MINI-REVIEW

Power and Promise of Ubiquitin Carboxyl-terminal Hydrolase 37 as a Target of Cancer Therapy

Yan-Jie Chen, Yu-Shui Ma, Ying Fang, Yi Wang, Da Fu*, Xi-Zhong Shen*

Abstract

Ubiquitin carboxyl-terminal hydrolase 37 (UCH37, also called UCHL5), a member of the deubiquitinating enzymes, can suppress protein degradation through disassembling polyubiquitin from the distal subunit of the chain. It has been proved that UCH37 can be activated by proteasome ubiquitin chain receptor Rpn13 and incorporation into the 19S complex. UCH37, which has been reported to assist in the mental development of mice, may play an important role in oncogenesis, tumor invasion and migration. Further studies will allow a better understanding of roles in cell physiology and pathology, embryonic development and tumor formation, hopefully providing support for the idea that UCH37 may constitute a new interesting target for the development of anticancer drugs.

Keywords: UCH37 - deubiquitination - proteasome - protein interaction - tumor therapy target

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Introduction

The ubiquitin-26S proteasome system is the main non-lysosomal route for intracellular protein degradation in eukaryotes. The 26S proteasome is a proteolytic complex which consists of two subcomplexes: the barrel-shaped core complex (the 20S proteasome) and the 19S regulatory complex (also known as PA700). The proteasome recognizes substrate via its multiubiquitin chain, followed by ATP-dependent unfolding and translocation of the substrate from the regulatory particle into the core particle to be degraded (Hershko and Ciechanover, 1998; Pickart, 2001; Glickman and Ciechanover, 2002; Wilkinson, 2002; Goldberg, 2003). But ubiquitin groups which bound with the substrate are mostly not delivered into the core particle and broken down with substrate, which is regulated by the deubiquitinating enzymes (DUBs). DUBs, which are capable of removing Ub from the protein substrates, are also involved in lots of biological processes such as transcriptional regulation, growth and differentiation, and oncogenesis (Wilkinson, 1997; Chung and Baek, 1999).

Discovery of UCH37

In 1997, Cohen and coworkers reported a 19S-associated isopeptidase that could selectively disassemble polyubiquitin chain from the distal end of poorly ubiquitinated protein conjugates. This isopeptidase, a protein with molecular mass of 37K named UCH37 (also called UCH-L5), functions to disassemble Lys48-linked poly-ubiquitin from the distal end of the chain, and is thought to be involved in editing ubiquitinated substrates according to the length of polyubiquitin chains rather than the structure of the target proteins themselves. The protein can also disassemble Lys6- and Lys11-linked polyubiquitin, but not α-linked di-ubiquitin or poly-ubiquitin with introduced mutations (Leu8Ala and Ile44Ala) (Lam et al., 1997a; Lam et al., 1997b).

Molecular structure

UCH37 gene is located in 1q32 of the chromosome, the full-length of the human UCH37 cDNA consisting of 1818 nucleotides, including a 236-nucleotide 5′-untranslated region (UTR), a 990-nucleotide open reading frame, and a 592-nucleotide 3′-UTR. The possible transcription promoter was calculated by NNPP version 2.2 (Reese, 2001) as “ctggggecgacaanaagctecacggectccgcaagtctcacc” in the -329 to -280 forward the 5′-UTR. The underline nucleotides were predicted as the methylated sites. Then the human UCH37 amino acid sequence was compared...
with those from other species deposited in GenBank database using ClustalW2 software (Larkin et al., 2007), we noticed that human UCH37 shared 98% (vs. Bos), 96% (vs. Mus), 94% (vs. Rattus), 92% (vs. Gallus), and 88% (vs. Danio) of identity (Figure 1). UCH37 in all of these species have conserved catalytic amino acid residues, which indicates that the UCH37 may perform ubiquitin C-terminal hydrolase activity. UCH37 consists of two functional domains, a catalytic domain (UCH-domain, residues 1-226) and a C-terminal domain (tail-domain, 227-329). The crystal structure of N-terminal catalytic domain shows that it is composed of a central six-stranded anti-parallel β-sheet, with seven α-helices on either side of the sheet, causing it to form a bilobal structure (Figure 2).

The S-shaped loop, which is the active-site crossover loop of UCH37, consists of residues 142-163, is disordered. It would be reordered if ubiquitin was bound and uncovering the S-shaped loop of ubiquitin just like UCH-L3, indicating that large substrates can not pass through the loop on UCH37N. Helix-3, which comprises a wall on the edge of the putative substrate-binding site (P'-site), is collapsed in UCH37N, resulting in a broader V-shaped trough when compared with other UCHs. This suggests that UCH37 can distinguish substrates with different features, such as larger substrates (Nishio et al., 2009). UCH37 has a long crossover loop (>14 residues). It is the loop length and potentially loop-chain flexibility which play an important role in the catalytic activity and substrate specificity of a UCH for isopeptide Ub chain (Zhou et al., 2011). The C-terminal domain comprises α-helices 8-10, and a helical segment comprising residues 306-311 (Burgie et al., 2011).

In biological systems, protein localization, activity, their interaction with other proteins and overall turnover is determined by post translational modifications (PTMs). Phosphorylation is one important PTM. Phosphorylation potential for human UCH37 and kinase specific phosphorylation sites were predicted using NetPhos 2.0 and KinasePhos 2.0 (Blom et al., 1999; Wong et al., 2007). The minimum threshold value used to predict phosphorylation is 0.5 for NetPhos 2.0. A total of 8 sites showed high potential for phosphorylations. Amongst these 5 were Ser, 2 Thr and 1 was Tyr (Table 1). In spite of Ser 156, 7 predicted sites were highly conserved in mammals (Figure 2). We drew the 3D structure of UCH37 and assessed the possible surface accessibility for phosphorylation. The Ser, Thr and Tyr residues are denoted by red, yellow and green colors.

### Table 1. Predicted phosphorylation sites on UCH37 protein

<table>
<thead>
<tr>
<th>Substrate Position</th>
<th>Score</th>
<th>Kinase prediction</th>
<th>Context</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ser 72</td>
<td>0.994</td>
<td>AKT1, PKA, PKB, ATM, GSK-3, PKC, IKK, PKG, RSK, STK4, CHK1, PDK</td>
<td>VVQDSRLDT</td>
</tr>
<tr>
<td>131</td>
<td>0.865</td>
<td>AKT1, PKA, ATM, PKC, PKG, PLK1, RSK, STK4, CHK1, CK1</td>
<td>GLALSNSDV</td>
</tr>
<tr>
<td>156</td>
<td>0.997</td>
<td>AKT1, PKA, ATM, Aurora, PKG, RSK, STK4, CHK1, CK1, PDK, CK2</td>
<td>DTKTSAKEE</td>
</tr>
<tr>
<td>212</td>
<td>0.991</td>
<td>AKT1, PKA, PKB, ATM, PKC, Aurora, PKG, CaM, MAPK, RSK,</td>
<td>IQKYSEGEI</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CKD, STK4, CHK1, PDK, CK2</td>
<td></td>
</tr>
<tr>
<td>258</td>
<td>0.909</td>
<td>AKT1, ATM, PKG, RSK, STK4, CHK1</td>
<td>NSMLSAIQS</td>
</tr>
<tr>
<td>Thr 76</td>
<td>0.638</td>
<td>GRK, PKB, PKC, CDK</td>
<td>SRLDTIFFA</td>
</tr>
<tr>
<td>110</td>
<td>0.576</td>
<td>GRK, PKB, PKC, CDK, CK2, PDK</td>
<td>HLGLETSEF</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tyr 168</td>
<td>0.515</td>
<td>Fgr, ALK, PDGFR, BTK, Ret, IGFR1, EPH, IR, JAK2, TYK2, Fes, ZAP70, FGFR1</td>
<td>HFVSYVPVN</td>
</tr>
</tbody>
</table>

### Figure 1. Comparison of the UCHL5 (UCH37) in Different Species

The underlined sequences indicate the KEKE-like motif. GeneBank accession numbers of each sequence are as follows: Homo sapiens, NP_057068.1; Bos Taurus, NP_776906.2; Mus musculus, NP_062508.1; Rattus norvegicus, NP_001012149.1; Gallus gallus, NP_001006530.1; Danio rerio, NP_998249.1

### Figure 2. The Crystal Structure of the UCH37 and the Phosphorylation Locations on the UCH37

The N-terminal catalytic domain is composed of a central six-stranded anti-parallel β-sheet and seven α-helices on either side of the sheet, causing it to form a bilobal structure, and the C-terminal domain comprises α-helices 8-10. This model shows that predicted Ser and Thr sites have high surface accessibility for phosphorylation. The Ser, Thr and Tyr residues are denoted by red, yellow and green colors.
structure. The structure is capped by the carboxy-terminal domain which consists of a seven-stranded β-sandwich canonical pleckstrin-homology fold in the amino-terminal chains and hRpn2. It has been revealed that hRpn13 has a N-terminal domain, binds the polyubiquitin (Hamazaki et al., 2006; Qiu et al., 2006; Yao et al., 2006). KEKE motifs are involved in their physical interaction C-terminal regions of hRpn13 and UCH37 containing enhancing its isopeptidase activity (Figure 3). The GP110, a subunit of the 19S particle, binds to UCH37. Recent studies have showed that hRpn13/Adrm1/Interacting protein 1). The C-terminal extension of UCH37 is vital for the interaction and furthermore, the interaction between Ulp1 and UCH37 was much stronger than that between S14 and UCH37.

Recent studies have showed that hRpn13/Adrm1/GP110, a subunit of the 19S particle, binds to UCH37 enhancing its isopeptidase activity (Figure 3). The C-terminal regions of hRpn13 and UCH37 containing KEKE motifs are involved in their physical interaction (Hamazaki et al., 2006; Qiu et al., 2006; Yao et al., 2006). The N-terminal domain of hRpn13, binds the polyubiquitin chains and hRpn2. It has been revealed that hRpn13 has a canonical pleckstrin-homology fold in the amino-terminal domain which consists of a seven-stranded β-sandwich structure. The structure is capped by the carboxy-terminal α-helix. So the authors called this domain “pleckstrin-like receptor for ubiquitin” (Pru) (Saeki and Tanaka, 2008; Schreiner et al., 2008). Interestingly, UCH37 can also bind to the proteasome through Rpn10/S5a, another ubiquitin receptor of the proteasome beyond hRpn13 (Deveraux et al., 1994; Stone et al., 2004). This receptor is located at the hinge between the lid and base of the 19S complex, and close to where UCH37 lies.

It is also found that in the nucleus UCH37 is combined with the human Ino80 chromatin-remodeling complex (hINO80), which is an ATP-dependent chromatin remodeling complex that alters nucleosome positioning on DNA during both transcription and DNA repair (Figure 3) (Cai et al., 2007). UCH37 is associated with hINO80 through its C-terminal tail and the N-terminal domain of NFRKB. In hINO80, UCH37 is held in an inactive state; however, it can be activated by transient interaction of the INO80 complex with the proteasome or hRpn13

Regulation of UCH37

Much literature has reported the structure and interactant of UCH37, but little focuses on the upstream regulations of UCH37. DNA methylation is an epigenetic mechanism regulates gene expression. The changes in the methylation pattern including the methylation of CpG islands and primers, which are normally unmethylated, may lead to the silencing of endogenic genes (Sulewska et al., 2007). It has been predicted that there are three possible methylation sites in the UCH37 promoter. When the promoter region has a high methylation status, the gene transcription is usually suppressed. MicroRNAs are small endogenous RNAs that derive from distinctive hairpin precursors in various organisms. After incorporation into a silencing complex, which contains at its core an Argonaut
protein, a miRNA can pair to an mRNA and thereby specify the post-transcriptional repression of that protein-coding message, either by transcript destabilization, translational repression, or both. Many sites that match the miRNA seed (nucleotides 2-7), particularly those in 3’ untranslated regions (3’UTRs), are preferentially conserved (Baek et al., 2008). For the prediction of possible sites for miRNA binding, TargetScan, microRNA.org and miRDB were used (Betel et al., 2008; Wang, 2008; Wang and El Naga, 2008; Friedman et al., 2009). A total of 3 conserved sites and 3 poorly conserved sites showed high potential possibility as the target region (Table 2).

Previous studies have shown that neither UCH37 itself nor UCH37-Adrm1 or UCH37-hRpn13-hRpn2 complexes can hydrolyse Lys48-linked di-ubiquitin efficiently; rather, conjunction with the 19S complex is necessary to enable hydrolysis of polyubiquitin chains (Yao et al., 2006). hRpn13 can bind the C-terminal tail of UCH37 and relieves its autoinhibition. It hasn’t been known how hRpn13 activates UCH37, but its strong ubiquitin-binding affinity may contribute by increasing UCH37’s affinity for the substrates when in the hRpn13 complex and by orienting neighboring ubiquitin moieties in a configuration that is optimal for hydrolysis. hRpn13’s ability to modulate the relative orientation of its Pru- and UCH37-binding domain may contribute a driving force in UCH37 catalysis (Chen et al., 2010). Although the Rpn10/ S5a subunit also appears to interact with UCH37 in the 19S complex, this interaction fails to activate UCH37 (Holzl et al., 2000; Stone et al., 2004; Liu et al., 2007). In hnNO80, UCH37 is held in an inactive state; however, it can be activated by transient interaction of the INO80 complex with the proteasome or hRpn13 in a “hit-and-run” manner without disrupting its association with INO80 (Figure 3) (Yao et al., 2008; Zediak and Berger, 2008).

A new study on the structure of C-terminal extension of UCH37 by Burgie SE et al found that the crystallographic tetramer of UCH37 predicted its autoinhibition, as Helix 9 would occlude the ubiquitin binding-site. Activation appeared to be regulated in part by the C-terminal domain of UCH37 as removal of the residues 238-329 provided enhanced hydrolase activity. In the absence of BSA, UCH37 specific activity was relatively low, and was appeared to be regulated in part by the C-terminal domain of UCH37 as removal of the residues 238-329 provided enhanced hydrolase activity. In the absence of BSA, UCH37 specific activity was relatively low, and was high was dependent upon the UCH37 concentration (Burgie et al., 2011). These results suggest that additives that could stabilize UCH37 solubility through a direct binding event, for example, Rpn13 or chemical modifications of UCH37 that may yield a more soluble form; for example, removal of the C-terminal tail could enhance UCH37’s activity. However, these hypotheses need further verification.

The degradation way of UCH37 has not been reported yet. Whether it is degraded by lysosomal route or ubiquitin-26S proteasome system also needs further investigation.

**Regulation effects**

Several studies, performed both in vivo and in vitro, have suggested that UCH37 can suppress protein degradation through disassembles polyubiquitin from the distal subunit of the chain, shortening it such that poorly ubiquitinated substrates can be rescued from being degraded (Lam et al., 1997b; Husnjak et al., 2008; Koulich et al., 2008; Schreiner et al., 2008; Jacobson et al., 2009). In contrast, a recent study has suggested that UCH37 may promote the degradation of specific proteasome substrates instead, such as nitric oxide synthase and IκB-α (Mazumdar et al., 2010). Little is known in addressing these seeming contradictions. It is likely that UCH37 may inhibit the degradation of some substrates while promote the degradation of others. Recent study showed that only ubiquitinated loosely-folded proteins, after becoming bound to the 26S, interacted with Ubp6/Usp14 or UCH37 to activate ATP hydrolysis and enhance their own destruction (Peth et al., 2013).

In vivo of hnNO80 as an ATP-dependent nucleosome remodeling complex which is involved in transcriptional regulation, possible substrates for UCH37 are the histones H1A and H1B and transcriptional factors. It is also possible that UCH37 activity affects nucleosome remodeling by hnNO80 (Cai et al., 2007; Zediak and Berger, 2008). TGF-β (transforming growth factor-β) signals through serine/threonine kinase receptors and intracellular Smad transcription factors. An important regulatory step involves specific ubiquitination by Smurfs (Smad-ubiquitin regulatory factors), members of the HECT (homologous to E6-associated protein C-terminus) ubiquitin ligase family, which mediate the proteasomal degradation of Smads and/or receptors. The interaction between Smads and UCH37 could potentially counteract Smurf-mediated ubiquitination. Importantly, Smad7 can act as an adaptor able to recruit UCH37 to the type 1 TGF-β receptor. Consequently, UCH37 dramatically up-regulates TGF-β-dependent gene expression by deubiquitinating and stabilizing the type 1 TGF-β receptor (Figure 2) (Wicks et al., 2005; Wicks et al., 2006). UCH37 knockdown significantly inhibits the activity of a TGF-β-dependent gene reporter and selectively decreases levels of some TGF-β-dependent target genes, notably p21, a protein which plays a key role in cell cycle arrest by preventing G1/S cell cycle progression and inhibits proliferation, and PAI-1, a scaffold protein that has been shown to act as a tumor suppressor and induce apoptosis via caspase-3, during the early phase of TGF-β receptor activation. Yet UCH37 knockdown significantly impairs cell migration through abolishes the TGF-β-induced expression of MMP-2 and PAI-1, which are thought to play a key role in TGF-β-dependent cell migration and tumor invasion, at both early and late stages of TGF-β receptor activation (Cutts et al., 2011). Thus, up-regulation of UCH37 and related DUBs observed in several cancers may play an important role in late stage of tumor development. Chen Z et al has showed that the ratio of Bax/Bcl-2 is higher in silencing of UCH37 than in that of control group after that of UCH37 in A549 cells. Meanwhile, experiments with the A549 cell line disclose that silencing of UCH37 could induce efficiently A549 cell apoptosis through activation of caspase-9 and caspase-3. On the other hand, over-expression of UCH37 leads to the opposite effect (Chen et al., 2011).
In addition to the impact of TGF-β-dependent gene expression and an important role UCH37 plays in apoptosis by altering Bax/Bcl-2 ratio and enzymatic activities of caspase-9 and caspase-3, some studies have shown its potential role in oncogenesis. Rolén et al. (2006) have found that the activity of the C-terminal hydrolases UCH37 is up-regulated in the majority of tumor tissues compared with the adjacent normal tissues. We have showed that the quantity of UCH37 rises in hepatocellular carcinoma (HCC) using a functional proteomic analysis to screen UCH37-interacting proteins in HCC, thus identifying glucose-regulated protein 78, essential for cell viability (Hirohashi et al., 2006), as one interacting with UCH37. It was also found that UCH37 was a predictor for time to recurrence of HCC. And in vitro, UCH37 could promote cell migration and invasion through deubiquitinating PRP19, an essential RNA splicing factor, in HCC cell lines (Fang et al., 2013). Kapuria V et al have found that WP1130, a partly selective DUB inhibitor which directly inhibits DUB activity of USP5, USP9x, USP14 and UCH37, could mediate inhibition of tumor-activated DUBs resulting in down-regulation of anti-apoptotic and up-regulation of proapoptotic proteins (Kapuria et al., 2010). The relationship between the UCH37 expression level and the outcomes of esophageal squamous cell carcinoma (ESCC) patients was found by our group recently (Chen et al., 2012). The protein expression level of UCH37 was higher in the cancer tissue than in para-tumorous tissue and was overexpressed in the tumor tissues of recurrent patients. The result of multivariate analysis also showed us that UCH37 can be a predictor for overall survival (OS) and disease-free survival (DFS) and has the potential power to predict the ESCC recurrence (Chen et al., 2012). All of the evidences suggest that the up-regulation of UCH37 maybe play an important role in oncogenesis through promoting some Proto-oncogenes’ expression and stem cell-like characteristics in the cell. It has been reported that UCH37 and Rpn13, the regulators of the proteasome pathway, also play a vital role in the mental development of mice; deleted UCH37 can result a severe defect in embryonic brain development in prenatal lethality in mice, which suggests the physiological role of UCH37 in murine development (Al-Shami et al., 2010). It will be interesting to find out whether lacking UCH37 would have significant impact on the development of other organs.

D’Arcy and his group (D’Arcy et al., 2011) discovered that b-AP15, a proteasome inhibitor that abrogates the deubiquitinating activity of the 19S regulatory particle, inhibited the activity of two 19S regulatory-particle-associated deubiquitinases, UCH37 and USP14, resulting in accumulation of polyubiquitin. The tumor progression and organ infiltration can be inhibited by the treatment of b-AP15 in four different solid tumor models in vivo and an acute myeloid leukemia model, indicating that the deubiquitinating activity of UCH37 maybe a new anticancer drug target.

Clinical significance

In addition to the impact of TGF-β-dependent gene expression and an important role UCH37 plays in apoptosis by altering Bax/Bcl-2 ratio and enzymatic activities of caspase-9 and caspase-3, some studies have shown its potential role in oncogenesis. Rolén et al. (2006) have found that the activity of the C-terminal hydrolases UCH37 is up-regulated in the majority of tumor tissues compared with the adjacent normal tissues. We have showed that the quantity of UCH37 rises in hepatocellular carcinoma (HCC) using a functional proteomic analysis to screen UCH37-interacting proteins in HCC, thus identifying glucose-regulated protein 78, essential for cell viability (Hirohashi et al., 2006), as one interacting with UCH37. It was also found that UCH37 was a predictor for time to recurrence of HCC. And in vitro, UCH37 could promote cell migration and invasion through deubiquitinating PRP19, an essential RNA splicing factor, in HCC cell lines (Fang et al., 2013). Kapuria V et al have found that WP1130, a partly selective DUB inhibitor which directly inhibits DUB activity of USP5, USP9x, USP14 and UCH37, could mediate inhibition of tumor-activated DUBs resulting in down-regulation of anti-apoptotic and up-regulation of proapoptotic proteins (Kapuria et al., 2010). The relationship between the UCH37 expression level and the outcomes of esophageal squamous cell carcinoma (ESCC) patients was found by our group recently (Chen et al., 2012). The protein expression level of UCH37 was higher in the cancer tissue than in para-tumorous tissue and was overexpressed in the tumor tissues of recurrent patients. The result of multivariate analysis also showed us that UCH37 can be a predictor for overall survival (OS) and disease-free survival (DFS) and has the potential power to predict the ESCC recurrence (Chen et al., 2012). All of the evidences suggest that the up-regulation of UCH37 maybe play an important role in oncogenesis through promoting some Proto-oncogenes’ expression and stem cell-like characteristics in the cell. It has been reported that UCH37 and Rpn13, the regulators of the proteasome pathway, also play a vital role in the mental development of mice; deleted UCH37 can result a severe defect in embryonic brain development in prenatal lethality in mice, which suggests the physiological role of UCH37 in murine development (Al-Shami et al., 2010). It will be interesting to find out whether lacking UCH37 would have significant impact on the development of other organs.

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Comparison with other DUBs

Substrate deubiquitination on the proteasome is mediated by three distinct deubiquitinating enzymes (DUBs) associated with the regulatory particle: RPN11, UCH37, and USP14. Here we compare the characteristics of the three DUBs (Table 3) (Lam et al., 1997b; Verma et al., 2002; Yao and Cohen, 2002; Hanna et al., 2006; Koulich et al., 2008; Jacobson et al., 2009; Lee et al., 2010; Lee et al., 2011).

An obvious question that arises is why there’re two DUBs, UCH37 and USP14, which share similar enzymatic properties on the proteasome. To answer this question, we shall first know the distinctions between UCH37 and USP14. RPN11 and UCH37 have been found to discriminate strongly among different types of chain linkages, and this may be true of USP14 as well. Chain length may be equally critical. A third substrate feature that may determine USP14 susceptibility is the amenability of the substrate to the proteasome-directed unfolding (Hanna et al., 2006; Lee et al., 2010). The persistence of the proteasome-substrate interaction can be controlled by USP14 in a noncatalytic function of the protein. And USP14 can also regulate the opening of the substrate translocation channel in the CP (Peth et al., 2009). So there’re three possible reasons to have both UCH37 and USP14 on the proteasome. Perhaps two DUBs on the proteasome can enhance the effect of protein degradation suppressing. And if one was inhibited, the other one can ensure the effects in the normal level. On the other hand, their substrates are mutually complementary which covers all kinds of features. Last but not least, the two DUBs may work in coordination. USP14 slowing substrate degradation allows a longer exposure of the substrate to the trimming activity by UCH37, which leads a more stable way to suppress substrate from degradation.

Future directions

Although the previous literature indicates a growing focus on deubiquitinating enzymes, the studies in this area are at a preliminary stage. UCH37, as a member of the DUBs, has received a lot of investigation on its structure, substrate, function and clinical significance. But questions

Table 3. Comparison of Three DUBs Associated with the Regulatory Particle

<table>
<thead>
<tr>
<th>RPN11</th>
<th>UCH37</th>
<th>USP14</th>
</tr>
</thead>
<tbody>
<tr>
<td>Family belonging</td>
<td>JAMM family</td>
<td>UCH family</td>
</tr>
<tr>
<td>Cleaving site</td>
<td>The base of the ubiquitin chain</td>
<td>The distal tip of the ubiquitin chain upon docking of the substrate to the proteasome</td>
</tr>
<tr>
<td>Deubiquitinating moment</td>
<td>Somewhat “late” in the reaction pathway</td>
<td>Promoting substrate degradation</td>
</tr>
<tr>
<td>Result</td>
<td>Promoting substrate degradation</td>
<td>Suppressing protein degradation</td>
</tr>
</tbody>
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still remain to be answered, such as how the quality of UCH37 is controlled; how UCH37 is activated; what role the phosphorylation plays; what the degradation way of UCH37 is; what role UCH37 plays in INO80 complex; what the target genes are; what role UCH37 plays in oncogenesis and what the pathway of UCH37 is to induce cancer.

Conclusions

In conclusion, UCH37, a member of the deubiquitinating enzymes, can suppress protein degradation by disassembling polyubiquitin from the distal subunit of the chain. It has been proved that UCH37 can be activated with proteasome ubiquitin chain receptor Rpn13 and via their incorporation into the 19S complex. UCH37, which has been reported to assist in the mental development of mice, may play an important role in oncogenesis, tumor invasion and migration. Further studies on UCH37 will allow us to get a deep insight into cell physiology and pathology, embryonic development and tumor formation, and further support the idea that UCH37 may constitute a new interesting target for the development of anticancer drugs.

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