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The role of aberrant proteolysis in lymphomagenesis

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Abstract

Purpose of review—Deregulated proteolysis is increasingly being implicated in pathogenesis of lymphoma. In this review, we highlight the major cellular processes that are affected by deregulated proteolysis of critical substrates that promote lymphoproliferative disorders.

Recent findings—Emerging evidences support the role of aberrant proteolysis by the ubiquitin proteasome system (UPS) in lymphoproliferative disorders. Several UPS mediators are identified to be altered in lymphomagenesis. However, the precise role of their alteration and comprehensive knowledge of their target substrate critical for lymphomagenesis is far from complete.

Summary—Many E3 ligase and Deubiquitinases that contribute to regulated proteolysis of substrates critical for major cellular processes are altered in various lineages of lymphoma. Understanding of the proteolytic regulatory mechanisms of these major cellular pathways may offer novel biomarkers and targets for lymphoma therapy.

Keywords

deubiquitinase; E3 ligase; lymphoma; ubiquitin proteasome system

INTRODUCTION

Lymphomas are clonal proliferations that arise from B,T or natural killer lymphoid cells at various stages of maturation. Lymphomas represent about 4% of the new malignancies in the western countries, making it the fifth most common cancer and the fifth leading cause of mortality. Lymphomas are classified on the basis of the clinical, histologic, immunophenotypic, and genetic features. B-cell lymphomas make up over 85% of lymphoma in the western hemisphere. Whereas the genetic derangements underlying the pathogenesis of malignant lymphomas are relatively well studied, the role of deregulation of the ubiquitin proteasome system in the pathogenesis of these neoplasms has not been fully characterized. In this review, we discuss derangement in the proteolytic system that contributes to lymphoma pathogenesis and evolution.

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[152].

Conflicts of interest

There are no conflicts of interest to declare.

UBIQUITIN-PROTEASOME SYSTEM

The ubiquitin proteasome system (UPS) is the major proteolytic machinery that controls the site and context-specific levels of cellular regulatory proteins via a stepwise cascade of action of proteolytic enzymes, leading to the ligation of multiple ubiquitin to a protein target [1,2]. Figure 1 illustrates a schematic of the series of reactions mediated by the cascade of enzymes in the ubiquitin-proteasome system for degradation of a target substrate and their protection by deubiquitinase enzymes.

First, the reaction begins with ATP-dependent ubiquitin activation by the ubiquitin activating enzyme (E1) followed by transfer of the activated ubiquitin to a cysteine residue of ubiquitin conjugating enzyme (E2) and finally, transfer of ubiquitin to a free amine group in either the amino terminus or an internal lysine of a protein substrate that is mediated via a ubiquitin ligase (E3) enzyme. This cascade can proceed repeatedly to result in long chain of ubiquitin (polyubiquitin) on substrate. Ubiquitin has seven internal lysines (K6, K11, K27, K29, K33, K48, and K63). Each of these lysine residues can be utilized to mark substrates with monoubiquitination or polyubiquitination to feature different topology and consequently different biochemical consequences. Polyubiquitination at K48 and rarely at K11 marks substrates for degradation by the proteasome. The process of ubiquitination is counterbalanced by the process of deubiquitination mediated by deubiquitinating enzymes. The counteracting activities of E3 ligases and deubiquitinases control the cellular homeostasis. Deregulated degradation of critical cellular substrate proteins via UPS interrupts normal proteostasis of the cell, and triggers aberrant progression of cell-division cycle, transcriptional regulation, DNA-damage response, and apoptosis (Table 1 [3–44]) [11,43,45,46,47■]. Deregulations of these critical cellular pathways culminate into multistep process of lymphoid transformation (Fig. 2).

REGULATION OF TRANSCRIPTION FACTORS

Hematopoiesis is a multistep process sustained by coordinated regulation of proliferation, self-renewal, and differentiation of stem and progenitor and lineage-committed cells to generate mature and functional lymphoid cells. The process of maturation of hematopoietic cells largely depends upon the establishment of correct gene expression patterns under the control of a limited set of transcription factors. These factors act as important cell-fate switches in the hematopoietic system. Hence their physiologic levels are tightly controlled by the ubiquitin proteasome system-mediated protein turnover. Deregulated proteolysis of these transcription factors leads to aberrant gene expression and contributes to lymphomagenesis. In this section, we will discuss the transcription factors and epigenetic modulators that significantly contribute to hematopoietic- cell lineage commitment, lymphoid maturation and proliferation, and how their aberrant proteolysis contribute to lymphoma pathogenesis.

Nuclear Factor κ B signaling components

Nuclear factor (NF)- κ B is a structurally and evolutionally conserved family of transcription factors that are critical for physiologic immune response and lineage commitment of lymphocytes into T cells or B cells [48■]. The family is comprised of five structurally

related activators (RelA or p65, RelB, c-Rel, p50, and p52) and five inhibitors [p100, p105 and Inhibitor of κ B (IkB α , IkB β and IkB ϵ)] [49].

Two cullin-RING type SCF E3 ligases Fbxw1 (β TrCP) and Fbxw7 α have been majorly implicated in the proteolytic regulation of the NF κ B components [3–5,48–50]. β TrCP polyubiquitinates IkB α as well as p105 for proteasomal degradation. It also activates the proteolytic processing of p100 to generate p52, the active component of NF κ B transcription factor, which directs activation of canonical as well as noncanonical NF κ B signaling [6–8]. The Fbxw7 α regulates the degradation of nuclear p100 and favors noncanonical pathway activation [3]. The functional dynamics of β TrCP and Fbxw7 α regulate the activation of canonical or noncanonical NF κ B pathway. However, the context or maturation stage of lymphoid lineage cells at which the specific E3 ligase activity prevails for canonical or noncanonical NF κ B pathway activation is not yet completely understood. Aberrant activation of NF κ B signaling is associated with lymphomagenesis and hence, a clear understanding of proteolytic mechanisms in this pathways is crucial to the design of specific therapies against NF κ B-driven lymphomas.

Notch signaling proteins

Notch signaling plays critical roles in lineage commitment of T lymphocytes and B lymphocytes [50]. Accordingly, aberrant activation of Notch signaling has been associated with several hematologic malignancies [51–54]. Somatic mutations leading to gain-of-function of Notch signaling is associated with oncogenesis in many lymphoid neoplasms. In myeloid malignancies, however, loss-of-function mutations implicate a tumor suppressor role of Notch signaling components [55]. From this we can surmise that oncogenic or tumor suppressor activities of Notch signaling pathways are highly context dependent [55]. Notch signaling is significantly regulated by the UPS. Aberrant proteolysis of Notch1 due to activating mutations in Notch1 receptors impair its recognition and degradation by SCF^{Fbxw7} E3 ligase and promote lymphomagenesis [9,10]. The C-terminal PEST domain of Notch is highly conserved among different Notch proteins. Independent studies have identified Notch2 mutations in splenic marginal zone lymphoma (SMZL) patients using next-generation sequencing suggesting a mechanism analogous to that observed with Notch1 mutations. Most of the identified mutations targeted the conserved C terminal PEST region and are predicted to be recognition sites for E3 ligase(s) [51,52]. Accordingly, frameshift and deletion mutations targeting the PEST domain could increase the stability of mutant Notch2 protein with attendant Notch hyperactivity contributing to SMZL pathogenesis. Although Notch1 proteolysis is well understood, the machinery and regulation of Notch2 are not completely characterized. Thus, the identification of E3 ligase(s) and molecular mechanism that regulate Notch2 proteolysis might offer novel insights for therapeutic intervention against SMZL.

Myc

The Myc family of transcription factors is one of the most frequently deregulated oncogenes in human cancer [56]. It is a leucine zipper transcription factor that modulates several critical cellular processes including growth, metabolism, cell proliferation, apoptosis, genomic instability, stem cell self-renewal, and differentiation [57]. With the cooperation of

other genetic lesions, myc deregulation derives tumorigenesis in several subtypes of hematopoietic malignancy and human cancer. Overexpression and chromosomal translocation-mediated hyperactivation of c-Myc oncoprotein has been observed in large number of hematologic malignancies including Burkitt lymphoma, Diffuse Large B-Cell Lymphoma (DLBCL), follicular lymphoma, Acute Lymphoblastic Leukemia (ALL), B-cell lymphoma unclassifiable with features intermediates between DLBCL and Burkitt lymphoma (BCLU), plasma-cell myeloma, mantle-cell lymphoma (MCL), chronic lymphocytic leukemia, and plasmablastic lymphoma [58–74]. Myc levels are regulated posttranslationally by SCF^{Fbxw7} E3 ligase. Several mutations identified in the coding region of c-Myc center around Thr 58, which undergoes phosphorylation by GSK3 β and facilitates recognition and polyubiquitination of c-Myc by Fbxw7 for degradation [12]. Degradation of c-Myc is significantly impaired in Burkitt lymphoma harboring Thr58 or other mutations critical for Fbxw7-mediated recognition of the transcription factor [12,13]. The counteracting activity of c-Myc ubiquitination has been shown to be mediated by the USP28 deubiquitinase in colorectal cancer [14]. However, the deubiquitinase that regulates c-Myc abundance in hematologic malignancy has not been clearly established and offers a potential avenue for further studies. Apart from c-Myc, SCF^{Fbxw7} also regulate several other transcription factors involved oncogenic transcription, such as c-Myb, Jun, Notch, and KLF5 and thereby control growth-regulating pathways [75–81]. Consequently, mutational inactivation of Fbxw7 has been observed and implicated in the development and evolution of many subsets of malignant lymphoma [82–84].

Epigenetic regulators

The polycomb group (PcG) proteins are evolutionarily conserved epigenetic regulators of development [83]. Deregulated expression of PcG proteins is associated with several forms of cancer including hematologic malignancies [84–86]. The critical catalytic subunits of PcG protein; BMI1 and EZH2 are most frequently altered in several hematologic malignancies. BMI1 is recurrently upregulated in MCL and chronic myelogenous leukemia and a novel gene translocation t(10;14)(p12;q32) resulting in the IGH-BMI1 juxtaposition has been reported in chronic lymphocytic leukemia [87–89]. EZH2, a SET domain containing histone methyltransferase is a critical enzymatic subunit of the polycomb repressive complex 2 (PRC2), which trimethylates histone H3 (H3K27) to mediate gene repression [90]. Somatic mutations, overexpression, and hyper activation of *EZH2* have been reported in the pathogenesis of several types of lymphoma [84]. Genome wide sequencing studies identified heterozygous somatic and recurrent gain-of-function mutations targeting EZH2^{Y641} occurring most frequently in germinal center derived follicular and aggressive diffuse large B-cell lymphoma. This mutation is associated with H3K27me3 hyperactivation promoting lymphomagenesis [91–94]. These mutations have been reported to alter the enzymatic activity of EZH2 (with preference for trimethylation of H3K27) and increase its stability, resulting in a protein with prolonged half-life. SCF ^{β TrCP} E3 ubiquitin ligase controls the rapid proteolysis of BMI1 and EZH2 [15,16,82–84]. Although the complete molecular mechanism and context of their proteolysis is not completely understood, SCF ^{β TrCP} E3 ligase has been shown to recognize Y641 phosphorylated EZH2 for polyubiquitination and degradation [15]. The mutations at Y641 abrogate EZH2 phosphorylation by JAK2 tyrosine kinase and compromise its recognition by SCF ^{β TrCP}

rendering the EZH2 protein long-lived with attendant increase in H3K27 trimethylation activity. Similarly, the polycomb group protein Yin Yang 1 is targeted for degradation by smurf2 (smad ubiquitination regulatory factor 2) E3 ligase in germinal center and smurf2 is reported to be downregulated in germinal center derived DLBCL [17]. Mice deficient in smurf2 develop B-cell lymphoma. In a different context, smurf2 is also reported to regulate EZH2 proteolysis [18]. The possibility of novel smurf2 targets in the germinal center that may contribute to lymphomagenesis remains an intriguing. Further studies on the detail molecular mechanism of proteolytic regulation of PRC components may provide potential new therapeutic opportunities for treatment of hematopoietic malignancies driven by aberrant activity of PcG proteins.

PcG group-mediated transcriptional repression is counteracted by the multisubunit complex of trithorax group (TrxG) proteins. Mutational inactivation of TrxG complex components are identified in several B-cell and T-cell malignancies. The trithorax group histone methyl transferase mixed-lineage leukemia (MLL) is posttranslationally regulated by E3 ligases SCF^{Skp2} and anaphase-promoting complex, APC^{CDC20} during cell-cycle progression [19]. However, the posttranslational regulations of other TrxG proteins are poorly understood. As several hematologic malignancies are associated with mutational inactivation of TrxG proteins [95–98], understanding their proteolytic mechanism might provide significant insight on lymphomagenesis driven by increased stability of these epigenetic modifiers.

In concert with histone modifiers, DNA methyl transferases also play significant role in epigenetic regulation of gene expression. Several DNA methyl transferases have been implicated in hematologic malignancies [99]. DNA methyl transferase DNMT1, implicated in acute lymphoblastic leukemia and malignant T-cell lymphoma is regulated at the posttranslational level by UHRF1 E3 ligase and HAUSP deubiquitinase in response to acetylation [20,21]. Given the importance of the field, the identification of posttranslational regulatory mechanisms for DNA methyl transferases and demethylases warrants detailed investigation in relation to their possible roles in the pathogenesis of hematopoietic neoplasms.

BCL6

BCL6 is a transcriptional repressor required for the establishment of the germinal center during B-cell maturation [100]. BCL6 deregulation has also been associated with B-cell lymphomagenesis [100]. BCL6 regulates the germinal center reaction by transcriptional repression of genes required for cellular proliferation and differentiation, and thus prevent premature activation and differentiation of B-cell toward memory and plasma cells [101–109]. Overexpression of BCL6 through promoter hypermutation (~15%) and chromosomal translocations involving BCL6 (~40%) have been identified in DLBCL [22,110–113]. Another regulatory mechanism involving proteasomal degradation of BCL6 has been recently identified. [22]. The SCF^{Fbxo11} E3 ubiquitin ligase regulates BCL6 degradation, and thus controls its levels required for germinal center formation [22]. Fbxo11 silencing in a DLBCL-cell line promotes tumorigenesis in immunodeficient mice and its reconstitution suppresses tumor growth [22]. Fbxo11 deletion and mutations are found in several DLBCL-cell lines and primary DLBCL-patient samples. Loss of Fbxo11 promotes BCL6 stability.

Fbxo11 mutations identified in DLBCL are unable to trigger BCL6 degradation, and thus potentially contribute to lymphomagenesis through BCL6 stabilization. The identification of regulatory mechanisms that control BCL6 abundance in GC B-cell may offer a potential avenue for targeted therapeutic intervention against BCL6-deregulated lymphoma.

GENOTOXIC STRESS AND CELLULAR APOPTOSIS

P53

The cellular response following DNA damage is largely controlled by tumor suppressor p53 by blocking cell-cycle arrest for repair or alternatively inducing apoptosis. P53 is mutated in, approximately, 50% of human malignancies; however, its mutational inactivation is relatively less frequent in hematologic malignancies [23]. Instead, p53 levels are regulated at other levels including proteasomal degradation. Whereas MDM2 is the major E3 ligase for p53, other E3 ligases are also involved in p53 stability and activity [11]. Similarly, genotoxic stress also triggers the phosphorylation and proteolysis of cyclin D1 to regulate cell-cycle progression in order for DNA damage repair machinery to detect and repair [114]. The proteolytic regulatory mechanism of cyclin D1 is discussed in later section of this review.

BCL2 family

Two major signaling pathways namely the extrinsic or death receptor and intrinsic or mitochondrial pathway trigger apoptosis [115]. The intrinsic pathways are more commonly perturbed in lymphoid malignancies. This pathway is largely regulated by BCL2 family proteins.

This family constitutes three subfamilies: prosurvival (BCL2, BCLx1, BCLw, MCL1, and BFL1/A1), the subfamily that promote cell death; the initiator BH3-only proteins (BIM, PUMA, BAD, or NOXA); and the cell death mediators (BAX and BAK) [116,117].

Overexpression of BCL2 induced by the t(14;18)(q32;21) is characteristic of follicular lymphoma [118,119]. However, it is also overexpressed in CLL [120,121], MCL [122], DLBCL [123], ALL [124], MM and other plasma-cell dyscrasias [125], and some T-cell lymphomas [126]. Proteins of this family are regulated at posttranslational level by several E3 ligases and deubiquitinases. The deregulation of corresponding degradation machinery components has been documented in several forms of lymphoma. SCF^{Fbxo10} has been implicated in BCL2 protein degradation and reported to be compromised by mutational inactivation or deletion in germinal center type DLBCL [24]. Similarly, the BCL2 family protein BIM is targeted for degradation by two E3 ligases namely β TrCP and APC^{CDC20} in different cellular contexts [25,26]. Overexpression of the BCL2 family protein myeloid-cell leukemia sequence 1 (MCL1), cooperates with Myc and to promote lymphomagenesis [127]. Four E3 ligases: Mule, β TrCP, Fbxw7, and Trim17 trigger MCL1 proteolysis and its degradation is prevented by the deubiquitination activity of USP9X [27]. Targeting MCL1 through increased proteolysis might be a potential avenue of investigation for MCL1 overexpression-mediated lymphomagenesis. Thus, while several apoptosis intermediates are regulated by the UPS, the regulatory mechanisms of many are yet to be explored and may offer novel opportunities for targeted therapeutic interventions in malignant lymphomas.

TNFAIP3

The ubiquitin ligase TNFAIP3 (A20), a known effector of apoptosis, is a unique ubiquitin ligase that also possesses deubiquitinating activity and controls its own degradation in a negative feedback loop [128]. TNFAIP3 is primarily responsible for attenuation of NF κ B signaling and thereby inhibits inflammation and tumorigenesis and TNF-mediated apoptosis [128]. Mutational inactivation of TNFAIP3 by deletions, frameshift or nonsense mutations, and by promoter hypermethylation has been reported in several forms of B-cell and T-cell lymphoma [129–137]. TNFAIP3 inactivation by any mechanism contributes to lymphoma pathogenesis by promoting unchecked NF κ B signaling and enhanced-cell survival [132]. Considering the critical role played by TNFAIP3 in hematopoiesis, the studies involving its regulatory mechanisms and other novel substrates targeted by this enzyme might offer an opportunity for therapeutic interventions in TNFAIP3 dysregulated lymphomas.

CELL-CYCLE CONTROL

Deregulation of the cell cycle fundamentally underlies the development and evolution of various forms of malignant lymphoma. Cell-cycle progression is precisely regulated by timely synthesis and degradation of cell-cycle regulatory proteins; cyclin-dependent kinases (CDK1, CDK2, CDK4, and CDK6), their essential activating coenzymes, the cyclins (cyclin A, B, D, and E), interaction of CDK-inhibitory proteins (CDKIs) and the signaling networks that control their function via posttranslational modifications. The abundance of these intermediates during the different phases of cell-division cycle is tightly controlled by the ubiquitin proteasome system [138]. Mutational inactivation of proteolytic machinery components that control critical cell-cycle regulators contribute to the pathogenesis of malignant lymphoma. Additionally, the genetic lesions in cell-cycle regulators that enable them to bypass proteolytic turnover also promote aberrant lymphoid-cell growth and malignant transformation. Two major ubiquitin ligase complexes; the APC or cyclosome (APC/C) and the SCF complex are primarily involved in the regulated proteolysis of several cell-cycle regulatory proteins [43,139].

Cyclin and cyclin-dependent kinases

Cell-cycle progression is principally driven by cyclins and their respective CDK and regulated by cyclin-dependent kinase inhibitors (CKIs) in different phases of cell cycle. Several E3 ligases that participate in physiologic cell-cycle progression have been shown either to be deregulated in specific types of lymphoma or contribute to lymphoma pathogenesis in mouse models. APC/C^{Cdh1} E3 ligase targets cyclin A and B for degradation along with many other factors associated with M to G1 phase transition [140]. Cdh1 heterozygous mice develop B-cell lymphoma and a myelodysplastic syndrome-like disorder [141]. Further, the reduced expression of CDH1 has been described in the malignant progression of B lymphoma cell line suggesting a plausible role APC/C complex components in lymphomagenesis [142]. Cyclins are often overexpressed in several types of cancer and promote cancer progression by accelerating the cell-division cycle [143–147]. Thus, failure to degrade cyclins is associated with tumor development and progression. For example, neoplasia of diverse lineages overexpress cyclin E and this overexpression

correlates with increased tumor aggressiveness. Cyclin E is known to promote entry into S phase and the cyclin E-CDK2 complex phosphorylates retinoblastoma to promote G1 progression. The cyclin E is a prototypic substrate of SCF^{Fbw7} E3 ligase [28]. The regulation of cyclin E protein abundance is compromised by mutational inactivation of Fbw7 that contributes to several forms of lymphoid neoplasia [29]. Frequent inactivation of *Fbw7* by deletions or point mutations occurs in diverse hematopoietic malignancies [9,10,30,148]. Specifically, the most frequent *Fbw7* mutations are identified in T-ALL (~30%) and cholangiocarcinomas (~35%) [149]. Commonly, missense mutations of *Fbw7* occurring at R465C, R479Q, and R505C within WD40 repeats 3 and 4 (from Fbw7 α) diminish its capacity to recruit substrates to the E3 ligase complex by loss of interaction [10]. Further, during G1 to S phase transition cyclin D1 is targeted for degradation by several SCF E3 ligases including FBXO4, FBXO8, FBXO31, SKP2, β TRCP, and APC [31–36,150]. It is anticipated that studies investigating the pathogenic deregulation of these E3 ligases will be informative on their role in the pathogenesis of lymphoid malignancies.

Cyclin-dependent kinase inhibitors

CKIs are the critical regulator of cyclin-CDK activities. CKIs function by inhibiting CDK activity and promoting cell-cycle arrest and/or delaying the response to antimitogenic stimuli. These CKIs fall into two families: the INK4 inhibitors and the CIP/KIP inhibitors. There are four known INK4 family members: p16^{INK4A}, p15^{INK4B}, p19^{INK4D}, and p18^{INK4C}. The three mammalian CIP/KIP CKIs: namely p21^{CIP1}, p27^{KIP1}, and p57^{KIP2} play different role in cell-cycle regulation [138,151]. The SCF^{SKP2} E3 ligase targets all three CKIs: p21^{CIP1}, p27^{KIP1}, and p57^{KIP2} (all widely accepted tumor suppressors) at different stages of the cell cycle for degradation [37–42]. However, p27 seems to be a principal target of SKP2 as the prominent phenotypes apparent in *Skp2* $-/-$ mice including nuclear enlargement, polyploidy, and an increased number of centrosomes. This phenotype is ameliorated in *Skp2* $-/-$ p27 $-/-$ double mutant mice [2,153]. As SKP2 target p27 and other CKIs for degradation, it can be considered an oncogene. Apart from CKIs, SKP2 also targets p130, cyclin A, cyclin D1, free cyclin E, ORC1, CDK9, MYC, B, Myb, SMAD4, RAG2, UBP43, FOXO1, and papillomavirus E7(139). SKP2 over expression has been associated with poor prognosis in human lymphoma patients [154,155].

CONCLUSION

The controlled degradation of cellular proteins involved in cell-cycle progression, response to genotoxic stress, signaling pathways, and transcriptional control of gene expression is prerequisite for normal hematopoiesis. In this context, the UPS plays a pivotal role by degradation of regulatory proteins in a precisely timed and context-dependent manner. Deregulation of the UPS results in complex outcomes in term of tumorigenesis. Ubiquitin ligases control a remarkable diversity of substrates for the control of cellular homeostasis and hence, it is not surprising that these E3 ligases are deregulated by multiple mechanisms cumulatively resulting in lymphoproliferative disorders. Although E3 ligases have been implicated in the regulation of a diverse array of substrates, the knowledge on the subcellular location, context, and cofactors that dictate the degradation of these substrates in particular metabolic states, as well as, lineage and cellular contexts is far from complete.

The main goal of studying proteolytic mechanisms in lymphopoiesis and lymphoid malignancies is to develop a more sophisticated understanding of the regulation of these processes and the phenomena that play a role in their perturbation resulting in malignancy. Such knowledge could be exploited in the development of therapeutic strategies targeting lymphomas driven by aberrant proteolysis of critical cellular substrates. Advances in this arena include the FDA approval of Velcade (Bortezomib, a general proteasome inhibitor) and the use of the neddylation inhibitor (MLN4924) in the management of cancers. Inhibition of specific components of the proteolytic machinery in cell lineage and context-dependent settings offers plausible options for novel lymphoma therapies.

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KEY POINTS

- Proteolytic regulatory mechanisms that control several critical cellular processes maintain cellular homeostasis.
- Deregulation of the proteolytic machinery by mutational inactivation or hyperactivation contributes to lymphoma pathogenesis.
- Somatic mutations in critical cellular substrates that result in failure to degrade the substrates also contribute to lymphoma pathogenesis.

FIGURE 1.

A multistep enzymatic cascade attaches ubiquitin (Ub) to its Substrate. An E1 (ubiquitin activating enzyme) activate ubiquitin using energy from ATP hydrolysis and transfers it to an E2 (ubiquitin conjugating enzyme). The E2 subsequently transfer the activated ubiquitin to a substrate that is specifically recruited by an E3 (ubiquitin ligase). Polyubiquitination comprising four or more ubiquitin protein linked either through K48 or K11 undergo degradation in 26S proteasome. The ubiquitination mark can be reversed by deubiquitinase enzymes (DUBs) to protect substrate from degradation. The dynamic equilibrium of E3 ligase and DUBs dictates the level of substrate steady state levels and turnover.

FIGURE 2.

Aberrant proteolysis of critical substrates involved in cell-cycle progression, genotoxic stress, apoptosis, or cellular machinery such as epigenetic modulators and transcription factors that control gene expression contribute to lymphoma development and evolution.

Table 1

Cellular substrates and associated E3 ligases/deubiquitinases implicated in lymphoma pathogenesis

Substrates	Lymphoma subtype associated	E 3 ligase and Deubiquitinases	References
Transcription factors and epigenetic modulators			
NF κ B components	T-PLL, ABC-DLBCL,	SCF ^{Fbxw7α} , SCF ^{βTrCP} ,	[3–8]
Notch signaling components	T-ALL, B-ALL SMZL,	SCF ^{Fbxw7α}	[9,10]
Myc	BL, DLBCL, FL, ALL, BCLU, MCL, CLL, PBL	SCF ^{Fbxw7α} , SCF ^{βTrCP} , SCF ^{Skp2} , Truss, Huwe1, USP28	[11–14]
Polycomb group proteins	GCB DLBCL, FL,	SCF ^{βTrCP} , Smurf2	[15–18]
MLL	B-ALL, DLBCL, AML, MCL	SCF ^{Skp2} , APC ^{CDC20}	[19]
DNMT1	TCL, ALL	UHRF1, HAUSP	[20,21]
BCL6	GCB-DLBCL, FL	SCF ^{Fbxo11}	[22]
Genotoxic stress and Apoptosis			
p53	TCL, ATLL, FL, DLBCL, MCL, MZL,CLL	MDM2, Pirh2, SCF ^{βTrCP} , USP10 and HAUSP	[11,23]
BCL2	FL, DLBCL, CLL, MCL, ALL, TCL, MM	SCF ^{Fbxo10}	[24]
BIM		SCF ^{βTrCP} , APC ^{CDC20}	[25,26]
MCL1	MCL, DLBCL, BL, CLL, AML, ALL and MM	SCF ^{βTrCP} , SCF ^{Fbxw7α} , USP9X	[27]
Cell-cycle regulators			
Cyclins	BL,MCL,DLBCL,	APC/C ^{Cdh1} ,SCF ^{Fbxw7α} , SCF ^{Fbxo4} , SCF ^{Fbxo8} , SCF ^{Fbxo31} , SCF ^{Skp2} and SCF ^{κTrCP}	[28–36]
CKI	BL, DLBCL, FL, ALL, MCL, CLL, PBL, MZL,cHL, TCL	SCF ^{Skp2}	[37–42]
CDK	TCL	SCF ^{Skp2} , SCF ^{βTrCP}	[43,44]

ALL, Acute Lymphoblastic Leukemia; BCLU, B-cell lymphoma unclassifiable; BL, Burkitt lymphoma; CDK, cyclin-dependent kinases; CKI, cyclin-dependent kinase inhibitors; FL, follicular lymphoma; MCL, mantle-cell lymphoma; MLL, mixed-lineage leukemia; SMZL, splenic marginal zone lymphoma.