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The role of the ubiquitin-proteasome pathway in cancer development and treatment

Fangbao Ding[1], Haibo Xiao[1], Mingsong Wang[1], Xiao Xie[1], Fengqing Hu[1]

[1]Department of Cardiothoracic Surgery, Xinhua Hospital, School of Medicine, Shanghai Jiaotong University, Shanghai, China

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1. ABSTRACT

Ubiquitination is a post-translational modification that plays a role in several cellular processes including cell cycle progression, cell proliferation, DNA replication and apoptosis. Ubiquitin-mediated signaling is frequently altered in cancer cells. Several tumor suppressors and oncogenes interact with enzymes of the ubiquitin-proteasome pathway that function in ubiquitin conjugation and deconjugation. Increasing evidence indicates that the ubiquitin-proteasome system (UPS) plays an important role in cancer development. Several small molecule inhibitors of the UPS have been applied to the treatment of cancer. The current review focuses on the role of the UPS in cancer development and the development of UPS inhibitors for cancer treatment.

2. INTRODUCTION

The balance between protein synthesis and degradation is important for the maintenance of homeostasis in eukaryotic cells (1, 2). Protein degradation is essential for the removal of excessive proteins (such as enzymes and transcription factors that are no longer needed) or exogenous proteins transported into the cells. Two major protein degradation systems exist in cells, the authophagy-lysosome and the ubiquitin-proteasome systems (3, 4). The ubiquitin-proteasome system (UPS) controls the degradation of intracellular proteins, whereas the lysosomal pathway degrades extracellular proteins imported into the cell by endocytosis or pinocytosis (5). Ubiquitination-proteasome-deubiquitination is an important regulatory mechanism that balances the responses to the

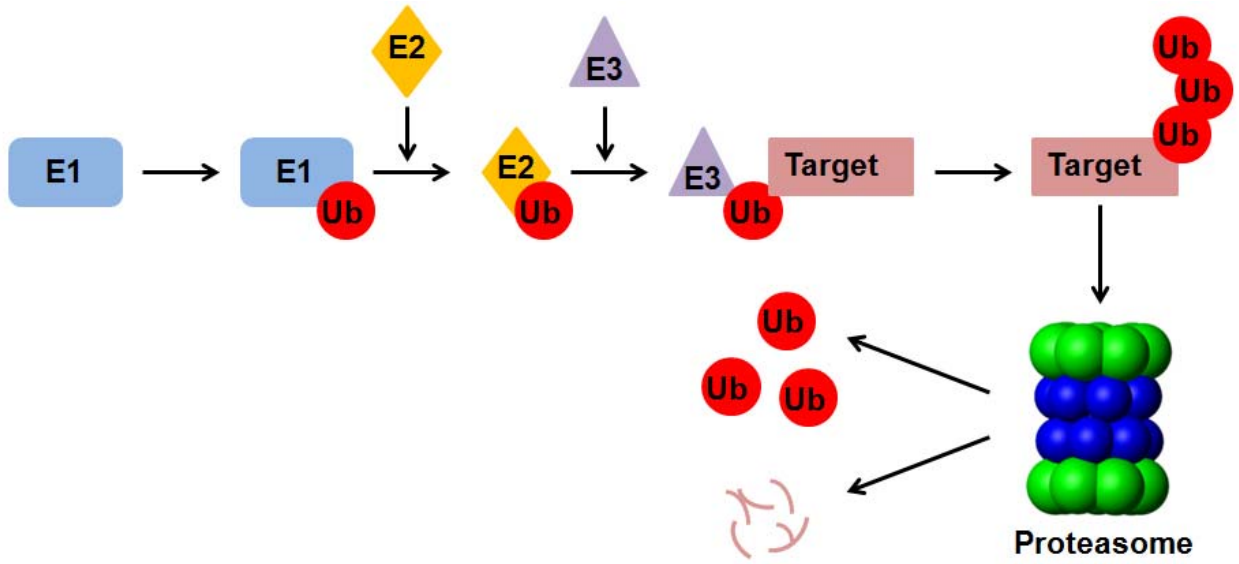

Figure 1. Enzymatic cascade involved in Ubiquitination. Ubiquitination occurs through an enzymatic cascade that involves three steps, activation, conjugation, and ligation, which are separately catalyzed by E1, E2 and E3 enzymes

environment *in vivo* (6, 7). Certain types of diseases such as cancers and diabetes are caused by system imbalances in the body (5).

Ubiquitin (Ub) was first identified in 1975 as an 8.5 kDa protein of unknown function expressed in all eukaryotic cells (8). The basic functions of ubiquitin and the components of the ubiquitination pathway were elucidated in the early 1980s (9). Ubiquitination (also known as ubiquitylation) is an enzymatic, post-translational modification (PTM) process in which an ubiquitin protein is attached to a substrate protein. The UPS regulates multiple biological aspects of cell survival by mediating the degradation of target proteins and thereby maintaining cellular homeostasis (10, 11). Defects in the UPS are responsible for a variety of human diseases, including cancers and metabolic disorders. The deregulation of UPS components has been observed in numerous cancers and their overexpression is often associated with chemoresistance and poor prognosis (10, 11). For example, the E3 ubiquitin ligase murine double minute 2 (MDM2), which is involved in the regulation of p53 levels, is frequently overexpressed in tumors and is predicted to be a negative prognostic marker for the development of several human cancers including breast carcinoma and prostate carcinoma (12-14).

3. THE CHARACTERISTICS OF UBIQUITINATION

Ubiquitination is crucial for such cellular processes as protein degradation, apoptosis, autophagy, and cell cycle progression. Approximately 80−90% of intracellular proteins are degraded though the UPS. The remaining 10−20% of intracellular proteins, composed of membrane-associated proteins and the alien proteins captured during endocytosis, are degraded in the lysosome (7). Ubiquitination is a process in which one or multiple ubiquitin moieties are covalently attached to a substrate through an enzymatic cascade involving an ubiquitin-activating enzyme (E1), an ubiquitin-carrier protein (E2), and an ubiquitin-protein ligase (E3). The proteasome and deubiquitinases (DUBs) are essential components of the system. Formation of an ubiquitin Lys48 chain on the ε-NH2 group of a substrate's internal Lys residue (polyubiquitination) can target the substrate for degradation by the 26S proteasome in an ATP-dependent manner. The enzymes in the ubiquitination process are critically regulated to control many cellular programs (15, 16).

3.1. Ubiquitination enzymes

Ubiquitination occurs through an enzymatic cascade that involves three steps, activation, conjugation, and ligation, which are separately catalyzed by E1, E2 and E3 enzymes (Figure 1) (1, 17). E1 enzymes, also known as ubiquitin-activating enzymes, catalyze the first step in the ubiquitination reaction. Ubiquitin is activated in a two-step reaction by an E1 ubiquitin-activating enzyme in an ATP-dependent manner (18). The initial step involves production of an ubiquitin-adenylate intermediate. The E1 binds both ATP and ubiquitin and catalyzes the acyl-adenylation of the C-terminus of the ubiquitin molecule. In the second step, ubiquitin is transferred to an active site cysteine residue and AMP is released. This step is mediated by the formation of a thioester linkage between the C-terminal carboxyl group of ubiquitin and the E1 cysteine sulfhydryl group. The human genome contains two genes that produce enzymes capable of activating ubiquitin, UBA1 and UBA6 (19). E2 ubiquitin-conjugating enzymes catalyze the transfer of ubiquitin from E1 to the active site cysteine of the E2 via a trans (thio)esterification reaction (20, 21). To perform this reaction, the E2 binds to both activated ubiquitin and the E1 enzyme. Humans possess 35 different E2 enzymes, whereas other eukaryotic organisms have between 16 and 35. They are characterized by their highly conserved structure known as the ubiquitin-conjugating catalytic (UBC) fold (22). E3 ubiquitin ligases catalyze the final step

of the ubiquitination cascade. Most commonly, they create an isopeptide bond between a lysine of the target protein and the C-terminal glycine of ubiquitin. In general, this step requires the activity of one of the hundreds of E3s present in cells (23-25). E3 enzymes function as the substrate recognition modules of the system and are capable of interaction with both E2 and substrate. Some E3 enzymes also activate the E2 enzymes. E3 enzymes possess one of two domains: the homologous to the E6-AP carboxyl terminus (HECT) domain and the really interesting new gene (RING) domain (or the closely related U-box domain). HECT domain E3s transiently bind ubiquitin in this process, whereas RING domain E3s catalyze the direct transfer of ubiquitin from the E2 enzyme to the substrate (26, 27). The anaphase-promoting complex (APC) and the Skp1-Cullin-F-box protein (SCF) complex are two examples of multi-subunit E3s involved in recognition and ubiquitination of specific proteins targeted for degradation by the proteasome. E3 ubiquitin ligases catalyze the final step of the ubiquitination cascade (28, 29).

3.2. Proteasomes

Upon modification by ubiquitin, substrates can be degraded by the 26S proteasome in an ATP-dependent manner (30, 31). The executioner of the ubiquitin-proteasome pathway is the 26S proteasome, which consists of a proteolytic core particle (20S proteasome) and two regulatory particles (19S regulatory complex) (32, 33). The 20S proteasome has a barrel shape characterized by two-fold symmetry and contains multiple catalytic centers located within the inner cavity of a molecular cage. It comprises 28 subunits arranged in four seven-membered rings that stack upon each other, yielding a $\alpha_{1-7}\beta_{1-7}\beta_{1-7}\alpha_{1-7}$ complex. Proteasomes participate in many cellular degradation processes, including cell cycle, responses to oxidative stress, inflammation, and regulation of gene expression (34, 35). Inhibitors of the proteasome have been developed to study the mechanism of the ubiquitin-proteasome pathway and treat diseases by targeting the proteasome (36). Bortezomib (N-acyl-dipeptidyl boronic acid), an inorganic compound, is the first and, at present, the only proteasome inhibitor approved by the FDA for the treatment of relapsed multiple myeloma (MM) and mantle cell lymphoma. It is a small boronic acid dipeptide molecule that binds reversibly to the chymotrypsin-like β5 subunit of the catalytic cavity of the 20S proteasome (37, 38).

3.3. De-ubiquitination enzymes

Ubiquitination is a reversible modification mediated by the concerted action of a large number of specific ubiquitin ligases and ubiquitin proteases, called deubiquitinating enzymes (39, 40). The balance of the activity of these enzymes determines the localization, function, and stability of target proteins. While some DUBs counter the action of specific ubiquitin ligases by removing ubiquitin and editing ubiquitin chains, other DUBs function more generally to maintain the cellular pool of free ubiquitin monomers (41-43). The DUBs oppose the role of ubiquitination by removing ubiquitin from substrate proteins. They are cysteine proteases that cleave the amide bond between the two proteins (44, 45). They are highly specific, as are the E3 ligases that attach the ubiquitin, with only a few substrates per enzyme. They can cleave both isopeptide (between ubiquitin and lysine) and peptide (between ubiquitin and the N-terminus) bonds. In addition to removing ubiquitin from substrate proteins, DUBs have many other roles within the cell. Ubiquitin is expressed either as multiple copies joined in a chain (polyubiquitin) or attached to ribosomal subunits. DUBs cleave these proteins to produce active ubiquitin. They also recycle ubiquitin that has been accidentally bound to small nucleophilic molecules during the ubiquitination process. Monoubiquitin is generated by DUBs that cleave ubiquitin from free polyubiquitin chains that have been previously removed from proteins. Approximately 100 DUBs have been described in the human genome (46, 47). These cysteine proteases can be classified into four categories according to their protease domains: ubiquitin-specific proteases (USP); ubiquitin C-terminal hydrolases (UCH); ovarian tumor (OTU)-type proteases; and Machado-Joseph disease proteases (MJD). The ubiquitination-deubiquitination balance is important in mammalian physiology (48). For example, the NF-κB pathway is regulated by DUBs. Deubiquitination factors negatively regulate IKK activity, and abolish the function of many enzymes that have deleterious consequences (49, 50).

3.4. Variety of ubiquitin modifications

Ubiquitination involves the attachment of ubiquitin to lysine residues on substrate proteins or itself, which can result in protein monoubiquitination or polyubiquitination. Polyubiquitination through different lysines (seven) or the N-terminus of ubiquitin can generate different protein-Ub structures. These include monoubiquitinated proteins, polyubiqutinated proteins with homotypic chains through a particular lysine on Ub or mixed polyubiquitin chains generated by polymerization through different Ub lysines (51). Monoubiquitination is the addition of one ubiquitin molecule to one substrate protein residue. The monoubiquitination of a protein has different effects than the polyubiquitination of the same protein (52). Monoubiquitination affects cellular processes such as membrane trafficking, endocytosis and viral budding (51). The addition of a single ubiquitin molecule is required prior to the formation of polyubiquitin chains. Multi-monoubiquitination is the addition of one ubiquitin molecule to multiple substrate residues. Polyubiquitination is the formation of a ubiquitin chain on a single lysine residue on the substrate protein. These chains are made by linking the glycine residue of a ubiquitin molecule to a lysine of ubiquitin bound to a substrate (53, 54). In addition to its N-terminus, ubiquitin has seven lysine residues that may serve as points of ubiquitination, namely K6, K11, K27, K29, K33, K48 and K63. Following the addition of a single ubiquitin moiety to a protein substrate, further ubiquitin molecules can be added to the first, yielding a polyubiquitin chain. Lysine 48-linked polyubiquitin chains target proteins for degradation by a process known as proteolysis (55, 56). At least four ubiquitin molecules must be attached to a lysine residue on the condemned protein for it to be recognized by the 26S proteasome. Lysine 63-linked chains are not associated with proteasomal degradation of the substrate protein. Instead, they allow the

coordination of other processes such as endocytic trafficking, inflammation, translation and DNA repair (57).

4. RELATIONSHIP BETWEEN THE UPS AND CANCER DEVELOPMENT

Recent studies have clarified the relationship between ubiquitination and human diseases, especially the development of cancer (10, 11). The role of E1 enzymes in different cancers has not been described in detail, and only a few reports have focused on the role of E2 in tumors. However, accumulating evidence strongly suggests a link between E3 enzymes and cancer development. E3 ubiquitin ligases are overexpressed in a number of human cancers, such as lung and breast cancer (58-60). The overexpression of E3 ubiquitin ligases is associated with a poor prognosis regarding patient survival. In addition, many E3 ligases play an essential role in carcinogenesis or are required for the maintenance of the cancer cell phenotype. The proteasome has emerged as a target for the treatment of several types of cancer. Bortezomib, the first and only proteasome inhibitor approved by the FDA, inhibits the enzyme complex in a reversible manner and has demonstrated clinical efficacy in the treatment of multiple myeloma and mantle cell lymphoma (7). Nevertheless, despite its effectiveness, some patients do not respond to bortezomib when it is used as a single agent, and the majority of patients that do respond, ultimately relapse.

4.1. The role of E3 ubiquitin ligases in cancer development

Numerous evidences indicate that the deregulation of ubiquitin pathways can directly and indirectly contribute to the development and progression of human cancers. One of the most studied aspects is linked to defects in E3 ligases that are essential for the removal of damaged organelles and misfolded or aggregated proteins. In general, E3 ubiquitin ligases are divided into the following two major types: HECT domain ligases, which favor the E6-associated protein carboxyl terminus for linkage with ubiquitin (61), and RING finger domain ligases (62). Several well-known E3 ligases are either aberrantly activated or display reduced function in human cancers. MDM2 is the E3 ligase that ubiquitinates the tumor suppressor protein p53, targeting it for proteasomal degradation (63). Increased MDM2 activity antagonizes the tumor suppressor function of p53 resulting in loss of function of p53. Overexpression of MDM2, principally due to genomic amplification, has been identified in a variety of human cancers including soft tissue sarcoma or lung cancer (64, 65). F-box and WD repeat domain-containing 7 (FBW7), an F-box protein, is another well-studied ubiquitin E3 ligase (66, 67). FBW7 is the substrate-specific component of this composite E3 ligase. FBW7 binds to phosphorylated regions of the substrate proteins, leading to their polyubiquitination and subsequent proteasomal degradation. Various oncogenes and key signaling mediators of cell growth and proliferation are among the target proteins of FBW7 including Myc, Jun, cyclin E, krueppel-like factor 5, Notch homolog 1, translocation-associated (Drosophila) (Notch1) and TGFβ -induced factor 1. Loss of FBW7 is frequently detected in various malignancies, including breast or colon cancer and T-cell acute lymphoblastic leukemia (68, 69). Genetic inactivation of FBW7 in mouse T-cells promotes lymphomagenesis, validating FBW7 as a tumor suppressor gene (68, 69). Overexpression of several FBW7 target proteins such as Jun, Myc or Notch 1 can not only promote proliferation but also induce cell death (70). The recent identification of myeloid cell leukemia sequence 1 (BCL2-related) (MCL1) as a FBW7 target protein has provided a plausible explanation for this open question. Casitas B-lineage lymphoma (CBL), another well-known ubiquitin E3 ligase, has been shown to be involved in cancer pathogenesis (71). CBL plays a role in the downregulation of receptor tyrosine kinases such as FLT3 or c-KIT, via multiple ubiquitination events. Deregulation of CBL has been identified in various cancers including acute myeloid leukemia, lymphoma and gastric carcinoma and has been linked to insufficient termination of receptor tyrosine kinase signaling (59, 72). Neural precursor cell-expressed developmentally down-regulated gene 4-1 (Nedd4-1) mediates the downregulation of the epithelial sodium channel in the collecting ducts of the kidneys by catalyzing its ubiquitination (73, 74). Phosphatase and tensin homolog (PTEN) is a target of Nedd4 (73). PTEN can function as a tumor suppressor by negatively regulating the Akt/PKB signaling pathway, and negatively regulates intracellular levels of phosphatidylinositol-3,4,5-trisphosphate. PTEN is a tumor suppressor protein that is inactivated in many human cancers. A single ubiquitin molecule attached to PTEN can lead to its nuclear translocation, whereas polyubiquitination of PTEN by Nedd4-1 promotes its proteasomal degradation (73). Although controversy still exists regarding the interaction between Nedd4-1 and PTEN, these findings provide evidence that Nedd4-1 may be an important target during cancer development (74).

4.2. The role of deubiquitinating enzymes in cancer development

Mammalian genomes encode approximately 100 DUBs including the USP, UCH, OTU, MJD, and the jab1/MPN domain-associated metalloisopeptidase class (JAMM) (75, 76). Aside from the JAMM enzymes, which are metalloproteases, all DUBs are cysteine proteases with a classical papain active-site structure composed of the catalytic triad of cysteine, histidine, and a third residue consisting of either aspartic acid, asparagine or rarely serine. Although the DUB family is large, only a subset is characterized to any degree at the molecular level. There is a growing recognition of DUBs that are mutated in human cancers, suggesting their roles as oncogenes and tumor suppressors (75, 76).

Cylindromatosis (CYLD) is a deubiquitinating enzyme that can cleave the lysine 63-linked polyubiquitin chains from target proteins and regulate cell survival or cell proliferation (77). Since loss of CYLD expression can be observed in different types of human cancer, it is now well established that CYLD acts as a tumor suppressor gene (78). CYLD interacts with NEMO (or IKK-γ) and TRAF2 in HeLa cells after tumor necrosis factor (TNF) α stimulation (79). Forced expression of CYLD in colon and hepatocellular carcinoma (HCC) cell lines significantly

decreases NF-κB activity. Overexpression of CYLD in HCC increases the antitumor effect of TNF-α-related apoptosis-inducing ligand (TRAIL). Accordingly, deubiquitination of TRAF2 by CYLD *in vivo* and *in vitro* promotes apoptosis. Besides the NK-κB signaling pathway, CYLD can interfere with both JNK and p38MAPK signaling to limit inflammation and survival (80).

USP2 is another well-studied deubiquitinating enzyme involved in cancer development. USP2 was linked to cancer in a study designed to isolate androgen sensitive DUBs from the rat prostate (81, 82). The rat DUB Ubp69 was isolated as well as its human orthologue USP2 from a human prostate cancer cell line. USP2 promotes the malignant transformation of immortalized human prostate epithelial cells and enhances tumorigenicity in an NIH3T3 *in vivo* tumor assay (81, 82). Other effects of USP2 may enhance its role in tumor formation. MDM2 was used as bait in a yeast two-hybrid screen and it formed a complex with USP2, which deubiquitinates and stabilizes MDM2. USP2-depleted cells show reduced MDM2 and increased p53 levels (83). USP2 was also found to bind to fatty acid synthase (FAS), a protein that is often overexpressed in aggressive prostate cancers. Tumor cells disproportionately synthesize their fatty acids de novo instead of deriving them from nutritional sources, making FAS an important tumor gene that protects prostate cancer cell lines from apoptosis. At the biochemical level, the core domain of USP2 is highly promiscuous and this DUB is commonly used as a generic Ub-removing enzyme in *in vitro* assays (84). Several cancers have reduced expression of USP2 including cancers of the colon, pancreas and head/neck. Unfortunately, no animal model exists with modulated USP2 expression.

4.3. The role of the proteasome in cancer development

Recent evidence suggests that the proteasome plays an important role in cancer development (7). Proteasome inhibition has been shown to suppress tumor growth, especially tumor angiogenesis (7). Angiogenesis, which is defined as the formation of new blood vessels, is an important and necessary function under both normal physiological conditions such as embryonic development and wound repair, and pathological conditions such as inflammation and cancers. Angiogenesis is necessary for tumor growth, survival, and metastasis (85). The progression of angiogenesis is regulated by proangiogenic factors and angiogenesis inhibitors. Proangiogenic factors include vascular endothelial growth factors (VEGFs), fibroblast growth factors (FGF) 1, FGF2, transforming growth factors (TGF) α, TGFβ, granulocyte macrophage colony stimulating factor (GM-CSF), epidermal growth factor (EGF), interleukin-1 (IL-1) and IL-8 (86).

Proteasome inhibitors can downregulate key angiogenic factors such as VEGF, whose mRNA expression is dependent on the cellular levels of p53 (87, 88). Induction of p53 downregulates the expression of VEGF, and proteasome inhibition can block VEGF expression by promoting the accumulation of p53. Recent studies show that p53 promotes MDM2-mediated ubiquitination and proteasomal degradation of hypoxia inducible factor (HIF) 1α, a transcription factor that regulates angiogenesis in response to oxygen deprivation (88). Inactivation of p53 in tumor cells enhances HIF-1α levels and increases HIF-1-dependent transcriptional activation of the VEGF gene in response to hypoxia. VEGF is also regulated by the NF-κB pathway. The endogenous inhibitor of NF-κB (IκBα) is regulated by the UPS, and the NF-κB pathway is known to be essential for many biological processes in cancers including angiogenesis. Inhibition of proteasome activity results in the accumulation of IκBα, which inhibits NF-κB and in turn downregulates the angiogenic factor VEGF and other pathways related to cancer (89). Animal studies have shown that bortezomib can suppress blood vessel development in tumor xenografts by more than 50%, resulting in a more than two-fold increase in survival time (34 days) in treated mice compared with untreated mice (14 days). Bortezomib was also shown to inhibit the growth of human pancreatic tumor xenografts through the inhibition of angiogenesis in nude mice and the downregulation of NF-κB-dependent proangiogenic cytokine expression in squamous cell carcinoma and human myeloma xenografts (90).

5. SMALL MOLECULE INHIBITORS OF THE UBIQUITIN PROTEASOME SYSTEM IN CANCER TREATMENT

5.1. Ubiquitin E1 activating enzyme inhibitor

PYR-41 is the first cell permeable inhibitor shown to specifically inhibit Uba1, a ubiquitin E1 activating enzyme (91). PYR-41 stabilizes p53 by preventing its ubiquitination and proteasomal degradation, thereby preferentially killing transformed cells with wild-type p53 (92). Increasing evidence suggests that PYR-41 functions by covalently modifying Uba1, perhaps on its active site cysteine. Functional studies revealed that PYR-41 also inhibits cytokine-induced NF-κB activation through the inhibition of both upstream TRAF6 ubiquitination (required for its E3 ligase activity) and downstream IκB ubiquitination (required for its proteasomal degradation) (92). PYZD-4409, which is structurally related to PYR-41, is another Uba1 inhibitor. PYZD-4409 induced cell death preferentially in hematologic malignant cell lines and primary patient samples over normal hematopoietic cells. The antitumor effect of PYZD-4409 was validated in a mouse leukemia model via interperitoneal injection (92).

5.2. Ubiquitin E2 carrier protein inhibitor

NSC697923 is an inhibitor of the Ubc13–Uev1A E2 enzyme identified in a screen for small-molecule compounds that may inhibit NF-κB activation in diffuse large B-cell lymphoma cells (93). Ubc13–Uev1A is involved in the formation of K63-linked poly-ubiquitin chains that are required for IKK activation. NSC697923 specifically inhibits the formation of the Ubc13–Ub thio-ester conjugate (93).

5.3. Ubiquitin E3 ligase inhibitor

Several series of non-peptide small molecule MDM2 antagonists have been developed to mimic the Phe19, Trp23 and Leu26 residues in p53 and their

interaction with MDM2 in the well-defined deep hydrophobic pocket (11). Spiro-oxindoles are a class of compounds that were discovered in a search for chemical moieties that can mimic the interaction of Trp23 with MDM2, with MI-63 being the most potent prototype drug (94). MI-63 is highly effective in activating p53 and inhibiting cancer cell growth when p53 is wild-type (95). MI-63 has excellent specificity for cancer cells with deleted p53 and shows minimal toxicity to normal cells (96). JNJ-26854165 is another MDM2 antagonist that inhibits the binding of the MDM2-p53 complex to the proteasome (97). The Skp2-p27 axis is an attractive target for cancer drug discovery. Compound A (CpdA) was identified in an *in vitro* high-throughput screen for compounds that could inhibit $p27^{Kip1}$ ubiquitination (98). It specifically targets SCF^{Skp2} by interfering with the Skp1/Skp2 interaction and thereby preventing the incorporation of Skp2 into the SCF complex. By stabilizing the SCF^{Skp2} substrate p27, CpdA induces G1cell-cycle arrest as well as SCF^{Skp2}- and p27-dependent cell killing (98).

5.4. Proteasome inhibitors

Several types of proteasome inhibitors have been developed in the last decade including peptide boronates (e.g., bortezomib, delanzomib and MLN9708), peptide epoxy ketones (e.g., carfilzomib, oprozomib, ONX-0914 and PR-924), peptide aldehydes (e.g., MG132 and IPSI-001), and non-peptidic β-lactones (e.g., marizomib) (11). Treatment with bortezomib results in the stabilization of two important negative regulators of the cell cycle, $p27^{KIP1}$ and p53, which are both known proteasome substrates. Inhibition of proteasomal activity by bortezomib also suppresses NF-κB signaling by preventing IκB degradation and the generation of the NF-κB subunits p50 and p52 from their precursors, p105 and p100, respectively (99). Bortezomib treatment also leads to the accumulation of the pro-apoptotic protein Bax, thereby shifting the pro-apoptosis and anti-apoptosis balance towards apoptosis (100). Additionally, proteasome inhibition has been shown to induce endoplasmic reticulum stress and oxidative stress in cancer cells.

6. CONCLUSION

The ubiquitin-proteasome system is an important mechanism regulating protein degradation. It is involved in the regulation of cell proliferation, differentiation and survival, and dysregulation of this system often leads to pathologies such as cancers. Recent studies have focused on the relationship between the UPS and cancer. Dysregulation of ubiquitination can lead to the development of several types of cancer. Targeting ubiquitination is therefore a promising strategy for cancer therapy. Several small molecule inhibitors of the UPS such as bortezomib and delanzomib have been applied to the treatment of cancer.

7. ACKNOWLEDGEMENT

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Abbreviations: APC: anaphase-promoting complex; CBL: casitas B-lineage lymphoma; CpdA: compound A; CYLD: cylindromatosis; DUBs: deubiquitinases; E1: ubiquitin-activating enzyme; E2: ubiquitin-carrier protein; E3: ubiquitin-protein ligase; EGF: epidermal growth factor; FAS: fatty acid synthase; FGF: fibroblast growth factors; FBW7: F-box and WD repeat domain-containing 7; TRAIL: TNF-α-related apoptosis-inducing ligand; Ub: Ubiquitin; UBC: ubiquitin-conjugating catalytic; UCH: ubiquitin C-terminal hydrolases; UPS: ubiquitin-proteasome system; USP: ubiquitin-specific proteases; VEGFs: vascular endothelial growth factors.

Key Words: Ubiquitination, Ubiquitin-Proteasome System, Cancer, Review

Send correspondence to: Fangbao Ding, Department of Cardiothoracic Surgery, Xinhua Hospital School of Medicine, Shanghai Jiaotong University, 1665 Kongjiang Road, Shanghai 200092, China, Tel: 86-13661715410, Fax: 86-021-65792951, E-mail: drnail@yeah.net