

Review

The role of deubiquitinating enzymes in hematopoiesis and hematological malignancies

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Abstract

Hematopoietic stem cells (HSCs) are responsible for the production of blood cells throughout the human life span. Single HSCs can give rise to at least eight distinct blood cell lineages. Together, hematopoiesis, erythropoiesis and angiogenesis coordinate several biological processes, such as cellular interactions in development and proliferation, guided migration, lineage programming and reprogramming by transcription factors. Any dysregulation of these processes may result in hematological disorders and/or malignancies. Several studies of the molecular mechanisms governing HSC maintenance have demonstrated that protein regulation by the ubiquitin proteasomal pathway is crucial for normal HSC function. Recent studies have shown that the reversal of ubiquitination by deubiquitinating enzymes (DUBs) plays an equally important role in hematopoiesis; however, there is only limited additional information regarding the biological function of DUBs. In this review, we focus on recent discoveries that have led to a better understanding of the physiological roles of DUBs in hematopoiesis, erythropoiesis and angiogenesis. In addition, we discuss the DUBs associated with common hematological disorders and malignancies, which may potentially be therapeutic drug targets.

Keywords: DUB's, HSC's, Myeloid, erythroid, leukemia, lymphoma, cell differentiation.

1. Introduction

The blood system consists of red blood cells, megakaryocytes, myeloid cells (monocyte/macrophage and neutrophil) and lymphocytes. All these blood components are produced by rare cells in bone marrow called hematopoietic stem cells (HSCs) as a result of the process termed hematopoiesis [1]. The properties of self-renewal and differentiation into various progenitor cells allow HSCs to reconstitute the entire blood system. The progenitor cells further mature into lineage-specific precursors by specific pathways. The hematopoietic system originates from two sites: the yolk sac (primitive, generating nucleated erythrocytes) and the aorta-gonad mesonephros (AGM) region (definitive, generating HSCs giving rise to all blood lineages) [2,3].

Erythropoiesis is the differentiation of multipotent hematopoietic stem cell to unipotent stem cells which are primitive erythroid progenitors [4]. Primitive or embryonic erythropoiesis is the maturation of erythroid progenitors from yolk sac in the fetal liver. After birth, definitive erythropoiesis is initiated in the bone marrow in successive waves of erythroid progenitor cell maturation, including generation of burst-forming unit-erythroid (BFU-E), Colony forming Unit-erythroid (CFU-E), proerythroblast, and basophilic, polychromatic, and orthochromatic erythroblasts derived from HSCs [5,6]. The CFU-E undergoes many substantial changes, such as chromatin condensation and enucleation, and progressively gives rise to erythrocytes or Red Blood Cells (RBCs). Erythrocyte production is regulated at each stage of development through various transcription factors, post-translational modification of histones, and the interplay between the cell cycle and RBC differentiation [7,8].

Angiogenesis is the formation of blood vessels from the existing vascular system. Mesodermal stem cells are the source of HSCs and angioblasts in the embryo. Mesodermal cells in the embryo form aggregates of endothelial precursor cells or angioblasts called blood islands [9,10]. These blood islands fuse to form hierarchical networks of arteries, capillaries, and veins, whereas HSCs mature to form all the components of blood [9]. The complex network of blood vessels produced by angiogenesis carries oxygenated RBCs throughout the body along with other blood cells, macromolecules, gases, and fluids [9,10]. It is essential to circulate blood to all tissues to enable diffusion exchange of nutrients and metabolites within the large and complex bodies of vertebrates. Angiogenesis is essential for both normal growth and development and for the growth of tumors and metastasis [11]. It is apparent that identifying the regulators of angiogenesis is of potential therapeutic benefit.

HSC differentiation is a tightly controlled process, and recent studies suggest that post-translational modification of protein substrates plays an essential role in its regulation. Many studies have established the roles of ubiquitination and deubiquitination in regulating a wide range of transcription factors, signal transduction pathways, and niche factors [12]. Normal hematopoiesis requires tight regulation of the expression of lineage-specific genes and of epigenetic and post-translational modifications, and any perturbations in this processes may result in myeloid or lymphoid disorders or malignancies [1].

2. Ubiquitination and deubiquitination

Ubiquitination is the process whereby an ubiquitin molecule is covalently attached to a protein substrate. Ubiquitin is a 76-residue polypeptide. Conjugation of

ubiquitin to its substrate protein is carried out by large enzymatic complexes: these enzymes are the ubiquitin-activating enzymes (E1), ubiquitin-conjugating enzymes (E2), and ubiquitin ligases (E3). The ubiquitin molecule is first activated by E1 enzymes in an ATP-dependent manner forming a thiol ester bond with the C-terminus of ubiquitin, and is then transferred to E2 through a thioester-linked E2-ubiquitin intermediate. Next, the E2 and E3 enzymes position the target protein substrate and transfer this activated ubiquitin to its lysine residue (Fig. 1) [13]. Ubiquitin has certain specific lysine residues for ubiquitin conjugation, which modify the protein in a specific way. Protein modification by attachment of a single ubiquitin is termed monoubiquitination, while conjugation of single or multiple lysine residues by a chain of ubiquitin oligomers is termed polyubiquitination. Monoubiquitination of a protein is associated with DNA repair, vesicle sorting, signal transduction and receptor endocytosis, whereas polyubiquitination is associated with protein degradation by the 26S proteasome. The addition of ubiquitin is a reversible process. Deubiquitinating enzymes (DUBs) are proteases that remove ubiquitin from ubiquitin-protein conjugates prior to proteolysis (Fig. 1). DUBs are a very important class of enzymes, as they can negatively regulate protein degradation and help to balance the pool of free ubiquitin in circulation [14-16].

DUBs belong to the human family of proteases, which catalyse the removal of ubiquitin from substrate proteins and also play a vital role in ubiquitin recycling, editing and maturation [17,18]. DUBs also play a key role in modulating various cellular pathways, including gene expression [19], apoptosis [20], cell cycling [21], cellular reprogramming [22], oogenesis [23], spermatogenesis [24], endosomal trafficking and endocytosis [25], and proteostasis [26].

Approximately 100 different types of DUBs have been identified in the human genome, which can be subdivided into six different sub-families according to sequence conservation in the catalytic domain: they are (1) ubiquitin-specific proteases (USP), (2) ubiquitin C-terminal hydrolases (UCH), (3) OTU domain-containing ubiquitin aldehyde-binding protein 1 (OTUB1), (4) ataxin-3/Machado-Joseph domain proteases (MJD), (5) JAB1/Pad/MOV34/MPN-domain containing metalloenzymes (JAMM), [27] and (6) monocyte chemotactic protein-induced proteases (MCP/IP) [28]. Rehman et al. reported the discovery of new family of DUBs called MINDY (motif interacting with Ub-containing novel DUB family), which shows high selectivity for cleavage of K48-linked polyubiquitin chains [29]. In addition to these families, M48^{USP}, a novel class of protease which functions as a DUB, has also been documented [26]. However, the precise functions and substrates for most DUBs have not yet been elucidated.

A growing body of evidence indicates that DUBs play a very important role in the differentiation of hematopoietic stem cells to all blood cell lineages, including lymphoid-lineage T and B cells, and myeloid-lineage neutrophils, eosinophils, basophils, monocytes, macrophages, megakaryocytes, and platelets [30,31]. Thus, in this review, we discuss the evolving understanding of the role of DUBs at the interface of hematopoiesis, erythropoiesis and angiogenesis, and the diseases associated with these processes.

3. Importance of DUBs in hematopoiesis

DUB-1, DUB-2A, DUB-3

Recently, a hematopoietic-specific cytokine-inducible growth-regulatory subfamily of DUBs has been identified. Within this family, DUB-1, an immediate-early gene, is induced by interleukins-3 and -5 (IL-3 and IL-5) in the murine hematopoietic progenitor cell line Ba/F3. DUB-1 regulates the ubiquitin-dependent proteolysis which arrests the cell cycle in S phase. DUB-1 is specifically expressed in hematopoietic cells and may play a role in growth suppression [32]. Another immediate-early gene, DUB-2, is induced by IL-2 in the IL-2-dependent murine hematopoietic progenitor cell line CTLL. DUB-2 inhibits apoptosis after cytokine withdrawal [33] and prolonged STAT5 phosphorylation [34]. DUB-2 influences STAT5 activation, which is important for the expression of various oncogenes [34]. DUB-2A, which is similar to DUB-2, is induced by IL-2 and regulates intracellular cytokine-induced growth proteins such as CBL E3 ubiquitin protein ligase [35] and Cytokine induced STAT inhibitor (CIS) protein [36,37]. The proteins involved in cytokine-induced signaling pathways are regulated by ubiquitin-dependent proteolysis in hematopoietic cells. This regulation involves two important processes: ubiquitin-dependent internalization and turnover of cytokine receptors [38,39] and STAT1 degradation [40].

DUB-3 or USP17, induced by IL-4 and IL-6, plays important role in blocking cell proliferation and inducing apoptosis in hematopoietic cells [41,42]. DUB-1 and DUB-2 are specifically expressed in either B or T cells, respectively, whereas DUB-3 is found in numerous hematopoietic tumors [34,42]. These DUBs are induced by hematopoietic cytokines to initiate a cytokine-specific growth response; thereafter, DUB-1 and DUB-2 are degraded as the cytokine response is down-regulated [32,33,43].

MYSM1

MYSM1 was originally identified as a histone H2A deubiquitinase, playing an important role in activation of several genes regulated by Androgen Receptor (AR) in prostate cancer cells [44]. Transcription factors are key determinants of the complex orchestration of hematopoiesis; however, little is known about the underlying mechanisms by which these transcription factors are regulated [45]. Transcription of a gene is critically regulated by epigenetic histone modifications. EBF1 is one of the master transcription factor for B cell lineage commitment and development, and its deficiency leads to a blockage in early pro-B cell development [46]. EBF1 plays an important role in activation of many genes, such as Pax5, Foxo1, Cd79a, Cd79b, Igll1, and others which are important for B cell development [47,48]. MYSM1 plays a broad role in the hematopoietic system and regulates the transcription of Ebf1, as well as other genes essential in B cell development. [49]. Recently Huo et al. and Le Guen et al. have identified that MYSM1 plays an essential role B cell development, hematopoietic development and lymphocyte generation in bone marrow of both humans [50] and mice [51]. Several studies have found that MYSM1 deficiency or mutation may lead to defect in development and function of HSC's, B cells, Natural Killer (NK) cells and dendritic cells and it also resulted in development of lymphopenia, anemia and thrombocytopenia, low B cell and NK cell counts in mice as well as humans [51-56].

USP3

USP3 regulates the ubiquitin-dependent DNA damage response (DDR) to double-stranded DNA breaks [57]. In USP3-knockout HSCs, defective ubiquitination has been shown to decrease HSC function, and increase cumulative DNA damage

and hypersensitivity to ionizing radiation [58]. Due to the loss of USP3, HSCs in USP3 knockout mice are under chronic genotoxic stress, causing shortened life span and associated functional decline of the hematopoietic stem and progenitor compartment. The function of USP3 therefore appears to be to protect HSCs against DNA damage by regulating DDR signaling.

USP16

Another H2A deubiquitinase, USP16 regulates many genes involved in hematopoiesis [59]. USP16 regulates cell cycling during hematopoiesis through the polycomb repressive complex 1 (PRC1), a major H2A ubiquitin ligase. Some studies have suggested that deletion of USP16 may impact HSC lineage commitment by reducing the number of mature progenitor cells [60]. USP16 also plays an important role in the expression of genes involved in HSC differentiation, chromosome organization immune response and hematopoietic organ development [60,61]. Additionally, USP16 has been found to regulate the transition between HSCs with long-term regeneration capacities (long-term HSCs) to those with short-term regeneration capacities (short-term HSCs) during fetal hematopoiesis [62].

USP1 and USP10

During normal development, HSCs are prone to undergo apoptosis due to fluctuations in cytokine availability as they move from the fetal liver (FL) to bone marrow (BM). USP10 inhibits apoptosis by two distinct mechanisms: one is deubiquitinases-independent/ROS-dependent and the other is deubiquitinase-dependent/ROS-independent. Furthermore, the latter mechanism inhibits cytokine-deprivation-induced apoptosis of HSPCs including long-term HSCs in the FL. BM

failure with pancytopenia and anemia due to pronounced reduction of HSCs and progenitor cells is also observed in USP10-knockout mice [63]. Another DUB involved in bone marrow failure is USP1, which is associated with a chromosome instability syndrome called Fanconi anemia (FA). USP1 regulates the FA pathway by deubiquitinating FANCD2. USP1 inhibition causes accumulation of monoubiquitinated FANCD2 and protects cells against certain types of DNA damage [64,65].

Other DUBs

BAP1 is an essential component of the polycomb repressive deubiquitinase complex (PR-DUB), in which it deubiquitinates monoubiquitinated histone H2A at lysine 119 (H2AK119ub), a modification that is catalyzed by the PRC1. The mammalian PR-DUB complex contains ASXL family proteins, which are required for its deubiquitinating activity. The PR-DUB complex has increasingly attracted the interest of medical researchers, as somatic mutations in ASXL1 occur in various myelodysplastic syndromes [66]. Another DUB, USP42 is expressed in bone marrow and is associated with RUNX1 expression (a key regulator of hematopoiesis) in acute myeloid leukemia (AML) [67]. Several DUBs, including USP16, MYSM1, USP21, and BAP1, have been identified as H2A-specific DUBs, whereas others, such as USP3, USP12, and USP46, display dual specificity toward both ubH2A and ubH2B [49].

4. Importance of DUBS in erythropoiesis and angiogenesis

Erythropoiesis involves reorganization of a complex cellular compartment in support of the differentiation and maturation of RBCs. This reorganization is

regulated in part by programmed protein degradation [68]. During erythropoiesis, protein ubiquitination and deubiquitination guides the removal of proteins and organelles within proteasomes or lysosomes. However, the role of DUBs in erythropoiesis needs further investigation.

Among the USP subfamily, USP50 is considered to be catalytically inactive due to the unavailability of one of the canonical residues required for catalysis [69]. USP50 is upregulated during the terminal stages of erythropoiesis, and hence can be involved in cell-cycle arrest [8]. USP50 is involved in Ku70-mediated deubiquitination of Mcl-1, which plays an important role in regulating apoptosis in the later stages of erythropoiesis. The Ku70 protein is a DNA binding protein and is expressed in CD34⁺ hematopoietic progenitor cells (HPCs) [8,70]. USP7 ubiquitinates and stabilizes the erythroid transcription factor-GATA. While originally identified as a potential anti-cancer target in a genome-wide RNAi (RNA interference) screen of catalytically active USP's, USP7 has recently attracted attention as a potential therapeutic target. According to a recent study, USP7 expression was significantly upregulated during erythropoiesis, and was associated with delayed terminal erythroid differentiation, inhibition of hemoglobin expression and cell proliferation, and induction of apoptosis [71].

Angiogenesis refers to the migration, growth and differentiation of vascular endothelial cells to form new capillary blood vessels. This process is tightly regulated by a range of angiogenic factors and inhibitors, the most important of which is vascular endothelial growth factor (VEGF). Protein ubiquitination regulates virtually every aspect of the angiogenesis signaling pathway. Both the canonical and non-canonical Wnt signaling pathways have been found to be of importance for angiogenesis. The key component of Wnt signaling is the disheveled protein (DVL2),

which helps to cleave the linear ubiquitin linkages [12]. Linear ubiquitination linked via Ub Met-1 (M1) chains regulates NF- κ B-dependent inflammation and adaptive immunity. The linear ubiquitin chain assembly complex (LUBAC) consists of HOIL-1/1I, HOIP and sharpin proteins which together produce M1-linked chains. Certain DUB's, such as CYLD and OTULIN (also known as Gumby or *Fam105b*), are to known to negatively regulate LUBAC. OTULIN binds to LUBAC and decreases linear ubiquitination, thereby activating NF- κ B-dependent transcription [12,72].

5. DUBs in hematological malignancies

The ubiquitin proteasome system (UPS), along with DUBs, is involved in catalyzing destruction of many protein substrates involved in the pathogenesis of several types of cancers. Deregulation of this proteolysis-regulating machinery may result in uncontrolled cell proliferation, accumulation of harmful proteins, and genetic instability leading to malignancy [73,74]. Several DUBs have been identified which are deregulated by various processes in hematological malignancies. These perturbations in the turnover of regulatory proteins lead to disruptions of cellular homeostasis and disturb the balance of various signaling pathways contributing to the multistep process of carcinogenesis [75]. However, there is limited evidence regarding direct links between neoplastic transformation and deregulated deubiquitination [76]. The potential for therapeutic targeting of the DUBs that are linked to various hematological malignancies is described in the preceding section.

A20

A20 was identified as a protein that protects against TNF-induced cytotoxicity, and has been shown to have both E3 ligase and deubiquitinase activity. Inactivation

or deletion of A20 is associated with several types of hematological malignancies [77]. As discussed in the previous section, activation of the NF- κ B pathway plays a central role in the pathogenesis of various hematological malignancies. Several studies have demonstrated that NF- κ B activation is negatively regulated by A20 through interactions with proximal signaling proteins such as tumor necrosis factor receptor associated factor 1 (TRAF1), TRAF2, TRAF6, RIPK1, RIPK2, NEMO and MALT1 [78,79]. In several types of hematological malignancies, inactivation of A20 by genomic deletion, somatic mutation or epigenetic hypermethylation results in impaired NF- κ B suppressor function [80-82]. Re-expression of A20 in different B-cell lymphomas with no functional A20 alleles resulted in apoptosis and suppression of cell growth, along with downregulation of the NF- κ B pathway [83,84].

Knockdown or inactivation of A20 resulted in cell proliferation in acute T cell lymphocytic leukemia [81], B cell lymphomas [83], mucosa-associated lymphoid tissue (MALT) lymphoma [85,86], marginal zone lymphoma [87,88], primary mediastinal B cell lymphoma (PMBL) and classic Hodgkin's lymphoma [89,90], suggesting A20 has tumor suppressor activity [79]. Inactivation of A20 by biallelic mutation was detected in more than 20% of cell lines derived from patients with diffuse large B-cell lymphoma (DLBCL), MALT lymphoma, Hodgkin's lymphoma or marginal zone lymphoma [82,84,87,91].

Although the molecular mechanism or mode of action of A20 has not been completely elucidated, its involvement in regulation of ubiquitin-dependent signaling indicates A20 may be a potential therapeutic target in various hematological malignancies.

USP7

USP7 was initially identified as ICP0 (Herpes Simplex Virus protein)-stabilizing protein [92]. Several studies have reported USP7 mediates stabilization of ICP0 enzyme-inducing proteasome-dependent degradation of a number of proteins, including p53 and promyelocytic leukemia protein (PML) [93]. In addition, overexpression of USP7 in various cancers correlates with tumor aggressiveness [94]. MDM2, murine double minute oncogene (HDM2-human orthologue), is a substrate for USP7 which negatively regulates the tumor-suppressor protein p53. Under normal conditions, USP7 stabilizes intracellular MDM2 concentrations, which in turn drive steady ubiquitination of p53, which targets it for proteasome-mediated degradation [95]. In multiple myeloma (MM), reduction in p53 expression occurs at the later stages of cancer progression, along with overexpression of USP7. Downregulation of USP7 by P5091 (USP7 inhibitor) in MM cell lines, an MM xenograft model and patient-derived tumor cells has been demonstrated to create a potent, specific and selectively enhanced degradation of HDM2, as well as upregulation of p53 and p21 expression, resulting in cell cytotoxicity [96]; USP7 is also implicated in human lymphomas. The overexpression of USP7 regulates turnover of p53, which induces p53-dependent apoptosis. The N-terminal domain of USP7 is involved in p53-USP7 interactions, and also contains a TRAF (tumor necrosis factor receptor associated factor) domain and an EBNA 1 binding domain. Human TRAF regulates lymphocyte survival, while EBNA1 is a viral onco-protein responsible for the immortalization of cells and development of B-cell lymphomas [97]. Recent studies have reported that USP7 modulates the stability of RAD18, a DNA damage-responsive E3 ubiquitin ligase, which in turn regulates p53 expression. Inhibition of USP7 in chronic lymphocytic leukemia (CLL) with inactivated ATM-p53 pathway-

induced tumor cell killing through genotoxicity. This suggests USP7 may be a potential pharmacological target even in p53-defective cells [98].

USP9X

USP9X is a substrate-specific DUB showing a highly conserved sequence in *Drosophila* and humans. Overexpression of DUB USP9X has been reported in various cases of lymphoma, chronic myeloid leukemia (CML), B cell malignancies, and MM, and is associated with a poor prognosis [99]. MCL1 (induced myeloid leukemia cell differentiation protein), an essential apoptotic regulator protein for survival of stem cells and progenitor cells of multiple lineages, is expressed at abnormally high levels in B and mantle cell lymphomas, CML, and MM. The mechanism of overexpression of MCL1 in cancer is not completely clear; however, USP9X is thought to stabilize MCL1 by removing degradative Lys-48-linked polyubiquitin chains. Increased expression of USP9X is highly correlated with increased MCL1 in diffuse B cell lymphomas and multiple myeloma. Knockdown of USP9X resulted in downregulation of MCL1, which enhances cell apoptosis in human follicular lymphomas and B-cell lymphomas [100]. Increased MCL1 and USP9X protein expression has been detected during relapses of acute myelogenous leukemia (AML), acute lymphocytic leukemia (ALL) [101] and multiple myelomas [102], and is associated with reduced survival. Ubiquitin cycle inhibitor WP1130 directly inhibits USP9X, which results in down-regulation of MCL1 protein and facilitation of apoptosis of various CML cell lines [103]. The novel small molecule EOAI3402143 (with properties similar to WP1130) selectively inhibits USP9X and USP24, induces apoptosis in malignant B cell lines and also blocks or regresses myeloma tumors in

mice [104]. Hence, inhibition or knockdown of USP9X may be a potential therapeutic target in various hematological malignancies with abnormal USP9X activity.

USP9X also demonstrates mitotic activity due to its role in the regulation of chromosome alignment and segregation by targeting survivin and Aurora B and other inhibitor of apoptosis proteins (IAP) [105]. USP9X shows specificity towards various substrates in different types of cells. It also plays an important role in T cell proliferation, T helper cell differentiation, and cytokine production. [97,106]. Studies conducted by Engel et al. demonstrated that USP9X deubiquitinates the X-linked inhibitor of apoptotic protein (XIAP) in order to promote mitotic survival in aggressive B cell lymphomas through RNAi-mediated knockdown of USP9X. Overexpression of USP9X is also correlated with increased expression of XIAP, which is identified as a predictive biomarker for chemotherapy resistance in diffuse B cell lymphomas [106]. Spindle assembly checkpoint (SAC)-induced mitotic arrest coupled with knockdown of USP9X are important targets for anti-neoplastic therapies.

USP14

USP14 is a DUB associated with 19S proteasome which dynamically regulates magnitude and nature of its activity, though its role in disease development is still not clear [107]. Various studies have revealed association of USP14 with various types of cancer. Specifically, it was reported that upregulated expression of USP14 was associated with Leukemia and may perhaps be implicated in apoptosis [108]. Various proteasome inhibitors like Bortezomib [109], Carfilzomib [110], MLN9708 [111] has contributed significantly towards treatment and survival in MM [112] and B cell malignancies patients [104]. However, increasing development of resistance of cancer cells against chemotherapy has been a main roadblock in development

treatment of malignancies. Studies have shown that multiple myeloma cells can be protected from chemotherapy induced apoptosis by phenomenon called cell adhesion mediated drug resistance (CAM-DR) [113]. USP14 reported to contribute to CAM-DR by upregulating antiapoptotic protein Bcl-x1 and Wnt 3 signalling pathways. Studies have shown that USP14 is significantly overexpressed in CAM-DR model and downregulated in apoptotic model of MM. Moreover, upregulation of USP14 in MM model could enhance anti apoptotic cell adhesion abilities, thus promoting drug resistance in MM [114].

Co-inhibition USP14 and UCHL5 by novel DUB's inhibitor VLX1570 revealed a potent tumor specific apoptotic activity in drug resistant tumor cells of Waldenstrom macroglobuliemia (WM), an incurable Non-Hodgkin Lymphoma (NHL) [115]. Recently it was also established that targeted inhibition of USP14 and UCHL5 with small molecule inhibitor b-AP15 induced proteotoxic stress and apoptosis in tumour cells of WM, without affecting proteolytic activity of 20S proteasome [116]. b-AP15 mediated inhibition of proteasome deubiquitinating activity also suppressed tumor progression and organ infiltration in different *in vivo* solid tumor models of an acute myeloid leukaemia [117]. Tian et al demonstrated that b-AP15 mediated inhibition along with siRNA knockdown of USP14 and UCHL5 induced synergistic apoptotic activity MM tumor cells and overcomes Bortezomib resistance [118]. Above data provides us with idea about implications of USP14 in various hematological malignancies and its potential in targeted therapy. Therefore, further investigation of the role of USP14 will provide preliminary theoretical basis for its application in clinical research.

USP24

Studies have demonstrated that USP24 promotes cancer malignancy by inducing IL-6 transcription in tumor infiltrating leukocytes (TILs), vascular endothelial cells and cancer associated fibroblast [119]. In another study, selective inhibition of USP9x by inhibitor WP1130 reduced Mcl-1 levels and induced apoptosis in MM cells. However, significant upregulation of USP24 was observed when USP9x was inhibited. Thus emphasizing its role in MM cell survival [112]. Interestingly, USP24 was found to regulate survival of MM cells in absence of USP9X. Direct USP24 knockdown resulted in apoptosis of myeloma cell associated with reduction in Mcl-1 levels. Dose dependent inhibition of USP9X and USP24 activity by modified compound of WP1130, EOAI3402143 increased cells apoptosis and completely regressed myeloma tumors in mice models [104].

CYLD

Nuclear factor-kB (NF-kB) transcriptional factors and associated signaling pathways play a central role in activation of the innate and adaptive immune responses, and are also involved in cancer development, tumor angiogenesis and progression [120]. CYLD is a negative regulator of NF-kB signaling and its loss inhibits apoptosis by activation and expression of NF-kB-dependent cells pro-survival genes necroptosis [121]. The CYLD gene was first identified in association with suppression of multiple skin tumors in cases of familial cylindromatosis [122]. CYLD is an essential mediator of RIPK1- and RIPK3-dependent necroptosis [121].

Proteolytic cleavage of CYLD through the para-caspase MALT-1 tissue results in NF-kB activation, which is a key step in the initiation of T-cell acute lymphoblastic leukemia (T-ALL) [123,124]. Notch (transcription regulator) signaling regulates activation of the NF-kB signaling cascade and facilitates NF-kB nuclear

retention during T cell activation [125]. Dysregulated Notch gene expression is a common feature of acute T cell lymphoblastic leukemia (T-ALL) [126]. Recent evidence has suggested that Notch-induced activation of NF- κ B pathways plays a key role in T-cell leukemia, and the degree of downregulation of NF- κ B is correlated with the severity of the disease [127]. CYLD-mediated suppression of NF- κ B signaling and I κ B kinase (IKK) expression and function has a negative impact on the survival of human T-ALL cells and also repressed tumor growth in animal models [128].

Given CYLD negatively regulates mitosis and cytokinesis [129,130], and plays an important role in the regulation of microtubule dynamics and cell migration [131,132] and apoptosis, CYLD may be a novel target for treating hematological malignancies. As evident from previous studies, regulation of NF- κ B signaling plays an important role in the initiation and pathogenesis of hematological malignancies. Additional DUBs such as USP10 [133], USP11 [134], USP21 [135], USP15 [136] and OTULIN [137] which play an important role in activation or inhibition of the NF- κ B pathway, might also play an as yet undiscovered role in pathogenesis of hematological malignancies.

6. Deubiquitinases as emerging target against Hematological malignancies

Ubiquitination and deubiquitination are known to play critical role in various biological pathways closely associated with development of various cancer. Even though knowledge about exact role of DUB's in cancer pathology has been limited, the list of DUB's that are altered genetically in human cancer cases is growing rapidly in recent years [138]. Recent studies have presented DUB's as a true oncogene and tumor suppressor. DUB's have been identified to regulate cellular expression and turnover of oncogenic protein in various hematological malignancies. In recent years' inhibitors of the Ubiquitin proteasome system has emerged as

therapeutic target for treatment of various cancers. However, role of most of these inhibitors has shown limited application with low efficacy in hematological malignancies. Recent novel approach targeting DUB's have emerged to be promising therapeutic target against different hematological malignancies[139]. The ability of DUB's to modulate fate of protein specifically and selectively gives advantage over targeting UPS system. For example, DUB's may increase or maintain level of tumor suppressor protein by decreasing its degradation by UPS or can boost pathogenesis by reversing fate of oncogenic protein in the cell [26]. Considering the advantages and ease of developing inhibitors over enzyme activators, the research towards development of DUB's inhibitors against hematological malignancies have been emphasized.

Recent approach targeting DUBs through various small molecule inhibitors has showed promising results against various hematological malignancies. The novel regulatory particle b-AP15 together with lenalidomide, or dexamethasone induces synergistic anti-MM activity [140]. According to recent studies b-AP15 could also be a potential therapy for leukemia and WM by inhibiting 19S proteasome-associated DUBSs such as USP14/UCHL5 and inducing tumor cell apoptosis. Another potent DUB inhibitor WP1130, known as Degrasyn previously, targets deubiquitinases such as USP5, USP9x, USP14, USP24 and UCHL5. Recent study concludes that WP1130 mediated inhibition of USP9X increases ubiquitination of an anti-apoptotic protein myeloid leukemia-1 (MCL-1) which is highly expressed in drug resistant MM tumors [141,142]. The rapid degradation of MCL-1 results in increase in the sensitivity of these tumor cells to chemotherapy [26,139,143]. USP24 which is closely related to USP9X also plays a critical role in the survival of myeloma B cell by regulating MCL-1 protein levels. Peterson and colleagues suggested that dual

inhibition of USP9X and USP24 by WP1130 provides greater anti-myeloma activity. However, they developed a threefold more effective inhibitor called EOAI3402143 (G9) which had an improved therapeutic index than WP1130. G9 also inhibits USP5 increasing p53 accumulation and hence prove to be a promising approach towards B-cell malignancies [142,144]. At present there are studies regarding USP7 and USP10 inhibitors (HBX19818, P22077) which play a key role in many cellular processes. A lead-like inhibitor, HBX41108 and HBX19818 has been found to inhibit the catalytic activity of USP7 and induce p53-dependent apoptosis. [145] [146]. Preclinical data from Chauhan et. al. demonstrated anti-tumor efficacy of P5091 with lenalidomide, HDAC inhibitor SAHA, or dexamethasone by inducing tumor cell-apoptosis in MM disease models [96]. It also stabilizes p53 by inhibiting USP7 mediated-deubiquitination of MDM2 which degrades p53 tumor suppressor, [147-149], thus inhibiting cancer cell proliferation. P045204, P22077 are the analogs of HBX19818, P5091 and HBX41108 and are proved to be potent inhibitors of USP7 [150]. P217564, a second generation inhibitor, binds to the active site of USP7 inhibiting its activity [151]. Along with USP7, P22077 and HBX19818 has also been reported to inhibits USP10, promoting degradation of FLT3-mutant AML cells [152]. A small molecule inhibitor named by Liu, Xia et al. as “spautin-1” (for *specific and potent autophagy inhibitor-1*) which inhibits autophagy and two DUBs USP10 and USP13 which deubiquitinates two tumor suppressors Beclin1, subunit of Vps34 complexes and p53 [153].

A better understanding of the regulatory DUBs involved in inhibition or activation of hematopoietic processes and pathologies is expected to open new frontiers in the development of novel therapeutic drugs targeting hematological malignancies and disorders. The goal is to enhance our understanding of

dysregulated DUBs in hematopoiesis in order to design new therapeutic targets and to establish biomarkers that could be used in diagnosis and prognosis

7. Conclusions

Since its discovery, the UPS has emerged as one of the key regulators of various proteins and factors involved in hematopoiesis, erythropoiesis and angiogenesis. The roles of E1, E2 and E3 enzymes in governing the various pathways involved in hematopoietic regulation and pathologies have been studied extensively; however, knowledge about the reversal of the activity of DUBs and their involvement in various hematological processes is limited. Several studies have provided insight regarding dysregulated functioning of DUBs in various hematopoietic cells, which contribute to hematological pathologies. In this review, we have described various DUBs that are directly or indirectly involved in the regulation of various hematopoietic processes.

Selective inhibition or overexpression of DUBs has helped to elucidate their roles in hematopoiesis, erythropoiesis, angiogenesis and related abnormalities. Potent selective inhibitors of DUBs have shown promise for the treatment of hematological malignancies. Hematological disorders are the result of defective function of one or many components in the blood caused by intrinsic factors. DUBs are thought to play a very important role in the etiology of various diseases and disorders and are therefore potential drug targets. However, limited knowledge about the molecular mechanisms and substrate specificity of DUBs currently restrict their potential as novel therapeutic targets (Fig 2).

In Table 1 we have described a list of DUBs associated with certain blood disorders. Identification of other DUBs involved in the pathogenesis of other

hematological disorders and more complete insight into the regulatory mechanisms of DUBs that govern disease progression will provide new perspectives in therapeutics.

Although evidence suggests DUBs play an importance role in the regulation of hematopoiesis, many questions about their involvement in the hematopoietic system remain unexplored. Further investigation of the localization and substrate specificity of DUBs, their interactions with other hematopoietic factors and other data gaps will help to improve our knowledge about their importance in hematopoiesis.

Abbreviations:

DUBs: Deubiquitinating enzymes; UPS: Ubiquitin proteasome system; HSCs: Hematopoietic stem cells; USP: Ubiquitin-specific proteases; UCH: Ubiquitin C-terminal hydrolases; MJD: Ataxin-3/Machado-Joseph domain proteases; OUT: Otu-domain ubiquitin aldehyde-binding proteins; JAMM: JAB1/Pad/MOV34/MPN-domain containing metalloenzymes; MINDY: Motif interacting with Ub-containing novel DUB family; MCPIPP: Monocyte chemotactic protein-induced proteases; AGM: Aorta-gonad mesonephros; BFU-E: Burst-forming unit-erythroid; CFU-E: Colony forming Unit-erythroid; RBCs: Red Blood Cells; AR: Androgen Receptor; NK: Natural Killer; DDR: DNA damage response; PRC1: Polycomb repressive complex 1; PR-DUB: Polycomb repressive deubiquitinase complex; FL: Fetal liver; BM: Bone marrow; CIS: Cytokine induced STAT inhibitor; AML: Acute myeloid leukemia; HPCs: Hematopoietic progenitor cells; VEGF: Vascular endothelial growth factor; LUBAC:

Linear ubiquitin chain assembly complex; MALT-1: Mucosa-associated lymphoid tissue; NF- κ B: Nuclear factor- κ B; TRAF: Tumor necrosis factor receptor associated factor; RIPK: Receptor-interacting serine/threonine-protein kinase; NEMO: NF- κ B essential modulator; PML: Promyelocytic leukemia protein; IL: Interleukin; FA: Fanconi Anaemia; SAC: Spindle assembly checkpoint; CAM-DR: Cell adhesion mediated drug resistance; WM: Waldenstrom macroglobuliemia; NHL: Non-Hodgkin Lymphoma; CYLD: Cylindromatosis; MM: Multiple myeloma; LT-HSC: Long term Hematopoietic stem cells;

Author's contribution

SR conceived the idea. NS and JK searched the literature and wrote the manuscript. The author read and approved the final manuscript. All authors read and approved the final manuscript.

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Conflict of interests

The authors declare no conflict of interests.

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Table 1. List of DUBs involved in hematological disorders

Disorder	Associated Substrate	Regulatory DUB	Reference
Fanconi Anemia	FANCD2	USP1	[154,155]
Anemia	Ku70	USP50	[8]
β -thalassemia	α -Globin	USP15	[156]
Pancytopenia	Reduction in LT-HSC	USP10	[31]
Myeloproliferative diseases	ASXL1, EZH2, JAK2, TET2	PR-DUB, BAP1	[157,158]
Waldenstrom macroglobulinemia (WM)	Overexpression of USP14 and UCHL5 in drug-resistant WM-tumor cells	USP14 and UCHL5	[115,159,160]
Bone marrow failure	B-cell factor 1 (Ebf1), paired box 5 (Pax5), and other B-lymphoid genes	MYSM1	[51,161]
Malaria	CD8+ T cells	CYLD	[162]

Figures

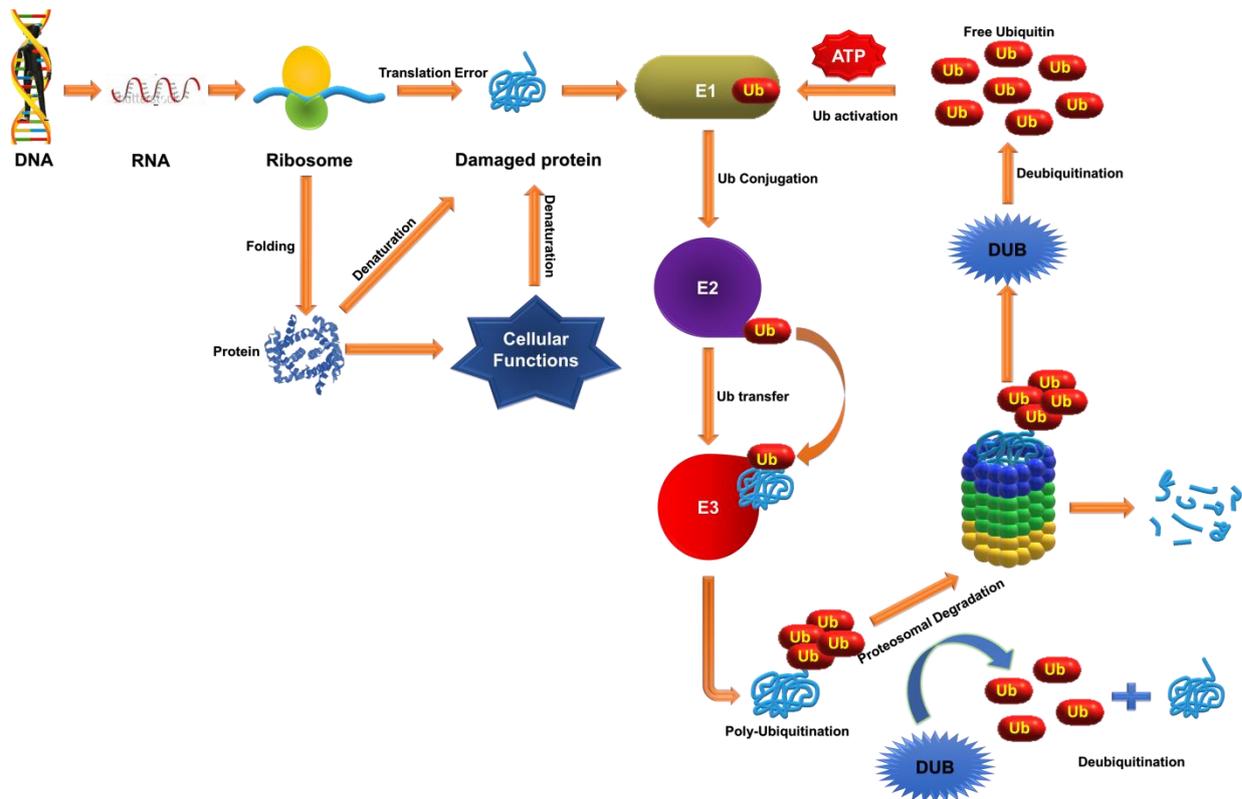


Figure 1. Protein quality control and degradation by the Ubiquitin Proteasome System (UPS)

The nascent polypeptides and the misfolded proteins, which have arisen from the translational error, are the targets of UPS system balancing the myriad of intracellular protein levels. The UPS system mainly consists of Ubiquitination of the target protein by E3 ligases and degradation of ubiquitinated proteins by the proteasome. Ubiquitination is the process of tagging the target protein by ubiquitin molecule/s. This cascade of enzyme reaction is catalyzed by sequential activity of three enzymes: E1 (Ubiquitin activating enzyme), E2 (Ubiquitin conjugating enzyme) and E3 (Ubiquitin ligases). This process is counter balanced by Ub proteases belonging to either metalloprotease or cysteine protease family referred to as

deubiquitinating enzymes (DUBs). These DUB's cleaves the ubiquitin molecule from the substrate protein maintaining the pool of mono-Ub which is supplied for the ubiquitination of misfolded proteins. Any disturbance in the equilibrium between ubiquitination and deubiquitination persuades proteotoxicity.

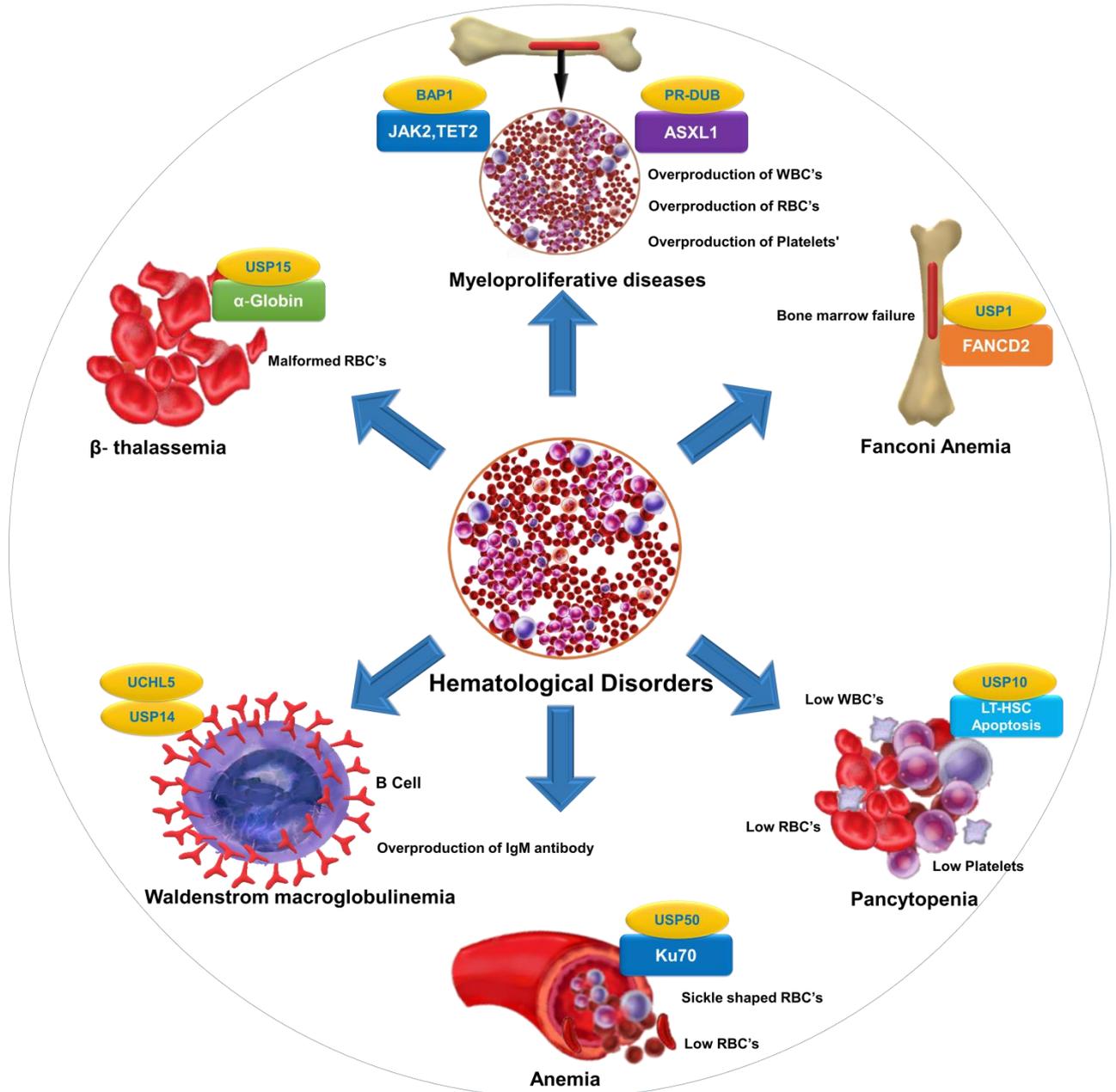


Figure 2. DUB as a novel target in hematological diseases

DUB's regulates level and function of protein by catalyzing removal of ubiquitin from the substrate protein. Thus dysregulation of DUBs contributes to the pathogenesis of various hematological disorders. The figure illustrates different hematological disorders and the associated DUBs that can provide novel target for the therapeutic interventions to treat these disorders.