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Review Articles

Targeting the ubiquitin pathway in lymphoid malignancies

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ABSTRACT

Ubiquitination and related cellular processes control a variety of aspects in human cell biology, and defects in these processes contribute to multiple illnesses. In recent decades, our knowledge about the pathological role of ubiquitination in lymphoid cancers and therapeutic strategies to target the modified ubiquitination system has evolved tremendously. Here we review the altered signalling mechanisms mediated by the aberrant expression of cancer-associated E2s/E3s and deubiquitinating enzymes (DUBs), which result in the hyperactivation of oncoproteins or the frequently allied downregulation of tumour suppressors. We discuss recent highlights pertaining to the several different therapeutic interventions which are currently being evaluated to effectively block abnormal ubiquitin-proteasome pathway and the use of heterobifunctional molecules which recruit the ubiquitination system to degrade or stabilize non-cognate substrates. This review aids in comprehension of ubiquitination aberrance in lymphoid cancers and current targeting strategies and elicits further investigations to deeply understand the link between cellular ubiquitination and lymphoid pathogenesis as well as to ameliorate corresponding treatment interventions.

1. Background

Ubiquitination is an intricately orchestrated process which refers to the transfer of a small 76 amino acid residue ubiquitin to a substrate protein leading to the alteration of protein stability, localization, or function. These alterations are essential to maintain cellular integrity and homeostasis through the regulation of various cellular processes including signal transduction, transcriptional regulation, or antigen presentation among others [1]. Ubiquitination to the targeted protein is ATP-dependent and sequentially requires the catalysation of E1 activating enzymes, E2 conjugating enzymes and E3 ligases in a harmoniously coordinated fashion (Fig. 1) [1–3]. There are over 600 E3 ligases coded from the human genome separated into 3 main families. The homologues to E6-associated protein carboxy terminus (HECT) family and the really interesting new gene (RING) family are the most abundant in the genome, with the third family being the RING-Between-RING (RBR) family. All three families function by linking E3 ligases with their cognitive substrates; however, the process of ubiquitin transfer within each of the families is unique (see review Walma et al. [4]). The transfer of ubiquitin can occur as a single moiety resulting in the monoubiquitination or multi-monoubiquitination; however, as ubiquitin itself contains a number of lysine residues ubiquitin chains can be generated either through E2/E3 processing and then transferred as blocks, or built up sequentially on the substrate itself [5]. The two most well-studied of these chain topologies are the K48 and K63 ubiquitin chains which are the archetype of homotypic chain formation (chain formation through a single lysine residue). In addition, heterotypic or mixed-linkage polyubiquitination also exists, in which two or more linkage types (ex. K48-K63-K27) are present in the same polyubiquitin chain. Interestingly, the ubiquitin chain topology can also exhibit branched formations. The function of these distorted structures remains to be determined (Fig. 1). Poly-ubiquitin chains, most notably K48-linked chains, mark substrate proteins for proteasome-mediated degradation (Fig. 1). Therefore, the accessibility and susceptibility to the proteasome greatly impacts protein half-life [6]. All 26S proteasomes contain a common catalytic core also known as 20S and one or

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two 19S regulatory cap subunits. The 20S core is formed by four rings, outer α and inner β, with each containing seven subunits. Three of those subunits, β1, β2 and β5, are catalytically active and possess the caspase-like, trypsin-like and chymotrypsin-like activities required for protein degradation, respectively [7,8]. It is important to note that monoubiquitination, multi-monoubiquitination, and K63-specific poly-ubiquitin chains lead to primarily non-proteolytic distinct roles.

Counteracting the effect of E2/E3 ligases, deubiquitinating enzymes (DUBs) cleave ubiquitin from protein substrates (Fig. 1). The human genome encodes approximately 80–100 DUBs classified into seven families, including the ubiquitin-specific proteases (USPs), the ubiquitin carboxy-terminal hydrolases (UCHs), the ovarian tumor-related proteases (OTUs), the Machado-Joseph disease protein domain proteases (MJDs), the JAB1/PAB1/MPN-domain containing metallo-enzyme (JAMMs), the motif interacting with Ub-containing novel DUB family (MINDYs) and ZUFSP [9–12]. Like the E3 ligases, DUBs have highly selective activity on different substrates and ubiquitin chain linkages [13]. Functions of deubiquitination are multidimensional, encompassing apoptosis, protein trafficking, cell cycle regulation, DNA damage repair and chromatin remodelling [13–15]. Frequent aberrance of the ubiquitin-proteasome system (UPS) components is observed in cancers including lymphoid related malignancies and therefore are considered attractive targets for therapeutic interventions [16]. In this review, we have summarized recent progress of ubiquitination study in malignant lymphoid context and current therapeutic strategies. For comprehensive evaluation of disease prognosis, developing therapies independent of the UPS, and patient management we recommend the following reviews [17–20].

2. Deregulation of ubiquitinating enzymes in lymphoid disorders

Using both genome- and proteome-wide approaches, a number of alterations have previously been identified in the UPS in lymphoid disorders [21,22]. Green and colleagues used a large targeted hybrid-capture sequencing approach to interrogate the genetic landscape of 685 cases of B cell non-Hodgkin's lymphoma (NHL), encompassing diffuse large B cell lymphoma (DLBCL), mantle cell lymphoma (MCL), follicular lymphoma (FL) and Burkitt's lymphoma (BL). Ubiquitin-proteasome-specific genes have been found to be deregulated in the majority of tumours of each B cell NHL subtype [23]. More specifically in BL, temporal alterations in ubiquitination levels have been found at approximately 150 sites proteome-wide, with the upregulated events associated with proteins participating in RNA processing and the downregulation of events related to proteins involved in apoptosis and DNA repair [24]. These results suggest ubiquitination abnormalities are not strictly associated with individual cases but pervasive in lymphomas and possessed profound downstream influences. It is also important to note that components of the UPS are likely to undergo post-translational modifications which are likely to affect their activity or substrate binding. Although few examples have been published to date it is likely that a greater exploration into ubiquitin modifying enzyme activity will identify modifications contributing to disease progression.

2.1. Expression alterations

Altered expression of components of the UPS either through chromosomal mutations or aberrant epigenetic modifications are associated with poor clinical outcomes in lymphoid malignancies. Notably, the E2

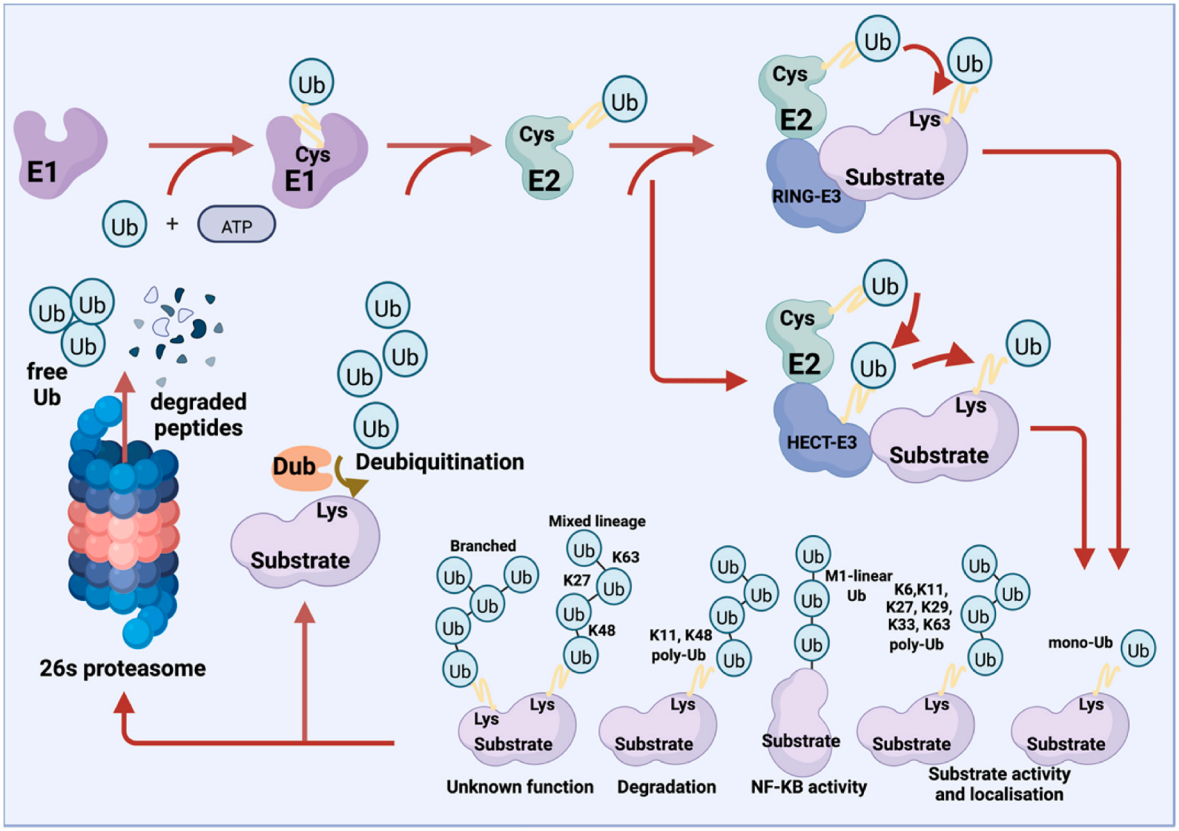

Fig. 1. Schematic representation of the ubiquitination and deubiquitination process. Ubiquitination occurs through a hierarchical set of three types of enzymes: ubiquitin-activating (E1), ubiquitin-conjugating (E2) and ubiquitin ligase (E3) enzymes. Two of the major classes of E3s depicted are RING and HECT. This cascade results in different ubiquitin topologies affecting changes in protein function, the most well studied of which is K48 that targets the protein for proteasome-mediated degradation. Deubiquitination occurs through a family of deubiquitinating enzymes which cleave Ub from targeted protein substrates.

enzyme UBE2T is associated with poor survival and prognosis in multiple myeloma (MM) and increases with MM deterioration, especially in the early stage [25]. In DLBCL, the E3 ligase PELI1 participates in lymphomagenesis and is significantly associated with bone marrow involvement and shorter relapse-free survival [26]. Similarly, the DUB UCH-L1 has been identified as a poor prognostic factor essential for myeloma progression and is suggested to be a biomarker of aggressive MM [27]. Correspondingly, in mouse models UCH-L1 overexpression strongly accelerates lymphomagenesis [28]. The DUB USP14 negatively regulates apoptosis of MM cell lines, with its expression correlated to Bcl-xl [29]. These reports indicate that overexpression of key oncogenic components in UPS drives tumorigenic phenotypes and suggest the potential benefit of targeting these components.

2.2. Mutations

Loss-of-function mutations in (de)ubiquitinating enzymes in lymphomas and lymphoblastic leukemia have also been observed. In a Chinese cohort of primary and relapsed DLBCL patients, 13% non-synonymous mutations of E2 enzyme UBE2A have been identified [30]. In MCL, 18% of the patients harbour mutations in the E3 ligase UBR5. Interestingly, the majority of these mutations result in frameshifts and are located within the ubiquitin-binding HECT domain, leading to the reorientation of the conserved catalytic cysteine residue required for its E3 ligase activities. UBR5 mutations are also a critical pathogenic event in a subgroup of MCL [31,32]. In acute lymphoblastic leukemia (ALL), somatic mutations in the RING finger E3 ligase CBL have been identified in three children with an overall incidence of 1.7% that involve small deletions of exon 8, leading to a skipping of exon 8 and elimination of E3 ligase function [33]. In classical Hodgkin's lymphoma (cHL) and B cell NHLs, the ubiquitin-modifying enzyme A20 is frequently inactivated via deletions and mutations, most notably affecting ubiquitin-binding domains limiting the ability to catalyse ubiquitination [34,35]. In spite of these identified mutations, very few follow-up studies have been done limiting our understanding of their importance.

2.3. E3 ligase deficiency

Downregulation of E3 ligases was also detected in lymphomas. In cHL, the ubiquitin ligase component SKP2 and PDLIM2 is frequently lost [36,37]. HACE1 acts as a haploinsufficient tumor suppressor gene in NK cell neoplasm and B cell lymphomas. Deletion of HACE1 has been detected in 67% of malignant NK cell lines, 33% of primary NK cell lymphoma biopsies and 40% of B cell lymphoma samples. Mechanistically, deregulation of HACE1 levels is associated with a significant decrease in apoptosis and an accumulation of S and G2/M phases in cells [38,39]. These results reveal that an intact ubiquitination system is physiologically required for tumorigenesis and hint that these tumor suppressor E3 ligases might be responsible for ubiquitinating and degrading potentially tumorigenic substrates.

3. (Non)- proteolytic ubiquitination in lymphoid malignancies

3.1. Ubiquitination-related MYC oncogenesis

The transcription factor MYC is tightly regulated in normal tissues at the transcriptional, post-transcriptional, translational and post-translational levels [40]. Multiple lines of evidence have demonstrated ubiquitination pressures influence the deregulation of MYC and pathologically enhances tumorigenicity of lymphoid neoplasms.

Deregulation of several E3 ligases have been demonstrated to limit MYC degradation accelerating lymphoma and myeloma onset. In NHL, the E3 ligase UBE3B mediates MYC ubiquitination and degradation attenuating the transcriptional capability of MYC. This process is hindered by the interaction between MYC and the pseudokinase TRIB3. TRIB3 expression correlates with MYC expression in NHL and has been suggested as a therapeutic target in NHL [41]. The E3 ligase HUWE1 has been demonstrated to catalyse non-proteolytic ubiquitination and stabilization of MYC. HUWE1 expression positively correlates with MM staging and genetic or pharmacological inhibition of HUWE1 reduces MYC expression and supresses MM cell growth without significantly affecting normal bone marrow cells [42]. During lymphomagenesis, CSN6 facilitates ubiquitination and degradation of the Cullin ring ubiquitin ligase complex substrate adaptor Fbxw7, resulting in aberrant MYC stabilization [43]. Similarly, the oncoprotein vIRF-3 modulates MYC stability and activation via interaction with the SCF E3 ligase SKP2, blocking SKP2-mediated ubiquitination and contributing to MYC-induced lymphomagenesis [44].

Similarly, DUBs directly stabilize MYC and promote lymphoid tumorigenesis. The DUB USP29 deubiquitinates and stabilizes MYC, enabling adaptive response and survival of B lymphoma cells under both normoxia and hypoxia conditions. Knockout of USP29 depletes MYC and markedly prolongs survival of lymphoma xenografts [45]. Moreover, elevated OTUB1 levels are correlated with poor clinical outcome in the MYC-dependent MM and OTUB1 overexpression accelerates growth of MM cells. OTUB1 directly regulates MYC protein level by catalysing deubiquitination and stabilization [46]. However, the precise mechanism remains to be elucidated.

These reports indicate the indispensable role of MYC ubiquitination in lymphoma- or myeloma-genesis. It is still confusing why the ubiquitinated status of MYC is regulated by so many E3s and DUBs in all cancers. Determining the relative affinities of interactions between MYC and the abovementioned ubiquitination regulators and whether they function sequentially, cooperatively or are truly specific for a type of malignancy would fill in important knowledge gaps and undoubtedly lead to new therapeutic avenues to target MYC.

3.2. Ubiquitination of/by chromatin modifiers

Deregulated histone methyltransferase subunits owing to aberrant loss- or gain-of-ubiquitination drive the survival and chemo-resistance of lymphoma cells. The MLL family of methyltransferases regulate H3K4 methylation and epigenetically mark chromatin for active transcription. The stability of different MLLs is regulated by both the DUB USP7 [47] and the E3 ligase FBXW7 [48], thereby turning on or off target gene transcription critical for DLBCL cell fate and metabolism. Inhibition of these ubiquitin-modifying enzymes greatly represses survival of tumor cells and sensitizes them to chemotherapeutics [47,48]. The histone methyltransferase EZH2 catalyses H3K27 tri-methylation at the gene promoter and inhibits gene transcription. Gain-of-function mutations of oncogenic EZH2 have been well characterized in DLBCL and EZH2 with some of these mutations exhibited increased tendency to bind to DUB USP47 [49] and decreased tendency to bind to E3 ligase β-TrCP [50], both of which lead to EZH2 stabilization and favour H3K27 tri-methylation-mediated oncogenesis. Pan-EZH2 is also mediated by DUBs like USP21 in DLBCL [51] and USP36 in extranodal natural killer/T-cell lymphoma (ENKTL) [52], resulting in enhanced lymphoma cell proliferation and chemo-resistance.

Other chromatin modifiers may also exert E3-like roles to assist ubiquitination and degradation of downstream target proteins. In MCL, ATM, which phosphorylates histone H2AX to initiate the DNA damage response pathway, promotes proteasomal degradation of Parkin and induced mitophagy [53]. The histone demethylase KDM2A augments ubiquitination and degradation of the glycolysis-associated enzyme PFKFB3, supressing MM cell proliferation and angiogenesis [54]. In DLBCL, the histone deacetylase HDAC6 is frequently upregulated and has been demonstrated to interact with and downregulate HR23B. This interaction reduces the level of E3 ligase c-Cbl and stabilizes the MET oncoprotein [55].

Aberrant ubiquitination associated with chromatin modifiers profoundly affects chromatin states and decides fate of malignant lymphocytes, indicating the potential of epigenetic manipulation for the

treatment of lymphoma and myeloma. It is important to note that DNA or histone modifications tend to be genome-wide and future studies may look at how bivalent chromatins are modulated by ubiquitination associated with the abovementioned chromatin modifiers.

3.3. NF-κB-related ubiquitination

The transcription factor NF-κB is increasingly recognized by its essential role in a variety of steps during tumorigenicity and inflammation. A total of five members of NF-κB family have been characterized, designated p65, RelB, c-Rel, p105 and p100. Among them, p105 and p100 are pro-proteins and are proteolytically processed to p50 and p52, respectively [56]. All of these NF- κB proteins form homo- or hetero-dimers and bound to IκB (inhibitor of NF-κB) family proteins [57]. Bolstered NF-κB activation is frequently seen in B cell lymphomas including DLBCL and Waldenstrom macroglobulinemia as a result of aberrant ubiquitination. Both canonical and noncanonical NF-κB signalling are constitutively activated in DLBCL [58]. The NF-κB pathway is canonically activated by the failure of ubiquitination and degradation of roquin2 driven by KLHL6 with loss-of-function mutations [59], and noncanonically activated by deregulated and aberrantly-accumulated NIK due to BR3 activation and TNF-3 degradation [58], both of which favour DLBCL cell survival. MYD88 is a critical adaptor protein that transduce signals to NF-κB. MYD88 L265P gain-of-function mutations is non-proteolytically poly-ubiquitinated by RNF138 and assembles with TLR9 and BCR to form a super-complex, resulting in elevated NF-κB activation and B-cell oncogenesis [60,61]. Aberrant activation of NF-κB associated with poor patient survival is similarly noted in other lymphoid malignancies with or without the crosstalk with other pathways. In MM, NF-κB is deubiquitinated and stabilized by USP family deubiquitinases with tumorigenic activities [62,63]. And this prevents MM cells from apoptosis and is related to poor event-free and overall survivals [62,63]. In adult T-cell leukemia/lymphoma (ATL), a crosstalk between NF-κB pathway and Hippo pathway has been identified. NF-κB p65 abolishes the interaction between Hippo effector YAP and LATS1, leading to an inhibition of ubiquitination-induced degradation of YAP and constitutive survival of ATL cells [64]. In chronic lymphocytic leukemia (CLL), ATM interacts with TCL1, resulting in an enhancement of IκBα phosphorylation and ubiquitination and subsequent NF-κB activation, thereby promoting CLL pathogenesis [65]. Thus, abnormal NF-κB activation appears to be regulated in different contexts driven by both oncogenic mutations or aberrant ubiquitination.

The linear ubiquitin chain assembly complex (LUBAC) is required for the activation of NF-κB signalling. LUBAC, consisting of two RBR type ligases HOIP and HOIL1 and an adaptor subunit SHARPIN, is the only known E3 ligase complex able to initiate linear ubiquitination, in which inter-ubiquitin linkage is formed through ubiquitin amino-terminal methionine [66]. The LUBAC complex attaches linear polyubiquitin chains to IKKγ, a necessary event that engages NF-κB [67]. Both LUBAC and IKKγ are recruited by the E3 ligase cIAP1/2, which interacts with CARD11-MALT1-BCL10 adaptor complex for K63-linked poly-ubiquitination [68] (Fig. 2). Germline polymorphisms of the catalytic LUBAC subunit HOIP rarely happen among healthy individuals but are enriched in activated B cell-DLBCL (ABC-DLBCL). These polymorphisms increase HOIP-HOIL1 association as well as LUBAC enzymatic activity [67]. HOIP impedes cell apoptosis and magnifies NF-κB signalling to facilitate lymphomagenesis of ABC-DLBCL [69]. Therefore, LUBAC acts as a molecular scaffold to recruit and bind to other signaling complexes likely involved in lymphomagenesis. Therefore, HOIP should be considered as a suitable therapeutic target to intervene LUBAC and subsequent NF-κB activation (see Fig. 2).

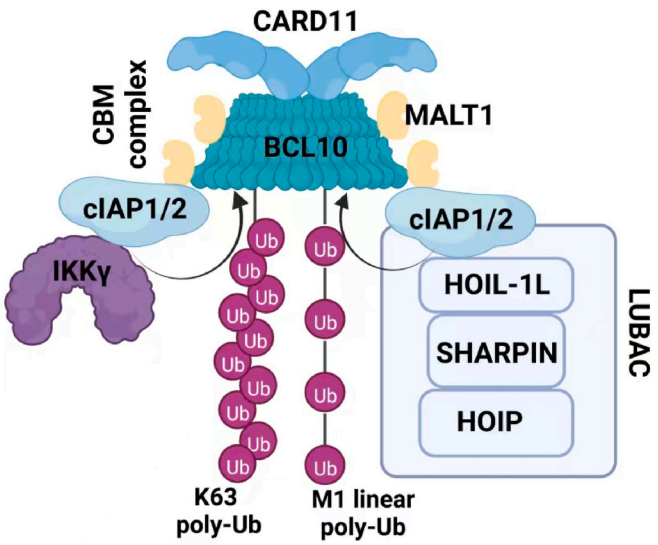

Fig. 2. CARD11-BCL-10-MALT1 complex. Upon activation CARD-11oligomerizes permitting the nucleation of both BCL-10 and MALT1 subunits. This results in the CARD11-BCL-10-MALT1 complex which then recruits various ubiquitin ligases including cIAP1, cIAP2 and LUBAC E3 ligase complex (HOIP, HOIL1, SHARPIN). Both cIAP2 and LUBAC mediate K63-linked and M1-linked ubiquitination of the CBM signalsome resulting in downstream pathway activation.

4. Targeting ubiquitination machineries

4.1. Proteasome inhibitors (PIs)

The proteasome is the endpoint of the UPS and the principal proteolytic machine. In cells of hematopoietic origin, it is important to note the immunoproteasome, a special class of proteasome which possesses additional functions like MHC presentation. Proteasome inhibitors (PIs) have been developed as a unique class of drugs and approved for the treatment of MM and MCL. PIs are also currently under investigations for other lymphoid malignancies. Bortezomib was the first PI approved by the US Food and Drug Administration, and second generation PIs carfilzomib and ixazomib were subsequently approved in recent years [70]. Here we review the action of PIs and immunoproteasome inhibitors.

4.1.1. Function and toxicity of bortezomib

Bortezomib inhibits the chymotrypsin-like site, and to a smaller extent, the caspase-like site of the 20s proteasome core [71]. Bortezomib is an indispensable part of anti-MM therapeutics demonstrating good clinical efficacy and manageable toxicities [72]. The efficacy of bortezomib is linked to a putative induction of apoptosis by blocking pro-survival signals like NF-κB and activation of JNK and p53 [73]. Bortezomib has been included in more than 500 clinical trials worldwide to treat MM or MCL either as a single agent or in combination with conventional therapies like melphalan in newly-diagnosed and relapsed or refractory cases. Treatment with bortezomib in B-NHL like DLBCL has also entered clinical trials, mostly for relapsed or refractory cases, suggesting a common proteosome malfunction in lymphoid cancer patients.

4.1.2. Bortezomib resistance, refractoriness, and limitations

As with all targeted therapies, resistance to Bortezomib is frequently observed upon treatment over time. In B-cell lymphoma and MM refractory to proteasome inhibition, a proteolytic switch from the UPS to autophagy-lysosome system appeared partly owing to USP7-mediated deubiquitination of Beclin-1 [74]. This paves the way for genetic or pharmacological inhibition of USP7 [75] and the usage of autophagy-associated p62 inhibitors in bortezomib-resistant cases [76,

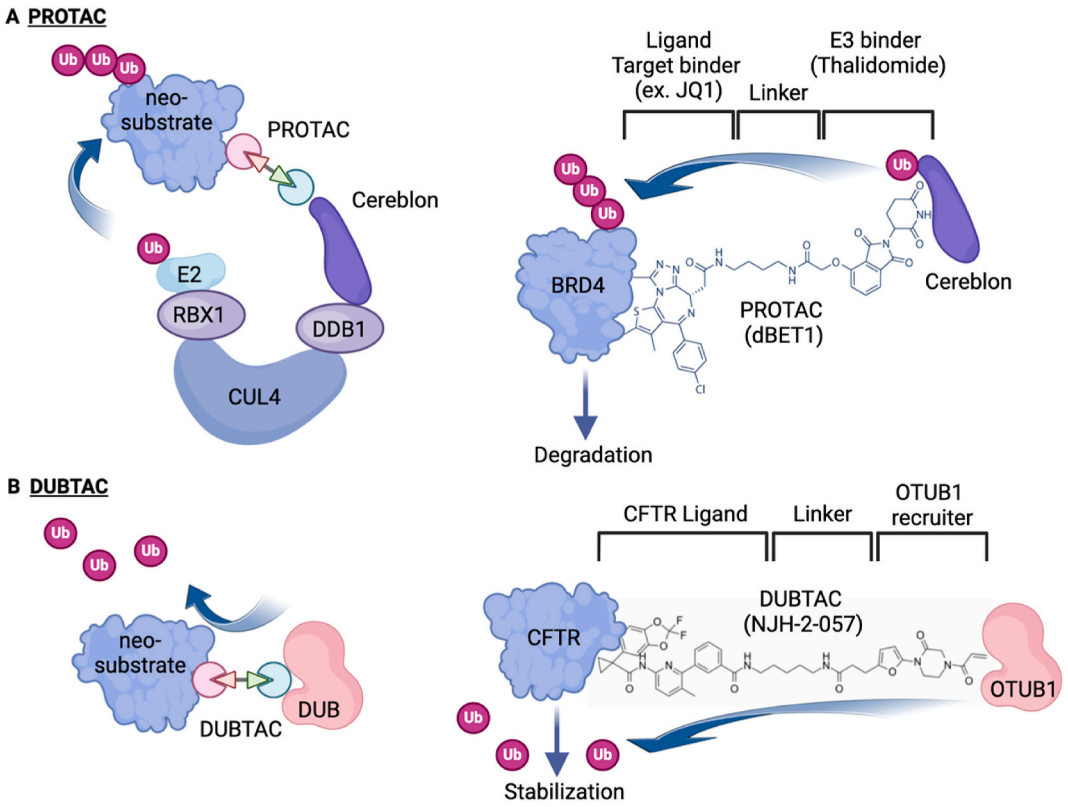

Fig. 3. A) Schematic of substrate recruitment to the E3 ligase CUL4-RBX1-DDB1-CRBN ($CRL4^{CRBN}$) complex by a heterobifunctional proteolysis-targeting chimera (PROTAC; left). Example of PROTAC dBET1 targeting BRD4 for degradation (right). B) Schematic of substrate recruitment to a deubiquitinating enzyme by a heterobifunctional molecule (DUBTAC; left). Example of DUBTAC NJH-2-057 targeting CFTR for stabilization (right).

77]. Likewise, Hedgehog pathway activation due to DKK1-abrogated GLI2 degradation [78,79] and SIRT1-mediated deacetylation and stabilization of GLI2 [80] contribute to bortezomib resistance in MM. Moreover, endothelin and its receptor [81], HSPB8 [82], LonP1 [83], cIAP2 [84], NF-κB [85,86], NGLY1 [87], EIF2, and mTOR [88] signalling worsen resistance to PIs. In contrast, XBP1s [89], Ω3 fatty acids [90], p53 [86], SENP2 [91], Pirh2 [92], miR-29b [93], PA28α [94] and Nrf-2 [88] all ameliorate PI sensitivity in MM. The abundance of these regulators highlights the ongoing need to establish effective clinical biomarkers for PI efficacy. However, it must be noted that all of the other mechanisms of bortezomib resistance, beyond those highlighted here, are still not fully understood. Furthermore, downstream inhibition of the UPS can lead to accumulation of upstream ubiquitinated proteins leading to potential undesirable side effects and may explain dose limiting toxicities such as peripheral neuropathy observed in a sub-set of patients. This explains the growing interest in targeting E1 enzymes in drug-resistant lymphoid malignancies.

4.1.3. *New-generation PIs and immunoproteasome inhibitors*

To overcome bortezomib resistance and toxicity, other PIs have recently come to the forefront. Carfilzomib is ten times more active than bortezomib in inhibiting B lymphoma cell survival and inducing apoptosis [95]. In MM, the new PI delanzomib exhibits higher proteasome inhibitory activity than bortezomib, and delanzomib overcomes bortezomib resistance in xeno-transplants [96]. In addition to marketed PIs, a couple of new-generation PIs and immunoproteasome inhibitors are currently under pre-clinical investigation, which target proteasome at different sites, show high specificity and superior anti-MM or anti-lymphoma activities *in vitro* and *in vivo* and are demonstrated to overcome resistance to commercialized PIs [97–106] (Table 1).

PIs are also commonly utilized together with other therapies. For MM patients, PIs are usually given in combination with dexamethasone, or in certain cases with dexamethasone and immunomodulatory drug (IMiD). Other combinational approaches with marked effectiveness are mostly still under clinical and pre-clinical evaluation. Chemo-regimens consisting of PIs and other agents have been synergistically used to ameliorate conventional therapies [107–109], to augment the effects of targeted therapeutics [110–114], to block pro-survival autophagy [115–118] or aggresome formation [116,119,120] induced by PIs, to induce ER stress [121], to further accumulate ubiquitinated proteins [121–123], to inhibit other subunits of proteasome [124], to mitigate the increase of oncoproteins [125,126], or to abolish the transcription of proteosome subunits [127] (Table 2). All the above chemo-amalgamations brings better efficacy to patients than mono-therapy by targeting several different pathways to ameliorate PI

Table 1
New generation of PIs.

PI	Target	Disease	Citation
M3258	proteasome subunit LMP7	MM, MCL	[127, 128]
Di-peptide inhibitor	proteasome subunit β5	B cell lymphoma	[129]
Tripeptide propylene oxide derivatives	20S proteasome	MM	[130]
LC53-0110	20S proteasome	Resistant/ Refractory MM	[131]
BSc2118	proteasome subunit β5	MM	[132, 133]
Compound 6	proteasome core	MM	[134]
K-7174	proteasome core	MM	[135]
MLN2238	proteasome subunit β5	MM	[136]

Abbreviations: PI(s): proteasome inhibitor(s); MM: multiple myeloma; MCL: mantle cell lymphoma.

Table 2
Combination of PIs with other chemo-agents.

Combination	Disease	Synergistic mechanisms	FDA approval	Citation
Bortezomib, melphalan and prednisone	MM	–	✓	[138]
Bortezomib, mephalan, daratumumab and prednisone	MM	–	✓	[139, 140]
Bortezomib, lenalidomide and dexamethasone	MM	–	✓	[141, 142]
Bortezomib, daratumumab and dexamethasone	MM	–	✓	[143]
Bortezomib, selinexor and dexamethasone	MM	–	✓	[144, 145]
Bortezomib and bafilomycin A1	MM	Bafilocycin A1 inhibited pro-survival autophagy aroused by bortezomib	–	[146]
Bortezomib and clarithromycin	MM	clarithromycin inhibited pro-survival autophagy aroused by bortezomib	–	[147, 148]
Bortezomib and orlistat	MCL	Orlistat inhibited pro-survival autophagy aroused by bortezomib	–	[149]
Bortezomib/ carfilzomib and ricolinostat/ vorinostat/ MPT0G413	MM	Ricolinostat/ vorinostat/MPT0G413 blocked the formation of aggresome formed by PIs	–	[150, 151]
Bortezomib and chidamide	MM	Chidamide further increased accumulation of ubiquitinated proteins, induced excessive ER stress	–	[152]
Bortezomib and tanespimycin	MM	Tanespinmycin further increased accumulation of ubiquitinated proteins	–	[153]
Bortezomib and curcusone D	MM	Curcusone D further increased accumulation of ubiquitinated proteins	–	[154]
Bortezomib and VR23	MM	Collectively inhibited β1, β2, β5 subunits of proteasome	–	[155]
Carfilzomib/ Bortezomib and SMI-16a/ AZD1208	MM	SMI-16a/AZD1208 Inhibited the increase of PIM2 proteins caused by proteosome inhibition	–	[156, 157]
PI and CB5083	MM	CB5083 inhibited the transcription of proteasome subunit genes	–	[158]
Bortezomib and Nelfinavir	MM	–	–	[159]
Bortezomib/ carfilzomib and TRAF6 dominant-negative peptides	MM	–	–	[160]
Bortezomib and DT204	MM	–	–	[161]
Bortezomib and Reolysin	MM	Dual accumulation of oncolytic viral and host ubiquitinated proteins	–	[162]
Bortezomib, Nelfinavir and dexamethasone	MM	–	–	[163]

Abbreviations: PI(s): proteasome inhibitor(s); MM: multiple myeloma; MCL: mantle cell lymphoma.

resistance.

4.2. DUB inhibitors

DUBs cleave ubiquitin signals from the substrate proteins to regulate their stability and function, and have been implicated in all of the hallmarks of cancer [12]. Therefore, effective targeting of DUBs represents a novel therapeutic approach in disease including lymphoid malignancies.

The oncoprotein USP7 plays an integral role in regulating the MDM2-p53 axis. USP7 is overexpressed in MM correlating with poor outcome and short overall survival [128] and correspondingly, treatment with USP7 inhibitors reduced viability and induced apoptosis of MM cells [129–131] even in bortezomib resistant cells [128]. Moreover, USP7 inhibitor in addition to conventional therapies like dexamethasone triggered synergistic anti-MM effects [130] (Table 3).

Numerous studies have demonstrated that targeting DUBs degrades proteins involved in driving lymphoid malignancies (Table 3). However, the majority of these early experiments were done with first-generation DUB inhibitors. Recent comprehensive evaluations have indicated that the majority of these early DUB inhibitors lack specificity within USP family members and likely act as pan-inhibitors, greatly limiting the potential significance of these early findings. Re-evaluation of the studies listed in Table 3 with chemical and genetic knockdown studies are required prior to progression of these inhibitors into early clinical trials.

4.3. IMiDs

The class of IMiDs currently consist of thalidomide, lenalidomide and pomalidomide, and the latter two drugs are derived from thalidomide. Thalidomide was introduced as a sedative in the 1960s to cure pregnant nausea, but it was soon withdrawn due to teratogenicity. Despite these dreadful side effects, a healing role of thalidomide in MM by immunoactivation of T and NK cell was reported 50 years later. Subsequently, two second-generation IMiDs lenalidomide and pomalidomide were developed with more potent immunomodulatory and anti-MM, and additionally, anti-MCL effects. The IMiD class of drugs has also been preclinically and clinically evaluated for the treatment of other lymphoid cancers, including DLBCL, MCL, PEL, T-cell ALL and CLL [132]. The mechanisms of action of IMiDs have been reviewed below.

Table 3
DUB inhibitors.

Compound	DUB	target	Disease	Citation
–	USP7	MDM2	MM	[166]
P5091	USP7	MDM2	MM	[167]
pentacyclic triterpenes	USP7	MDM2	MM	[168]
Compound 1	USP7, USP47	MDM2, DNA polymerase β	MM, B cell leukemia	[169]
Mebendazole	USP5	c-Maf	MM	[170]
lanatoside C	OTUB1	c-Maf	MM	[171]
WP1130	USP5	c-Maf	MM	[172]
EOAI3402143	USP9X, USP24	MCL-1	MM	[173]
T5165804, CP2005	USP9X	MCL-1	MM, MCL	[174]
b-AP15	USP14, UCHL5	CDC25C, CDC2, and CCNB1	MM	[175]
ML364	USP2	CCND1	MCL	[176]
–	USP29	MYC, HIF1α	B cell lymphoma	[40]
SJB3-019A	USP1	Notch 1/2, SOX2/ 4	MM	[177]

Abbreviations:DUB: deubiquitinating enzyme; MM: multiple myeloma; MCL: mantle cell lymphoma.

4.3.1. Action mechanisms of IMiDs

The Cul4-Rbx1-DDB1-Cereblon (CRL4) E3 ubiquitin ligase complex is the common target of IMiDs [133]. By binding to the E3 ligase Cereblon, lenalidomide acts as molecular glue and causes selective ubiquitination and degradation of IKZF1 and IKZF3, two essential transcription factors required for the survival of MM cells. A single amino acid substitution of IKZF3 (Q147H) confers relative resistance to the effects of lenalidomide and annuls lenalidomide-induced inhibition of MM cell survival [134]. The degradation of IKZF1/3 following IMiD treatment in MM leads to the sustained downregulation of IKZF target genes MYC and IRF4 required for the inhibition of MM cell survival [135]. MEIS2, ZFP91 and ARID2 are also *bona fide* endogenous substrates of Cereblon in MM context. IMiDs blocks MEIS2 from binding to Cereblon when it is recruiting IKZF1 and IKZF3 for degradation [136]. Conversely, ZFP91 is critical for IMiD-dependent Cereblon binding [137]. ARID2 is a pomalidomide-dependent neo-substrate of Cereblon and ARID2 degradation has been suggested to be the potential cause for the improvement of lenalidomide resistance [138]. However, the targets of Cereblon vary in other lymphoid malignancies. A genome-wide CRISPR/Cas9 screen in PEL to identify novel IMiD effectors has found out that CK1α and IRF4 are essential for PEL cell survival, whereas IKZF3 is dispensable [139]. Whether IKZF1 degradation is needed for the anti-PEL effects of IMiDs still remains controversial [139,140]. In DLBCL, lenalidomide exerts antitumor effects mainly by Cereblon-mediated degradation of IRF4 and blocking of BCR-NF-κB signalling, and ABC-DLBCL cells are more responsive than germinal center B cell-DLBCL (GCB-DLBCL) [141]. In T-cell acute lymphoblastic leukemia (T-ALL), PLZF1/RARα and its fusion proteins are identified as IMiD-dependent neo-substrates of Cereblon. In accordance, pomalidomide treatment degrades PLZF1/RARα and exhibits antiproliferative effect in T-ALL [142]. Altogether, IMiDs work primarily by inducing Cereblon-dependent ubiquitination and degradation of substrate oncoproteins to exert anti-tumor effects.

4.3.2. Predictive markers of IMiDs

Generally, patients with lymphoid cancers especially MM respond well to IMiDs treatment, but as with all targeted therapies, a significant portion of patients develop resistance. The responsiveness and sensitivity to IMiDs in these patients is correlated with Cereblon levels. In MM patients and patients with another plasma disorder POEMS syndrome, Cereblon levels significantly and positively correlate with the outcome of IMiD treatment [143–148] (Table 4). Patients with low Cereblon expression do not respond to IMiD [149]. CUL4, DDB1 and IKZF1 expression may also predict responses and outcomes of IMiD treatment [150–152]. Mutations, copy number loss, transcript variants, Cereblon chromosome deletion and loss of Cereblon expression are common in IMiD-refractory MM cases [153–159] (Table 4). Importantly, Cereblon is expressed in all myeloma cell lines independent of their sensitivity to IMiDs likely indicating that the bone marrow environment may contribute to therapeutic resistance [160].

4.3.3. Modulation of IMiD effects

Several other factors may also affect response to IMiD via an interplay with Cereblon pathway proteins. USP15 is overexpressed in IMiD-resistant cells and antagonizes ubiquitination of Cereblon substrates, involving IKZF1/3 and CK1α. Inhibition of USP15 represents a valuable therapeutic opportunity to overcome lenalidomide resistance in MM [161]. RUNX1/3 interacts with IKZF1/3, inhibiting Cereblon-dependent binding, ubiquitination and degradation of IKZF1/3 upon lenalidomide treatment. Genetic or pharmacological inhibition of RUNXs re-sensitizes myeloma cells to lenalidomide [162]. KPNB1 affects the effects of pomalidomide in MM by impacting the nuclear import of Cereblon and Cereblon-directed degradation of IKZF3 [163]. SCF ligase complex targets Cereblon for degradation, and loss-of-function of CSN9 signalosome activates SCF complex, resulting in enhanced Cereblon degradation and IMiD resistance [164]. All the findings above confirm the central role of

Table 4
Biomarkers related to IMiD treatment outcomes.

Cohort	Treatment	Outcome related to Biomarkers	Citation
49 newly-diagnosed MM patient	Lenalidomide and dexamethasone	Median Cereblon expression: complete response > very good partial response > partial response > stable disease > progressive disease	[197]
89 elderly patients with MM	Thalidomide-based regimen	Cereblon-positive patients better responded than did cereblon-negative patients	[198]
96 patients with newly diagnosed MM	Daily thalidomide (50 mg) for 2 years	Increase of Cereblon expression was significantly associated with longer PFS	[199]
40 relapsed/ refractory MM and 22 newly diagnosed MM patients	lenalidomide/ dexamethasone (LD) (relapsed/refractory); thalidomide/ dexamethasone and (TD) melphalan/ bortezomib/ prednisolone (MVP) (newly diagnosed)	The response rate was higher in Cereblon positive patients than Cereblon negative patients	[200]
92 MM patients	Thalidomide-based regimen (83.7%), bortezomib-based regimen (16.3%)	83.7% of patients achieved treatment response, mainly in patients treated with thalidomide	[201]
41 patients with newly diagnosed POEMS syndrome	Lenalidomide and dexamethasone	Patients with high cereblon expression tended to achieve better hematologic response compared to those with low expression	[202]
53 refractory MM patients	Pomalidomide and dexamethasone	The highest Cereblon quartile group had a significantly higher PFS and OS than the lowest Cereblon quartile group	[203]
130 MM patients	Thalidomide or lenalidomide-based regimens	Cereblon and CUL4 was associated with the superior IMiD-based treatment response. CUL4 was associated with improved PFS. DDB1 negatively impacted on OS	[204]
60 MM patients	Lenalidomide in combination with chemotherapy	Patients in the lowest quartile of IKZF1 expression had a superior PFS compared with patients in the remaining quartiles	[205]
44 refractory MM patients	Pomalidomide and dexamethasone	Low IKZF1 gene expression predicted lack of response. Cereblon, IKZF1, and KPNA2 levels correlated significantly with OS	[206]
50 multidrug refractory MM patients	IMiDs and proteasome inhibitors	An increased prevalence of Cereblon and cereblon pathway mutations appeared compared with newly diagnosed MM cases	[211]

(*continued on next page*)

Table 4 (*continued*)

Cohort	Treatment	Outcome related to Biomarkers	Citation
167 Polish patients with refractory/ relapsed MM	Lenalidomide-based regimen	Germline Cereblon allelic variants might affect lenalidomide efficacy and significantly associated with lower possibility of at least partial remission in patients	[212]

Abbreviations: MM: multiple myeloma; PFS: progression-free survival; OS: Overall survival; HR: hazard ratio; CI: confidence interval; IMiD: immunomodulatory drug; OR: odds ratio.

Cereblon and its substrates in IMiDs sensitivity, and modulation of their stability and intracellular localization may markedly affect IMiD treatment outcomes. One of the interesting perspectives in future study is to examine how the crosstalk between Cereblon pathway and other well-known tumorigenic signalling cascade, like NF-κB, affects IMiD sensitivity.

4.3.4. Cereblon-independent action of IMiDs

In addition to binding to Cereblon to degrade its substrates, IMiDs also function by other means in both Cereblon-dependent and -independent manners. Cereblon may perform a co-chaperone-like function that brings together other chaperone proteins to affect their positioning or maturation. Certain IMiDs outcompete Cereblon to bind to these chaperones to exert anti-tumor effects [160,165]. Corresponding to their nomenclature, IMiDs promote secretion of immunostimulatory factors IL-2 and IFNγ to enhance T and NK cell activation and to reduce regulatory T cell suppressor function. IMiDs function by downregulating peroxidase-mediated intracellular H_2O_2 decomposition, which is believed as a causative event of Cereblon-dependent degradation of IKZF1/3 [166]. Other machineries behind the demonstrated efficacy of IMiDs encompass an enhancement of PU.1 expression via promoter demethylation [167] and a switch of myeloma-associated macrophages from M2 to tumoricidal M1 within bone marrow [168]. All these studies well supplement the connotation of action mechanisms of IMiDs. However, it is still not known how the abovementioned mechanisms are internally linked together to promote the effectiveness of IMiDs.

4.3.6. New generation IMiDs

Given the marked anti-tumor effects of IMiDs upon administration and acquired resistance and compromised effects over time, a couple of third generation IMiDs have been developed to overcome resistance observed in patients. These include CC-220, which exhibits notable anti-MM activities in lenalidomide- and pomalidomide-resistant MM cells through sustained suppression of Cereblon targets IKZF1/3 and transcription factors MYC/IRF4. The increased suppression by CC-220 compared to thalidomide or its analogues is dependent on the increased binding capacity to Cereblon [169,170]. Other newly-developed IMiDs CC-885, CC92480 and CC-122 are demonstrated to selectively induce ubiquitination and degradation of CDK4 or IKZF1/3 and inhibit tumor cell survival in MM, T-cell lymphomas and DLBCL via Cereblon-mediated pathways with optimized efficiency and kinetics [171–174]. These studies reveal high level of enthusiasm in IMiD therapeutics, and investigators have made their efforts to ameliorate resistance, efficacy and kinetics by developing new IMiDs. And continuous endeavour to dissect the cellular action mechanisms of these new IMiDs may assist to unveil novel applications of IMiDs.

4.4. Man-made proteolysis strategy

Due to the undruggable structure of some proteins-of-interest (POIs), Proteolysis-Targeting Chimeras (PROTAC) have been developed as a useful way to utilize the cells ubiquitination machinery to degrade target proteins. A heterobifunctional PROTAC molecule includes a small-molecule inhibitor of the POI which is covalently linked to a ligand recognized by an E3 ligase. Once bound to the POI, the PROTAC may recruit E3 ligase to target the POI for ubiquitination and subsequent degradation [175] (Fig. 3). The PROTAC strategy is a remarkable complement for traditional pharmacological inhibition of POIs and several PROTAC molecules are currently tested pre-clinically or in clinical trials for the treatment of lymphoid cancers.

Specifically in the context of lymphoid malignancies, PROTACs have been developed to target tumorigenic and pro-survival BETs [176–179], CDK6 [180,181], Bcl-xl [182,183], MCL1 [184], HDAC6 [185] and p300/CBP [186] (Table 5), which directly correlate with disease onset and are either previously nondruggable or the related inhibitors yield severe and unmanageable toxicities like thrombocytopenia [182]. These PROTAC agents potently and persistently degrade the abovementioned protein targets. Conversely, deubiquitinase-targeting chimeras (DUBTAC), enhancement-targeting chimeras (ENTAC), or survival targeting

chimeras (SURTAC) have been demonstrated in proof-of-concept experiments to stabilize non-cognate substrates [187]. Notably, the DUBTAC method has already been utilized as therapeutic strategy by linking a DNA oligonucleotide to a ligand of the deubiquitinase OTUB1 to selectively stabilize the cystic fibrosis transmembrane conductance regulator (CFTR) with variations of this technology now being utilized to stabilize tumour suppressors like p53 [187,188] (Fig. 3). Although other targeted-protein stabilizers are yet to be implemented in pre-clinical studies in lymphoid malignancies, this avenue presents a promising frontier for therapeutic intervention. It is important to note that similar to mechanisms of resistance to IMiDs, the mechanism of action of PROTACs and DUBTACs will likely require an intact UPS including sufficient expression of a non-mutated ligase or DUB, respectively.

Table 5
PROTACs in treating lymphoid cancers.

POI	Disease	Action mechanisms	Citation
BRD4 and other BETs	MM	Decreased cellular MYC, CDK4 and CDK6 levels, increased p21, induced cell cycle arrest and apoptosis and overcame the resistance of PIs and IMiDs	[251]
BRD4	BL	Better suppression of MYC levels and more efficient induction of apoptosis than BRD4 inhibitors	[252]
BRD2 and BRD4	MM	Rapidly degraded BRD2 and BRD4, down-regulated CCR1, RGS, MYB and MYC, inhibited the growth of MM xenografts and well synergized with several anti-MM drugs	[253]
BETs	MCL	Depleted MYC, CDK4, CCND1 Bcl-xL, XIAP and BTK, enhanced HEXIM1, NOXA and p21 and induced more apoptosis than BET inhibitors	[254]
CDK6	MM	Robustly degraded CDK6 and induced MM cell apoptosis	[255]
CDK6	MM	Potently degraded CDK6 and suppressed MM proliferation	[256]
Bcl-xl	TCL	Selectively killed Bcl-xl dependent TCL cells without significant platelet toxicity	[257]
Bcl-xl	TCL	Efficiently degraded BCL-XL in malignant TCL cells and demonstrated cell killing effects with less platelet toxicity compared with Bcl-xl inhibitors	[258]
MCL1	MM	Successfully degraded MCL1	[259]
HDAC6	MM	Improved potency in degrading HDAC6, and promising anti-MM effects	[260]
p300/CBP	MM	Potent in killing MM cells and abolishing the expression of MYC	[261]

Abbreviations: POI: protein of interest; MM: multiple myeloma; PI: proteasome inhibitor; IMiD: immunomodulatory drugs; BL: Burkitt's lymphoma; MCL: mantle cell lymphoma; TCL: T cell lymphoma.

4.5. Targeting E1/E2/E3 enzymes and ubiquitin receptors

4.5.1. Targeting E1/E2/E3 enzymes

As a result of the therapeutic impact of proteasome inhibitors in lymphoid malignancies, an effort has been made to investigate the use of E1/E2/E3 inhibitors with the thought being that downregulation of these ubiquitin cascades may replicate some of these patient outcomes while circumventing therapeutic limitations associated with targeting the proteasome.

TAK243 was the first small-molecule E1 enzyme inhibitor to enter clinical development. TAK243 interferes with global ubiquitination signalling in DLBCL, CLL and MM and induces endoplasmic reticulum stress and the unfolded protein response. TAK243 treatment successfully inhibited the proliferation capacity of cell lines and xenografts from the abovementioned illnesses and importantly overcomes resistance associated with conventional therapeutics [189–191]. NSC697923, which inhibits the E2 conjugating enzyme Ubc13-Uev1A, impedes the formation of ubiquitin chain on Ubc13, therefore suppressing constitutive NF-κB signalling and blocking DLBCL cell survival [192]. Compound 10e designed from a series of 1,4-naphthoquinones targets the HECT E3 ligase Itch. Treatment with 10e significantly down-regulates ITCH levels in MM and exhibits remarkable anti-MM effects in xenografts [193].

Similarly, IAP inhibitors such as Birinapant and LCL161, which target the ubiquitin ligases cIAP1/2, have been used in early phase clinical trials in haematological malignancies; however, overall response rates were limited [194]. Recent evidence has also indicated that the NEDD8-activating enzyme inhibitor Pevonedistat (MLN4924) displays a tolerable safety profile and potential activity in relapsed or refractory lymphoma patients [195]. A number of MDM2 inhibitors have been tested in clinical trials including Nutlin and its derivatives (e.g. RG7112, RG7388) and the dual MDM2/MDMX inhibitor ALRN-6924 which has shown potent activity in early phase clinical trials in lymphomas [196]. As indicated above HUWE1 is aberrantly expressed in MM resulting in MYC stabilization. HUWE1 inhibition by BI8622 shows anti-MM activity as a single agent and synergizes with lenalidomide in preclinical models. However, these results have not expanded into early phase clinical trials as of yet.

As genomic alterations of several other E1/E2/E3 enzymes have been robustly observed in lymphoma and myeloma, therapeutic interventions should be continued to be pursued either as monotherapy or in combination with PIs to effectively block lymphoma and MM cell survival and overcome resistance to existing therapies.

4.5.2. Targeting ubiquitin receptors

Apart from ubiquitinating modifying enzymes, ubiquitin receptor proteins aid in the transport of ubiquitinated proteins to the proteasome or other destinations for recognition and final degradation. One of these ubiquitin receptors Rpn13 is overexpressed in MM cells compared to normal plasma cells. Genetic ablation or pharmacological inhibition of Rpn13 using a small-molecule inhibitor RA190 [197] decreased MM cell viability [198], activated plasmacytoid dendritic cells and induced the proliferation of MM-specific cytotoxic T cells [199]. Although abnormality of Rpn13 has been observed and targeted, pathophysiology of Rpn13 and other ubiquitin receptors in protein quality control in lymphoid cancers still remains to be delineated, which will undoubtably yield new insight into lymphoid pathogenesis and shed light upon the search to look for novel therapeutic approaches to combat against lymphomas and myeloma.

5. Concluding remarks

In this review, we sought to outline the dysregulation of the UPS in lymphoid malignancies, and discuss how the ubiquitination or deubiquitination processes of key oncoproteins and tumour suppressors contribute to lymphomagenesis. Furthermore, we delve into how the ubiquitin-proteasome pathway can be effectively exploited to target oncoproteins or to protect tumour suppressors to yield cytotoxic effects. The UPS intricately governs the turnover and function of substrate proteins and its malfunction due to mutations, promoter hypermethylation or altered splicing results in aberrant protein digestion, with these alterations impacting clinical outcomes in lymphomas and myeloma. Dysfunctional UPS also compromises tumour suppressor functions and amplifies tumorigenic signals from host oncoproteins or virus-infected oncoproteins, highlighting the therapeutic potential of targeting all components of the UPS including ligases, DUBs or ubiquitin receptors. Even more tantalizing is the hijacking of the ubiquitin modifiers for artificial proteolysis of previously inaccessible oncoproteins, in terms of PROTAC, or in the emerging field of targeted-protein stabilisers, DUBTAC, ENTAC and SURTAC. The past few years has observed a renaissance in the study of UPS, E3 ligases, and DUBs. These initial studies utilising IMiDs-dependent PROTACs will likely pave the way to future explorations analyzing the potential of hijacking any of other 600–700 ubiquitin ligases beyond cereblon and VHL. For example, the identification of tumour-enriched E3 ligases that can be co-opted for targeted protein degradation would significantly improve tumour specificity and therapeutic indexes while alleviating some dose-dependent toxicities. A second area of great study is antibody drug conjugates where the PROTAC/DUBTAC is coupled to a tumour specific antibody. Given the continuing advancement of targeting protein stability, it is likely that we are only observing the first wave of therapeutic modalities adopting the UPS for therapeutic purposes in lymphoid malignancies. Future studies are expected for better mechanistic comprehension and therapeutic strategies upon utilising the UPS.

Ethics approval and consent to participate

Not applicable.

Consent for publication

All of the readers read and approved the final manuscript.

Availability of data and materials

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CRediT authorship contribution statement

Boheng Li: Writing – original draft. **Pieter Johan Adam Eichhorn:** Writing – original draft. **Wee-Joo Chng:** Writing – original draft.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Pieter Eichhorn reports financial support was provided by Curtin University. If there are other authors, they declare that they have no

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Abbreviations

ABC-DLBCL	activated B cell-diffuse large B cell lymphoma
ALL	acute lymphoblastic leukemia
ATL	adult T-cell leukemia/lymphoma
BL	Burkitt's lymphoma
cHL	classical Hodgkin's lymphoma
CLL	chronic lymphocytic leukemia
DLBCL	diffuse large B cell lymphoma
DUBs	deubiquitinating enzymes
ENKTL	extranodal natural killer/T cell lymphoma
ENTAC	enhancement-targeting chimera
FL	follicular lymphoma
GCB-DLBCL	germinal center B cell-diffuse large B cell lymphoma
HECT	E6-associated protein carboxy terminus
IMiDs	immunomodulatory drugs
JAMMs	JAB1/PAB1/MPN-domain containing metallo-enzymes
LUBAC	linear ubiquitin chain assembly complex
MCL	mantle cell lymphoma
MINDYs	Ub-containing novel DUB family
MJDs	Machado-Joseph disease protein domain proteases
MM	multiple myeloma
NHL	non-Hodgkin's lymphoma
OTUs	ovarian tumor-related proteases
PIs	Proteasome inhibitors
POIs	proteins-of-interest
PROTAC	Proteolysis-Targeting Chimeras
RBR	RING-between-RING
RING	really interesting new gene
SURTAC	survival targeting chimeras
T-ALL	T-cell acute lymphoblastic leukemia
UCHs	ubiquitin carboxy-terminal hydrolases
UPS	Ubiquitin-proteasome system
USPs	ubiquitin-specific proteases

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