Subject Review

Ubiquitin Hubs in Oncogenic Networks

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Abstract

Ubiquitin is an important regulator of diverse biological functions including cell cycle progression, apoptosis, cell proliferation, and DNA damage responses. Crucial proteins involved in the control of such diverse functions are modified by ubiquitin and are frequently altered during oncogenesis. Here, we define such proteins as key-nodes regulated by ubiquitin, discuss examples of their oncogenic aberrations, and indicate how pharmacologic manipulation of such molecular hubs might improve anticancer therapy.

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Introduction

Ubiquitin is an evolutionarily conserved 76–amino acid protein that is used to label and alter the fate of cellular proteins, and are thus known as small protein modifiers (1, 2). A large number of proteins including cell cycle regulators, transcriptional activators and inhibitors, cell surface receptors, oncogenes, and tumor suppressor products are modified by ubiquitin via a process known as ubiquitination or ubiquitylation. In this reaction, a covalent bond is generated between its most COOH-terminal amino acid residue, a glycine, and one of the lysines in the modified protein (3, 4). More than one lysine in a given protein may be tagged by a single ubiquitin, producing monoubiquitylated (one lysine, one ubiquitin) or multiple-monoubiquitylated (many lysines, one ubiquitin per lysine) species (5). Additionally, as ubiquitin contains seven lysine residues, it can itself undergo ubiquitylation to form polyubiquitin chains of different lengths and shapes. For example, K48-type chains, in which Lys<sup>48</sup> is used in the chain-forming process, are required for proteolysis, whereas Lys<sup>63</sup>-type chains are used, for instance, in cytokine signaling cascades (3).

Ubiquitin may be seen as a prototypic intracellular signal that can be attached to a wide spectrum of proteins and subsequently recognized by a variety of ubiquitin-binding proteins. The discovery of domains able to bind to ubiquitin (commonly known as ubiquitin-binding domains, UBD) and of enzymes that cleave it off its targets (deubiquitylating enzymes, DUB), indicated that ubiquitin may function in vivo as a reversible and highly versatile regulatory signal. This diversity of reversible modifications and broad range of specific interactions enables ubiquitin to convey different information at different locations in the cell. Apparently, ubiquitylation could control the subcellular localization and catalytic activity of various proteins in addition to the regulation of their half-life. Furthermore, the formation of ubiquitin signaling networks translates signals from the cellular environment into proper cellular functions (Fig. 1).

The Ubiquitin System

Ubiquitylation of proteins occurs through a three-step process involving three types of enzymes. First, ubiquitin is activated in an ATP-dependent manner by a ubiquitin-activating enzyme (E1), then transferred to a ubiquitin-conjugating enzyme (E2) via a thiol-ester bond, and finally conjugated to a target protein through the ε-amino group of a lysine residue via ubiquitin-protein ligases (E3). Although only one enzyme (E1) is known in humans to catalyze the first step of ubiquitylation, approximately 60 enzymes (E2) could perform the second step and approximately 1,000 (E3) enzymes could perform the third, making the number of possible combinations and substrate specificities very high (4). E3 ligases are the most abundant group of enzymes involved in ubiquitylation and could be constituted of a single protein or protein complexes. Thus far, E3 enzymes have been grouped into four classes: HECT-type, U-box-type, PHD finger-type, and RING-type, the most abundant type, which can still be divided into several subclasses. The largest subclass is represented by cullin-based E3s, with the Skp1-CUL1-F-box protein (SCF) complex and the anaphase-promoting complex/cyclosome (APC/C) as the best characterized examples (3, 6).

Ubiquitylation is a reversible process governed by enzymes specialized in cleaving ubiquitin off its targets. The human genome contains approximately 90 putative DUBs belonging to a family of cysteine proteases that can be divided into four subclasses based on their ubiquitin protease domains: ubiquitin-specific proteases (USP), ubiquitin COOH-terminal hydrolases, Otubain proteases, and Machado-Joseph disease proteases. All other DUBs are metalloproteases with a ubiquitin protease domain called JAMM (JAB1/MPN/Mov34 metalloenzyme; ref. 7).

The next layer of complexity in the ubiquitin system is built up by proteins that specifically interact with ubiquitylated substrates in cells. Since the annotation of the first UBD, called ubiquitin-associated domains, the UBD list has expanded rapidly and it now contains 16 additional members, such as UIM, CUE, UEV, GAT, GLUE, NZF, VHS, PAZ, MIU, A20...
Governed by networks of proteins, displaying one or more functions such as signaling, endocytosis, transcription, and DNA damage repair, a single molecule could orchestrate processes as different as cell cycle progression, apoptosis, growth factor and cytokine receptor activation, when it is modified, and which UBD recognizes it. In this way, the target protein that undergoes ubiquitylation, where and when it occurs, can be regulated by different domains. However, in spite of these similarities, their target proteins and are all presumably recognized by ubiquitin or ubiquitin-like modifiers, meaning that they may undergo different types of ubiquitylation or modification by ubiquitin-like modifiers, interact with several E2s, E3s, DUBs, or UBD-containing proteins; and alteration of their regulation by ubiquitin, as sometimes found in cancers, causes loss- or gain-of-function phenotypes. Here, we describe some currently known KNUBs (Fig. 2) and provide evidence that mutations or altered expression of such critical nodes or of their regulating ubiquitin machinery are found in several human malignancies. Lastly, we discuss how pharmacologic manipulation of critical nodes regulated by ubiquitin may improve anticancer therapy and perhaps set a paradigm for the treatment of other ubiquitin-associated diseases.

**Cycling with Ubiquitin**

The physiologic order of cell cycle phases is regulated by cyclin-dependent kinases (CDK), which are activated by periodic variations of the concentration of their regulatory subunits, cyclins. The CDK2 inhibitor p27 and cyclins B, D1, and E are the main force that drives transitions through the cell cycle by undergoing periodic ubiquitin-dependent degradation (13). p27, cyclins B, D1, and E may be classified as KNUBs as they are critical for cell cycle progression and their levels periodically oscillate due to ubiquitin-dependent degradation. The breakdown of their ubiquitin “brakes” results in cell cycle dysregulation, which is a universal property of human cancers (14).

The essential roles of p27 and cyclins B, D1, and E were deduced from experiments in which these proteins were either knocked down or overexpressed (15, 16). The interpretation of ubiquitin signals varies depending on the target protein that undergoes ubiquitylation, where and when it is modified, and which UBD recognizes it. In this way, a single molecule could orchestrate processes as different as cell cycle progression, apoptosis, growth factor and cytokine signaling, endocytosis, transcription, and DNA damage repair or tolerance (Fig. 1; ref. 2). Each of these functions are governed by networks of proteins, displaying one or more critical nodes. Such key-nodes regulated by ubiquitin (KNUB) share important characteristics: (a) they occupy a crucial position in the molecular network and are indispensable for its function; (b) they show a rich repertoire of regulation by ubiquitin or ubiquitin-like modifiers, meaning that they may undergo different types of ubiquitylation or modification by ubiquitin-like modifiers, interact with several E2s, E3s, DUBs, or UBD-containing proteins; and (c) alteration of their regulation by ubiquitin, as sometimes found in cancers, causes loss- or gain-of-function phenotypes. Here, we describe some currently known KNUBs (Fig. 2) and provide evidence that mutations or altered expression of such critical nodes or of their regulating ubiquitin machinery are found in several human malignancies. Lastly, we discuss how pharmacologic manipulation of critical nodes regulated by ubiquitin may improve anticancer therapy and perhaps set a paradigm for the treatment of other ubiquitin-associated diseases.

**FIGURE 1.** Different types of protein modifications by ubiquitin (blue circles) signal different cellular outcomes. More than a lysine in a given protein may be tagged by a single ubiquitin, producing mono- (one lysine, one ubiquitin) or multiple-monoubiquitylated (many lysines, one ubiquitin per lysine) species. Several proteins involved in processes as different as endocytosis and trafficking of cargos (such as epsins, Hrs, Eps15), transcription (e.g., histone H2B), or response to different DNA damages (such as PCNA or FANCDD) are monoubiquitylated. Multiple-monoubiquitylation has also been implicated in endocytosis and trafficking of transmembrane receptors. Because ubiquitin contains seven lysine residues, it can undergo ubiquitylation itself to form polyubiquitin chains of different lengths and shapes. For example, K48-type chains are branched and required for protein degradation in proteasomes, whereas Lys63-type chains are more linear and used in cytokine signaling cascades for instance.

ZnF, UBM, and UBZ (2, 8, 9). This list is likely to increase because there are several new domains on the block. Even though the structures of all these domains differ a lot from one another, the majority recognize the same surface on ubiquitin called the hydrophobic patch. Such interactions are of very low affinity (in the micromolar range), implying an in vivo requirement for multiple interactions or additional sites of contact between ubiquitylated and UBD-containing proteins (9, 10).

Another layer of complexity involves ubiquitin-like modifiers such as SUMO, NEDD8, ISG15, or FAT10. In analogy to ubiquitin, all ubiquitin-like modifiers are covalently attached to their target proteins and are all presumably recognized by specialized domains. However, in spite of these similarities, ubiquitin-like modifiers are believed to play different roles in the cell (11). For instance, sumoylation can regulate subcellular protein localization, DNA repair, chromatin remodeling, or gene transcription. Neddylation, on the other hand, has been implicated in the control of several E3 ligases, such as MDM2, Cbl, and cullins, providing a close link between the addition of the ubiquitin-like modifier NEDD8 and ubiquitylation (12).

The interpretation of ubiquitin signals varies depending on the target protein that undergoes ubiquitylation, where and when it is modified, and which UBD recognizes it. In this way, a single molecule could orchestrate processes as different as cell cycle progression, apoptosis, growth factor and cytokine signaling, endocytosis, transcription, and DNA damage repair or tolerance (Fig. 1; ref. 2). Each of these functions are governed by networks of proteins, displaying one or more critical nodes. Such key-nodes regulated by ubiquitin (KNUB) share important characteristics: (a) they occupy a crucial position in the molecular network and are indispensable for its function; (b) they show a rich repertoire of regulation by ubiquitin or ubiquitin-like modifiers, meaning that they may undergo different types of ubiquitylation or modification by ubiquitin-like modifiers, interact with several E2s, E3s, DUBs, or UBD-containing proteins; and (c) alteration of their regulation by ubiquitin, as sometimes found in cancers, causes loss- or gain-of-function phenotypes. Here, we describe some currently known KNUBs (Fig. 2) and provide evidence that mutations or altered expression of such critical nodes or of their regulating ubiquitin machinery are found in several human malignancies. Lastly, we discuss how pharmacologic manipulation of critical nodes regulated by ubiquitin may improve anticancer therapy and perhaps set a paradigm for the treatment of other ubiquitin-associated diseases.
overexpressed or genetically ablated. Overexpression of cyclin D1 causes in vitro transformation, mammary hyperplasia, and low-penetration breast carcinomas in transgenic mice. Additionally, mice knocked-out at the KIP1 locus, encoding for p27, develop pituitary adenomas and hyperplasia in multiple organs. Interestingly, high levels of B-type cyclins, such as A or B1, have been found in human carcinomas of the colon and lung. Additionally, both cyclins D1 and E are frequently overexpressed in different types of human cancers, where their levels correlate with a poor *quoad vitam* prognosis (6, 13).

The levels of these KNUBs are under strict ubiquitin regulation for which three cullin-dependent ubiquitin ligases are crucial: SCF/Skp2 (Skp1-CUL1-F-box protein), SCF/Fbw7, and the APC/C. SCF/Skp2, which contains the Skp2 F-box protein, binds to and polyubiquitylates phosphorylated p27 and possibly cyclin D1, whereas SCF/Fbw7 targets phosphorylated cyclin E for proteosomal degradation. On the other hand, APC is required for the polyubiquitylation and degradation of securin and cyclin B, which are indispensable for sister chromatid separation and exit from mitosis, respectively (6, 15).

Given their central role in cell cycle progression, it is not surprising that mutations of both APC and SCF/Skp2 or Fbw7 have been reported in several malignancies. Mutations that inactivate the APC subunits Cdc16 and Cdc23 have been described in colon carcinomas and high levels of its inhibitor Emi have been detected in several human tumors (13). Additionally, the E3 ligase β-TrCP, which targets Emi1 for proteosomal degradation, has been found to be overexpressed in several tumor cell lines and in samples of human colorectal carcinoma. The targeted expression of β-TrCP in the mouse mammary epithelium causes hyperplasia (16). Skp2 was found to be overexpressed in a large number of cancer types, where its levels correlated with a poor prognosis. Additionally, Skp2 alone or in association with oncogenic Ras could induce tumor formation in two mouse models. On the other hand, Fbw7 has the features of a tumor suppressor, and indeed, inactivation mutations of the *FBW7* gene have been detected in several ovarian and breast cancer cell lines expressing high levels of cyclin E. Furthermore, these mutations occur in primary endometrial carcinomas, where they may correlate with high tumor aggressiveness and scarce prognosis (6, 13, 15).

**Ubiquitin Nodes in Nuclear Factor κB, Transforming Growth Factor β, and WNT Signaling**

Many components of signal transduction pathways for growth factors or cytokines have been found to be modified by ubiquitin or ubiquitin-like modifiers in various physiologic or pathologic settings, but only a few have the characteristics of KNUBs such as IκB kinase (IKK) in the nuclear factor κB (NF-κB) pathway (which is activated, among others, by the proinflammatory cytokines tumor necrosis factor-α and interleukin 1[β]), β-catenin in the Wnt signaling cascade, and SMADs in the transforming growth factor β (TGF-β) pathway.

The transcription factor NF-κB mediates the expression of several genes involved in certain immune responses, inflammation, and apoptosis. Proinflammatory cytokines such as tumor necrosis factor-α or interleukin 1[β lead to the activation of the IKK complex, which phosphorylates the inhibitor of NF-κB, IκB. In turn, this becomes polyubiquitylated by the ligase SCF-βTrCP, and is degraded in the proteasome. Consequently, NF-κB is released and translocates into the nucleus where it triggers the expression of its target genes (17).

IKK is a crucial node in the molecular network that emanates from members of the tumor necrosis factor-α receptor superfamily. In fact, genetic ablation of the mouse gene encoding for the IKK α subunit resulted in premature death soon after birth, whereas disruption of the β subunit led to embryonic lethality between days 12.5 and 14, due to massive apoptosis in the liver (18, 19). Very interestingly, the activation of both IKK and TAK1, the IKK activating kinase, requires their modification by ubiquitin. In the case of IKK, its regulatory subunit NEMO needs to become polyubiquitylated with Lys63-type chains, whereas the subunit β becomes mono-ubiquitylated at Lys163 following phosphorylation at two specific serine residues (17). Additionally, TAB2 and TAB3, two TAK1-interacting partners, harbor a ubiquitin-binding zinc finger domain that preferentially associates with Lys63-type ubiquitin chains and is required for the ability of these proteins to activate TAK1. Another essential component of the tumor necrosis factor-α receptor signaling complex, receptor-interacting protein, becomes modified by the ubiquitin ligase TRAF2 with Lys63-type ubiquitin chains upon tumor necrosis factor-α stimulation. A20, a potent inhibitor of NF-κB signaling, is a fascinating chimeric enzyme that acts both as a DUB that removes Lys63-type ubiquitin chains from receptor-interacting proteins and as a ubiquitin ligase that attaches Lys48 chains, sending receptor-interacting protein for proteosomal degradation. The E3 ligases TRAF2 and TRAF6, which target IKK and TAK1, are also modified by Lys63 chains, a prerequisite for their stability and activation of the NF-κB pathway. Therefore, there is a rich repertoire of ubiquitin modifications and UBDs in the NF-κB network, involving the key-node IKK or its interaction partners (17).

Aberrant NF-κB signaling has been found in many cancers and is believed to play a major role in the increased incidence of cancer-associated anorexia-cachexia syndrome. In several cases, aberrant oncogenic signaling through the NF-κB pathway were the consequence of mutations in components of the ubiquitin system (20). Bcl10 for instance, the E3 ligase that targets NEMO for polyubiquitylation, is frequently overexpressed as a result of chromosomal translocations in marginal zone B-cell lymphomas, including those of the mucosa-associated lymphoid tissue (21). In another example, the tumor suppressor CYLD, originally cloned as the cause of the rare familial cylindromatosys syndrome, was later found to be a DUB. CYLD removes Lys63-type ubiquitin chains from TRAF2, TRAF6, and NEMO, leading to the down-regulation of NF-κB signaling (20).

The TGF-β pathway is another signaling cascade in which ubiquitin plays a crucial role. TGF-β superfamily ligands bind to Ser/Thr kinase receptors that propagate the signal by phosphorylation of receptor-regulated Smads (R-Smads) -1, -2, -3, -5, and -8. Phosphorylation of the R-Smads permits their association with the common Smad (co-Smad) Smad4, to form R-Smad/Smad4 complexes that regulate transcriptional
responses. The TGF-β superfamily controls a plethora of biological functions, such as cell proliferation or differentiation and apoptosis, particularly during embryonic development (22, 23).

Smads are critical for TGF-β signaling, as shown for instance by genetic ablation of the mouse Smad4 gene, which resulted in embryonic lethality for homozygous mutants, whereas heterozygous animals showed no abnormality (24). The size of the Smad pool in nonstimulated cells, as well as the Smad protein levels subsequent to activation of the pathway, are tightly controlled by ubiquitylation. Three HECT-type ubiquitin ligases mediate Lys48 polyubiquitylation of Smads: Smad ubiquitination-related factor 1 (Smurf1), Smurf2, and SCF/Roc1. In the absence of stimulation by TGF-β or bone morphogenic protein–type ligands, the WW domains of Smurf1 mediate a specific interaction with the phosphotyrosine motif of Smad1 and Smad5, thereby targeting them for ubiquitylation and subsequent proteasomal degradation. Similarly, Smurf2 polyubiquitylates inactive Smad1, Smad2, and Smad3. On the other hand, the SCF/Roc1 E3 ligase complex has been shown to trigger the ubiquitylation and degradation of phosphorylated, active, Smad3 (22, 23). Smad4 undergoes ubiquitylation as well, and interestingly, the E3 ligase responsible seems to be different between wild-type Smad4 and cancer-associated point mutants. Wild-type Smad4 is ubiquitylated by the RING-finger ligase ectodomain TIF-1γ (24), whereas tumor-derived point mutants that are polyubiquitylated with K48-type ubiquitin chains are targeted by the Skp2 complex (25).

Alterations in the TGF-β signaling pathway have been associated with a broad range of human diseases, particularly cancers. In comparison with the wild-type protein, various missense mutations in the MH1 domain of tumor-derived Smad4 lead to its increased polyubiquitylation and proteasomal degradation. Similarly, a nonsense mutation at position 515 in the MH2 domain of Smad4 has been described in pancreatic adenocarcinomas, which results in the truncation of the last 38 amino acids, and targets Smad4 for ubiquitin-dependent proteasomal degradation in addition to preventing it from associating with Smad2 and binding to DNA. Alterations in Smurfs have also been described in some human cancers as associated with increased Smad degradation and decreased TGF-β signaling (23).

Another KNUB is β-catenin, a core effector of WNT signaling. These glycoproteins are secreted during embryonic development and are crucial for stem cell maintenance in the adult. WNTs interact with members of the Frizzled family of serpentine receptors, and possibly, with the single-pass transmembrane protein LDL-receptor-related proteins 5 and 6 (26). β-Catenin is critically regulated by ubiquitin in vivo. In the absence of WNT ligands, β-catenin is recruited to a complex containing the previously described ubiquitin ligases, APC and AXIN, which promote the phosphorylation of β-catenin by casein kinase 1 and then by glycogen synthase kinase 3. In turn, phosphorylation primes β-catenin for ubiquitylation and proteasomal degradation. Upon binding of WNTs to Frizzled receptors, Dishevelled gets phosphorylated and recruited to the plasma membrane, where it attracts AXIN. In turn, AXIN directly binds to the cytoplasmic tail of LRP5/6 and is then degraded, which results in the reduction of β-catenin degradation. The activation of Dishevelled also inhibits glycogen synthase kinase 3, which further reduces the phosphorylation and degradation of β-catenin. Thus, in the “on” state, upon ligand stimulation, the levels of β-catenin increase and it accumulates in the nucleus, where it interacts with DNA-bound TCF and LEF family members to activate the transcription of target genes (27).

The impairment of the ubiquitin regulation of β-catenin is associated with several pathologies in humans, including cancer, and causes severe phenotypes in mouse models. Inherited and sporadic mutations in the tumor suppressor APC reduce the degradation of β-catenin, causing an increase in β-catenin levels and transcription of target genes such as the proto-oncogenes cyclin D1 and c-MYC. Similarly, gain-of-function mutations in the amino terminal phosphorylation sites of β-catenin, and loss-of-function mutations in AXIN that reduce β-catenin degradation, have been described in a variety of human cancers (28).

**Tolerating DNA Damages with Ubiquitin**

Cells needed to evolve mechanisms to cope with damages in DNA that blocked the progression of replication forks. When a fork stalls at the site of damage, processive polymerases are replaced by one of the so-called Y polymerases, such as η or Rev1. These polymerases possess more open catalytic sites allowing them to replicate across different types of lesions, a process known as translesion synthesis. Thanks to this “polymerase switch,” cells could quickly replicate the whole genome, even in the presence of some damage, and lesions could be repaired afterwards (29).

The proliferating cell nuclear antigens (PCNA) are another example of KNUBs that are indispensable for life. It forms a platform that brings different proteins, including polymerases, in contact with DNA, enabling DNA replication, repair, and damage tolerance processes. Depending on the function it needs to perform, PCNA undergoes different types of posttranslational modifications. For instance, upon UV treatment, it becomes monoubiquitylated by the action of Rad6 (E2) and Rad18 (E3) enzymes, and the ubiquitin moiety can then be recognized by the UBZ domain of Polη, which mediates the lesion bypass. Indeed, the ubiquitin-binding ability of Y polymerases is crucial because ablation of UBZ of Polη, for example, or of UBMs of Rev1 causes hypersensitivity to UV (10, 30). Additionally, Rad18 knockout mice ES cells have been reported to be hypersensitive to DNA damage–inducing agents and having defective damage tolerance (31). Interestingly, PCNA has been shown to undergo Lys63-type polyubiquitylation as well, which can mediate an alternative pathway of damage tolerance upon stalling of replication forks. However, it is not yet known how polyubiquitylated PCNA is recognized in a specific manner. Recently, USP1 was shown to be the DUB cutting off ubiquitin from the PCNA, and the interplay between USP1 and ubiquitylating enzymes has been envisioned to tightly regulate PCNA ubiquitylation. The regulation of USP1 itself is very elegant as its levels are constant during S phase, but drop down upon UV treatment due to UV-mediated self-destruction of the protein. In turn, this allows for a more stable modification of PCNA by its ubiquitin

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ligases (32). This mechanism was likely selected during evolution to prevent the unwanted replacement of replicative polymerases by Y polymerases in the absence of DNA damage. In fact, because translesion synthesis polymerases are devoid of proofreading activity and are therefore of a very low fidelity, their inappropriate deployment during normal S phase would lead to the accumulation of mutations in the genome, potentially facilitating carcinogenesis (32, 33).

Targeting KNUBs in Human Tumors

Given their crucial role in controlling the functions that are typically altered in human malignancies, KNUBs seem to be a reasonably good target for new anticancer drugs. Because computer-aided drug design is much easier towards clefs or pockets on the surface of proteins, such as enzymatically active sites, KNUBs may offer several possibilities, either because they are themselves enzymes, as in the case of IKK, or because components of their regulation such as E3s or DUBs contain catalytically active sites. Additionally, contact sites between KNUBs and components of the ubiquitin machinery might be amenable for drug design, provided that they can offer some degree of steric specificity (Fig. 2).

Targeting E3 ligases seems to be an intelligent approach as they are the major determinants of specificity of ubiquitylation, and the E3s of the above discussed KNUBs are already quite well structurally characterized. For instance, the crystal structure of a Skp1-Skp2-CKS1-phospho-p27 peptide complex has been resolved, providing clues for the rational development of inhibitors of p27 degradation, useful in the treatment of cancers associated with Skp2 overexpression. Contacts between the p27 phosphorylation site and Skp2 seem to be the most promising because they are more stereospecific than the contacts between CKS1 or Skp1 and the F-box Skp2 (34).

Targeting downstream of ubiquitin ligases can also be a worthwhile strategy, as shown by the recent success of the proteasomal inhibitor bortezomib (Velcade) in some clinical settings. Surprisingly, despite proteasomes being ubiquitous and degrading a plethora of proteins involved in multiple functions, bortezomib has a very favorable selectivity profile towards cancer cells versus normal ones. Based on the positive results of the SUMMIT trial, the American Food and Drug Administration, and its cousin, the European Medicines Evaluation Agency, have approved the use of bortezomib for patients with relapsed multiple myeloma, who received one prior type of chemotherapy or bone marrow transplant, and for patients with other cancers in the setting of approved, well-designed clinical trials (35).

Lastly, developing drugs to target interaction sites between KNUBs and components of the ubiquitin machinery that regulates them may also represent an innovative avenue of discovery. Structural information on the surface surrounding the lysine where ubiquitin gets attached in a given protein could allow for stereospecific drug design. In the case of PCNA, for example, targeting Lys$_{164}$ where ubiquitin is linked is predicted to result in a loss of the DNA damage tolerance potentials of cancer cells, thus making them more vulnerable to the toxic activity of conventional chemotherapeutic agents. Besides computer-aided design, we also envision the use of more classic, compound library–based screens to search for drugs that affect interaction sites between KNUBs and one of their regulatory components (Fig. 3; ref. 36).

Conclusions

In the age of molecular-targeted therapies for cancer and other diseases, the design of smart drugs against components of the ubiquitin system may seem to be a difficult challenge. The major dilemma revolves around the issue of how to target a ubiquitous signal, which is affected in human diseases but also controls many physiologic cellular functions, without paying a tremendous burden of toxicity. However, the recent success of the proteasomal inhibitor bortezomib (Velcade), which inhibits some of the proteasomal catalytic sites, has clearly shown that under some circumstances, the clinical benefits may outweigh the side effects. It is also becoming evident that a better understanding of ubiquitin signaling pathways and their involvement in cancers provides new avenues for the development of new, more specific, antitumor therapeutics (36). Our goal in this review was to describe a few KNUBs that operate crucial functions such as cell cycle progression, signaling, or DNA repair, and KNUBs that are often altered in human malignancies, thus, representing good targets for ubiquitin-directed anticancer drugs.

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References
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