New Insights into the Role of the Ubiquitin-proteasome Pathway in the Regulation of Apoptosis

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The ubiquitin-proteasome pathway (UPP) is the major system responsible for degradation of intracellular proteins in eukaryotes. By controlling the levels of key proteins, it regulates almost all of the cellular activities, including cell cycle progression, DNA replication and repair, transcription, protein quality control, immune response, and apoptosis. UPP is composed of the ubiquitination system that marks proteins for degradation and the proteasome which degrades the ubiquitinated proteins. The 26S proteasome is a 2400 kDa complex consisting of more than 40 subunits. Following ubiquitination catalyzed by the ubiquitin activating enzyme (E1), a ubiquitin-carrier protein (E2), and one of the cell's many ubiquitin-protein ligases (E3s), the protein substrates are targeted to the proteasome for degradation into small peptides. E3s regulate the degradation of protein substrates indirectly by determining both the specificity and timing of substrate ubiquitination, whereas the deubiquitinating enzymes can inhibit this process by releasing ubiquitin from substrates. In this review, we attempt to highlight the recent progress in research on UPP and its role in the regulation of apoptosis by focusing on several of its important components, including the ubiqutin ligase Nrdp1, which regulates ErbB/EGFR family of receptor tyrosine kinases, the ubiquitin-carrier protein BRUCE/Apollon (an Inhibitor of Apoptosis Protein), and the novel proteasome subunit hRpn13 (a binding site for the deubiquitinating enzyme, UCH37). *(Chang Gung Med J 2007;30:469-79)*

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Degradation of proteins by the ubiquitin (Ub)-proteasome pathway (UPP) is critical in regulating the levels of most cellular proteins and in the rapid elimination of misfolded proteins.[1-3] The conjugation of a polyubiquitin chain into a protein substrate leads to rapid binding and adenosine triphosphate (ATP)-dependent hydrolysis by the 26S proteasome. In the ubiquitin-proteasome pathway (Fig. 1), ubiquitin is activated by the ubiquitin-activating enzyme (E1) with the formation of a highly reactive thiol ester linkage, and it is then transferred to the active site Cys of a ubiquitin-carrier protein (E2). Formation of isopeptide bonds between the C-terminus of Ub and lysines on a substrate is catalyzed by a

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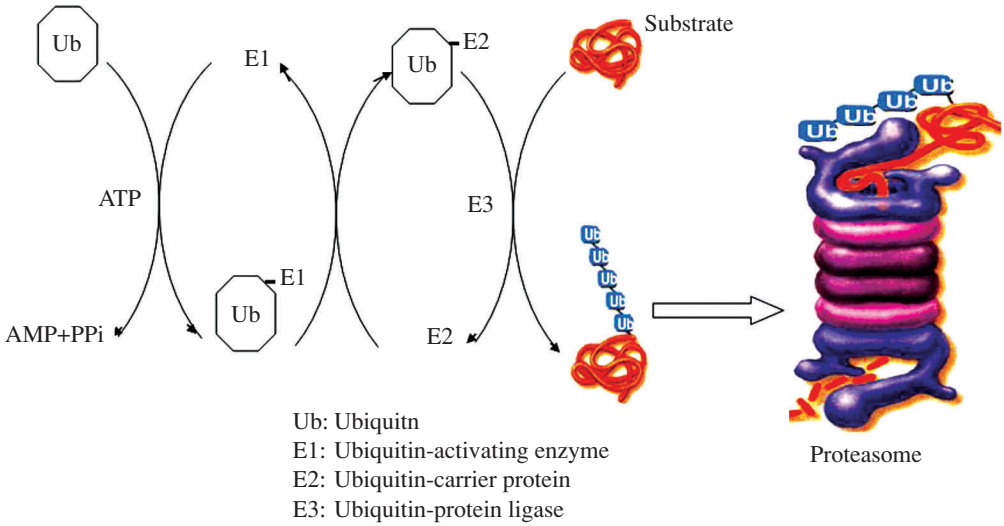

Fig. 1 The ubiquitin-proteasome pathway

ubiquitin-protein ligase (E3), which binds the substrate and catalyzes the transfer of the Ub from a specific E2 to the substrate. However, in some cases, multiubiquitin chain assembly requires the additional activity of certain ubiquitin chain elongation factors. Enzymes possessing these specific activities have been proposed to be called E4 enzymes.[4] The formation of a chain of Ub molecules on the substrate generally targets it for degradation by the 26S proteasome. The specificity of this degradation process depends upon which E2s and E3s are functioning during ubiquitination. Mammalian cells contain 20-40 different E2s and between 500 and 1000 different ubiquitin ligases. E3s vary widely in structure: some are small monomeric proteins, e.g., Mdm2, while others are large multisubunit complexes, e.g., the SKP1-CUL1-F-box (SCF) or the anaphase promoting complex (APC) that regulate the cell cycle. E3s bind different classes of protein substrates depending on their specific sequences, structural features or covalent modifications most often by phosphorylation. As a consequence of different rates of ubiquitination, cell proteins can have very different half-lives and can be selectively eliminated under very specific conditions.

The 26S proteasome consists of two sub-complexes, the 20S core particle, within which proteolysis takes place, and the 19S regulatory particle, which binds the ubiquitinated substrate.[5] The 20S proteasome is composed of two outer α-rings and two inner β-rings, each containing seven different, but homologous, subunits. The β-subunits confer six peptidase sites, which differ in specificity but function together in protein breakdown.[6] The proteasome inhibitors widely used as research tools (e.g., MG132 or lactacystin) or in the treatment of certain cancers (e.g., Velcade/PS-341) all inhibit these active sites, primarily two chymotrypsin-like active sites.[6] The 19S regulatory complex, which binds to one or both ends of the 20S particle, is composed of a base and a lid.[7,8] The base contains a ring of six homologous ATPases, which mediate the unfolding and translocation of substrates into the 20S.[9] The lid contains at least eight subunits including multiple isopeptidases which catalyze the rapid disassembly of the ubiquitin chain.[3]

By influencing the levels of critical proteins, the ubiquitin-proteasome pathway regulates almost all the cellular processes, including cell cycle progression, DNA replication and repair, transcription, protein quality control, and immune responses. In addition, UPP appears to play multiple important roles in promoting and inhibiting apoptosis.[10] Therefore, it is not surprising that aberrations in UPP directly or indirectly lead to many human diseases, such as tumors and neurodegenerative disorders. Autosomal

recessive juvenile Parkinsonism (AR-JP) is the most frequent form of familial Parkinson's disease. Mutations in the gene of the ubiquitin ligase, parkin, which result in the loss of its ubiquitin ligase activity, have been found to be associated with AR-JP.[11] Alterations in UPP also play critical roles in the pathogenesis of various types of tumors. For example, the ubiquitin ligase Cbl is involved in the down-regulation of the epidermal growth factor (EGF) receptor, and its deregulation is involved in lymphoma and gastric carcinoma. The substrate binding component of the SCF ubiquitin ligase complex, SKP2, is involved in cell cycle control, and its up-regulation contributes to the development of malignant melanoma and lymphoma.[12,13] The transcription factor p53 is a tumor suppressor that functions by controlling cell cycle progression or promoting apoptosis under a genotoxic stress. Under normal conditions, nuclear p53 is kept at low levels mainly by the E3 ubiquitin ligase, Mdm2, and the upregulation of Mdm2 is associated with non-small-cell lung cancer, soft-tissue carcinoma, and colorectal cancer.[13,14] This review will address the recent progress on UPP, especially the role of several new components of this pathway in the regulation of apoptosis and their relevance to the development of tumors or Parkinson's disease.

Nrdp1-catalyzed ubiquitination and initiation of apoptosis

Nrdp1 is an E3 for ErbB3, a member of the epidermal growth factor receptor family

Nrdp1 (referred to as FLRF in mice) belongs to the large RING finger family of E3 ubiquitin ligases. Nrdp1 mRNAs are expressed in a variety of human tissues. Its N-terminal region contains a RING finger variant. RING fingers are zinc-binding domains thought to mediate a variety of protein-protein interactions and are found in most ubiquitin ligases.[15] Nrdp1 associates with ErbB3, a member of the epidermal growth factor (EGF) receptor family of receptor tyrosine kinases.[16]

The EGF receptor family, including EGFR, ErbB2 (HER2/neu), ErbB3 and ErbB4, play fundamental roles in the regulation of cell survival, proliferation, and differentiation in response to specific growth factors. Numerous researchers have documented that overexpression or amplification of ErbB receptors is associated with the development of various types of human cancer.[17,18] Consequently, blocking the activation or accelerating the degradation of ErbB proteins is an attractive approach for cancer therapy.[19] There are more than 10 EGF-like growth factors, which bind the extracellular domains of ErbB receptors and cause the formation of receptor homo- and hetero-dimers. Dimerization eventually stimulates autophosphorylation of specific tyrosine residues in the cytoplasmic tails of the receptors, which act as docking sites for signaling molecules.[20] The unique C-terminal domain of ErbB3 binds many important signal-transducing proteins, such as phosphatidylinositol (PI) 3-kinase and Shc.[21,22] In contrast to the other members of the ErbB family, ErbB3 lacks catalytic activity and only functions by heterodimerizing with other ErbBs. In fact, dimers of ErbB3 and ErbB2, the latter of which has no direct ligands, are the most potent in causing cell transformation.[23-25] Recent evidence suggests that ErbB3 is implicated in tumor resistance to certain therapeutic drugs.[26] Unlike most other membrane receptors, ErbB3 does not undergo degradation by lysosomes.[27,28]

ErbB3 is degraded through the ubiquitin-proteasome pathway, and Nrdp1 catalyzes its ubiquitination and degradation by proteasomes. While the atypical RING finger domain of the N-terminal half of Nrdp1 is required for enhancing ErbB3 degradation, its C-terminal half by itself associates with ErbB3 and raises ErbB3 levels in cells, probably by acting as a dominant-negative form of Nrdp1. In cell-free systems, Nrdp1 has E3 activity and ubiquitinates ErbB3, in the presence of the E2, UbcH5, E1 and ATP.

Interestingly, the human Nrdp1 gene, like erbB3, is located at 12q13, a chromosome region frequently rearranged in human tumors,[29,30] suggesting a possible important physiological role of Nrdp1 in growth regulation or tumor suppression. Consistent with this notion, Yen et al.[31] recently analyzed spontaneous mammary tumors induced in a transgenic mouse model of active ErbB2/neu expression, and suggested that a loss of Nrdp1 expression contributed to a substantial up-regulation of both ErbB3 and ErbB2 receptors. Their observations raised the possibility that whereas ErbB2 and ErbB3 collaborate in the progression of breast cancer, loss of Nrdp1 expression may also be a factor in mediating receptor up-regulation. Thus, it is possible that Nrdp1 acts as an endogenous suppressor of tumor cell growth

and/or invasion.

Nrdp1-mediated degradation of BRUCE and initiation of apoptosis

Most E3s catalyze ubiquitination and degradation of multiple proteins. It seemed likely that Nrdp1 might also target other proteins in addition to ErbB3 for degradation, since Nrdp1 is conserved in Drosophila, which lacks a close homolog to ErbB3. In a search for other substrates in mammalian cells, Qiu et al.[32] demonstrated that Nrdp1 also binds and catalyzes the ubiquitination of BRUCE/Apollon. BRUCE is a giant (528 kDa) membrane-associated protein with a BIR domain at its N-terminal region and an E2 motif at its C-terminus. Zhong et al.[33] also showed that Nrdp1 did interact with and regulate the stability of Parkin, an E3 ubiquitin ligase whose absence leads to a early onset hereditary form of Parkinson's Disease.

The primary mediators of apoptosis are caspases, cytosolic cysteine proteases that, once activated, initiate an irreversible cascade of events resulting in rapid cell death.[34,35] The only known cellular caspase inhibitors are the Inhibitor of Apoptosis Proteins (IAPs), which are characterized by the presence of one to three tandem baculoviral IAP repeats (BIRs). Overexpression of almost all of the known IAPs suppresses apoptosis. Several human IAPs (e.g., XIAP, c-IAP1, c-IAP2, and NAIP) and Drosophila IAP1 directly bind and inhibit caspases.[36-40] In addition to the BIR domain, certain IAPs, including c-IAP1, XIAP and Drosophila IAP1, contain a RING-finger domain, which is characteristic of many E3s. In certain cells, these IAPs catalyze ubiquitination and degradation of themselves and other proteins important for apoptosis, such as caspase 3 and TRAF2.[41-44] In addition, certain IAPs can promote ubiquitination of the pro-apoptotic RHG motif-containing proteins (e.g., Rpr in Drosophila or Smac/DIABLO in mammals), which interact with and inhibit several IAPs.[37,45-47]

Qiu et al.[48] demonstrated that in the presence of an exogenous E2, UbcH5c, purified Nrdp1 catalyzes BRUCE ubiquitination. In vivo, overexpression of Nrdp1 promotes ubiquitination and proteasomal degradation of BRUCE, and the net loss of BRUCE can play a critical role in inducing apoptosis. The Drosophila IAP, DIAP1, binds and inhibits Drosophila caspases, and the results of genetic studies have indicated that the cellular content of DIAP1 determines the threshold for apoptosis.[49] Perhaps in an analogous way, the level of BRUCE may also determine the sensitivity of certain mammalian cells to apoptotic stimuli. In fact, reducing BRUCE by overexpression of Nrdp1 also caused caspase 3 activation and promoted apoptosis.[48] Furthermore, accelerated degradation of BRUCE appears to be a key event in apoptosis. During the etoposide-induced apoptosis, the levels of c-IAP1 and XIAP fell markedly in thymocytes,[43] but did not change in HeLa or 293T cells. In MCF-7 cells, the levels of both BRUCE and XIAP, but not of c-IAP-1, decreased sharply in response to another apoptotic stimulus called camptothecin. The levels of BRUCE also fell dramatically in HeLa, 293T, HT1080 and NIH/3T3 cells upon treatment with either etoposide or camptothecin. Thus, degradation of BRUCE appears to be a general event during initiation of apoptosis in many cell types, while degradation of other IAPs may or may not occur, depending on the nature of the cell and, perhaps, the apoptotic stimulus. Since the loss of BRUCE was inhibited by RNAi for Nrdp1 and by lactacystin, the results indicate that Nrdp1 catalyzes proteasomal degradation of BRUCE in response to these apoptotic stimuli.

BRUCE/Apollon is an essential IAP

Unlike other mammalian IAPs, BRUCE/Apollon is essential for the viability of various cell lines,[48] and knockout of BRUCE in mice causes embryonic or neonatal lethality.[50] Studies by Hao et al.[50] and Bartke et al.[51] demonstrated that overproduction of BRUCE suppressed apoptosis in mammalian cells, in accord with the findings by Qiu et al. that decreasing endogenous BRUCE promoted apoptotic cell death.[48] It is clear from the results of various studies that BRUCE has multiple anti-apoptotic actions that antagonize the pro-apoptotic actions of Smac and caspases. Hao et al. reported that BRUCE is essential to inhibit Smac-induced apoptosis by promoting ubiquitination and degradation of the mature Smac.[50] Qiu et al.[32] presented complementary evidence that BRUCE promotes degradation of mature Smac. However, their study demonstrated that BRUCE, unlike other IAPs, also binds to the precursor of Smac and promotes its degradation. Furthermore, they showed that BRUCE binds to procaspase-9 and inhibits its cleavage. Overexpression

of the Smac precursor has been shown to promote the apoptosis induced by certain apoptotic stimuli,[45,52] although this precursor by itself is probably inactive in promoting apoptosis. Presumably, the enhancement of apoptosis is because higher amounts of this precursor in the cytosol lead to increased levels of Smac in the mitochondria, and therefore the cellular sensitivity to apoptotic stimuli rises. Thus, BRUCE-mediated degradation of the Smac precursor can be important in making cells more resistant to apoptotic stimuli. It is noteworthy in this regard that under normal conditions, the levels of Smac in various tissues are inversely correlated with the content of BRUCE, presumably because of the BRUCE-mediated degradation of the Smac precursor. The additional capacity of BRUCE to bind and destroy mature Smac after its release from mitochondria[50] should inhibit the apoptotic process once it has been activated. Pro-caspase-9 in complex with Apaf-1 plays a key role in the initiation of the caspase cascades, and is resistant to other IAPs.[53] The exceptional ability of BRUCE to antagonize the precursors of caspase-9 and Smac, whose ectopic expression promotes apoptosis,[45,54] might explain why BRUCE is essential.

The requirement of BRUCE for viability has also been confirmed by Ren et al.,[55] who showed that deletion of the C-terminal half of BRUCE, including the UBC domain, causes activation of caspases and apoptosis in the placenta and yolk sac, leading to embryonic death. This apoptosis is associated with up-regulation and nuclear localization of the tumor suppressor p53 and activation of mitochondrial pathway for apoptosis, which includes upregulation of Bax, Bak, and Pidd, translocation of Bax and caspase-2 onto mitochondria, release of cytochrome c and apoptosis-inducing factor, and activation of caspase-9 and caspase-3. Mutant mouse embryonic fibroblasts are sensitive to multiple mitochondrial death stimuli but resistant to tumor necrosis factor (TNF). They concluded that p53 is a downstream effector of BRUCE.

In summary, Nrdp1 and BRUCE regulate apoptosis, most likely through the mitochondrial pathway (Fig. 2), and changes in their activity are probably involved in multiple major human diseases, including cancers, where there is generally a failure of apoptotic mechanisms, and Parkinson's Disease, where there is excessive death of critical neurons.

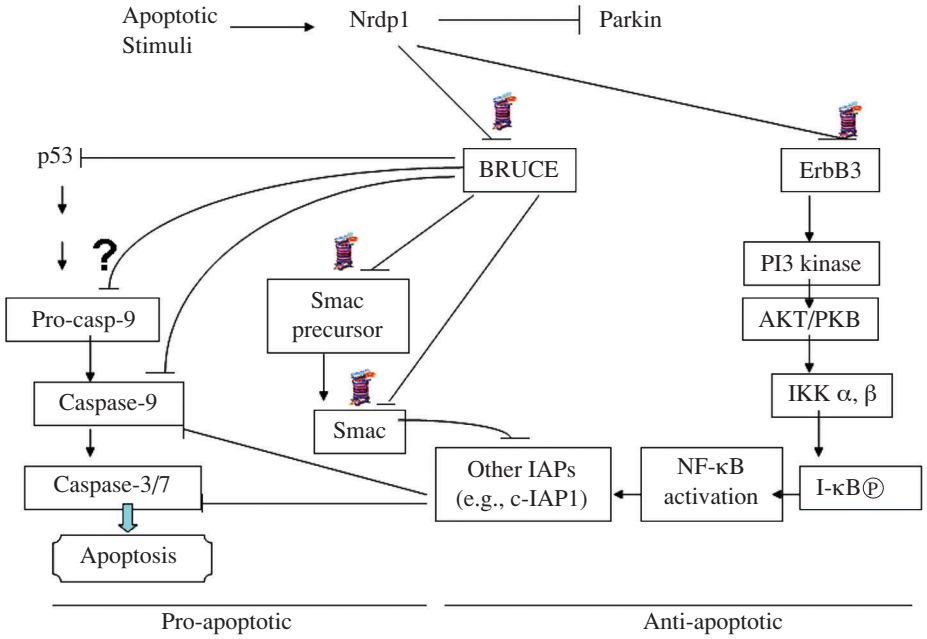

Fig. 2. The model mechanisms by which Nrdp1 and BRUCE modulate apoptosis

Regulation of the proteasome

Ubiquitination and deubiquitination at the proteasome

Finley and his colleagues used affinity isolation of the 26S proteasome from yeast and recently found several key proteasome-associated proteins which were removed during standard multistep purifications of the proteasome. One of the proteins is the deubiquitinating enzyme Ubp6, which possesses the capacity to delay the degradation of ubiquitinated substrate proteins independent of its catalytic activity, indicating that it has both deubiquitinating activity and proteasome-inhibitory activity.[56] This delay of degradation appears to allow gradual deubiquitination of the substrate by Ubp6. Proteasomes also contain other deubiquitinating enzymes, such as Rpn11.[56,57] In contrast to Ubp6, Rpn11 is an integral proteasome subunit that promotes protein breakdown through degradation-coupled deubiquitination. Rpn11 seems to catalyze substrate-proximal en bloc chain cleavage, and Ubp6 interferes with degradation upstream of this step, so that the degradation delay by Ubp6 is accompanied by a switch in the mode of ubiquitin chain processing.

Another proteasome-associated protein in yeast is Hul5, a ubiquitin ligase, which functions as an E4 enzyme and promotes the elongation of multiubiquitin chains at the proteasome. The results of a study by Crosas et al.[58] showed that the binding of Hul5 to the proteasome was promoted by Ubp6, and progressive deubiquitination of the substrate by Ubp6 was antagonized by Hul5. Moreover, hul5 mutants showed reduced degradation of multiple proteasome substrates in vivo, suggesting that the polyubiquitin signal targeting substrates to the proteasome can be productively amplified at the proteasome. However, the products of Hul5 conjugation are subject to disassembly by Ubp6. A hul5 null mutation suppresses ubp6 null mutation, suggesting that a balance of chain-extending and chain-trimming activities is required for proper proteasomal function. Based on these observations, Crosas et al.[58] proposed that through dynamic remodeling of ubiquitin chains, proteasomes actively regulate substrate commitment to degradation. Thus, governed especially by the functional interactions among Ubp6, Hul5, and Rpn11, ubiquitin chains are in a highly dynamic state at the proteasome, and regulate substrate selection by the proteasome.[58]

Regulation of the proteasome by phosphorylation

Phosphorylation of proteasome subunits has been shown in several organisms. The phosphorylation of proteasomal PSMA7 subunit at serine/threonine sites was demonstrated in yeast using proteomic approaches.[59] The results of recent studies on phosphorylation of fish oocyte proteasomal PSMA7 subunit by casein kinase Ia, a serine/threonine kinase, suggest that phosphorylation plays a role in the regulation of proteasomal activity during the meiotic cell cycle.[60] Liu et al.[61] revealed that the human proteasomal subunit PSMA7 is a specific substrate of Abl tyrosine kinases. In addition, they showed that c-Abl and Arg control the constitutive phosphorylation on PSMA7 Y153. The phosphotyrosine 153 moiety may facilitate PSMA7 and c-Abl/Arg interaction through the binding of c-Abl and Arg SH2 domains. Consequently, proteasome-dependent proteolysis may be compromised. Notably, cells expressing phosphorylation mutants of PSMA7 (Y153F) display impaired G1/S transition and S/G2 progression, highlighting the biological significance of tyrosine phosphorylation of the proteasome.

Novel proteasome subunit hRpn13 interacts with the deubiquitinating enzyme, UCH37

Although the proteasome structure and properties are highly conserved in eukaryotes,[9] a number of differences exist between proteasomes of higher and lower eukaryotes, and several specializations in mammalian proteasomes have been identified, such as the immunoproteasomes that are important in antigen presentation.[62] Also, the 26S particles in lower eukaryotes seem to contain unique subunits, such as Daq1/Rpn13, a 156 amino acid subunit of the 19S in budding yeast that appears important for degradation of certain model substrates.[63]

Based upon the approach of Leggett et al.[64] for isolating yeast proteasomes, Qiu et al.[65] recently described an affinity method for purifying mammalian 26S proteasomes. Using this approach, they discovered a novel human 19S subunit, a 407 residue protein that corresponds to gene products previously termed ADRM1 or ARM1 for "adhesion regulating molecule 1"[66] or GP110[67] for a putative surface glycoprotein. However, Qiu et al.[65] showed that this protein was primarily a subunit of the 26S proteasome, and three other groups[68-70] also demonstrated, using other approaches, its presence within the 26S

proteasome. It was renamed hRpn13 because its N-terminal region shares 28% identity with budding yeast Daq1/Rpn13, which was identified as a subunit of the 19S particle.[63,71]

Purified hRpn13 binds to UCH37 and enhances its isopeptidase activity. Two other isopeptidases, the cysteine peptidase, Ubp6/USP14, which is structurally related to UCH37, and the metallopeptidase, POH1/Rpn11, are also located in the 26S proteasome.[8,72] It is noteworthy that the C-terminal region of hRpn13 (residues 201-407), which binds to UCH37, is partially conserved in fission yeast, but not in budding yeast. Interestingly, UCH37 can also bind to the proteasome through Rpn10/S5a,[73] which is located at the hinge between the lid and the base of the 19S complex,[7] close to where UCH37 has been located.[74] Although the Rpn10/S5a subunit thus appears to interact with UCH37 in the 19S complex, this interaction fails to activate UCH37. Presumably both interactions function within the 19S complex, but the C-terminal region of hRpn13 evolved specifically to activate UCH37. Although there is no homolog of UCH37/UCH2 in budding yeast, Daq1/Rpn13 is still required for degradation of certain ubiquitinated proteins (e.g. substrates of the UFD pathway).[63] Therefore, hRpn13 also seems important in the assembly of the 19S complex or its function in some UCH37/UCH2-independent steps.

In frogs, the homolog of hRpn13, Xoom, is required for embryonic development,[75] which presumably reflects a critical role for protein degradation or for UCH37 during frog development. The knockdown of hRpn13 in 293T cells, though incomplete, reduced overall degradation of short-lived protein reproducibly, and this two-fold inhibition caused a large accumulation of the rapidly degraded model substrate Ub-R-GFP, which is degraded by the proteasome after ubiquitination by the "N-end rule" ligase E3α/Ubr1.[76] Furthermore, similar decreases in proteolysis were seen upon expression of high amounts of the C-terminal half of hRpn13, which probably acts as a dominant-negative form that inhibits UCH37 binding but allows 19S assembly. What is more significant is that the expression of the C-terminal half of hRpn13 led to the condensation of the nuclei and a marked aggregation of the mitochondria, as were observed during apoptosis induced by TNFα and cycloheximide. At high levels, the C-terminal half of hRpn13 appears to induce cell death, probably by preventing UCH37, but not hRpn13, from binding to the proteasome.[65] However, the more conclusive physiological function of hRpn13, especially its role in the regulation of apoptosis, awaits more intensive study.

Concluding remarks

The ubiquitin-proteasome pathway is critical to the life of eukaryotes. Therefore, aberrations in this pathway have been implicated in the pathogenesis of major human diseases, such as cancers, muscle atrophy, and neurodegenerative disorders. In this review, we described a few novel players in this pathway, especially Nrdp1 and Bruce/Apollon, which represent a novel pathway for initiating apoptosis. Notably, this new pathway is probably implicated in cancer and Parkinson's disease. Nevertheless, the way by which this pathway is controlled remains largely unknown.

It is clear that the ubiquitin-proteasome pathway plays a critical role in the regulation of apoptosis. Many cellular proteins with important functions in apoptosis are degraded by the ubiquitin-poteasome pathway. The proteasome inhibitor, Velcade/PS-341, is now widely used to treat multiple myeloma and mantle cell lymphoma, and other proteasome inhibitors are in clinical trials for the treatment of cancers and other major human disorders, where manipulation of apoptosis is desirable. In order to develop more specific drugs targeting the ubiquitin-proteasome pathway, it is important to understand the mechanism by which this pathway is regulated and the specific roles of different ubiquitin ligases in normal and diseased states.

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泛素－蛋白酶體通路及其對細胞凋亡調控研究的最新進展

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泛素-蛋白酶體通路 (The ubiquitin-proteasome pathway, UPP) 是真核細胞內蛋白質降解的主要途徑。它調節著幾乎所有的細胞活動，包括細胞週期、DNA 複製和修復、轉錄、蛋白質質量控制、免疫應答，以及細胞凋亡。UPP 由泛素化系統和一個巨大的多亞基 26S 蛋白酶體組成。蛋白質底物需首先在泛素激活酶 (E1)、泛素載體蛋白 (E2) 和泛素-蛋白連接酶 (E3) 的作用下與泛素共價結合形成複合物，然後在蛋白酶體中被降解成小肽段並通過去泛素化酶釋放出泛素以供重新利用。E3 通過決定底物泛素化的時間性和特異性而間接調控泛素-蛋白酶體通路介導的蛋白底物降解，而去泛素化酶則通過對泛素化的逆轉而實現對此通路的調節。在本綜述中，我們通過著重介紹幾個泛素-蛋白酶體通路的新組份 (如泛素連接酶 Nrdp1、泛素載體蛋白 BRUCE/Apollon，及蛋白酶體亞單位 hRpn13) 及其與細胞凋亡的相關性，對近年來在此通路的研究進展，尤其是它在細胞凋亡過程中所起的作用作一回顧，從而提供此通路及其對細胞凋亡調控機理的新認識。(長庚醫誌 2007;30:469-79)

關鍵詞：蛋白酶體，細胞凋亡，泛素連接酶，Nrdp1，BRUCE，hRpn13

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