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Ubiquitin Proteasome System as Target for Tumor Therapy

Mohamed Hassan [1,2,3*], **Abdelouahid El-Khattouti** [1], **Youssef Haikel**[2,3], **Mosaad Megahed** [4]

[1]*Cancer Institute, University of Mississippi Medical Center, Jackson, MS 39216, USA*

[2]*Institut National de la Santé et de la Recherche Médicale, U 977*

3Department of Operative Dentistry and Endodontics, Dental Faculty, University of Strasbourg, 67000 Strasbourg, France

4Clinic of Dermatology, University Hospital of Aachen, Pauwelsstr. 30, 52074 Aachen, Germany

[*]***Corresponding authors:*** *Dr. Mohamed Hassan Cancer Institute, University of Mississippi Medical Center, Jackson, MS 39216, USA,*

Tel.: +1 601 815 8945; Fax:+1 601 984 29 81 E-mail: dr.hassan@gmx.de

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Abstract

Targeting the ubiquitin-proteasome pathway gained more attention as a rational approach in the treatment of human cancer. The 26S proteasome (2000-kDa) complex, which degrades ubiquitinated proteins, contains in addition to the 20S proteasome a 19S regulatory complex composed of multiple ATP ases and components necessary for binding protein substrates. Accordingly, proteasome is considered an exciting target for the development of anticancer therapies. Inhibition of proteasome machinery has shown a positive clinical benefit for cancer patients. Thus, the highlight of the mechanistic role of proteasome regulators, both inhibitors and activators, may help to improve the outcome of tumor treatment. In this review, we will focus on the molecular action of proteasome regulators in tumor treatment.

Keywords: Ubiquitin; Deubiquitin; Proteasome; Tumor therapy

Introduction

The ubiquitin-proteasome system (UPS) is a conserved pathway responsible for the selective degradation of the majority of nuclear and cytosolic proteins in normal and tumor cells. The function of the ubiquitin system (UBS) is mediated by a group of E1, E2, E3 and E4 enzymes that are characterized by their highly binding affinity to poly-ubiquitin chains conjugated protein substrates [**1**]. Thus, the binding of these enzymes to ubiquitinylated substrates facilitate their transport to approximate proteasomes, where they degrade into small peptides [**2**]. The 26S proteasome complex consists of a 20S core particle that is associated with one or two 19S regulatory particles [**3**], the 20S proteasome is the central proteolytic machinery of the UPS [**4**]. It is cylindrical in shape and composed of four heptameric rings that are ordered as follows: α7β7β7α7 [**5**]. The outer α-rings are essential for proteasome gating, and the two β rings contain three catalytic sites arranged in the β1, 2 and 5 subunits, forming six active sites in both β-heptamers. The gate opening of 20S is regulated by the binding of the regulatory 11S and 19S complexes to α rings [**6**]. Thus, the binding of the poly-ubiquitylated substrates to 19S regulatory unit as well as the ATP binding to the ATPase hexameric ring is important for the enhancement of gate opening leading to the increase of the proteolytic activity of the 20S [**7**]. Accordingly, the ubiquitin-proteasome pathway plays an essential role in cellular homeostasis [**8**], and the levels of proteasome activity in cancer cells are higher when compared with normal cells [**9**]. Thus, targeting proteolytic and regulatory particles of the proteasome system is an efficient strategy for tumor treatment. Figure 1 outlines the ubiquitin-proteasome system mediating protein degradation. Because of the importance of the proteasome in common cellular functions such as, protein turnover, DNA repair, and intracellular trafficking [**10-13**], inhibition or activation of the proteasome is considered as an ideal therapeutic strategies for a variety of diseases including, cancer. Besides the inhibition of proteasome as a strategy for tumor treatment, small molecules that can block the function of proteasome activators may become a relevant therapeutic approach for tumor treatment. The degradation efficiency of ubiquitinated substrates depends on the efficiency of unfolding and removal processes of polyubiquitin chains [**14**]. These processes are derived by the translocation of ubiquitin-tagged proteins into the proteolytic core by a mechanism, in which the deubiquitinase (DUB) activity of the 19SRP plays an essential role [**15**]. Thus, the inhibition of deubiquitination by specific inhibitors such as β-AP15, is expected to block the function of proteasome through the disruption of the gate opening to prevent the entry of the substrate into the 20S core particle (20SCP) chamber. Accordingly, the inhibition of the proteasome is expected to destroy the balance between the proliferative and anti-proliferative signals leading to cell-cycle arrest and/or induction of apoptosis [**16**]. Thus, the highlight of the mechanistic role of proteasome regulators may provide an insight for the development of a novel tumor therapeutic strategy.

Molecular mechanism of proteasome-mediated protein degradation

The ubiquitin-proteasome pathway is a conserved pathway that is required for the targeted degradation of most short-lived proteins in eukaryotic cells [**17**,**18**]. The main targets of this pathway are cell cycle regulatory proteins, whose timely destruction is essential for controlled cell division, and the miss-folded protein within the endoplasmic reticulum[**19-21**] The proteolysis of cellular proteins is a highly complex, temporally controlled and tightly regulated process that is essential for the regulation of the basic cellular processes[**22**,**23**]. The proteolysis of cellular proteins by proteasome pathway is outlined in Figure 2. This process is mediated by a complex cascade of enzymes that are highly specific towards their substrates [**24**,**25**]. These substrates include cell cycle and growth regulators, components of

signal transduction pathways, enzymes of housekeeping and cell specific metabolic pathways, miss-folded, mutated or damaged proteins [**19-21**]. The degradation of a protein by the ubiquitin-proteasome pathway is mediated by two distinct and successive steps, including, covalent attachment of multiple ubiquitin molecules to the target protein and the subsequent degradation of the tagged protein [**26**]. The conjugation of ubiquitin to its substrate is regulated by a three-step mechanism. This mechanism is initiated by ubiquitin - activating enzyme, E1 that has the ability to enhance the binding activities of the C-terminal Gly of ubiquitin, through thiol ester intermediate, to the substrate that has the specificity to bind to a member of the ubiquitin –protein ligase family, E3. The transfer of ubiquitin to the substrate can be mediated directly or indirectly via another E3 ubiquitin thiol ester intermediate. These E3 intermediates serve as a cofactor that facilitates and catalyzes the covalent attachment of ubiquitin to its substrate [**27**,**28**]. Once the first moiety is transferred to the ε–NH2 of the internal Lys residue, the α-NH2 group or Lys group of the substrate creating a linear peptide or isopeptide bond, respectively [**29**,**30**]. The propose of this reaction is to form a polyubiqutin chain by transferring additionally activated ubiquitin moieties to the internal Lys residue of the beforehand conjugated ubiquitin molecules.

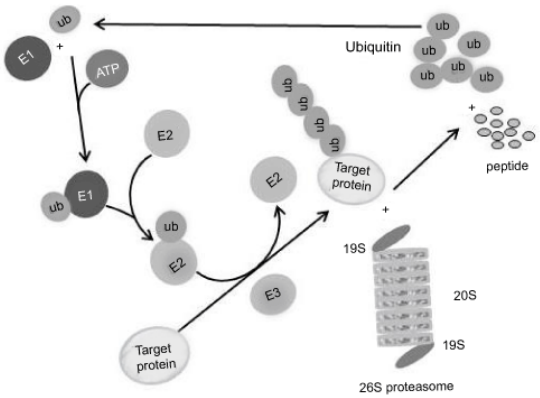

Figure 1: The ubiquitin- proteasome pathway. The activation of ubiquitination process is mediated by the addition of ubiquitin moiety to E1 enzyme, and E1 transfers ubiquitin to E2 enzyme that subsequently interacts with E3 leading the formation of polyubiquitin chain. Ultimately, substrate proteins tagged with a multiple-ubiquitin chain are then degraded by the 26S proteasome that is composed of a 20S catalytic core and two 19S subunits.

The ubiquitin proteolytic system plays an essential role in a wide range of basic cellular functions, in which, proteases/deubiquitinases (DUBs) serves as a fundamental roles in the regulation of many biological and pathological processes including, cancer[**31**,**32**]. These deubiquitinases are essential for the regulation of ubiquitin homeostasis and protein stability by enzymatic activities-dependent mechanisms [**33**,**34**]. This regulatory process is divided into three different steps namely, ubiquitin precursor processing, ubiquitin deconjugation and editing of ubiquitin conjugates [**35**,**36**]. Thus, DUBs contributes to the processes that leads to the ubiquitin chains from ubiquitinated proteins and rescue them from degradative pathways or mediate the revision of ubiquitin signaling [**37**,**38**]. Based on its pivotal potency in ubiquitin homeostasis and control of protein stability, DUB activity seems to be tightly regulated by different cellular mechanisms including, transcriptional control of gene expression, post-translational modification and alterations in subcellular localization via a process mediated by interacting proteins [**37**,**38**].

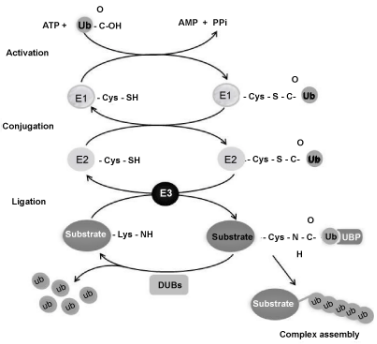

Figure 2: The ubiquitin-proteasome pathway. Ubiquitination of the substrate proteins are mediated serial and coordinated ubiquitin-activating (E1), ubiquitin-conjugating (E2), and ubiquitin-ligating (E3) enzymes. E1 enzymes (E1s) activate ubiquitin (Ub) in an ATP-dependent manner via the acyladenylation of the ubiquitin C terminus. The activated Ub is then released from charged E1 to form second thioester complex with the E2 catalytic Cys. E2 enzymes (E2s) interact with E3 enzymes (E3s) that incorporate protein substrates for Ub ligation. E3s modify substrates by sequential addition of Ub moieties. Conjugation of monoubiquitin or polyubiquitin chains determines the biological consequences of the substrate proteins. Accordingly, the addition of linear Ub chains or the acceptor lys residue (K63)-linked polyubiquitin chains is mainly associated with substrate activation or subcellular localization. Whereas the attachment of Lys residues K48, or K11 is essential for the enhancement of proteasome-dependent of the substrate proteins. Ubiquitination can be reversed through a tightly regulated process mediated by deubiquitinases (DUBs). DUBs generate free ubiquitin through the process of ubiquitin precursors maintaining ubiquitin homeostasis. DUBs can edit ubiquitin chains, a mechanism for the alteration of ubiquitin signals in addition to the rescue of substrate proteins from degradation as well as the removal of a nondegradative ubiquitin signal via ubiquitin deconjugation.

Based on their functional diversity, nature and pattern, DUBs are implicated in the regulation of many biological processes including, cell cycle control, DNA repair, chromatin remodeling and intracellular signaling pathways [**37**,**38**]. As result, the involvement of DUBs in tumor development and progression is expected [**20**,**39**]. Accordingly, these DUBs become emerging targets for anti-cancer therapies.

Proteasome activators

Activation of ubiquitin-proteasome system is an essential step in the degradation process of normal, damaged, or mis-folded proteins [**40-42**]. Thus, the accumulation of polyubiquitinated proteins is the consequences of UPS activation. The ubiquitin-proteasome system-mediated degradation is a tightly regulated process, in which the contribution of proteasome activators, PA28, PA200 and PA700 are essential [**43**,**44**]. Therefore, the activation of the proteasome is carried out by proteasome activators, through the binding to their regulatory

subunits [45,46], 50]. The involvement of the proteasome activators, PA28α,β,γ and PA28γ in the regulation of cell proliferation, apoptosis, and carcinogenesis has been reported [46,47]. For example, PA28γ has been shown to mediate the turnover of p53 via MDM2-mediated proteasomal degradation via the interaction between MDM2 and p53 [48,49]. This mechanism causes the inhibition of p53-dependent apoptosis, an evidence for an essential role of PA28γ in the modulation of apoptosis and cell proliferation. Thus, targeting PA28γ consequently increase the activity of p53 and, in turn, enhances apoptosis as an attractive therapeutic strategy for tumor treatment.

Also, the involvement of the proteasome activator PA200 in the regulation of DNA damage via its ability to function as an adapter between the proteasome and chromatin proteins, is required for DNA repair [50-52]. Moreover, as a component of 26S proteasome, PA200 is able to recruit an ATP-dependent protease to DNA damage sites, an essential step in the activation process of the 26S proteasome to initiate the degradation of chromatin proteins, and thereby facilitates the exposure of DNA to the required repair enzymes[52]. Thus, based on its potential role in the modulation of proteasome-mediated efficient DNA repair, PA200 is considered as an attractive therapeutic target for tumor treatment.

In addition to the proteasome activators PA28 and PA200, the ATP-dependent 20S proteasome activator, PA700 has been intensively studied in the context of its ability to trigger the activation of the 26S proteasome. Accordingly, PA700 is essential for substrate selection and processing [53,54]. Thus, apart from its molecular action, PA700 plays a crucial role in the regulation of UPS [55]. Since alterations of UPS function have been reported to trigger many pathological processes including cancer, PA700 subunit is considered as a potential therapeutic target for tumor treatment.

Proteasome inhibitors

Of note, the main function of the UPS is not only the degradation of structural and housekeeping proteins, but also the removal of many regulatory proteins, which are essential to control the biosynthetic pathways, cell cycle control, and transcription factors, oncoproteins and proteins that are essential for the regulation of the immune system. Thus, the design and synthesis of chemical agents based on proteasome inhibition that serves as an antitumor agent could be an efficient therapeutic strategy for tumor treatment. The inhibition of the cellular proteins turnover by the inhibition of the proteasome function is a mechanism that cannot be tolerated in any cell. The inhibition of the proteasome consequently results in the accumulation of unwanted proteins that, in turn, become toxic for the cell. Thus, the utilization of such mechanisms as a therapeutic strategy to kill tumor cells showed success in the treatment of multiple myeloma and mantle cell lymphoma[56]. Accordingly, the first reported proteasome inhibitors are Acetyl-Leucyl-Leucyl-Norleucinal (ALLN) and leupeptin [57,58]. Also, a wide variety of natural and synthetic compounds have been approved or under clinical evaluation. These compounds are able to inhibit the proteasome activity by either reversible or irreversible binding to the 20S catalytic subunit of the proteasome [59,60].

Based on their chemical structure and molecular action proteasome inhibitors are divided into specific classes. Covalent inhibitors that are electrophilic and react with the catalytic –hydroxyl of Thr1 in the active sites of the proteasome via mechanism-mediated by reversible or irreversible binding. Most of these natural inhibitors such as, syringolin A, lactacystin and epooxomicin belong to the class of covalent inhibitors [61,62]. Whereas, inhibitors that lacking the reactive group belong to non-covalent inhibitors that are mostly associated with less specificity and low stability [63].

The molecular action of proteasome inhibitors are mediated by different cellular mechanisms including, the control of cell cycle, regulation of pro-and antiapoptotic proteins, enhancement of cell sensitivity to ligand-induced apoptosis and autophagy associated pathways [16,64,65].

Although their therapeutic efficiency are higher than other antitumor agents, most of these proteasome inhibitors show low specificity and insufficient metabolic stability [66,67]. However, the most promising proteasome inhibitors for clinical utilization belong to the class of peptide boronates [68]. Thus, in addition to their high specificity to proteasome, their therapeutic potency is greater than those of the analogues of peptide aldehydes [69].

The establishment of bortezomib in the treatment of multiple myeloma encouraged researchers and clinician to identify and assess the clinical reliability of new proteasome inhibitors. Most of these inhibitors are either approved for clinical utilization or are still under clinical evaluation [70,71]. These include MLN-9708 and CEP-18770 that are known to be reversible inhibitors that offer more benefit for patients than bortezomib [72].

Although bortezomib is established as a first-line therapy for the treatment of multiple myeloma patients, relapse often occurs in patients who initially responded to the treatment with bortezomib making the acquisition of bortezomib resistance into a serious problem [73]. Thus, based on its reliability as therapeutic target for tumor treatment, the development of a therapeutic strategy depends on the inhibition of the USP14/UCHL5 deubiquitinases of 19S regulatory particle is considered. These inhibitors include the small molecular inhibitor, β-AP15 that has been shown to induce a distinct cellular response like those induced by the inhibitors of 20S core particle[74]. The killing efficiency of β-AP15 is associated with the induction of both endoplasmic reticulum- and oxidative stress- mediated pathways to apoptosis [75,76]. Although the inhibitors of 20S core particle and 19S regulatory particle blocks the function of the proteasome, the mode of their mechanistic action is quite different [77]. Although ubiquitin system is believed to be highly druggable, the development of therapeutic approaches based on the destruction or inhibition of proteasome system still remains under the expectation. The identification of β-AP15, an inhibitor of the USP14 and UCHL5 DUBs of the 19SRP and its subsequent application in tumor treatment has gained more attention. The Inhibition of both USP14 and UCHL5 by β-AP15 in tumor cells results in the accumulation of various proteasome substrates that, in turn, trigger tumor cell death [78]. β-AP15-induced cell death is mediated by a mechanism that is similar to those of bortezomib [74]. The clinical use of β-AP15 is thought to be reliable for the treatment of multiple myeloma patients who have developed resistance to bortezomib [79]. Although the clinical outcome of bortezomib and β-AP15 is similar, the molecular action is quite different. For example, β-AP15-induced apoptosis is not influenced by the overexpression of Bcl-2 or by the genetic disruptions of proapoptotic proteins such as, BAX and P53 [75,80]. Whereas, proteasome inhibitors-induced apoptosis depends on the stability of various proteasomal substrates such as the inhibitor of NF-kB kinase, IkB [81], p53 [82], as well as the stability of the proapoptotic proteins Bid and Bax [83].

Ubiquitin proteasome system as target for tumor therapy

Although in cancer E1s and E2s are not targets for mutation or any other genetic changes and they do not appear to play any essential role in cancer development and progression, the deregulation of E3 ligases is more important for tumor development and progression [**84-86**]. The inactivation of E3s is thought to be essential for stabilization of oncogene products or the degradation of tumor suppressor proteins. Up to date, the most established proteasome inhibitor is the bortezomib that mediates its antitumor activity through the inhibition of the proteolytic activity of the proteasome, and in turn, the degradation of multi-ubiquitinated proteins [**87**]. Although bortezomib inhibits only the chemotrypsin-like activity of the proteasome, the inhibition of this activity is enough to block all proteasome- associated activities [**88**, **89**]. The molecular action of bortezomib-induced effects on tumor cells is mediated by the inhibition of NF-KB activation, inhibition of myeloma cell adherence to bone marrow stroma, reduction of the production of angiogenic factors, decrease of IL-6 signaling, mitochondrial dysregulation, endoplasmic reticulum stress and the accumulation of multi-ubiquitinated proteins [**90-92**]. Although bortezomib has emerged as a therapeutic target for tumor treatment, there are remarkably undesired adverse effects such as, neuropathy. Also, most of tumor patients who do not show any response to bortezomib, have been shown to develop resistance to proteasome inhibitors [**93**]. Apart from the mentioned therapeutic limitation of bortezomib, the proteasome inhibitors, carfilzomib showed a promising antitumor activity in multiple-myeloma (MM) with limited side effects [**94**]. Carfilzomib is a selective proteasome inhibitor that is approved for the treatment of patients with Relapsed/Refractory multiple myloma (RRMM) who the failed first line therapies and have disease progression after the completion of the last therapy [**95**]. Thus, besides being well tolerated as evidenced by low rates of dose reductions and discontinuations in response to the adverse effects, single-agent treatment with carfilzomib is promising and demonstrated improved overall patients'response and an increased in median duration of the response [**96**]. Although its therapeutic reliability in tumor patients is shown in phase II studies, the most common adverse events include fatigue, anemia, nausea, dyspnea, and diarrhea have been observed [102]. In addition, Carfilzomib also shows the hematologic adverse events including, thrombocytopenia, anemia, lymphopenia, and neutropenia [**97**]. Whereas nonhematologic adverse effects that have been observed include, pneumonia, acute renal failure, pyrexia, and congestive heart failure [**97**]. Thus, apart from the associated adverse effects carfilzomib offers an alternative therapeutic approaches for the treatment of patients with RRMM, particularly, who are heavily pretreated or refractory to bortezomib and/or immunomodulatory agent. Carfilzomib mediates its antitumor activity through the inhibition of cell growth and induction of apoptosis via a mechanism that is mediated by the activation of c-Jun-N-terminal kinase, mitochondrial dysregulation leading to the loss of mitochondrial membrane potential, cytochrome c release and activation of caspases-associated with the induction of either intrinsic or extrinsic pathways[**16**]. NPI-0052 is another potent inhibitor of proteasome which demonstrated promising antitumor activity in vitro [**98**]. This inhibitor has been found to mediate its antitumor activity through mechanisms- mediated by both mitochondrial dysregulation and endoplasmic stress-depended pathways leading to apoptosis of tumor cells [**99**]. Also, this proteasome inhibitor has the ability to inhibit migration of MM cells as well as angiogenesis [**100**]. Thus, the improvement of current proteasome inhibitors or the development of novel and more effective proteasome-related inhibitors is urgently needed.

Immunoproteasome as a therapeutic target for tumor therapy

Besides being a target for tumor treatment, immunoproteasome is an emerging biological target that constitutes a key element not only in antigen presentation but also in T cell and cytokine regulation as well as cellular homeostasis. As the major proteolytic machinery in the cell, proteasome system is responsible for generating antigenic peptides that can be presented to cytotoxic T cells by the major histocomputability (MHC) class I molecules [**101**]. Generally, 20S core of the 26S that harbors the three catalytic subunits β1, β2, and β5 in the inner β-rings, the constitutive subunits of the proteasome, are mainly responsible for caspase-, trypsin-, and chymotrypsin-like activities, respectively [**102**], can be replaced by the immunoproteasome subunits including β1i, low molecular mass polypeptide (LMP); β2i multicatalytic endopeptidase complex-like (MECL)-1; and β5i (LMP7), respectively, in heamopoietic cells or in response to the stimulation of nonhematopoietic cells by proinflammatory cytokines such as TNF-α and IFN- [**103**]. Thus, in addition to their role in the antigen presentation, immunoproteasomes determine the repertoire of T cells besides being responsible for their survival and expansion [**104**].

The main function of immunoproteasomes in the cells of hematologic origin and their primary function is to improve MHC Class I antigen presentation by the cleavage of proteins after hydrophobic and basic amino acids through their chymotrypsin-like and trypsin-like activities[**105**]. Therefore, immunoptoteasome-generated peptides are thought to be more efficient in T-cell activation than those that are generated from the constitutive proteasome. Thus, the involvement of the immunoproteasome in protein degradation during the course of the immune response has been reported and the immunoproteasome was found to be more efficient in controlling the protein degradation process, when compared with the constitutive proteasome [**106**]. Of note, the expression of immunoproteasome in B-cell malignancies is markedly higher than the level of constitutive subunits, emphasizing the potential importance of the immunoproteasome in the homeostasis of hematologic diseases. Although the pre-clinical activity of the β5i-specific proteasome inhibitor ONX 0914 has been approved in the autoimmune disease models, the clinical use of ONX 0914 in the treatment of hematologic malignancies is limited [**107**,**108**]. The ability of tumor cells to modulate immunoproteasome function is considered to be a tumor strategy to escape immune surveillance [**109**]. These strategies may consist of different genetic alterations including mutation in genes encoding for the constitutive β5 subunit. In contrast, the analysis of the immunoproteasome β5i did not reveal any mutation in its encoding gene suggesting that the resistance of hematologic tumor cells to bortezomib is attributed to the downregulation immunoprteasome rather than mutation. Accordingly, the elevated expression of immunoproteasome in B-cell malignancies, compared to those of constitutive subunits suggesting a potential role for the immunoproteasome in regulation of the homeostasis in hematologic diseases [**109**]. Thus, the modulation of immunoproteasome in tumor cells is thought to be a tumor protective strategy to escape immune surveillance [**109**]. These mechanisms seem to arise in hematologic tumor cells with acquired bortezomib resistance that may result from genetic alteration of the proteasome (prosome, macropain) subunit beta type 5 (PSMB5) gene that encodes for the constitutive β5 subunit

[**109**]. Since the immunoproteasome β5i the counterpart of the constitutive β5 subunit does not harbor mutations, the downregulation of immunoproteasome in bortezomib-resistant hematologic tumor cell lines is thought to be the mechanism whereby tumor cells escape targeting from bortezomib [**109**]. Accordingly, the upregulation of immunoproteasome expression is expected to sensitize the hematologic tumor cells to bortezomib or proteasome inhibitors that are designed to target immunoproteasomes. However, the induction of immunoproteasome in multiple myloma derived cell lines in response to the exposure to inflammatory cytokines, such as IFN-γ and TNFα has been reported [**109**]. Although the exposure of B-cell lines to IFN-γ has been shown to enhance their bortezomib-sensitivity, the underlying mechanism still remains to be explored. To that end, targeting inhibition of the immunoproteasome has been suggested to be a potent strategy to overcome resistance of multiple myeloma to conventional drugs and nonspecific proteasome inhibitors [**110**]. More importantly, IFN-γ-induced upregulation of immunoproteasome expression in bortezomib-resistant tumor cells, in which both immunoproteasome expression is downregulated and the mutated β5 subunits are upregulated can accommodate as a therapeutic strategy to reconstitute tumor sensitivity to bortezomib, and proteasome and immunoproteasome inhibitors.

Ubiquitin-like proteins as therapeutic target for tumor treatment

The discovery of ubiquitin-like proteins (ULP), functionally and mechanistically parallel to the established ubiquitin pathways, adds a new opportunity for the development of relevant therapeutic strategies for tumor treatment [**111**]. These ULPs are characterized by their ability to bind covalently to the protein substrates in addition to their individual cellular function [**112**]. Although ULPs such as, the small ubiquitin-like modifier (SUMO) and the related to ubiquitin (RUB) pathways have been reported in all eukaryotic cells, other ULBs such as, ISG15 pathway is restricted in their distribution [**113**]. The function of ULPs are highly regulated in all eukaryotic cells and involved in different cellular functions including, nuclear transport, transcriptional regulation, chromosome segregation and cell- cycle control [**112**]. In addition to the protein transport from the cytoplasm to the nucleus, the post-translational modification process of SUMO (SUMOylation) also regulates the transcriptional activities proteins and mediates the binding of protein to the corresponding proteins [**114**,**115**]. Accordingly, the SUMOylation pathway is essential to target Ran GTPase-activating protein 1 (RANGAP1 to the nuclear pore complex, as mechanism whereby SUMO mediates the protein transport from the cytoplasm to the nucleus [**116**]. Unlike Ub, SUMO does not target proteins for proteasome degradation; instead it can act as a signal for the recruitment of E3 Ub ligases that are essential for the ubiquitylation and subsequent degradation of the targeted substrates [**117**].

Interestingly, the enhancement of SUMOylation pathway and its effectors were noted in melanoma patients compared to normal plasma cells (PCs)[**118**]. Thus, the induction of the SUMOylation pathway did confer multiple properties on myeloma cells and, in turn, promotes tumorgenesis [**119**]. Unlike Ub-pathway where conjugating enzymes exist with limited substrate specificity, UBE2I encodes the sole SUMO-conjugating enzyme is an evidence for the fundamental role of UBE2I and the SUMOlyation pathway in the regulation of the critical cellular processes [**78**,**120**,**121**]. Figure 3 outlines the potential therapeutic targets and inhibitors of the ubiquitin–proteasome system.

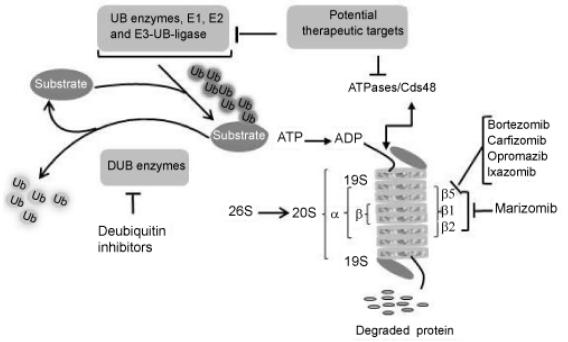

Figure 3: Potential therapeutic targets and inhibitors of the ubiquitin-proteasome system. DUB: deubiquitylating enzyme; E1: Ubiquitin-activating enzyme; E2: Ubiquitin-conjugating enzyme; E3: Ubiquitin ligase enzyme; Ub: Ubiquitin.

Conclusions

The discovery of the ubiquitin-proteasome pathway opened a new era for tumor therapy. Laboratory studies, preclinical and clinical evaluation of proteasome inhibitors revealed the reliability of ubiquitin-proteasome pathway as a therapeutic target for the treatment of a variety of solid and hematological malignancies. Proteasome inhibitors in the form of monotherapy or combination therapy exhibited their ability to potentially overcome chemo- or radio-resistance. Although the therapeutic potential of proteasome inhibitors in the treatment of hematological malignancies is high, many disadvantages and limitation of proteasome inhibitors have been noted in solid tumors. Of note, observations such as, the expected severe side effects, insufficient efficacy in addition to the acquisition of chemo-resistance in cancer patients may help clinicians to modify their therapeutic strategies to reduce proteasome inhibitors-associated disadvantages, and encourage researchers to develop new generation of proteasome inhibitors that broaden the spectrum of activity and able to produce a more durable clinical response.

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