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DUBbing down translation: The functional interaction of Deubiquitinases with the translational machinery

Bandish Kapadia¹, Ronald Benjamin Gartenhaus^{1,2}

¹University of Maryland School of Medicine, Baltimore, MD, 21201,

²Veterans Administration Medical Center, Baltimore, MD, 21201

Abstract

Cancer cells revamp the regulatory processes that control translation to induce tumor-specific translational programs which can adapt to a hostile microenvironment as well as withstand anti-cancer therapeutics. Translational initiation has been established as a common downstream effector of numerous deregulated signaling pathways which together culminate in pro-oncogenic expression. Other mechanisms including ribosomal stalling as well as stress granule assembly also appear to be rewired in the malignant phenotype. Therefore, better understanding of the underlying perturbations driving oncogenic translation in the transformed state will provide innovative therapeutic opportunities. This review highlights deubiquitinating enzymes that are activated/dysregulated in hematologic malignancies thereby altering the translational output and contributing to tumorigenesis.

Keywords

Hematological Malignancy; Protein Translational Machinery; Deubiquitinase; USP9X; USP10; USP11

Introduction

Despite advances in our treatment of hematological cancers(1), a large cadre of patients remain refractory to tumoricidal agents, while others require prolonged and intensive treatment to achieve continuous remission, which may lead to serious sequelae. Indeed, in recent years, better understanding of the molecular pathogenesis has spawned a revolution in next-generation therapeutics from the newly identified genes whose products are suitable for targeted therapy. Our focus herein is to provide a concise overview on the newly identified deubiquitinases which regulate the protein levels of key effectors driving tumor growth and survival.

Correspondence: **Ronald B. Gartenhaus**, 655 West Baltimore Street 9-014, Marlene and Stewart Greenebaum Cancer Center, University of Maryland School of Medicine, Baltimore, MD 21201; rgartenhaus@som.umaryland.edu, Ph:(410) 328-3691 or **Bandish Kapadia**, 655 West Baltimore Street 9-014C, Marlene and Stewart Greenebaum Cancer Center, University of Maryland School of Medicine, Baltimore, MD 21201; BKapadia@som.umaryland.edu, Ph:(410) 328-3691.

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In the last two decades, it has become dogmatic that the deregulated protein biosynthetic machinery promotes a specific subset of mRNAs which encodes protein regulating cell growth and survival and have a high degree of secondary structure in the 5' UTR which are sensitive cap-dependent translation initiation(2). Significantly, translational machinery output is observed to be directly correlated with hyperactivated cellular proliferation pathways increasing overall biosynthesis. Previously, we and others summarized the protein machinery components and its regulatory signaling pathway in hematologic malignancies and suggested them to be ideal candidates for therapeutic intervention(2–5). Several small molecule inhibitors which regulates cap-dependent as well as cap-independent translational regulation are undergoing phase I or phase II clinical trials and have shown promising results in preclinical studies(6–8).

Ubiquitination is a complex process whereby ubiquitin molecules are covalently linked with protein substrate(s) which predominantly alters its half-life along with the interactome, functionality as well as sub-cellular localization. Ubiquitination reaction is comprised of three steps orchestrated by ubiquitin-activating enzyme (E1), ubiquitin conjugating enzyme (E2) and ubiquitin ligase (E3) that mediate ATP-dependent thiol ester covalent bond formation between C-terminus of the Ubiquitin molecule and its substrate protein(s) (9). Successive ubiquitin molecules are attached to the lysine residue at positions 6, 11, 27, 33, 48 and 63, each of which are known to regulate different cellular responses, prominent among them is K-48 polyubiquitination which leads to 26S proteasomal degradation(10). Deubiquitination is a hydrolytic reaction in which the ubiquitin molecules are cleaved from the conjugated protein substrates by deubiquitinating enzymes (DUBs) and thus counteracts the ubiquitin ligase activity. Ubiquitination-Deubiquitination collectively regulate a plethora of cellular functions including; protein degradation (proteasome and lysosome), apoptosis, cellular survival, cell cycle progression chromosome segregation, gene expression, etc.(11). Numerous reviews in the literature have described the importance of ubiquitin ligase and DUBs in various cellular processes(12–15). However, there is still a relative paucity of literature on the impact of this reversible post-translational mechanism on protein/ribosomal machinery functioning, a key cellular driver for transformation.

Several genetic, biochemical and structural studies have enhanced our understanding on the upregulation of components of the translational and/or ribosomal machinery. A prominent event is the reversible ubiquitination-deubiquitination protein quality control with regulated degradation in order to maintain stringent qualitative output of the nascent polypeptide, an event which is sometimes hijacked in cancerous conditions. There are a series of reports(16–18) as well as mini review by Wang et al. where they have listed various E3 ligases which act on the ribosomal machinery for efficient scanning of newly synthesized proteins(19). The translational impact of DUBs, which remove the covalent linkage of ubiquitin from their substrate protein(s), is currently poorly understood. Emerging data reveals that the activity of DUBs appear to control the translational, as well as ribosomal protein activity thereby, play an essential role in effective regulation of nascent polypeptide synthesis (Fig. 1). Below, we provide information on specific DUBs, their substrate(s) in the translational complexes as well as their potential impact on hematopoiesis and/or hematological malignancies.

USP 10

USP10 is a member of the ubiquitin-specific protease family of cysteine proteases. The deubiquitinase was identified in a yeast two-hybrid screen using G3BP (GAP SH3-binding protein) as bait(20). USP10 is highly conserved protein encompassing conserved cysteine and histidine boxes in the central region and C terminal of protein. Interestingly, USP10 lacks deubiquitinase activity when enriched from bacterial lysates(20) suggesting a high dependence on protein folding under cellular conditions or presence of post-translational modification sites for its activity. The latter might result in increased protein resolving size in a denatured PAGE. Although initially being identified as G3BP bait, G3BP is unlikely to be a substrate due to its long protein half-life as well as the protein not found to be ubiquitinated(20). In contrast, addition of G3BP in a deubiquitinase assay, the activity of USP10 was found to be reduced, indicating the protein might act as scaffold/co-factor inhibitor in limiting the deubiquitinase activity under cellular conditions(20). USP10 is primarily localized in the cytoplasm, however upon modification by ATM at Thr42 and Ser337, it translocates to the nucleus(21).

USP10 has been shown to act as an anti-stress factor under several stress conditions, including oxidative stress, heat shock, and viral infection. USP10 has been reported to be downregulated in several cancers including renal carcinoma, ovarian cancer, hepatocellular carcinoma and is proposed to act as a tumor suppressor. USP10 is also reported to stabilize classical tumor suppressor proteins including, P53(21), Sirt6(22), IKK γ /NEMO(23) and others. Apart from regulating DNA damage response (DDR) and cellular proliferative pathways, USP10 is also an established DUB in the formation of mammalian stress granules(24). During cellular stress, adverse conditions lead to inhibition of translation initiation directing the formation of several stalled preinitiation complexes that condense to form non-membrane bound enclosed foci called stress granules(25). Stress granules (SG) are generally observed due to enhanced SG-nucleating proteins aggregation induced by overexpression or response to stress conditions like osmotic stress or heat shock (26). G3BP is nucleate SG assembly of caprin1 and USP10 which binds to 40S ribosomal subunit(24). Interestingly, USP10 induced stalled translation initiation upon eIF4A inhibition or phosphorylation of eIF2 α , however when the protein is overexpressed, USP10 blocks SG formation by preventing polysomal disassembly or mRNP condensation(24). Recently, it was established that USP10 deubiquitinates AMPK α to promote its interaction with LKB1, its master regulator and thus enhances its activity. Furthermore, under energy stress, AMPK phosphorylates USP10 at Ser76 which increases its hydrolase activity(27). Hyper AMPK activity under energy stress conditions are known to stunt global translational activity(28), however, the impact of USP10/AMPK axis in inducing SG formation is still unclear.

Nutrient limitations are emerging as vital tool for therapeutic targeting which limits proliferative mTOR activation and thus curtail overall protein biosynthesis and cancer outgrowth. One of the induced and well-studied mechanism is degradations of cellular organelle due to starvation. A recent publication indicates mono-ubiquitination, an efficient mechanism for protein trafficking, plays a significant role in selective autophagy/ribophagy. Peter and his group reported that deubiquitination of RPS125 by USP10/Ubp3p-BRE5/

Br5p activity triggers 60S ribosome uptake and degradation by autophagosomes under nitrogen starvation(29).

USP10 also plays a critical role in protein quality control by regulating the mono-ubiquitination of Rsp3(30). Misfolded proteins, a potential intracellular toxic species, are recognized by chaperones and eliminated from cellular environment broadly by the ubiquitin-proteasome system. It has previously been reported that ubiquitination of ribosomal proteins regulates the ribosomal quality control (RQC) activity. During active translation, Rsp3 is mono-ubiquitinated by Hel3p/RNF123 E3 ligase(30). It is well established that temporal stalling of the ribosome during translation activates RQC pathways. In fact, USP10 deubiquitinates the Rsp3p to stall active translation. Critically, both Hel3p/RNF123 and Ubp3p/USP10 are both recruited at the ribosome complex under basal conditions, representing a tight regulation of mono-ubiquitination of Rsp3 under RQC induction(29). There is a recent report that USP10 interacts with eIF4G1 and depletion of USP10 enhanced eIF4G1 protein levels(31). This would indicate that the deubiquitinase might have negative effects either directly or indirectly on regulation of the eIF4F scaffold protein, and thus translation initiation.

In addition to being a critical modulator of ribosome activity, USP10 expression is vital for normal hematopoiesis. Higuchi et al. noted that whole body deletion of USP10 in mice resulted in early death of the mice, due to lack of proper bone marrow development. USP10-KO mice displayed severe anemia due to depletion of long-term hematopoietic stem cells (LT-HSC, CD150⁺CD48⁻ LSK) both in fetal liver and bone marrow. Thus, USP10 appears as a critical deubiquitinase in proper development of bone marrow and maintenance of long-term hematopoietic stem cells for maintenance of erythropoiesis(23). Recent advances in understanding the pathology of AML highlighted the importance of leukemia stem cells (LSCs) which has properties similar to hematopoietic stem cells, making them difficult to eradicate(32). Furthermore, mutations in FLT3 kinases represent clinical challenges in curing AML(33). Recently, Weisberg et al. screened the library of 29 DUB inhibitors and noted that HBX19818 and P22077 showed robust reduction in FLT3 protein levels. Although the compounds were reported as irreversible inhibitors of USP7 and USP10, mechanistic analysis revealed that USP10 and not USP7 regulates FLT3 stability and promotes the AML growth(34). Recently, a case of pediatric relapsed AML with recurring translocation in t(11;16)(q23;q24) noted generation of a novel fusion gene product of KMT2A-USP10(35). K-specific methyltransferase 2A (KMT2A) gene, located in chromosome band 11q23 is a well-established hotspot for illegitimate chromosomal rearrangement(36), while USP10 is critical for pluripotency of the hematopoietic stem cells proposing that the novel fusion gene might act as a proto-oncogene which confers resistance to standard therapy(35). However, more mechanistic studies are required to delineate the functional implication of such novel fused genes.

Collectively, USP10 is one of the most studied deubiquitinases associated with protein biosynthetic machinery as it is recruited to both 40S and 60S ribosomal subunits and also plays a major role in protein quality control and ribophagy. USP10 may also have a direct impact on regulating the translational initiation machinery. Although functionally tasked as a tumor suppressor in several cancers, USP10 appears to act as proto-oncogene in AML to

maintain cancer cell stemness. The role of USP10 on other hematological cancers is still evolving. Further studies to define the role of USP10 on regulating ribosomal output are clearly indicated.

USP11

Ubiquitin carboxyl-terminal hydrolase or Ubiquitin-specific protease 11 (USP11) belongs to the Ubiquitin-specific proteases family (USPs), a subfamily of the DUBs. USP11 shares a high sequence homology with USP15 and USP4 harboring the same domain architecture: two internal ubiquitin-like (UBL) domains and an N-terminal domain present in ubiquitin-specific proteases (DUSP), proposed to act as functional paralogs(37). Several studies have reported that USP11 and USP4 is localized in nucleus (but not nucleolus) as well as cytoplasm, while USP4 is believed to localized predominantly in nucleus excluding nucleolus, and USP15 in expressed both in nucleolus and in cytoplasm, exemplifying analogously functioning enzymes in different subcellular domains(38).

Li et al. while delineating the molecular mechanism of HCV life cycle, noted that USP11 expression was vital for IRES-dependent HCV mRNA expression(39). Subsequently, it was noted that USP11 plays a vital role in stabilizing eIF4B protein expression(40). eIF4B acts as a co-factor in enhancing endogenous eIF4A helicase activity(41). A recent study also indicates that eIF4B also plays a vital role in loading mRNA at the P-site of ribosome to regulate the transcripts' translational capacity(42). The Gartenhaus lab demonstrated that USP11 activity is directly correlated with eIF4B's half-life and enhances both eIF4B driven cap-dependent as well as cap-independent translation output. Mechanistically, it was established that enhanced activity of oncogenic fatty acid synthase increases the transcript and thus protein levels of USP11 in NHL. Further, USP11 was noted to be directly recruited on the m⁷GTP cap complex wherein it stabilizes the eIF4B levels. Significantly, it was established that USP11 is bonafide substrate of S6Kinase and phosphorylation of USP11 at Ser⁴⁵³ regulates the recruitment of USP11 on cap complex as well as its interaction with eIF4B, thus increasing the eIF4B driven oncogenes expression. It also important to note that the activity of phosphorylated USP11, under experimental conditions, was more or less equivalent to the wild-type protein revealing phosphorylation plays an important role in stabilizing DUBs substrate interaction(40). Recently it was reported that USP11 is also a substrate of PRMT1, an established ribosomal methyltransferase. However, the impact of methylation on USP11 driven protein translational machinery is unclear at present(43). Apart from eIF4B, USP11 also stabilizes multiple other proteins like RAE1(44), ALK5(45), BRCA2(46), TGFβ receptor II(47) and thus plays vital roles in regulating proliferative TGFβ signaling, DNA double-strand repair, and chromatin segregation, positioning USP11 as an attractive therapeutic target.

Identification of USP11 inhibitors will further aid in delineating its functional impact on numerous cellular functions. Burkhart et al., using a fluorescent-based high-throughput assay, screened more than 2000 FDA approved chemical entities and reported that mitoxantrone inhibits USP11 activity under *in-vitro* conditions(48). Traditionally, mitoxantrone inhibits DNA synthesis by intercalating DNA, inducing DNA strand breaks, and causing DNA aggregation and compaction, delaying cell cycle progression, particularly

in late S phase and has been used clinically in AML for over three decades(49). The drug has shown several immunomodulatory effects, inducing macrophage-mediated suppression of B-cell, T-helper and T-cytotoxic lymphocyte functions(50). However, the drug has significant cytotoxic effects and it is, therefore, appealing to identify USP11 specific inhibitors with potentially more modest side effects in an anticancer therapeutic regimen. Structural analysis of USP11's N terminal domain and UBL domain reveals a conserved VEVY signature motif at the two domain's interface which might provide a potential substrate interaction site(51). Employing a ubiquitin chain cleavage assay, Harper et al. reported that USP11 may cleave a panel of Lys (48,63,6,33 and others) linked linear ubiquitin chains indicating that USP11 may function in regulating protein activity(51). Recently, Dreveny and her group reported the identification of peptide ligands that exclusively targeted the UBL domain of USP11 without impacting its functional paralogs USP4 and USP15, providing an ideal platform to next-generation biochemical tools for limiting USP11 activity(52). Thus, there are exciting opportunities to specifically target USP11 with minimal off target impact.

USP9X

USP9X is one of the highly evolutionary conserved DUBs. Although the protein is more over 2500 amino acids long, minimal information is available regarding its structure. The protein encompasses classical cysteine and histidine box dependent catalytic motifs, a ubiquitin-like module (Ubl) and N terminal nuclear transport signal. To date, more than 40 different substrates have been identified with USP9X regulating a wide array of cellular process including; transcription, apoptosis, chromatin remodeling and proliferative cellular signaling. A detailed study has been reported by Wood and colleagues elucidating the functional impact of USP9X activity on multiple cellular phenomenon(53). Herein, we will highlight the functional significance of USP9X in regulating the translational machinery.

Li et al. with an aim of identifying the potential interacting with the eukaryotic initiation factor performed tandem affinity purification with eIF4B and confirmed that USP9X was one of the interacting partners recruited to the cap complex. Biochemical characterization confirmed that intact protein and not individually mapped regions of eIF4B was necessary for efficient complex formation with USP9X. Further, USP9X was localized and captured in the cap complex enrichment along with eIF4B. Importantly, modulation of USP9X expression altered overall protein biosynthesis along with specific regulation of IRES-driven translation. Mechanistically, the authors reported that USP9X stabilizes eIF4A1 protein levels and regulates specific oncogenes cMYC and XIAP at the translational level(54). However, they didn't observe any specific interaction with eIF4A1 either endogenously or upon ectopic expression. It was proposed that eIF4B may act as a bridge in removing the ubiquitin chains from eIF4A1(54), however, depletion of eIF4B was shown to have minimal impact on overall eIF4A protein levels(40). Furthermore, Li et al. didn't report any *in vitro* deubiquitinase assay(s) to support their observations leaving it unresolved whether USP9X may or may not be the direct deubiquitinase regulating the eIF4A1 protein stability.

Employing a blindfold screening protocol to identify the potential inhibitor of Janus kinase pathway, Kapuria et al. reported that WP1130 (also known as degrasyn) irreversible

degraded the JAK1/2 protein(55). Later, it was reported that WP1130 is a partial selective inhibitor of USP9X, USP5, USP14, and UCH37(56). The Dixit group in describing the mechanism of enhanced MCL1 protein levels in follicular lymphoma and DLBCL reported that USP9X removes the K-48 polyubiquitin chain and prevents the protein from undergoing proteasomal degradation(57). Consistently, USP9X was also highly expressed in MM patient with poor prognosis and treatment with WP1130 significantly induced apoptosis in primary cells from patients with Drug-Refractory Multiple Myeloma in a MCL1 (eIF4A regulated gene) dependent manner(58). Similarly, they also reported that USP9X inhibition promotes BCR-Abl (known to regulated eIF4A activity) ubiquitination and apoptosis. Recently, it was reported that USP9X inhibition promotes cell apoptosis in FLT3-ITD AML cells(59). Engel et al. noted that depletion of USP9X significantly reduced the rate of lymphoma development in E μ -Myc mice in a XIAP (eIF4A regulated gene) dependent manner(60).

Thus, USP9X appears to be a critical target in some tumors and perhaps limiting its activity may have broad clinical application. Wp1130 has shown some ability to overcome the drug resistance, albeit under ex vivo conditions. However, the small molecule inhibitor also impacts USP5, USP14, and UCH-L5 supporting a need to generate more specific USP9X inhibitors. Also, USP9X impact on the translational machinery requires further in-depth investigation to define the target(s) regulating the translational readouts.

USP15

USP15 belongs to the USP family of deubiquitinase which shares close homology with USP4 & USP11, and are believed to act as functional paralogues(61). Evolutionary studies by Gray and colleagues proposed that a gene duplication event might have given rise to USP4 and USP15 in higher vertebrates(37). USP15 is most expressed in the cytoplasm and encompasses canonical Cys and His repeats in UBL domains along with DUSP domain in the N terminal region. Similar to USP11, USP15 has also been implicated in regulation of several cellular processes including COP9-signalosome, TGF β and NF κ B pathway(61).

USP15 is the first and only deubiquitinase known which regulates the newly synthesized peptide(s) from the ribosome. Faronato et al. in an unbiased siRNA screen to identify the DUB responsible for the stability of REST (RE1 silencing transcription factor) reported that USP15 regulated the protein half-life (62). REST is a critical protein which maintains stemness and inhibits differentiation, thus protein turnover rate is high which is regulated by β -TRCP mediated degradation(63). Generally, DUBs remove the ubiquitin-tagged from their protein substrate and prevent it from undergoing protein degradation. However, when the Coulson lab explored the precise mechanism, they identified two findings that were challenging; 1) REST is predominantly expressed in nucleus, while USP15 expressed in cytoplasm 2) inhibiting the protein translation, USP15 failed to alter the protein half-life of REST, indicating USP15 doesn't neutralize the β -TRCP mediated degradation, raising an alternative explanation that USP15 might alter the protein translation of REST(62,64). Indeed, the authors established that USP15 deubiquitinates the newly synthesized REST peptide on polysomes and thus aids in the mitotic exit of the cells(62).

The impact of USP15 on cancer has been not well defined. The expression of USP15 is noted to be upregulated in several cancer including lymphoma (65,66). It is known that TGF β upregulates the protein translation of USP15 in a PI3K/Akt dependent manner(67). Conversely, USP15 is also known to stabilize TGF β receptor for sustained cellular proliferation; thus, a feed-forward loop exists between USP15 and TGF β signaling in promoting oncogenesis(68). A recent study by Matsuura and group noted that USP15 augments HCV mRNA translation and thus viral propagation(69). We and others have postulated that HCV infected leads to lymphoproliferative disorder by upregulation of BCR signaling (70–72). Zhou et al. noted that depletion of USP15 in multiple myeloma enhanced the NF κ B transcriptional activity and reduced the rate of apoptosis(73). Importantly, identification of small molecules which modulates USP15 activity will be important to define its physiological function. Crystal structure analysis by Ward et al. highlighted minute differences between the paralogs and noted that mitoxantrone binds and partially inhibits USP15, similar to USP11. These structural insights will provide a strong framework for designing specific small molecule modulators that won't interfere with their functional paralogues(74).

USP21

Ubiquitin specific peptidase 21 (USP21) belongs to the USP family of DUB, cleaving both ubiquitin-conjugated proteins as well as NEDD8 conjugated proteins(75). Apparently, the protein impacts both ubiquitination as well as neddylation associated cellular processes (76). The protein has been studied in numerous tumors and is proposed to stabilize both tumor suppressors and oncogenes; BRCA2(77), MEK2(78), EZH2(79), NANOG(80) and others(81). Consequently, it affects multiple cellular processes including; DDB repair, ERK activity, transcriptional regulation as well maintaining stem cell pluripotency.

Garshott et al. while addressing the reversible ubiquitination of the stalled ribosomes reported that USP21 and OTUD3 (OTU deubiquitinase 3) removes the ubiquitin moieties from RPS10 and RPS20 respectively to re-initiate the translational machinery. Temporal stalling of the ribosomal machinery by reversible ubiquitination reaction provides efficient control in RQC pathway as discussed above. UV induced ribosomal stalling is induced by upregulation of ZNF598 activity which ubiquitinates several residues of the ribosomal complex. Using dual-fluorescence translation stall reporter plasmids, Garshott et al., reported that USP21 antagonizes the ZNF598 mediated ribosomal stalling and promotes the active translational complex formation(82).

Physiological characterization of the USP21 knockout mice revealed that USP21 expression is indispensable for hematopoiesis and lymphocyte differentiation(83). Interestingly, the mice developed spontaneous splenomegaly with equal distribution of dendritic cells, B-cells and T-cells in spleens of the knockout mice(84). Furthermore, USP21 also deubiquitinates GATA3, a transcription factor which limit T_{reg} induced pro-inflammatory responses, and its expression was noted to be upregulated in asthmatic patients(85). Also, USP21 deubiquitinates the dead-domain kinase RIG1 limiting the anti-viral interferon response signaling as well as TNF α induced NF κ B activation(84,86). Contrary to this observation, Tao et al. reported that USP21 stabilizes IL33 and thus activates P65. However, the study

was pursued in HEK293T, which might explain the different results(87). Interestingly, aged USP21 knockout mice exhibit spontaneous T-cell activation which was independent of GATA3 activity (83), indicating the protein might play a significant role in regulating T-cell responses as well TCR signaling. Indeed, using T_{reg} specific deletion of USP21 destabilized FOXOP3 induced T_{reg} cell stability *in vivo*(88).

Collectively, USP21 appears to exert vital regulation in protein quality control as well the inflammatory responses regulated by T-cells. However, its mechanistic link to hematologic malignancies is still unclear. It will be interesting to dissect the molecular function of USP21 in T-cell lymphoma given the protein expression is regulated by TCR signaling(88).

UCHL-1

Ubiquitin carboxy-terminal hydrolase L1 (UCHL-1) is the first discovered deubiquitination enzyme using a candidate gene approach involved in ubiquitin-mediated pathway (89). The protein is abundantly expressed in neurons and testis of mice with lower expression in other tissues but is readily detected in several B-cell malignancies(90,91). UCHL-1 is localized preliminary in cytoplasm and plasma membrane. The protein encodes N terminal C12 peptidase domain, a carboxy-terminal extension and unstructured loop which regulates the protein substrate interactions. UCHL1 efficiently releases amino acids from ubiquitin as well can cleave de-ubiquitin. Since the protein is predominantly expressed in neurons and induced in several cancerous conditions, the functional impact of UCHL-1 expression has been explored in detailed in numerous neurological diseases and other diseases(90).

Recently, Hussain et al. noted that UCHL-1 promotes the eIF4F translation complex formation and augments overall the protein biosynthesis which promotes lymphomagenesis. Using proximity-based proteomics approach, the authors reported that a panel of translation initiation proteins were observed in UCHL-1 proximity proteome supporting a role for the DUB in regulation of protein translation. Indeed, ectopically expressed UCHL-1 was noted to be recruited on the cap complex as well as precipitated with ribosomal subunit (40S, 60S, and 80S), but the recruitment was noted to be reduced upon overexpression on catalytically inactive mutant. Importantly, upon overexpression of UCHL-1, but not its inactive mutant, the recruitment of eIF4F complex protein on the cap was enhanced positioning UCHL-1 as a DUB involved in promoting translational initiation complex. The protein seems to play role in regulation of translation initiation but its substrate(s) on the translational complex are still unknown(92). Since many of these studies were performed with ectopically expressed protein, analysis of the endogenous UCHL-1 on the translational machinery will be essential to understand the physiology as well as the rewired pathological signaling in promoting tumors.

Although expressed at low levels in circulating cells, this enzyme is noted to be upregulated in several hematological cancers including; multiple myeloma, AML, DLBCL and others(66,93,94). The impact of the protein can be appreciated by the observation that transgenic expression in B-cell was sufficient to drive spontaneous B- cell malignancies which were further accelerated in disease models like E μ -Myc(91,95). Indeed, transcriptomic analysis of UCHL-1 driven B-cell lymphoma to that of E μ -MYC and PI3K

overexpressing mice model shows a high degree of similarity in gene expression patterns(92). Further, UCHL-1 downregulated mTOR activity but promotes Akt activity by deregulating PHLPP1 expression(95). UCHL-1 has also been proposed as a biomarker for multiple myeloma disease progression(96).

Future directions

In the past decade, significant progress has been made in delineating the molecular details altered by rewired translational machinery in the hematological cancers. Nevertheless, understanding the mechanisms regulating the protein turnover of the translational complex machinery is still nascent. While Phase I and Phase II clinical studies are underway to study the efficacy of compounds targeting the eIF4F complex demonstrating the feasibility of targeting translational machinery, the underlying processes regulating protein levels and function of translational machinery components is still an underexplored area. We are excited to see robust efforts from multiple research groups striving to delineate the deubiquitinase signature pattern of enhanced protein translation output that upregulates the core ribosomal protein levels/activity. It emerges that DUBs appear to regulate translation initiation, stabilize newly synthesized peptides, stress granules formation, RQC pathway, and ribophagy. However, the involvement of DUBs in regulating the translational process including; elongation, termination, re-initiation and translational machinery/ribosomal recycling is a ripe area for discovery. Conversely, deubiquitinases such as eIF3F(97,98) and OTUD6B(99) are reported to be recruited on the translational machinery but their corresponding substrate(s) on the protein biosynthetic machinery is not yet known (Table 1). Collectively, assessment of DUBs' impact on translational output (Fig. 2) may aid in determining the malignant potential, predict response to specific therapy and lead to refinement of our therapeutic approaches. A number of DUBs appear to be actionable through the use of small molecule inhibitors, at least based on *in vitro* and *ex vivo* studies supporting the further investigation and development of these targeted approaches. Finally, improved understanding of the DUBs associated with the bio-synthetic machinery aided by novel small molecule modulators will generate greater landscape of molecular insights providing knowledge into both their physiological functions as well as providing innovative clinical approaches in the treatment of hematologic malignancies.

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Fig. 1: DUBs on translational machinery.

The model represents the reported deubiquitinase recruited to cap complex and ribosomal machinery in regulation of protein translation. Based on the substrate(s) regulation/stability, we categorized DUBs into four groups. 1) DUBs which modulates translational and ribosomal proteins (USP9X, USP10, USP11, USP21, OTUD3) 2) DUBs which stabilizes the newly synthesized peptides (USP15), 3) Translational machinery proteins which can act DUB on substrate(s) on non-translational machinery proteins (eIF3F) and 4) Others (OTUD6B, UCHL-1) DUBs which are known to be recruited to the translational complex, but their substrates are not known.

Fig. 2: Role of deubiquitinase in protein translation.

The reversible deubiquitinase reaction by several indicated DUBs regulates 1) the proteins stability of translational complex proteins, 2) 43S protein initiation complex formation, 3) stress granules formation, 4) ribophagy, 5) ribosome quality control (RSQ) and 6) stabilizes newly synthesized peptides. Collectively, DUBs appear to have stringent regulation on the translational complex and regulated the overall protein biosynthesis.

Table 1:

Deubiquitinase enzymes involvement in translational regulation

DUB	translational machinery substrate	Ribosome process affected	Cancer-associated activity	Pharmacological inhibitor	Disease reference
USP10	G3BP	Stress granules	AML	HBX19818, P22077	(32–35)
	RPS125	Ribophagy			
	RPS3	RQC			
	eIF4G1	Translation initiation			
USP11	eIF4B	Translation initiation	DLBCL	Mitoxantrone	(40)
			FL		(100)
USP9X	eIF4A1	Translation initiation	DLBCL	WP1130	(57)
			MM		(58)
			AML		(59)
USP15	REST protein	Newly synthesized peptides	Lymphoma	Mitoxantrone	(65,66)
			MM		(73)
USP21	RPS10	RQC	-	-	-
	(eS10)				
OTUD3	RPS20	RQC	-	-	-
	(uS10)				
OTUD6B	-	Translation initiation	-	-	-
eIF3F	-	Translation inhibition	-	-	-
UCHL-1	-	Translation initiation	DLBCL	-	(91)
			Lymphoma		(95)
			MM		(96)