REVIEW

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Role of ubiquitin ligases in neural stem and progenitor cells

Cord Naujokat

Institute of Immunology, University of Heidelberg, Heidelberg, Germany

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Abstract

Ubiquitin ligases are central components of the ubiquitin-proteasome system (UPS), the major machinery for regulated proteolysis in eukaryotic cells. Proteins essential for regulating development, differentiation, proliferation, cell cycling, apoptosis, gene transcription, and signal transduction undergo posttranslational processing via selection by ubiquitin ligases and subsequent controlled proteolysis by the 26S proteasome, the proteolytic unit of the UPS. Neural stem cells (NSCs) are self-renewing multipotent cells of the embryonic and adult mammalian central nervous system. In the last few years, NSCs have generated considerable interest because of their potential to repair neurological damage in preclinical models of stroke, spinal cord injury, and neurodegenerative disease. Recent evidence reveals a central role of ubiquitin ligases in controlling the development, survival, differentiation, and programming of neural stem and progenitor cells. Here the current knowledge of the role and function of ubiquitin ligases in neural stem and progenitor cells is reviewed and insight into an important mechanism of NSC homeostasis by regulated proteolysis is provided.

Key words: ubiquitin ligase, ubiquitin-proteasome system, regulated proteolysis, neural stem cells, neural progenitor cells, neurogenesis.

Corresponding author: Cord Naujokat, Institute of Immunology, University of Heidelberg, Im Neuenheimer Feld 305, Heidelberg, Germany, e-mail: cord.naujokat@med.uni-heidelberg.de

THE UBIQUITIN-PROTEASOME SYSTEM

The ubiquitin-proteasome system (UPS) is an evolutionarily conserved and highly organized machinery for the proteolytic degradation of cytosolic and nuclear proteins in eukaryotic cells (Glickman and Ciechanover 2002; Schwartz and Ciechanover 2009). A plethora of cell proteins essential for the regulation of development, differentiation, proliferation, cell cycling, apoptosis, gene transcription, signal transduction, senescence, inflammation, and stress response undergo posttranslational processing via controlled and limited proteolysis by the UPS. The UPS therefore plays a key role in cellular regulation and homeostasis (Naujokat and Hoffmann 2002; Schwartz and Ciechanover 2009; Wolf and Hilt 2004).

The central proteolytic machine of the UPS is the 26S proteasome, a large multi-catalytic multi-subunit protease composed of a hollow barrel-shaped 20S catalytic core complex capped at one or both ends by a 19S regulatory complex (Baumeister et al. 1998; Naujokat et al. 2007; Voges et al. 1999; Wolf and Hilt 2004) (Fig. 1B). The proteolytic activities of the 26S proteasome occur in the 20S catalytic core complex composed of four axially stacked rings (Fig. 1B). Each outer ring consists of seven different non-proteolytic α subunits that allow conformational flexibility and substrate translocation into the central cavity of the 20S complex. The two inner rings are formed by seven different but related β subunits. Thus the 20S complex displays the stoichiometry $\alpha_{1\text{-}7}\beta_{1\text{-}7}\beta_{1\text{-}7}\alpha_{1\text{-}7}$ (Baumeister et al. 1998; Voges et al. 1999). Only the β1, β2, and β5 subunits harbor proteolytic sites formed by N-terminal threonine residues that face the central cavity of the 20S complex (Baumeister et al. 1998; Groll and Huber 2004; Voges et al. 1999). Based on their specificity toward oligopeptidyl substrates, the β1, β2, and β5 subunits have been defined to possess caspase-like, trypsin-like, and chymotrypsin-like peptidase activity, respectively (Groll and Huber 2004). However, 20S complexes are incapable of processing and degrading ubiquitin-conjugated and folded substrate proteins and require for this task one or two 19S regulatory complexes bound to the α rings of the 20S complex, leading to the assembly of a 26S holoparticle (Baumeister et al. 1998; Voges et al.

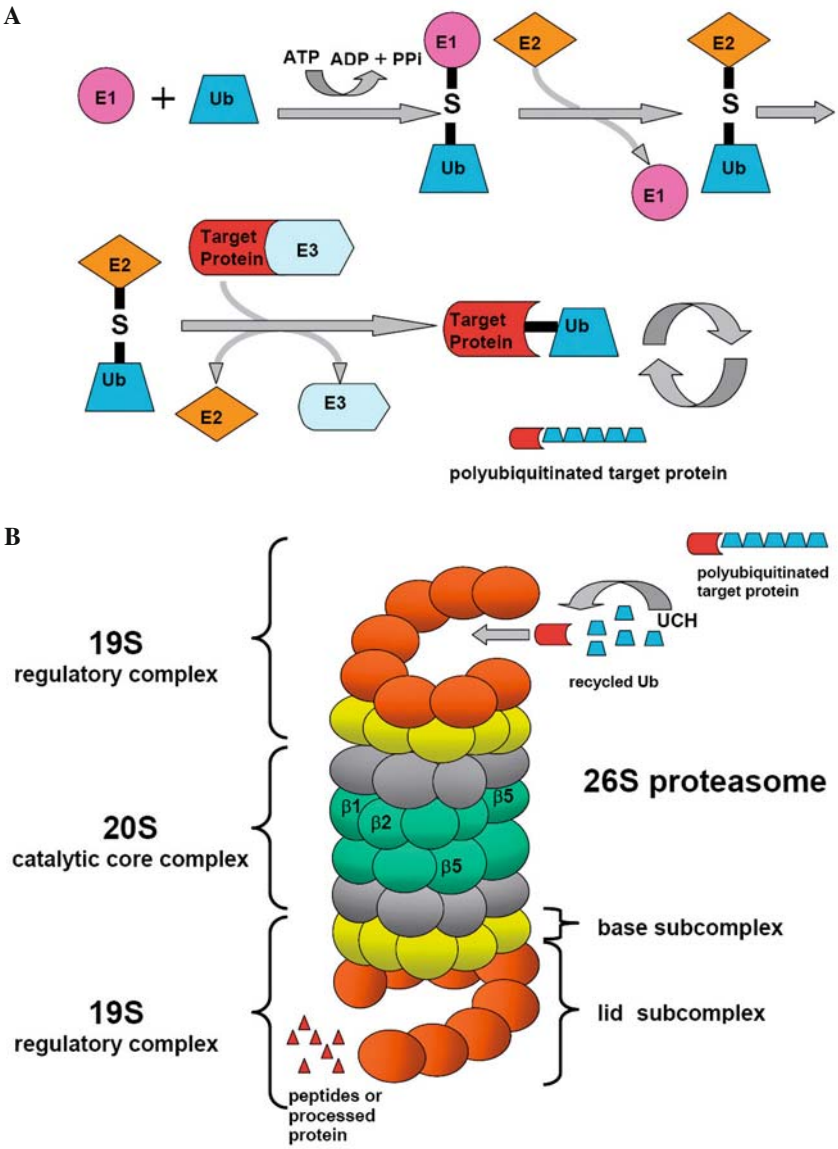

Fig. 1. The ubiquitin-proteasome system: components and mode of action. (**A**) Attachment of ubiquitin (Ub) to the target protein requires three enzymatic steps: ubiquitin-activating enzymes (E1) activate ubiquitin by forming a high-energy thiol esther bond between E1 and ubiquitin. This reaction requires energy provided by the hydrolysis of ATP and forms an activated ubiquitin moiety that is transferred and bound by an additional thiol ester bond to ubiquitin-conjugating enzymes (E2) that serve as carrier proteins. Ubiquitin ligases (E3) catalyze the covalent attachment of ubiquitin to the target protein by the formation of isopeptide bonds and finally provide substrate specificity. Multiple cycles of ubiquitination result in the synthesis and attachment of polyubiquitin chains that serve as a recognition signal for the degradation of the target protein by the 26S proteasome. (**B**) The 26S proteasome consists of the hollow barrel-shaped 20S catalytic core complex and one or two 19S regulatory complexes capping the 20S complex. The 20S complex is composed of four axially stacked rings. Each outer ring consists of seven non-proteolytic α subunits (grey). Each of the two inner rings is formed by seven β subunits (green), and only three of them, β1, β2, and β5, are proteolytically active and harbor proteolytic sites formed by N-terminal threonine residues that face the central cavity of the 20S complex. The 19S complex consists of the base and lid subcomplex. The base subcomplex contains six non-redundant ATPases of the AAA superfamily (yellow). The lid subcomplex (orange) contains at least eight subunits including deubiquitinating enzymes and receptors for ubiquitinated proteins. The polyubiquitinated target protein enters the 19S regulatory complex, is recognized, deubiquitinated, unfolded, and translocated into the central cavity of the 20S catalytic core complex where it is degraded by the hydrolytic activity of the N--terminal threonine residue of the β1, β2, or β5 subunits. Ubiquitin is recycled by ubiquitin carboxy terminal hydrolases (UCH). Processed proteins or peptide products of degradation are released from the 26S proteasome by diffusion.

1999). 19S complexes exhibit sophisticated multi-subunit assemblies consisting of six ATPase and at least eight non-ATPase subunits and are required for the recognition, deubiquitination, unfolding, and translocation of substrate proteins before their proteolytic degradation within the central cavity of the 20S complex (Pickart and Cohen 2004).

Cell proteins destined to undergo processing by the UPS must first be targeted for recognition and subsequent degradation by the 26S proteasome by covalent

attachments of multiple monomers of the 76-amino--acid polypeptide ubiquitin (Pickart and Eddins 2004). This process, called ubiquitination, takes place in a multistep reaction and requires three classes of enzymes (Fig. 1A): ubiquitin-activating enzymes (E1), ubiquitin--conjugating enzymes (E2), and ubiquitin ligases (E3). The ubiquitin-activating enzyme activates ubiquitin by forming a high-energy thiol ester bond between an active site cysteine residue of ubiquitin-activating enzyme and the C-terminal glycine residue of ubiquitin in a reaction that requires the hydrolysis of ATP. This activated ubiquitin moiety is subsequently transferred to the ubiquitin-conjugating enzyme via the formation of an additional thiol ester bond, and finally transferred to one of hundreds of distinct ubiquitin ligases, which catalyze the covalent attachment of ubiquitin to the target protein by the formation of isopeptide bonds. A single ubiquitin-conjugating enzyme can interact with multiple ubiquitin ligases to provide specificity in a combinatorial fashion. There are several distinct classes of ubiquitin ligases, including the HECT domain family (Bernassola et al 2008), the RING finger family (Petroski and Deshaies 2005), and the U-box family (Pickart and Eddins 2004). Ubiquitin ligases are key determinants of substrate specificity and are capable of recognizing a few or multiple substrate proteins through specific degradation signals, thereby selecting the respective substrate proteins for controlled proteolysis by the 26S proteasome (Pickart 2001; Pickart and Eddins 2004). Multiple cycles of ubiquination ultimately result in the synthesis and attachment of polyubiquitin chains that serve as a recognition signal for the proteolytic degradation of the substrate protein by the 26S proteasome (Glickman and Ciechanover 2002; Pickart 2001; Pickart and Eddins 2004).

The proteolytic degradation and processing of cellular regulatory proteins by the UPS is a ubiquitous, essential, and highly ordered process that is central to the physiology of various eukaryotic cell types, tissues, organs, and entire organisms (Bowerman and Kurz 2006; Glickman and Ciechanover 2002; Moon et al. 2004; Naujokat and Hoffmann 2002; Naujokat and Saric 2007). Due to this complexity, it is obvious that the UPS can undergo deregulation which contributes to the pathogeneses of various human diseases, including cancer, neurodegenerative, autoimmune, genetic, and metabolic disorders (Ciechanover and Schwartz 2004; Golab et al. 2004; Schwartz and Ciechanover 2009). In view of these points, it is not surprising that the UPS and many of its important components, including ubiquitin ligases, play an important role in the physiology of neural stem and progenitor cells.

MAMMALIAN NEURAL STEM AND PROGENITOR CELLS

Neural stem cells (NSCs) are self-renewing multipotent cells that exist in both the embryonic and adult mammalian central nervous system (Crane and Trainor 2006; Ming and Song 2005; Zhao et al. 2008a). Embryonic NSCs can be isolated from the embryonic mammalian mesencephalon, telencephalon, and cerebral cortex (Carpenter et al. 1999; Chalmers-Redman et al. 1997; Davis and Temple 1994; Kilpatrick and Bartlett 1993; Uchida et al. 2000) and from the vertebrate neural crest, a migratory cell population located between the dorsal ectoderm and the neural tube that arises during early embryonic development. The neural crest consists of primarily multipotent, bipotent, and unipotent progenitor cells but also contains a small proportion of pluripotent stem cells (Baroffio et al. 1991; Bronner-Fraser and Fraser 1988; Crane and Trainor 2006; Morrison et al. 1999; Stemple and Anderson 1992). Embryonic NSCs isolated from embryonic mammalian brain can give rise to neurons, astrocytes, and oligodendrocytes and are therefore classified as multipotent (Carpenter et al. 1999; Chalmers-Redman et al. 1997; Davis and Temple 1994; Delaunay et al. 2008; Uchida et al. 2000). Neural crest stem cells, however, exhibit a unique ability to generate different classes of neurons, glia, neuroendocrine cells, melanocytes, myoblasts, fibroblasts, osteoblasts, chondroblasts, and adipocytes, thus demonstrating their pluripotency (Baroffio et al. 1991; Crane and Trainor 2006; Stemple and Anderson 1992).

Adult NSCs are located in anatomically defined germinal zones of the mammalian brain and maintain neurogenesis throughout postnatal life (Basak and Taylor 2008; Duan et al. 2008; Zhao et al. 2008a). The vast majority of adult NSCs reside in the largest germinal zone of the adult mammalian brain, the subventricular zone (SVZ) along the lateral wall of the anterior lateral ventricle (Chiasson et al. 1999; Doetsch et al. 1999; Johansson et al. 1999; Quinones-Hinojosa et al. 2006). In the SVZ, adult NSCs reside in a specialized vascular niche and give rise to transient amplifying cells that differentiate into immature neurons (Alvarez-Buylla and Garcia-Verdugo 2002; Ming and Song 2005; Zhao et al. 2008a; Shen et al. 2008; Tavazoie et al. 2008). From the SVZ, immature neurons migrate together in chains along the rostral migratory stream to the olfactory bulb, where they migrate to the superficial cell layers and terminally differentiate into granule and periglomerular interneurons (Kornack and Rakic 2001; Lledo and Saghatelyan 2005; Lois and Alvarez-Buylla 1994; Pencea et al 2001). Adult NSCs located in different regions of the SVZ give rise to different subtypes of olfactory bulb interneurons, which is evidently determined by a spatial code established during embryonic brain development (Merkle et al. 2007). A complete turnover of the resident proliferating cell population occurs every 12 to 28 days in the mouse SVZ, with about 30,000 new immature neurons being produced every day and migrating to the olfactory bulb (Craig et al. 1999; Lois and Alvarez-Buylla 1994). Besides the SVZ, a large germinal layer corresponding to the caudal and medial extension of the posterior horn of the lateral ventricle, the subcallosal zone (SCZ), contains adult NSCs that

give rise to precursor cells migrating into the corpus callosum to become oligodendrocytes and astrocytes (Seri et al. 2006).

A third pool of adult NSCs in the mammalian brain constitutes the subgranular zone (SGZ) of the hippocampal dentate gyrus where mainly granule neurons, but also oligodendrocytes and astrocytes, are continuously generated from yet poorly defined multipotent progenitor cells (Eriksson et al. 1998; Gage et al. 1998; Kornack and Rakic 1999; Palmer et al.1997; Seri et al. 2004; Suh et al. 2007; Ueki et al. 2003; Zhao et al. 2008a). In the rat SGZ, more than 9000 immature granule neurons are generated every day that migrate a short distance to differentiate into mature neurons in the dentate gyrus (Cameron et al. 1993; Cameron and McKay 2001).

Recent evidence suggests that adult neurogenesis occurs in several additional areas of the mammalian brain, including the neocortex, striatum, amygdala, and substatia nigra (Gould 2007). However, neurogenesis in these areas has been observed to occur in response to growth factor supply and brain damage by focal ischemia or seizures (Bernier et al. 2002; Dayer et al. 2005; Jiang et al. 2001; Park et al. 2006; Van Kampen and Robertson 2005; Zhao et al. 2003). Therefore it remains controversial whether normal neurogenesis occurs in areas of the adult mammalian brain other than the SVZ, SGZ, and SCZ.

As demonstrated by immunocytochemical staining of lineage-specific markers, adult NSCs located in the SVZ, SGZ, and SCZ mainly correspond to astrocytes (Doetsch et al. 1999; Garcia et al. 2004; Ihrie and Alvarez-Buylla 2008; Imura et al. 2003; Seri et al. 2001; Seri et al. 2006). However, adult NSCs displaying an ependymal or subependymal phenotype have also been found in the SVZ (Chiasson et al. 1999; Johansson et al. 1999). Although the exact developmental origin of adult NSCs is not known, accumulating evidence suggests that adult NSCs gradually transform from embryonic neuroepithelial cells to radial glial cells to astrocyte-like NSCs (Anthony et al. 2004; Bonfati and Peretto 2007; Merkle et al. 2004). Since adult NSCs can give rise to neurons, astrocytes, and oligodendrocytes *in vivo* and *ex vivo* when cultured with epidermal growth factor and/or fibroblast growth factor 2, they have been classified as multipotent cells (Doetsch et al. 1999; Gage et al. 1995; Reynolds and Weiss 1992; Vescovi et al. 1993). *In vivo* and *ex vivo*, adult NSCs can give rise to cells that normally derive from germ layers other than the neuroectoderm, such as myeloid, lymphoid, and more primitive hematopoietic cells as well as myocytes and skeletal myotubes (Bjornson et al. 1999; Galli et al. 2000; Rietze et al. 2001; Shih et al. 2001). Moreover, adult NSCs can give rise to cells of all germ layers when cultured together with embryoid bodies, demonstrating their enormous plasticity and pluripotent nature (Clarke et al. 2000).

Germinal regions of the embryonic and adult mammalian brain that contain NSCs are of increasing interest because of their role in endogenous brain plasticity and cellular homeostasis and their potential use for brain repair. In the last few years, NSCs have generated considerable interest because of their potential to repair neurological damage in stroke, spinal cord injury, Parkinson's disease, Huntington's disease, motor neuron disease, demyelinating disease, lysosomal storage disease, metabolic leukodystrophies, and other rare neurological disorders (Barnabé-Heider and Frisén 2008; Goldman and Windrem 2006; Hess and Borlongan 2008; Kim 2007; Lindvall et al. 2004).

ROLE AND FUNCTION OF UBIQUITIN LIGASES IN MAMMALIAN NEURAL STEM AND PROGENITOR CELLS

Different ubiquitin ligases and their subunits as well as deubiquitinating enzymes have recently been shown to be essential for neurogenesis and neural stem and progenitor cell survival and differentiation (Table 1).

$SCF^{\beta\text{-}TRCP}$

$SCF^{\beta\text{-}TRCP}$ belongs to the superfamily of cullin-RING ubiquitin ligases and is a member of the subfamily of mammalian Skp1-Cul1-F-box-protein (SCF) ubiquitin ligases which represent multi-subunit enzymes with a modular architecture (Cardozo and Pagano 2004; Petroski and Deshaies 2005). Each SCF ubiquitin ligase contains a cullin protein scaffold that is required for ligase function and an F-box protein that acts as a receptor for the recruitment of phosphorylated substrates to the SCF ubiquitin ligase machinery (Frescas and Pagano 2008; Skowyra et al. 1997).

Two recent studies show that β-TRCP, the F-box protein of $SCF^{\beta\text{-}TRCP}$, binds and ubiquitinates REST (Guardavaccaro et al. 2008; Westbrook et al. 2008), a master repressor of neuronal gene expression (Johnson et al. 2008; Schoenherr and Anderson 1995) whose levels decline by means of proteasomal degradation during the differentiation of pluripotent embryonic stem cells to neural stem and progenitor cells (Ballas et al. 2005). During neural differentiation of mouse pluripotent embryonic stem cells, REST is ubiquitinated and targeted for proteasomal degradation by $SCF^{\beta\text{-}TRCP}$, thereby downregulating the levels of REST that are required for neural gene expression and proper neural differentiation (Westbrook et al. 2008). Conversely, suppression of β-TRCP expression by RNA interference or expression of a non-degradable REST mutant leads to inhibition of neural differentiation of mouse embryonic stem cells (Westbrook et al. 2008). These results clearly demonstrate that downregulation of REST by $SCF^{\beta\text{-}TRCP}$-mediated ubiquitination and subsequent proteasomal degradation is critical for the neural differentiation of embryonic stem cells, and the $SCF^{\beta\text{-}TRCP}$-REST axis may constitute an important regulatory pathway controlling neurogenesis.

Table 1. Role of ubiquitin ligases in mammalian neural stem and progenitor cells

Ubiquitin ligase	Cell type	Effects/mechanisms	References
$SCF^{\beta\text{-}TRCP}$ (Skp1-Cul1-F-box--protein (SCF) ubiquitin ligase)	Mouse pluripotent embryonic stem cells	Initiation of neural differentiation of pluripotent embryonic stem cells by downregulation of REST via $SCF^{\beta\text{-}TRCP}$-dependent ubiquitination and proteasomal degradation	Ballas et al. 2005; Westbrook et al. 2008
Huwe1 (LASU1/ARF--BP1/Mule/HectH9; HECT ubiquitin ligase)	Mouse embryonic neural stem cells, cortical progenitor cells	Regulation of differentiation of embryonic stem cells along the neuronal lineage; timing of cell cycle exit and proliferation arrest of neural stem cells and cortical progenitors	Zhao et al. 2008b
DDB1 (subunit of the cullin4A ubiquitin ligase)	Mouse embryonic neural stem and progenitor cells; mouse epidermal stem and progenitor cells	Maintenance of viability and genomic integrity of dividing neural progenitor cells; maintenance of neural stem cells in the ventricular zone, subventricular zone and the cerebellar granular layer; maintenance of genomic stability, cell cycle fidelity and viability of dividing epidermal stem and progenitor cells	Cang et al. 2006; Cang et al. 2007
Mind bomb1 (RING ubiquitin ligase)	Mouse embryonic neural stem and progenitor cells, cerebellar progenitor cells, intermediate progenitor cells	Activation of Notch signaling; promotion of differentiation and survival of neural stem and progenitor cells; formation and development of the neuro-epithelium, neural tube, and forebrain	Barsi et al. 2005; Koo et al. 2005; Koo et al. 2007; Yoon et al. 2008
UBR1 and UBR2 (ubiquitin ligases of the N-end rule pathway)	Mouse embryonic neural stem and progenitor cells	Activation of Notch signaling; promotion of differentiation, survival, and proliferation of neural stem and progenitor cells; formation and development of the neuroepithelium, neural tube, and forebrain	An et al. 2006
UCH-L1 (ubiquitin C-terminal hydrolase with ubiquitin ligase activity)	Mouse embryonic neural progenitor cells	Regulation of differentiation and morphology of neural progenitor cells; promotion of the transition from neurogenesis to gliogenesis	Sakurai et al. 2005

Huwe1

Huwe1, alternatively termed LASU1, ARF-BP1, Mule, or HectH9, is a 482-kDa HECT domain-containing ubiquitin ligase that catalyzes the polyubiquitination of various proteins targeted for proteasomal degradation, including core histones, the tumor suppressor protein p53, the antiapoptoic protein Mcl-1, and the oncoproteins c-Myc and N-Myc (Adhikary et al. 2005; Chen et al. 2005; Liu et al. 2005; Zhao et al. 2008b; Zhong et al. 2005). N-Myc, which is posttranscriptionally regulated by proteasomal degradation (Bonvini et al. 1998), is essential for the correct timing of cell cycle exit and the neuronal and astrocyte differentiation of neural progenitor cells (Kenney et al. 2003; Sanosaka et al. 2008). Mice with conditional disruption of *N-Myc* display abnormal neurogenesis with precocious differentiation and premature withdrawal of NSCs and cortical progenitors from the cell cycle, finally leading to a size reduction and disorganization of the cerebellum and cerebral cortex (Knoepfler et al. 2002). As demonstrated recently, Huwe1 catalyzes polyubiquitination and subsequent proteasomal degradation of N-Myc in a timely and spatially regulated fashion during the differentiation of mouse ES cells along the neuronal lineage and in the mouse brain during embryonic cortical development (Zhao et al. 2008b). This Huwe1-N-Myc pathway, in which Huwe1 mediates the post-transcriptional regulation of N-Myc by proteasomal degradation, allows the precise timing of cell cycle exit and proliferation arrest of NSCs and cortical progenitors that is required for neuronal differentiation and proper neurogenesis (Zhao et al. 2008b). Interestingly, duplicated regions and sequence changes of highly conserved residues in the Huwe1 gene have recently been detected in families with X-linked mental retardation (Froyen et al. 2008), a heterogeneous inherited condition that causes failure to develop cognitive abilities owing to mutations in genes located on the X chromosome (Ropers and Hamel 2005). This strongly suggests that Huwe1 contributes to neuronal and cognitive development in humans.

DDB1

DDB1 is a component of the cullin4A-based ubiquitin ligase complex that controls nuclear excision repair, DNA replication, and cell cycle progression (Angers et al. 2006; Bondar et al. 2006; Groisman et al. 2003; Lee and Zhou 2007). As an obligatory subunit of the cullin4A-based ubiquitin ligase machinery, DDB1 forms heterodimers with a large number of WD40-repeat proteins that serve as adaptors for the recruitment of several substrate proteins targeted for ubiquitination and subsequent proteasomal degradation (Higa et al. 2006; Higa and Zhang 2007; Lee and Zhou 2007). These substrate proteins include nuclear excision repair proteins, DNA replication licensing factors, STAT proteins, histones, protooncoproteins, and cell cycle regulators, all highlighting the importance of DDB1 in regulating DNA metabolism, gene expression, and the cell cycle (Higa et al. 2006; Higa and Zhang 2007).

As recently shown, DDB1 plays an essential role in maintaining viability and genomic integrity of dividing neural progenitor cells during embryonic brain development. Conditional inactivation of the DDB1 gene in mouse brain results in a nearly complete loss of neural stem and progenitor cells in the ventricular and subventricular zones and in the cerebellar external granular layer of newborn mice (Cang et al. 2006). However, only proliferating, but not postmitotic, neural progenitor cells of these germinal layers undergo DNA damage and massive p53-dependent apoptosis during embryonic brain development of mice bearing a conditional deletion of *DDB1*, indicating a crucial role for DDB1 in maintaining embryonic neurogenesis (Cang et al. 2006).

Interestingly, tissue-specific deletion of DBB1 in mouse epidermis leads to a nearly complete loss of epidermal stem cells and induction of apoptosis in proliferating epidermal progenitor cells, suggesting that DBB1 is essential for the maintenance and viability of stem and progenitor cells of different tissues (Cang et al. 2007).

Mind bomb1

The *mind bomb* gene was originally identified to ensure the formation of the correct number of primary neurons during neurogenesis in zebrafish embryos (Schier et al. 1996). Positional cloning of *mind bomb* revealed that it is a gene in the Notch signaling pathway that encodes a ubiquitin ligase of the RING type (Itoh et al. 2003). This RING-type ubiquitin ligase, termed Mind bomb1 (Mib1), interacts with the intracellular domain of the Notch ligand Delta to promote its ubiquitination and subsequent endocytosis that is required for the modulation of Notch activation and Notch-mediated proneural gene expression in Notch-expressing cells receiving signals from Delta-expressing neighboring cells (Itoh et al. 2003). Moreover, Mib1 regulates the endocytosis of all of the canonical Notch ligands (Delta-like 1, 3, and 4 and Jagged 1 and 2), thereby playing a pivotal role in the fine tuning of Notch signaling events that lead to the adoption of a neural fate of cells in proneural clusters and finally to proper neurogenesis in vertebrates (Androutsellis-Theotokis et al. 2006; Koo et al. 2005; Koo et al. 2007; Louvi and Artavanis-Tsakonas 2006; Yoon et al. 2008).

Accordingly, mice harboring a targeted mutation of Mib1 display dramatic neuroepithelial and cerebral defects, such as a compromised structural integrity of the embryonic neuroepithelium, a lack of neuroepithelial cells, neural tube and forebrain malformations, a lack of forebrain NSCs, and precocious neurogenesis accompanied by the induction of apoptosis in premature neurons soon after their differentiation (Barsi et al. 2005; Koo et al. 2005). This aberrant neurogenesis associated with early embryonic lethality appears as a direct consequence of disrupted Notch signaling due to the absence of Mib1, which ultimately impairs proper neural patterning and embryonic neurogenesis (Barsi et al. 2005; Koo et al. 2005).

Moreover, conditional inactivation of the Mib1 gene in mice leads to severe developmental defects of the cerebellum, including reduction of cerebellar size and foliation, a delayed migration of the postmitotic granule cell precursors from the external to the internal granule cell layer, and a truncation and disorganization of Bergmann glial fibers that fail to extend to the cerebellar pial surface (Koo et al. 2007).

Radial glial cells, which serve as a source of NSCs in all regions of the embryonic mammalian central nervous system (Anthony et al. 2004) and in restricted germinal zones of the adult mammalian brain (Merkle et al. 2004), are generated in response to Notch signaling during embryonic neurogenesis (Gaiano et al. 2000). Radial glial cells also arise from cultured ES cells and act as cellular intermediates during differentiation of ES cells toward neurons (Götz and Barde 2005). A recent study shows that Mib1 is required for the initiation of Notch activation and signaling in radial glial cells crucial for the self-renewal and maintenance of radial glial cells during embryonic mammalian neurogenesis (Yoon et al. 2008). In particular, conditional inactivation of the Mib1 gene in mice results in complete loss of Notch activation in radial glial cells of the mouse embryonic forebrain, leading to defective self-renewal and premature differentiation of the cells into intermediate progenitors and, finally, neurons (Yoon et al. 2008). These severe cellular defects result in progressive loss and degeneration of radial glial cells and finally in disorganization of the neocortex and the subcortical regions of the embryonic forebrain. Importantly, Mib1 expression is restricted to intermediate progenitors and newborn neurons which send the signal for Notch activation to neighboring radial glial cells, thereby maintaining self-renewal and the expanding pool of radial glial cells during embryonic neurogenesis (Yoon et al. 2008).

UBR1/UBR2

Similar to Mib1, the ubiquitin ligases UBR1 and UBR2 of the N-end rule pathway, which constitutes

a major regulatory proteolytic pathway of the UPS (Meinnel et al. 2006; Tasaki et al. 2005), are essential for the proper differentiation, proliferation, and survival of mouse embryonic neural stem and progenitor cells (An et al. 2006). Mice lacking both UBR1 and UBR2 exhibit impaired proliferation and increased apoptosis of neural progenitor cells of the neural tube and the ventricular zone of the embryonic forebrain, leading to the occurrence of thin neuroepithelial layers, a deformed neural tube, and a distorted forebrain morphology. Moreover, mitotically active neural precursor cells of *UBR1*$^{-/-}$*UBR2*$^{-/-}$ mice embryos prematurely migrate from the ventricular zone to the subventricular zone, apparently as a result of their precocious and deregulated differentiation. As in the case of Mib1 mutant mice, aberrant neurogenesis in *UBR1*$^{-/-}$*UBR2*$^{-/-}$ mice is associated with suppression of the Notch signaling pathway and the occurrence of early embryonic lethality, revealing an essential role of both UBR1 and UBR2 in mammalian neurogenesis and development (An et al. 2006).

However, mice lacking either UBR1 or UBR2 do not display the multiple and severe defects in neurogenesis observed in *UBR1*$^{-/-}$*UBR2*$^{-/-}$ mice (Kwon et al. 2001; Kwon et al. 2003), suggesting that UBR1 and UBR 2 can compensate for each other and may have redundant functions in promoting neurogenesis. Mice lacking UBR1 exhibit a phenotype comprising low body weight with reduced skeletal muscle and adipose tissue mass, defective regulation of fatty acid synthase, exocrine pancreatic insufficiency with increased susceptibility to pancreatic injury, and behavioral abnormalities (Kwon et al. 2001; Zenker et al. 2005). Consistently, a similar phenotype is observed in humans with Johanson-Blizzard syndrome, a rare autosomal recessive disorder caused by the deficiency of UBR1 and comprising intrauterine-onset destructive pancreatitis with exocrine pancreatic dysfunction, deafness, mental retardation, and multiple physical malformations (Gershoni-Baruch et al. 1990; Zenker et al. 2005).

UCH-L1

Ubiquitin C-terminal hydrolase L1 (UCH-L1), a member of the large family of deubiquitinating enzymes, catalyzes the hydrolysis of C-terminal ubiquitin ester and amide adducts, thereby generating free monomeric ubiquitin from ubiquitin proproteins or small ubiquitinated peptides (Larsen et al. 1998). UCH-L1 is one of the most abundant proteins in the adult mammalian brain (1–5% of total soluble proteins) and is localized exclusively in neurons (Wilkinson et al. 1989). Upon dimerization, UCH-L1 exhibits ubiquitin ligase activity that promotes the accumulation of α-synuclein in cultured cells, a mechanism implicated in the pathogenesis of Parkinson's disease (Liu et al. 2002). UCH-L1 ensures ubiquitin stability in neurons (Osaka et al. 2003), and mutations of the UCH-L1 gene and alteration of UCH-L1 catalytic activities have been found to associate with several neurodegenerative disorders, including Parkinson's, Huntington's, and Alzheimer's disease (Gong and Leznik 2007; Setsuie and Wada 2007). Conversely, UCH-L1 has been shown to rescue β-amyloid-induced decreases in synaptic function and contextual memory in the *APP/PS1* mouse model of Alzheimer's disease (Gong et al. 2006). This strongly suggests that UCH-L1 is essential for proper neuronal function.

UCH-L1 seems to promote differentiation of embryonic neural progenitor cells. In particular, expression of UCH-L1 has been detected in nestin-positive neural progenitor cells located in germinal zones of the mouse embryonic brain, such as the ventricular zone and the cortical plate (Sakurai et al. 2005). In these areas, UCH-L1 regulates the morphology of neural progenitor cells and modulates their differentiation (Sakurai et al. 2005). The temporal and spatial pattern of UCH-L1 expression suggest that UCH-L1 is required for the onset of neurogenesis, which is followed by glial differentiation (Sakurai et al. 2005). The ability of UCH-L1 to promote neurogenesis and regulate the differentiation of neural progenitors depends on the binding affinity of UCH-L1 for ubiquitin and the interaction between monoubiquitin and UCH-L1 (Sakurai et al. 2005), indicating a functional homology between UCH-L1 and the ubiquitin ligases discussed above in the regulation of mammalian neurogenesis.

SUBSTRATE PROTEINS OF THE UPS REQUIRED FOR MAMMALIAN NEUROGENESIS

Various proteins and components of signaling pathways directly involved in the regulation of mammalian neurogenesis and NSC differentiation have been shown to undergo proteolytic processing and degradation by the UPS. Such proteins include the Notch receptor (McGill and McGlade 2003; Qiu et al. 2000; Wu et al. 2001), the Notch ligand Delta (Song et al. 2006), the Notch antagonist Numb (Kuo et al. 2006; Nie et al. 2002), the neuronal adaptor protein Disabled-1 (Arnaud et al. 2003; Bock et al. 2004), the transcription factor E2F1 (Azuma-Hara et al. 1999), the inhibitor of cyclin-dependent kinases, p27 (Baldassarre et al. 2000; Zindy et al. 2006), cyclin D1 (Sundberg et al. 2006), the neuronal-specific activator of Cdk5, p35 (Patrick et al. 1998; Sahlgren et al. 2006), the regulator of neuronal proliferation NPDC-1 (Spencer 2004), the epidermal growth factor family member neuregulin-3 (Carteron et al. 2006), the NSC-specific intermediate filament protein nestin (Mellodew et al. 2004), and bone morphogenetic proteins and their receptors (Satow et al. 2006; Zhu et al. 1999). The specific functions, abundance, and homeostasis of these important neurogenic regulators are directly controlled by proteolytic degradation via the UPS, pointing out a central role for the UPS in the regulation of neurogenesis and NSC physiology.

CONCLUSION

The proteolytic degradation of cell proteins by the UPS is a highly complex and tightly regulated process that is central to the regulation of many basic processes in eukaryotic cells, including development, differentiation, proliferation, cell cycling, gene expression, signal transduction, and apoptosis. This elaborate and selective process plays a pivotal role in controlling the levels and activities of diverse regulatory proteins in neural stem and progenitor cells, especially in cells undergoing transcriptional regulation and signal transduction.

As demonstrated in recent studies in mice, several ubiquitin ligases and deubiquitinating enzymes, including $SCF^{\beta\text{-}TRCP}$, Huwe1, DDB1, Mind bomb1, UBR1/ /UBR2, and UCH-L1, play essential roles in embryonic and adult neurogenesis and neural stem and progenitor cell differentiation. Moreover, a considerable number of proteins required for the differentiation, proliferation, survival, and homeostasis of neural stem and progenitor cells are proteolytically processed by the UPS, indicating that the UPS constitutes a key regulator of embryonic and adult neurogenesis. The limited number of the currently known components and target proteins of the UPS involved in the regulation of mammalian neurogenesis may represent only a minor part of the plethora of neurogenic regulators awaiting identification as components or substrates of the UPS.

Future research dedicated to characterizing the multiple functions of ubiquitin ligases and the entire UPS in NSC physiology will improve our understanding of embryonic and adult neurogenesis and may provide a basis for the development of novel therapeutic and regenerative strategies in neurological disorders.

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