Review

The potential roles of deubiquitinating enzymes in brain diseases

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\textbf{ABSTRACT}

Most proteins undergo posttranslational modification such as acetylation, methylation, phosphorylation, biotinylation, and ubiquitination to regulate various cellular processes. Ubiquitin-targeted proteins from the ubiquitin-proteasome system (UPS) are degraded by 26S proteasome, along with this, deubiquitinating enzymes (DUBs) have specific activity against the UPS through detaching of ubiquitin on ubiquitin-targeted proteins. Balancing between protein expression and degradation through interplay between the UPS and DUBs is important to maintain cell homeostasis, and abnormal expression and elongation of proteins lead to diverse diseases such as cancer, diabetes, and autoimmune response. Therefore, development of DUB inhibitors as therapeutic targets has been challenging. In addition, understanding of the roles of DUBs in neurodegeneration, specifically brain diseases, has emerged gradually. This review highlights recent studies on the molecular mechanisms for DUBs, and discusses potential therapeutic targets for DUBs in cases of brain diseases.

1. Introduction

Ubiquitination is a common posttranslational modification (PTM) mediated by ubiquitin, and ubiquitin is consisted of 76 amino acids and is attached to a target protein with a covalent bond through three enzymatic processes; E1-activating, E2-conjugating, and E3-ligase enzymes (Fig. 1a) (Ciechanover, 2005). Firstly, the ubiquitin activating reaction with two E1 enzymes depends on an ATP to make thioester linkage on ubiquitin, and the activated ubiquitin is transferred to $\sim$ 40 E2 enzymes. Finally, the C-terminus of ubiquitin is bound to the ε-amino group of a lysine residue on its substrates by the interaction with E2 and E3 ligases (Deshaies and Joazeiro, 2009). Ubiquitin E3 ligases are structurally and functionally distinct for named as RING and HECT (Metzger et al., 2012). More than 600 E3 ligases are encoded in the human genome and they form as mono-, di-, and multicomplex with E2s to degrade target proteins (Ozkan et al., 2005). Unlike RING E3 ligases, $\sim$ 30 HECT E3 ligases are encoded in humans and are associated with cell growth and proliferation through the regulation of protein trafficking, transportation, and signaling pathways (Rotin and Kumar, 2009). Other ubiquitin-like modifiers (UBLs) such as NEDD8, SUMO, and ISG15 are also bound to targeted proteins through E1-E2-E3 enzyme cascades known as Neddylation, Sumoylation, and ISGylation, respectively (Hochstrasser, 2009). This reaction creates various types of ubiquitin chains through seven internal lysine residues on ubiquitin; K6, K11, K27, K29, K33, K48, and K63, while a K48-linked ubiquitin chain acts as a proteolysis marker for target proteins in the ubiquitin-proteasome system (UPS) (Lim et al., 2016). Because most ubiquitinated proteins undergo proteasomal degradation by 26S proteasome complex as a macromolecule, ubiquitination has been known as “a molecular kiss of death” since it was identified (Behuliak et al., 2005). However, a number of studies have revealed that the fate of ubiquitinated protein is determined by the types of ubiquitination or ubiquitin chain(s) such as monoubiquitination, multi-monoubiquitination, homogenous-ubiquitin chain, branched-ubiquitin chain, and mixed-ubiquitin chain (Komander and Rape, 2012). These types of ubiquitin can induce proteolysis for targeted proteins, as well as regulate several cellular processes or signaling pathways. They are involved in functions such as protein-protein interaction and activity, alteration of protein complex, and transporting of subcellular localization (Huang and D’Andrea, 2006). In addition, the expanding roles of ubiquitin by PTMs such as acetylation and phosphorylation have been demonstrated, recently (Herhaus and Dikic, 2015). For example, proteasomal degradation of target proteins was induced by K11-linked as well as K48-linked ubiquitin chain (Jin et al., 2008). In the case of K63-linked ubiquitin chains, it is mainly associated in the DNA double-strand break (DSB) repair process and translational regulation, and autophagy formation (Back et al., 2019; Lee et al., 2017; Xu et al., 2018). Although the intracellular functions of K6-, K27-, K29-, and K33-linked ubiquitin chains are currently uncleared, a recent proteomic analysis provides valuable information that helps the identification of cellular functions of these
ubiquitin codes (Michel et al., 2017).

The UPS becomes reversible through the action of deubiquitinating enzymes (DUBs) in a process that can edit and cleave monomeric modifiers such as ubiquitin from substrates (Fig. 1b) (Lim and Baek, 2013). Approximately ∼100 DUBs are encoded in humans and they are structurally classified into several subfamilies such as ubiquitin-specific proteases (USPs; 54 members), ovarian tumor proteases (OTUs; 16 members), ubiquitin C-terminal hydrolases (UCHs; 4 members), Machado-Joseph domain containing proteases (MJDs; 4 members), and JAB1/MPN/MOV34 metallocproteinases (JAMMs; 7 members) (Lim et al., 2016). A newly identified DUB, motif interacting with Ub-containing novel DUB family (MINDY), has been recently added as a DUB subfamily (Abdul Rehman et al., 2016). UBL-related DUBs also exist; for example, sentrin/SUMO-specific proteases (SENP), deSUMOylating isopeptidase (DeSI), and NEDD8-specific protease 1 (NEDP1) are targeted to SUMO and NEDD8, respectively (Hickey et al., 2012; Shin et al., 2012). To date, lots of research into the roles of DUBs have revealed their structures and mechanisms both in vivo and in vitro. In addition, many reviews well summarized the roles of DUBs, and have suggested the therapeutic target of DUBs in several diseases such as cancer (Kausal et al., 2018; Lim and Baek, 2013; Mevissen and Komander, 2017). With increased understanding of the function for DUBs in the central nervous system, this review provides insights into the role of DUBs in brain diseases by examining the emerging evidence that suggests potential cues to how DUBs can be used in the brain disease therapy.

2. DUBs in Parkinson’s disease

2.1. Overview of DUBs in Parkinson’s disease (PD) pathology

PD is a neurodegenerative disorder and is caused by aggregation of proteins into Lewy bodies (LBs) and Lewy neurites (LNs) which are located in the neuron soma and axons, respectively (Cookson, 2003). To understand PD pathology, it is important to identify PTMs or interaction partners, and to analyze inherited mutations on PD-related proteins and genes. For example, Parkin mutations in the early-onset PD show that a wide majority are defective in most PD patients (Marder et al., 2010). Several pieces of research have revealed that abnormal PTMs such as ubiquitination of Parkin and α-synuclein (SNCA) are mainly linked to PD (Schmid et al., 2013; Yasuda and Mochizuki, 2010). From the UPS axis, Lys12,21, and 23 on SNCA are related to ubiquitination for aggregation of LBs (Schmid et al., 2013). In addition, the proteasome, as well as the lysosome, cannot degrade A53T mutated SNCA, and this leads to promotion of fibrilization (Cuervo et al., 2004). It has been suggested that proteolytic regulation of SNCA is a main component of PD pathology.

As described previously, SNCA is one of the major components of LBs, and several clinical studies have reported that SNCA exists at higher levels in the brain and this can lead to aggregation and neurodegeneration (Luk et al., 2009; Parnetti et al., 2019). Abnormal expression of SNCA is subject to unbalanced regulation between accumulation and degradation in PD. Therefore, several E3 ubiquitin ligases induce considerable degradation of α-synuclein that leads to the selective elimination of α-synuclein protein. UCH-L1 was identified as the first DUB which is associated with PD through a autosomal mutation on 193M, and it works to decrease the enzymatic activity of UCH-L1. Since then various studies have added new mutations such as E7A and S18Y on UCH-L1 in PD (Lee and Hsu, 2017; Liu et al., 2002).

Leucine-rich repeat kinase 2 (LRRK2) and glucocerebrosidase (GBA) were also identified as high-linked proteins for PD progression by genome-wide association study (GWAS) (Nalls et al., 2014). Furthermore, α-synuclein, Ubiquitin carboxy-terminal hydrolase L1 (UCH-L1), LRRK2, GRB10 interacting GYF protein 2 (GIGYF2), High-temperature-regulated A2 (HTRA2), Vacular protein sorting-associated protein 35 (VPS35), and Eukaryotic translation initiation factor (EIF4G1) have been shown to be autosomal dominant, while Parkin, Pten-induced putative kinase 1 (PINK1), DJ-1, lysosomal type 5 ATPase (ATP13A2),

Fig. 1. The cascade of ubiquitination for target proteins with relating enzyme reactions. (A) Ubiquitin is activated by an E1 activating enzyme (E1) in an ATP-dependent manner and then transferred to an E2 conjugating enzyme (E2). Finally, E2 and E3 form a complex with the substrate, and ubiquitin chains are then formed with an isopeptide bond to Lys on the substrate. (B) Ubiquitinated proteins are determined by the types of ubiquitin chain associated with proteasomal degradation or with diverse intracellular functions.
Phospholipase A2 (PLA2G6), F-box only protein 7 (FBX7), and DNAJ/HSP40 homolog subfamily C member 6 (DNAJC16) have been shown autosomal recessive (Hernandez et al., 2016).

In order to find molecular insights for therapies of PD, advances in sequencing and analysis of protein structure have led to the discovery of diverse mutations on PD-related proteins such as the Parkin family in the PD. These mutations are now used as targets for therapies and clinical trials for PD and have been thoroughly summarized in a previous review paper (Elkouzi et al., 2019). Mutations of PD-associated proteins that are related to dysfunction for a single pathway might also affect other pathways, and it is particularly difficult to understand and target which molecular mechanisms for PD-related protein degradation ultimately underlie the key to disease modification (Elkouzi et al., 2019). In addition, a previous study has suggested that genetic inheritance may not be necessary for PD occurrence and could correspond with exposure to common environmental components (Sveinbjörnsdottir et al., 2000). This report indicates the importance of discovering proteins that are strongly involved in PD pathology. Despite the list of genetic mutations in PD patients is gradually growing, the clinical features of DUBs, such as UCL-L1, have not been fully identified. Identification of molecular mechanisms and protein signal transductions of DUBs in PD pathology may be further complicated by crosstalk with combinations of various factors.

2.2. Functional relationship between DUBs and mitochondrial dysfunction

Maintaining mitochondria-derived cellular homeostasis is critical for neuronal cell function and for suppressing mitochondrial dysfunction events that can lead to neurodegenerative diseases (NDs) (Mottis et al., 2019). NDs, including PD, contain biological hallmarks of ageing such as mitochondrial dysfunction; while Alzheimer’s disease (AD), as the second most common neuronal disease, has overlapping molecular characteristics with PD (Borizogan et al., 2013; Collaborators, 2019; Hou et al., 2019). Works of many model systems have made clear the role of mitochondria dynamics play in the generation of adenosine 5’-triphosphate (ATP) through oxygen, production of reactive oxygen species (ROS), mitophagy, and autophagy; all of which indicate the range of mitochondrial dysfunction (Mottis et al., 2019). In particular, the mitophagy and autophagy processes are required to clear mitochondria that were damaged by the failure of proteasomal or lysosomal degradation due to unfolded proteins from proteotoxic stresses (Mottis et al., 2019). The mitochondrial unfolded protein response (UPRmit) is a sensor for mitochondrial dysfunction and facilitates recovery of mitochondrial function (Naresh and Haynes, 2019). Importantly, proteolysis of unfolded protein and its proteasomal degradation seem to be functionally connected to mitochondrial dysfunction, as they are constitutively associated with the interaction of DUBs.

Indeed, several DUBs are localized to mitochondria and remove ubiquitin from the substrates (Duran et al., 2011; Kim et al., 2011). Perhaps there are fundamental mechanisms for localizing DUBs in mitochondria in mitophagy. For example, sequence analysis of DUBs showed that USP30 has a membrane topology and is localized to the mitochondrial outer membrane (MOM), and it is required for maintaining of mitochondrial morphology through regulation of mitochondrial elongation (Nakamura and Hirose, 2008). In addition, several studies have revealed that DUBs, such as Ataxin-3, USP8, USP15, USP30, USP33 and USP35, were associated with Parkin-mediated ubiquitination in mitophagy (Bingol et al., 2014; Cornelissen et al., 2014; Durcan et al., 2011; Nakamura and Hirose, 2008; Niu et al., 2019; Wang et al., 2015). Interestingly, Parkin E3 ligase has both RING and HECT domains and is localized in MOM, it can remove dysfunctional mitochondria by selective promotion of autophagy or mitophagy (Fig. 2) (Kubli and Gustafsson, 2012). USP8 was identified as a mediator for lysosomal degradation, and a recent study showed that clearance of SNCA is regulated by USP8 for lysosomal degradation (Alexopoulos et al., 2016; Balut et al., 2011). Although SNCA is regulated by USP8, Parkin/Park2 was initially identified as a USP8 interaction partner in mitochondria that is required for Parkin localization to depolarize mitochondria through ubiquitination of the K6-linked ubiquitin chain on Parkin protein (Durcan et al., 2014). In addition, further research has revealed that USP8 seems to probably promote removal of K6-linked ubiquitin chain in the regulation of mitophagy (Durcan and Fon, 2015). Recently, USP8, Nrdp1 as an E3 ligase, and Clec16a form a complex that has been proposed to maintain mitochondrial quality in β-cell mitophagy (Pearson et al., 2018).

The precise functions of USP30 in mitochondrial ubiquitination, which was carried out by Parkin targeting K6- and K11-linked ubiquitin chains, were revealed by biochemical and structural assays (Cunningham et al., 2015; Gersch et al., 2017). USP30-mediated mitochondrial regulatory mechanism that modulates the ubiquitin ligase activity as Parkin in MOM was identified (Bingol et al., 2014). Ubiquitination on damaged mitochondria is important to activate mitophagy. However, USP30 inhibits the E3 function of Parkin by removing K6-linked ubiquitin chains in mitochondria (Bingol et al., 2014; Sato et al., 2017). Loss of USP30 has an opposite effect, leading to significant rescue of the mitophagy under ROS conditions (Bingol et al., 2014). Therefore, USP30 inhibitors might be a potent drug for treating PD patients by inducing mitophagy. This strategy, to induce mitophagy by targeting USP30, is currently being investigated using MF-094, which is a substance that accelerates mitophagy (Riuge et al., 2018). Similarly, depletion of USP15 also rescues mitophagy defects in PD patient’s fibroblasts (Cornelissen et al., 2014). Using a fluorescent-based mitophagy reporter assay to monitor the role of USP30 in the absence or presence of Parkin, an interesting feature of USP30 in controlling autophagy was recently described (Marcassa et al., 2018).

2.3. Autophagy and DUBs

Autophagy conceptually includes mitophagy for mitochondrial clearance with protein degradation. Autophagy can be split into three types; macroautophagy (generally regarded for “Autophagy”), microautophagy, and chaperone-mediated autophagy through its substrates (Parzych and Klionsky, 2014). Autophagy is initiated with a mammalian target of rapamycin (mTOR) as the inhibitor and AMP-activated kinase (AMPK) as the activator, and proceeds by utilizing several autophagy-related (ATGs) and light chain 3/γ-aminobutyric acid receptor-associated proteins (LC3/GABARAPs) in the cytosol (Dikic and Elazar, 2018). The relationship between autophagy and mammalian diseases including neurodegenerative disorders has been thoroughly reviewed previously (Dikic and Elazar, 2018). Autophagy plays an important role in brain disorders such as PD for targeted protein degradation, and the molecular mechanisms of DUBs in each type of autophagy have been elucidated recently (Jacomin et al., 2018).

In some cases, the nature of DUBs and E3s in mTOR signaling has been summarized and candidates for their biochemical components have been proposed (Jiang et al., 2019). For example, USPs (USP1, USP4, USP7, USP8, USP9X, USP10, USP12, USP13, USP18, USP20, USP46, and USP52), OTUs (OTU1, OTUD3, and OTUD7B), and CYLD were suggested as counteracting DUBs for E3s in mTOR signaling (Jiang et al., 2019). Although mTOR signaling is involved in various intracellular events (such as cell growth, proliferation, autophagy, metabolism, and DNA damage), and the expression level of DUBs is frequently changed in malignant tumors, most mTOR-signaling-associated DUBs have been identified in neurodegenerative models as well as in cancers (Fraile et al., 2012). USP2 acts as an upstream regulator of mTOR ubiquitination in the autophagy procedure, while UCH-L1 has been identified as a biomarker for the pathogenesis of PD and regulates mTOR complex through counteracting DDB1-CUL4-mediated raptor ubiquitination (Hussain et al., 2013; Li et al., 2018). In addition, UCH-L1 enhances PDGF-BB-induced mTOR phosphorylation and increases p21WAF1/Cip1 protein expression leading to autophagy suppression.
function activates autophagy (Taillebourg et al., 2012). Although USP36 is not involved in mTOR pathway, loss of regulator for mTOR signaling in neuronal progenitors (Bridges et al., 2017). Although USP36 is not involved in mTOR pathway, loss of regulator for mTOR signaling in neuronal progenitors (Bridges et al., 2017). Moreover, USP9X has also been suggested as a significant contributor to the clearance of Parkin by the autophagic process. Beclin1 (also termed as Atg6) is required for nucleation of autophagy by forming a complex with class III PI3K Vacular protein sorting 34 (Vps34) and has been identified as a remover of Ataxin-3 (Nascimento-Ferreira et al., 2011; Zeng et al., 2006). Interestingly, Vps34 acts as a regulator for autophagy, and Vps34 complexes down-regulate USP10 and USP13 by Beclin1, suggesting that they are downstream of autophagy activation (Liu et al., 2011). Previous studies have shown that the expression of Beclin1 is decreased in neurological disorders such as Alzheimer’s, Huntington’s and Machado–Joseph disease, and treatment with Beclin1 leads to improvement of neuronal dysfunction, neurodegeneration, and mitochondrial function (Ashkenazi et al., 2017; Chang et al., 2016; Nascimento-Ferreira et al., 2013). These researches have used Ataxin-3 to show the effect of Beclin1 on autophagy activity. An interesting study has shown the proteolysis mechanism of Beclin1 at the cellular level in cancer cells; however, Beclin1 is stabilized by USP9X (Elgendy et al., 2014). In addition, USP14 regulates and suppresses Vps34 activity by interacting with Beclin1 (Min et al., 2017; Xu et al., 2016).

Fig. 2. The concept of ubiquitination by RING or HECT E3 ligase. (A) E2s are bound to E3s through RING domains on E3s and then transfer ubiquitin to the target protein. (B) HECT domain on E3s mediates ubiquitin transfer to the target protein. (C) The structure of Parkin/PARK2. Parkin has ubiquitin-like (UbL), in-between RING (IBR), and three RING domains. The RING0 domain is though to be as a HECT like domain on the Parkin protein.

(Aron et al., 2018). UCH-L1 interacts with the lysosome-associated membrane protein 2A (LAMP-2A) as a lysosomal receptor for autophagy and mutation of S18Y or I93M on UCH-L1, and this leads to an increment for SNCA by the inhibition of autophagy processing (Andersson et al., 2011; Kabuta et al., 2008; Kabuta and Wada, 2008). Also, the development of an assay that evaluates the expression rates of UCH-L1 that had been fused with a UCH-L1 promoter and eGFP conversion, showed the accumulation of autophagosomes endogenously (Yasvoina et al., 2013). Interestingly, UCH-L1 levels in PD patients were significantly decreased and at the same time UCH-L1 is targeted by Parkin for proteasomal degradation (McKeon et al., 2015). Mono-ubiquitination is considered as an essential step in autophagy targeting SNCA clearing and the lower level of USP9X is being affected to inhibit degradation of monoubiquitinated SCNA (Rott et al., 2011).

Ataxin-3, a member of the MJDs, was identified as an autophagy inducer by genome-wide screening (Bilen and Bonini, 2007). This function of Ataxin-3 targeting autophagy was shown with a Huntington’s disease model that is associated with expression of USP15 (Menzies et al., 2010). Parkin was identified as an Ataxin-3 interaction partner that is required for the clearance of Parkin by the autophagic pathway (Duran and Fon, 2011). Members of the DUBs are also down-regulated by autophagic proteins while abnormal or mutated DUBs are cleared in the autophagy process. Beclin1 (also termed as Atg6) is required for nucleation of autophagy by forming a complex with class III PI3K Vacular protein sorting 34 (Vps34) and has been identified as a remover of Ataxin-3 (Nascimento-Ferreira et al., 2011; Zeng et al., 2006). Interestingly, Vps34 acts as a regulator for autophagy, and Vps34 complexes down-regulate USP10 and USP13 by Beclin1, suggesting that they are downstream of autophagy activation (Liu et al., 2011). Previous studies have shown that the expression of Beclin1 is decreased in neurological disorders such as Alzheimer’s, Huntington’s and Machado–Joseph disease, and treatment with Beclin1 leads to improvement of neuronal dysfunction, neurodegeneration, and mitochondrial function (Ashkenazi et al., 2017; Chang et al., 2016; Nascimento-Ferreira et al., 2013). These researches have used Ataxin-3 to show the effect of Beclin1 on autophagy activity. An interesting study has shown the proteolysis mechanism of Beclin1 at the cellular level in cancer cells; however, Beclin1 is stabilized by USP9X (Elgendy et al., 2014). In addition, USP14 regulates and suppresses Vps34 activity by interacting with Beclin1 (Min et al., 2017; Xu et al., 2016).

3. DUBs in Alzheimer’s disease

A previous study suggests that AD widely occurs in the cerebral cortex and hippocampus, and abnormal phenotypes such as the insolubility of amyloid-β (Aβ) protein are mainly associated with AD (Masters et al., 2015). In addition, the levels of Aβ cortex can be used for confirming diagnosis markers in AD patients (Masters et al., 2015). In general, tauopathies are believed to occur by two distinct mechanisms. Primary tauopathies are associated with Pick’s disease (PiD) through neuronal and glial tau inclusion, and secondary tauopathies are shown in AD with aggregation of tau and Aβ plaques (Bloom, 2014). In addition, Aβ is regarded as an upstream factor of tau, and tau toxicity also accumulates toxic Aβ through a feedback loop (Bloom, 2014). Furthermore, aberrant phosphorylation of tau has been shown in AD (Marinkovic et al., 2019). The finding that tau aggregates degradation by autophagy or that the UPS is involved in the progressing of NDs such as AD has spurred research into the tauopathies (Wang and Mandelkow, 2012). However, fundamental questions about whether the DUBs regulate Aβ directly or indirectly remain to be answered. Therefore, we will summarize the most relevant DUBs in relation to Aβ and tau for AD in the following section.

As most proteins undergo proteasomal degradation, several studies have suggested that Aβ is also subject to proteolysis by the UPS (Saido...
and Leissring, 2012). As each ubiquitin chain regulates and decides the fate of its targeted protein (Lim et al., 2016), all ubiquitinated Aβ peptides are not completely undergoing the proteasomal degradation pathway and even affect the activity of proteasome conversely. Interestingly, nonfamilial AD shows mutation of ubiquitin proteins, resistance for disassembly, and inhibition of 26S proteasome (Lam et al., 2000). A previous study showed that accumulation of mutations in Aβ precursor protein results in inhibition of proteasome activity (Almeida et al., 2006). In addition, DUBs (such as UCH-L1 and UCH-L3) and proteasome activity are reduced in mutation of Aβ precursor protein (APP) neuron (Almeida et al., 2006). Furthermore, an interesting paper recently showed that the N-terminus of Aβ is a possible binding site of ubiquitin with Ub-K48 and -K63 chains, and ubiquitination of Aβ by the Ub-K63 chain causes aggregation and delays degradation of Aβ (Francesco Bellia et al., 2019). Therefore, studying DUBs as ubiquitin modifiers in the Aβ proteolytic mechanism is an important part of developing AD treatment. Although the enzymatic details of the Aβ degradation pathway with DUBs remain unclear, the increasing dataset on the cleavage, degradation, and expression for Aβ regulating proteins in AD suggests possibilities for therapeutics for AD (Oltzmann et al., 2008).

Despite studies prove the direct interaction of Aβ with DUBs, several DUBs have recently been suggested and identified as indirect regulators of Aβ in AD. As described before, AD and PD are interrelated with several shared proteins that regulate mitophagy and autophagy. UCH-L1 is a well-known protein that is associated with both AD- and PD (Choi et al., 2004). Recent evidence for the role of UCH-L1 has shown that Aβ may be upstream of UCH-L1 in an AD-affected brain (Poon et al., 2013; Zhang et al., 2012). However, several DUBs have been suggested as upstream factors of Aβ regulation. The β-site amyloid precursor protein-cleaving enzyme (BACE1) is positively regulated by USP8, and USP25 has been suggested as a binding partner for APP under ER stress (Jung et al., 2015; Yeates and Tesco, 2016). USP14 was identified as a proteasome complex pairing DUB and the enzymatic activity of USP14 is increased with proteasomal proteolysis during aging (Ponnappan et al., 2013). As described before, aberrant phosphorylation of tau has been observed in AD, and depletion of USP14 has increased phosphor-tau (Jin et al., 2012). Interestingly, inhibition of USP14 has decreased the level of ND-linked proteins such as tau, TDP-43, and Ataxin-3 (Boselli et al., 2017; Lee et al., 2010). These studies have indicated that USP14 has dual function for both autophagy and proteasomal degradation in AD (Kim et al., 2018).

4. DUBs in other neurodegenerative diseases and therapeutic perspective

NDs have several issues such as heterogeneity within the diverse clinical individual-cases, and these make it hard to reveal the identification and to achieve intracellular detection for any preclinical symptoms. Furthermore, a lack of biomarkers for diagnosis makes it harder to develop ND-targeted therapies. Clinically, NDs are classified with hallmarks such as impairment, memory loss, and movement-related disorders (Martin, 1999). Since ND patients share characterizing clinical phenotypes, this raises the possibility of various therapeutic strategies targeting proteolysis of misfolded core proteins for NDs such as Aβ, SNCA, and tau (Singh et al., 2020). As misfolding proteins cause the processing of NDs, we summarized the defects in proteolysis for NDs with the main clinical features of ND-related proteins in current understanding. The importance of achieving induction or inhibition of several stimulating signaling pathways to activate mitophagy and autophagy with the UPS is considerable for elimination of misfolded proteins as well as of nondegradable protein during ND processing (Huang and Figueiredo-Pereira, 2010). Thus, it is an important question whether the DUBs as sensitizers for the ND treatment with drugs can be effective targets for therapy.

Unlike cancer which is accompanied by abnormal cell proliferation and immortalization, most NDs are dependent on the failure of several degradation pathways during aging that leads to an accumulation of toxic peptides in the brain (Hossain et al., 2019). This gives an unexpected role to DUB inhibitors in NDs when compared to cancer. For example, IU1 as a USP14 inhibitor has been shown to effectively decrease the level of tau in cancer, but not in neurons targeting 26S proteasome (Kiprowska et al., 2017). Nevertheless, it is important to find the role where inhibition of the degradation pathway with DUBs will specifically affect NDs but have little or no effect on normal tissues, defining a proteolytic removal relationship. Huntington’s disease (HD) is a well characterized ND and is caused by the mutation of the huntingtin (HTT) gene and misfolded polyglutamine tail (polyQ-HTT) (Kaliszewski et al., 2015). In terms of HD pathology, it is not clear what processes control polyQ-HTT aggregation (Kaliszewski et al., 2015). A recent paper has suggested that the proteolytic mechanism with YOD1 as an OTU may be associated with inhibiting abnormal expression of HTT (Tanzi et al., 2018). Based on the proteomic and biochemical characteristics of PD, it has been proposed that abundant expression of DUBs such as USP9X in the brain can be an upstream protein for neurodegeneration (Murtaza et al., 2015; Zhang et al., 2010). Accordingly, the identification of small molecule inhibitors for USP9X activity may potentially offer a new therapeutic approach for NDs. Recent studies have also suggested that UCH-L1 may have potent effects as a PD targeting drug. For example, inhibition of UCH-L1 increased levels of BACE1 leading to reduction of Aβ levels and it also affects the SNCA expression (Liu et al., 2009; Pulliam et al., 2019; Zhang et al., 2012).

Currently, studies using DUB inhibitors have shown the sensitivities of DUSs in autophagy and mitophagy regulation (Jacomin et al., 2018). WP1130 (also known as Degrasyn) was screened as a novel class of agents that inhibits I6-induced phosphorylation for STAT3 and is regarded as an USP9X inhibitor (Bartholomeusz et al., 2007; Paemka et al., 2015). The treatment of WP113 shows increased ULK1 ubiquitination, leading to autophagy (Driessen et al., 2015). A more recent study revealed that USP1 inhibitor pimozide also regulates autophagy through targeting ULK1 (Raimondi et al., 2019). In addition, autophagy was accompanied by treatment with the USP7 inhibitor P5091 (Wang et al., 2017). The molecular mechanism was not clear, but it may be associated with USP7-p53-MDM2 regulation for autophagy processing (Wang et al., 2017). The UCH-L1 inhibitor, LDN-57444 (LDN), demonstrated that suppression of the enzymatic activity of UCH-L1 affects mitophagy through proteolytic degradation system (Pukass and Richter-Landsberg, 2015). We described before the negative role of the IU1 in neurons, but an in vivo study showed the usefulness of IU1 in that it corrects impaired mitophagy targeting PD (Chakraborty et al., 2018).

5. Conclusion remarks

Here, we have reviewed the current knowledge regarding DUBs for NDs and looked at possibilities for its clinical application (Table 1). Unfortunately, therapies for NDs have a diverse range of barriers. Above all, neuronal cell lines derived from patients and mouse models of NDs, both currently have quite extensive limitations. Studies of NDs in mammalians have been hampered by a lack of informative genetic systems. Moreover, possibilities for deregulation of ND-related proteins by DUBs have not been thoroughly compared to studies on the proteolytic mechanism. Furthermore, the expression patterns and mutations of DUBs in NDs are yet to be unveiled. Recently, a novel proteolytic molecule, known as immunoproteasome (IP, termed as proteasome variant), was suggested as a potential target for NDs. The IP is induced by the pro-inflammatory mediator signaling under specific stress conditions such as reactive oxygen species (Seifert et al., 2010). The increment of activity for IP levels suggested that the degradation of oxidized or damaged proteins is accumulated by inflammatory cell stress (Seifert et al., 2010). Interestingly, the expression levels of IP subunits were increased in AD and HD brains (Mishito et al., 2006; Njihof et al., 2011). It is unclear what conserved mechanisms of IP exist in NDs, but these findings can also be used for therapeutic purposes.
Table 1

A list of DUBs in neurodegenerative diseases.

| DUBs    | Disease Function                                                                 | Reference                        |
|---------|----------------------------------------------------------------------------------|----------------------------------|
| UCH-L1  | PD (Parkinson’s disease)                                                          | Lee and Hsu, 2017; Liu et al., 2002 |
|         | PD (Inhibition of autophagy processing by LAMP-2A interaction)                    | Andersen et al., 2011; Kabuta et al., 2008; Kabuta and Wada, 2008 |
| PD      | mTOR signaling regulation                                                         | Hussain et al., 2013             |
| PD      | Parkin degradation                                                                | McKeon et al., 2015              |
| AD      | Down-regulated                                                                   | Choi et al., 2004                |
| Axatin-3| PD (Parkinson disease)                                                            | Duncan and Fon, 2011             |
| USP1    | PD (Interaction of ULK1 in autophagy regulation)                                  | Raimondi et al., 2019            |
| USP2    | PD (mTOR signaling regulation)                                                    | Hussain et al., 2013             |
| USP8    | PD (Mediation for lysosomal degradation)                                          | Alexopoulou et al., 2016; Balat et al., 2011 |
| AD      | BACE1 protein regulation                                                         | Duncan et al., 2014              |
| USP9X   | PD (SCNA degradation)                                                             | Yeates and Tesco, 2016           |
| USP10   | PD (Autophagy regulation)                                                         | Rott et al., 2011                |
| USP12   | PD (Acceleration of autophagy)                                                    | Liu et al., 2011                 |
| USP13   | PD (Autophagy regulation)                                                         | Pearson et al., 2018             |
| USP14   | AD (Regulation of tau, TDP-43, and Ataxin-3)                                       | Boselli et al., 2017; Lee et al., 2010 |
| USP15   | PD (Recovery of mitophagy defect)                                                 | Cornelissen et al., 2014         |
| USP20   | PD (ULK1 binding DUB)                                                             | Khge et al., 2018                |
| USP25   | AD (Binding with APP under ER stress)                                             | Jung et al., 2015                |
| USP30   | PD (Deubiquitination on K-6 and K11-linked Ub chain on Parkin; Delays mitophagy)  | Cunningham et al., 2015; Gersch et al., 2017; Wang et al., 2015 |
| USP33   | PD (Acceleration of mitophagy)                                                    | Khge et al., 2018                |
| USP35   | PD (Acceleration of mitochondria)                                                 | Wang et al., 2015                |
| USP36   | PD (Autophagy regulation)                                                         | Taillebourg et al., 2012         |

PD: Parkinson’s Disease; AD: Alzheimer’s Disease.

GWAS technique has provided improved and precise information on functions or mechanisms in many human diseases that have been derived from target genes, non-coding RNAs (ncRNAs), or long non-coding RNAs (lncRNAs, included enhancer RNAs). As a result, many scientists have been able to find promising positive functions or mechanisms from big genetic information analysis through GWAS (Ding et al., 2018; Joo et al., 2016; Kim et al., 2010; Ren et al., 2017; Schaukowitch et al., 2014; Suzuki et al., 2017). Many studies have revealed much insight into the multiple phenotypes of ND pathway and molecular players have been uncovered by genetic and biochemical studies. Despite these advances, many questions remain. The multi-molecular players have been unveiled by genetic and biochemical approaches, which include proteomics and genomics analysis on NDs. This work was supported by Korea Brain Research Institute (K布RI) basic research program through KBrI funded by the Ministry of Science and ICT (20-BR-02-13), and Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education (2019R1F1A1059595, 2017R1D1A1B03030741, NRF-2019R1A6A1A03032888).

Funding

This work was supported by Korea Brain Research Institute (K布RI) basic research program through KBrI funded by the Ministry of Science and ICT (20-BR-02-13), and Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education (2019R1F1A1059595, 2017R1D1A1B03030741, NRF-2019R1A6A1A03032888).

Acknowledgments

We thank for Harrisco for editing the manuscript.

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