-3      | Implicated in Machado-Joseph Disease                                                                 | (Durcan et al., 2010; Jana et al., 2005; Matsumoto et al., 2004) |
|               | Associated with E3 ligases (CHIP, E4B, Parkin) of proteins involved in the regulation of several neurological conditions |

Getting a particular DUB without affecting the expression of other DUBs. Second, most of the standard assays used to identify DUB inhibitors are prone to non-selective redox or alkylating false positives as DUB activity on ubiquitin molecules is dependent on a reactive thiol group (Wrigley et al., 2011). Additionally, the mode of action of several DUBs comprises complex enzymatic activity via allosteric sites, substrate catalysis, and involvement of both the active and non-active forms of DUBs (Mevissen and Komander, 2017; Sahtoe and Sixma, 2015). Therefore, before targeting DUBs as a therapeutic strategy, we need to address the limitations associated with the development of DUB-based therapies.

**CONCLUSION AND PERSPECTIVE**

In nervous system, PTMs play critical roles in proteasomal degradation and vesicular trafficking of intracellular proteins. Degradation of proteins is critical for the structure, function, and plasticity of synaptic connections (DiAntonio and Hicke, 2004). Ubiquitin protein-aggregates are found in a wide spectrum of neurodegenerative diseases, including AD, Huntington’s disease, and PD. Ubiquitin protease system (UPS) components like E3 ligases, DUBs, chaperons, shuttling factors, and various subtypes of proteasomes form complex networks in neurons (Tai and Schuman, 2008). Moreover, several neurodegenerative disorders are characterized by the accumulation of misfolded proteins, which affects nerve cell function and survival. DUBs have been reported to maintain healthy nerve cells by regulating the degradation of toxic proteins (Todi and Paulson, 2011). DUBs have also been implicated in the regulation of synapses, synaptic plasticity, and several neurodegenerative diseases such as AD, PD, and epilepsy, as well as neuroblastoma and glioblastomas (Kowalski and Juo, 2012; Ristic et al., 2014; Todi and Paulson, 2011). Recently, several studies have identified the role of DUBs in the regulation of various functions of the nervous system and in neurological disorders (Anta et al., 2016; Aron et al., 2018; Ding et al., 2019; Fang et al., 2017; Goldmann et al., 2015;...
Hu et al., 2016; Melo-Cardenas et al., 2016; Schwabenland et al., 2019; Zhou et al., 2017) (Fig. 2).

To date, several DUBs have been shown to regulate the nervous system, which makes them an attractive therapeutic target for disease intervention. However, there are several questions that must be addressed before targeting the DUBs involved in neurological disorders. For instance, neurons are highly polarized cells and the DUB activity in neurons depends on localization or re-localization of DUBs to different cellular or sub-cellular compartments. Thus, before pharmacologically targeting DUBs, it is important to understand which DUBs are shared among excitatory and inhibitory synapses as well as between sensory and motor neurons (Todi and Paulson, 2011). Moreover, we lack information about the expression pattern of DUBs during development and in adults, during activity and resting, in different areas of the brain and spinal cord, and in different types of neuronal and glial cells (Ristic et al., 2014). Given the importance of DUBs in the nervous system and in neurological disorders including cancers, further investigation is needed to improve our understanding of the role of DUBs and UPP in neuronal physiology and pathophysiology (Ristic et al., 2014).

In this review, we summarized the roles of DUBs, which regulate the stability and function of several neuronal proteins (Table 1). Major advances have been made over the past decade in identifying the critical roles of DUBs in nervous system development, function, and disease. Given the importance of PTMs in the nervous system, DUBs could be an excellent target for treatments aimed at maintaining appropriate function of the nervous system and controlling brain-related disorders including cancers.

Disclosure
The authors have no potential conflicts of interest to disclose.

ACKNOWLEDGMENTS
This research was supported by a grant from National Research Foundation of Korea (2018M3A9H3022412 and 2017R1A2B2008727) and Medical Research Center (2017R1A5A2015395), funded by the National Research Foundation of Korea (NRF) of the Ministry of Science, ICT and Future Planning, Republic of Korea.

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REFERENCES
Abbracchio, M.P. and Cattabeni, F. (1999). Brain adenosine receptors as targets for therapeutic intervention in neurodegenerative diseases. Ann. N. Y. Acad. Sci. 890, 79-92.

Abdul Rehman, S.A., Kristariyanto, Y.A., Choi, S.Y., Nkosi, P.J., Weidlich, S., Labib, K., Hofmann, K., and Kulathu, Y. (2016). MINDY-1 is a member of an evolutionarily conserved and structurally distinct new family of deubiquitinating enzymes. Mol. Cell 63, 146-155.

Alexopoulou, Z., Lang, J., Perrett, R.M., Elschami, M., Hurry, M.E.D., Kim, H.T., Mazaraki, D., Szabo, A., Kessler, B.M., Goldberg, A.L., et al. (2016). Deubiquitinase Usp8 regulates α-synuclein clearance and modifies its toxicity in Lewy body disease. Proc. Natl. Acad. Sci. U. S. A. 113, E4688-E4697.

Chen, H., Polo, S., Fiore, P.P. and De Camilli, P. (2003). The deubiquitylase USP8 interacts with TrkA and inhibits neuronal differentiation in PC12 cells. Exp. Cell Res. 333, 49-59.

Chastagner, P., Israël, A., and Brou, C. (2008). AIP4/Itch regulates Notch receptor degradation in the absence of ligand. PLoS One 3, e2735.

Chen, F., Sugiura, Y., Myers, K.G., Liu, Y., and Lin, W. (2010). Ubiquitin carboxyl-terminal hydrolase L1 is required for maintaining the structure and function of the neuromuscular junction. Proc. Natl. Acad. Sci. U. S. A. 107, 1636-1641.

Chen, H., Polo, S., Fiore, P.P., and De Camilli, P.V. (2003). Rapid Ca2+-dependent decrease of protein ubiquitination at synapses. Proc. Natl. Acad. Sci. U. S. A. 100, 14908-14913.

Chen, R., Qin, L.N., Li, X.M., Walters, B.J., Wilson, J.A., Mei, L., and Wilson, S.M. (2009). The proteasome-associated deubiquitinating enzyme Usp14 is essential for the maintenance of synaptic ubiquitin levels and the development of neuromuscular junctions. J. Neurosci. 29, 10909-10919.

Chen, X., Zhang, B., and Fischer, J.A. (2002). A specific protein substrate for a deubiquitinating enzyme: liquid facets are the substrate of fat facets. Genes Dev. 16, 289-294.

Choe, E.A., Liao, L., Zhou, J.Y., Cheng, D., Duong, D.M., Jin, P., Tsai, L.H., and Peng, J. (2007). Neuronal morphogenesis is regulated by the interplay between cyclin-dependent kinase 5 and the ubiquitin ligase mind bomb 1. J. Neurosci. 27, 9503-9512.

Collard, F. (2010). The therapeutic potential of deubiquitinating enzyme inhibitors. Biochem. Soc. Trans. 38, 137-143.

Das, C.M., Taylor, P., Gireud, M., Singh, A., Lee, D., Fuller, G., Ji, L., Fangusaro, J., Rajaram, V., Goldman, S., et al. (2013). The deubiquitylase USP37 links REST to the control of p27 stability and cell proliferation. Oncogene 32, 1691-1701.
Regulation of DUBs in Neurobiology
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DiAntonio, A., Haighhigh, A.R., Portman, S.L., Lee, J.D., Amaranto, A.M., and Goodman, C.S. (2001). Ubiquitination-dependent mechanisms regulate synaptic growth and function. Nature 412, 449.

DiAntonio, A. and Hicke, L. (2004). Ubiquitin-dependent regulation of the synapse. Annu. Rev. Neurosci. 27, 223-246.

Ding, K., Ji, J., Zhang, X., Huang, B., Chen, A., Zhang, D., Li, X., Wang, X., and Wang, J. (2019). RNA splicing factor USP39 promotes glioma progression by inducing TAZ mRNA maturation. Oncogene 38, 6414-6428.

Ding, M. and Shen, K. (2008). The role of the ubiquitin proteasome system in synapse remodeling and neurodegenerative diseases. Bioessays 30, 1075-1083.

Dobson, TH., Hatcher, RJ., Swaminathan, J., Das, C.M., Shaik, S., Tao, R.H., Milite, C., Castellano, S., Taylor, PH., and Sbardella, G. (2017). Regulation of USP37 expression by REST-associated G9a-dependent histone methylation. Mol. Cancer Res. 15, 1073-1084.

Dupont, S., Mamidi, A., Cordenonsi, M., Montagner, M., Zacchigna, L., Adorno, M., Martello, G., Stinchfield, MJ., Soligo, S. and Morsut, L. (2009). FAM/USP9x, a deubiquitinating enzyme essential for TGfβ signaling, controls Smad4 monoubiquitination. Cell 136, 123-135.

Duran, T.M., Kontogiannea, M., Thorarinsdottir, T., Fallon, L., Williams, A.J., Djarmati, A., Fantaneanu, T., Paulson, H.L., and Fon, E.A. (2010). The Machado–Joseph disease-associated mutant form of ataxin-3 regulates stress. Front. Mol. Neurosci. 11, 18.

Everington, E.A., Gibbard, A.G., Swinny, J.D., and Seifi, M. (2018). Molecular restriction (UbiCRest). Nat. Protoc. 10, 349-361.

Fang, X., Zhou, W., Wu, Q., Huang, Z., Shi, Y., Yang, K., Chen, C., Xie, Q., Mack, S.C., Wang, X., et al. (2017). Deubiquitinaise USP13 maintains glioblastoma stem cells by antagonizing FBXL14-mediated Medc ubiquitination. J. Exp. Med. 214, 245-267.

Francis, F., Koulakoff, A., Boucher, D., Chahey, P., Schaer, B., Vinet, M.C., Friocourt, G., McDonnell, N., Reiner, O., and Kahn, A. (1999). Doublecortin is a developmentally regulated, microtubule-associated protein expressed in migrating and differentiating neurons. Neuron 23, 247-256.

Friocourt, G., Kappeler, C., Saillour, Y., Fauchereau, F., Rodriguez, M.S., Bahi, N., Vinet, M.C., Chahey, P., Poirier, K., and Taya, S. (2005). Doublecortin interacts with the ubiquitin protease DFFRX, which associates with microtubules in neuronal processes. Mol. Cell. Neurosci. 28, 153-164.

Goldmann, T., Zeller, N., Raasch, J., Kierdorf, K., Frenzel, K., Ketcher, L., Basters, A., Stasiewski, O., Bredecke, S.M., Spiess, A., et al. (2015). USP18 lack in microglia causes destructive interferonopathy of the mouse brain. EMBO J. 34, 1612-1629.

Gong, B., Cao, Z., Zheng, P., Vitolo, O.V., Liu, S., Staniszevska, A., Moorman, D., Zhang, H., Shenlans, M., and Arancio, O. (2006). Ubiquitin hydrolase Uch-L1 rescues β-amyloid-induced decreases in synaptic function and contextual memory. Cell 126, 775-788.

Guan, K.L. and Rao, Y. (2003). Signalling mechanisms mediating neuronal responses to guidance cues. Nat. Rev. Neurosci. 4, 941.

Hedde, A.N., Inokuchi, K., Pei, W., Casadio, A., Ghirardi, M., Chain, D.G., Adorno, M., Martello, G., Stinchfield, M.J., Soligo, S., and Morsut, L. (2009). βFAM/USP9x, a deubiquitinating enzyme essential for TGFβ signaling, promotes maintenance of neural progenitor cells. Nat. Cell. Biol. 13, 142-152.

Huo, Y., Khatri, N., Hou, Q., Gilbert, J., Wang, G., and Man, H.Y. (2015). The deubiquitinating enzyme USP46 regulates AMPA receptor ubiquitination and trafficking. J. Neurochem. 134, 1067-1080.

Ikeda, W., Nakanishi, H., Miyoshi, J., Mandai, K., Ishizaki, H., Tanaka, M., Towaga, A., Takahashi, K., Nishikoa, H., and Yoshida, H. (1999). Afadin: a key molecular essential for structural organization of cell–cell junctions of polarized epithelia during embryogenesis. J. Cell Biol. 146, 1117-1132.

Imai, S., Mamiya, T., Tuskada, A., Sakai, Y., Mouri, A., Nabeishima, K., and Ebitara, S. (2012). Ubiquitin-specific peptidase 46 (Usp46) regulates mouse immobile behavior in the tail suspension test through the GABAergic system. PLoS One 7, e39084.

Jana, N.R., Dikshit, P., Goswami, A., Kotliarova, S., Murata, S., Tanaka, K., and Nukina, N. (2005). Co-chaperone CHIP associates with expanded polyglutamine protein and promotes their degradation by proteasomes. J. Biol. Chem. 280, 11635-11640.

Jason, J.Y. and Ehlers, M.D. (2007). Emerging roles for ubiquitin and protein degradation in neuronal function. Pharmacological Rev. 59, 14-39.

Jiang, X., Yu, M., Ou, Y., Cao, Y., Yao, Y., Cai, P., and Zhang, F. (2017). Downregulation of USP4 promotes activation of microglia and subsequent neuronal inflammation in rat spinal cord after injury. Neurochem. Res. 42, 3245-3253.

Kaltenbach, L.S., Romero, E., Becklin, R.R., Chettier, R., Bell, R., Phansalkar, A., Strand, A., Torcassi, C., Savage, J., Hurlburt, A., et al. (2007). Huntingtin interacting proteins are genetic modifiers of neurodegeneration. PLoS Genet. 3, e82.

Karpel-Massifer, G., Banu, M.A., Shu, C., Halatsch, M.E., Westhoff, M.A., Bruce, J.N., Canoll, P., and Siegelin, M.D. (2016). Inhibition of deubiquitinasases primes glioblastoma cells to apoptosis in vitro and in vivo. Oncotarget 7, 12791-12805.

Kawaguchi, Y., Okamoto, T., Tanawai, M., Aizawa, M., Inoue, M., Katayama, S., Kawakami, H., Nakamura, S., Nishimura, M., and Aikiguichi, I. (1994). CAG expansions in a novel gene for Machado-Joseph disease at chromosome 14q32.1. Nat. Genet. 8, 211-222.

Kerrisk Campbell, M. and Sheng, M. (2018). USP8 deubiquitinates SHANK3 to control synapse density and SHANK3 activity-dependent protein levels. J. Neurosci. 38, 5289-5301.

Komander, D. and Rape, M. (2012). The ubiquitin code. Annu. Rev. Biochem. 81, 203-229.

Kon, N., Zhong, J., Kobayashi, Y., Li, M., Szabolcs, M., Ludwig, T., Canoll, PD., and Gu, W. (2011). Roles of HAUSP-mediated p53 regulation in central nervous system development. Cell Death Differ. 18, 1366-1375.

Kovalenko, A., Chable-Bessia, C., Cantarella, G., Israël, A., Wallach, D., and Courtois, G. (2003). The tumour suppressor CYLD negatively regulates NF-κB signalling by deubiquination. Nature 424, 801-805.

Kowalski, J.R., Dahlberg, C.L., and Joo, P. (2011). The deubiquitinating enzyme USP46 negatively regulates the degradation of glutamate receptors to control their abundance in the ventral nerve cord of Caenorhabditis elegans. J. Neurosci. 31, 1341-1354.

Kowalski, J.R. and Joo, P. (2012). The role of deubiquitinating enzymes in synaptic function and nervous system diseases. Neural. Plast. 2012, 892749.

Kulathu, Y. and Komander, D. (2012). Atypical ubiquitylation—the unexplored world of polyubiquitin beyond Lys48 and Lys63 linkages. Nat. Rev. Mol. Cell Biol. 13, 508.

Kwasna, D., Abdul Rehman, S.A., Natarajan, J., Matthews, S., Madden, R., De Hu, M., Chen, H., Han, C., Lan, J., Xu, Y., Li, C., Xue, Y., and Lou, M. (2016). Expression and functional implications of USP17 in glioma. Neurosci. Lett. 616, 125-131.

Huang, Z., Wu, Q., Guryanova, O.A., Cheng, L., Shou, W., Rich, J.N., and Bao, S. (2011). Deubiquitylase HAUSB stabilizes REST and promotes maintenance of neural progenitor cells. Nat. Cell. Biol. 13, 142-152.
Lasky, J.L. and Wu, H. (2005). Notch signaling, brain development, and human disease. Pediatr. Res. 57, 104-109.

Lee, B.H., Lee, M.J., Park, S., Oh, D.C., Elsasser, S., Chen, P.C., Gartner, C., Dimova, N., Hanna, J., and Gygi, S.P. (2010). Enhancement of proteasomal activity by a small-molecule inhibitor of USP14. Nature 467, 179.

Lennox, G., Lowe, J., Morrell, K., Landon, M., and Mayer, R.J. (1988). Ubiquitin is a component of neurofilibrillary tangles in a variety of neurodegenerative diseases. Neurosci. Lett. 94, 211-217.

Li, Z.H., Yu, Y., Du, C., Fu, H., Wang, J., and Tian, Y. (2013). RNA interference-deubiquitylating enzyme FAM/USP9X. J. Biol. Chem. 281, 38738-38747.

Matsumoto, M., Yada, M., Hatakeyama, S., Ishimoto, H., Tanimura, T., Ducza, E., Ogris, E., Boehm, S., Freissmuth, M., and Nanoff, C. (2006). The ataxia and induces cell cycle arrest. Oncol. Lett. 5, 1290-1294.

Melo-Cardenas, J., Zhang, Y., Zhang, D.D., and Fang, D. (2016). Ubiquitin-669.

Morsli, R., Wijnhoven, P., le Sage, C., Tjeertes, J., Galanty, Y., Former, J.V., Cagide, M.J., Urbé, S., and Jackson, S.P. (2014). Systematic characterization of deubiquitylating enzymes for roles in maintaining genome integrity. Nat. Cell Biol. 16, 1016-1018.

Ross, O.A., Braithwaite, A.T., Skipper, L.M., Kachergus, J., Hulihan, M.M., Middleton, F.A., Nishiooka, K., Fuchs, J., Gasser, T., and Maraganore, D.M. (2008). Genomic investigation of α-synuclein multiplication and Parkinsonism. Ann. Neurol. 63, 743-750.

Sahtoe, D.D. and Sixma, T.K. (2015). Layers of DUB regulation. Trends Biochem. Sci. 40, 456-467.

Saitoh, S. and Kondo, J. (2007). The functions of UCH-L1 and its relation to neurodegenerative diseases. Neurochem. Int. 51, 105-111.

Shih, R.H., Wang, C.Y., and Yang, C.M. (2015). α-kappaB signaling pathways in neurological inflammation: a mini review. Front. Mol. Neurosci. 8, 77.

Spillantini, M.G. and Goedert, M. (2000). The α-synucleinopathies: Parkinson's disease, dementia with Lewy bodies, and multiple system atrophy. Ann. N. Y. Acad. Sci. 920, 16-27.

Spillantini, M.G., Schmidt, M.L., Lee, V.M.Y., Trojanowski, J.Q., Jakes, R., and Goedert, M. (1997). α-Synuclein in Lewy bodies. Nature 388, 839.

Tai, H.C. and Schuman, E.M. (2008). Ubiquitin, the proteasome and protein degradation in neuronal function and dysfunction. Nat. Rev. Neurosci. 9, 826.

Tang, B.L. (2009). REST regulation of neural development: from inside-out? Cell Adh. Migr. 3, 1-2.

Tarpay, P.S., Smith, R., Pleasance, E., Whibley, A., Edkins, S., Hardy, C., O`meara, S., Latimer, C., Dicks, E., and Menzies, A. (2009). A systematic, large-scale resequencing screen of X-chromosome coding exons in mental retardation. Nat. Genet. 41, 543-462.

Qin, N., Han, F., Li, L., Ge, Y., Lin, W., Wang, J., Wu, L., Zhao, G., and Zhang, J. (2019). Deubiquitinating enzyme 4 facilitates chemoresistance in glioblastoma by inhibiting P53 activity. Oncol. Lett. 17, 958-964.
Regulation of DUBs in Neurobiology
Soumyadip Das et al.

Tavana, O., Li, D., Dai, C., Lopez, G., Banerjee, D., Kon, N., Chen, C., Califano, A., Yamashiro, D.J., Sun, H., et al. (2016). HAUSP deubiquitinates and stabilizes N-Myc in neuroblastoma. Nat. Med. 22, 1180-1186.

Taya, S., Yamamoto, T., Kanai-Azuma, M., Wood, S.A., and Kaibuchi, K. (1999). The deubiquitinating enzyme Fam interacts with and stabilizes β-catenin. Genes Cells 4, 757-767.

Tessier-Lavigne, M. and Goodman, C.S. (1996). The molecular biology of axon guidance. Science 274, 1123-1133.

Todi, S. and Das, C. (2012). Should deubiquitinating enzymes be targeted for therapy. Clin. Pharmacol. Biopharm. 1, 1000e108.

Todi, S.V. and Paulson, H.L. (2011). Balancing act: deubiquitinating enzymes in the nervous system. Trends Neurosci. 34, 370-382.

Todi, S.V., Williams, A.J., and Paulson, H.L. (2007). Polyglutamine disorders including Huntington's disease. In Molecular Neurology, S.G. Waxman, ed. (Cambridge: Academic Press), pp. 257-275.

Toews, M.L. (2006). Adenosine receptors find a new partner and move out. Mol. Pharmacol. 69, 1075-1078.

Tomida, S., Mamiya, T., Sakamaki, H., Miura, M., Aosaki, T., Masuda, M., Niwa, M., Kameyama, T., Kobayashi, J., and Iwaki, Y. (2009). Usp46 is a quantitative trait gene regulating mouse immobile behavior in the tail suspension and forced swimming tests. Nat. Genet. 41, 688.

Vaden, J.H., Bhattacharyya, B.J., Chen, P., Watson, J.A., Marshall, A.G., Phillips, S.E., Wilson, J.A., King, G.D., Miller, R.J., and Wilson, S.M. (2015). Ubiquitin-specific protease 14 regulates c-Jun N-terminal kinase signaling at the neuromuscular junction. Mol. Neurodegener. 10, 3.

Wey, A. and Knoepfler, P.S. (2010). C-myc and N-myc in the developing brain. Aging (Albany NY) 2, 261-262.

Wilkinson, K.D., Deshpande, S., and Larsen, C.N. (1992). Comparisons of neuronal (PGP 9.5) and non-neuronal ubiquitin C-terminal hydrolases. Biochem. Soc. Trans. 20, 631-637.

Williams, A.J. and Paulson, H.L. (2008). Polyglutamine neurodegeneration: protein misfolding revisited. Trends Neurosci. 31, 521-528.

Wilson, S.M., Bhattacharyya, B., Rachel, R.A., Coppola, V., Tessarollo, L., Householder, D.B., Fletcher, C.F., Miller, R.J., Copeland, N.G., and Jenkins, N.A. (2002). Synaptic defects in ataxia mice result from a mutation in Usp14, encoding a ubiquitin-specific protease. Nat. Genet. 32, 420.

Wood, M.A., Kaplan, M.P., Brensinger, C.M., Guo, W., and Abel, T. (2005). Ubiquitin C-terminal hydrolase L3 (Uch3) is involved in working memory. Hippocampus 15, 610-621.

Wrigley, JD., Eckersley, K., Hardern, I.M., Millard, L., Walters, M., Peters, S.W., Mott, R., Nowak, T., Ward, R.A., Simpson, P.B., et al. (2011). Enzymatic characterisation of USP7 deubiquitinating activity and inhibition. Cell Biochem. Biophys. 60, 99.

Xiao, N., Li, H., Luo, J., Wang, R., Chen, H., Chen, J., and Wang, P. (2012). Ubiquitin-specific protease 4 (USP4) targets TRAF2 and TRAF6 for deubiquitination and inhibits TNFα-induced cancer cell migration. Biochem. J. 441, 979-987.

Ye, Y. and Rape, M. (2009). Building ubiquitin chains: E2 enzymes at work. Nat. Rev. Mol. Cell Biol. 10, 755.

Yeates, E.F.A. and Tesco, G. (2016). The endosome-associated deubiquitinating enzyme USP8 regulates BACE1 enzyme ubiquitination and degradation. J. Biol. Chem. 291, 15753-15766.

Yi, L., Cui, Y., Xu, Q., and Jiang, Y. (2016). Stabilization of LSD1 by deubiquitinating enzyme USP7 promotes glioblastoma cell tumorigenesis and metastasis through suppression of the p53 signaling pathway. Oncol. Rep. 36, 2935-2945.

Yoon, K. and Gaiano, N. (2005). Notch signaling in the mammalian central nervous system: insights from mouse mutants. Nat. Neurosci. 8, 709.

Yuasa-Kawada, J., Kinoshita-Kawada, M., Wu, G., Rao, Y., and Wu, J.Y. (2009). Midline crossing and Slit responsiveness of commissural axons require USP33. Nat. Neurosci. 12, 1087-1089.

Zhadanov, A.B., Provance, D.W., Jr, Speer, C., Coffin, J.D., Goss, D., Blixt, J., Reichert, C.M., and Mercer, J.A. (1999). Absence of the tight junctional protein AF-6 disrupts epithelial cell–cell junctions and cell polarity during mouse development. Curr. Biol. 9, 880-882.

Zhang, C.W., Hang, L., Yao, T.P., and Lim, K.L. (2016). Parkin regulation and neurodegenerative disorders. Front. Aging Neurosci. 7, 248.

Zhou, A., Lin, K., Zhang, S., Ma, L., Xue, J., Morris, S.A., Aldape, K.D., and Huang, S. (2017). Gli1-induced deubiquitinase USP48 aids glioblastoma tumorigenesis by stabilizing Gli1. EMBO Rep. 18, 1318-1330.