UPS in Human Malignancies

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The ubiquitin proteasome system (UPS) governs the non-lysosomal degradation of oxidized, damaged, or misfolded proteins in eukaryotic cells. This process is tightly regulated through the activation and transfer of polyubiquitin chains to target proteins which are then recognized and degraded by the 26S proteasome complex. The role of UPS is crucial in regulating protein levels through degradation to maintain fundamental cellular processes such as growth, division, signal transduction, and stress response. Dysregulation of the UPS, resulting in loss of ability to maintain protein quality through proteolysis, is closely related to the development of various malignancies and tumorigenesis.

ubiquitin proteasome system | dysregulation | chemoresistance | cancer | therapy | inhibitors

1. The Ubiquitin Proteasome System

The ubiquitin proteasome system (UPS) is essential for the regulation of protein homeostasis and control of eukaryotic cellular processes including cell cycle progression, stress response, signal transduction, and transcriptional activation [1][2]. UPS controls the degradation of approximately 80% of intracellular proteins which are oxidized, damaged, or misfolded in eukaryotic cells [3]. Though the UPS and autophagy are both important systems of degradation of proteins, the sizes of substrates critically influence the choice of degradation pathway [4]. The UPS typically degrades single unfolded polypeptides, whereas autophagy deals with larger cytosolic complexes, cellular aggregates, and organelles.

Degradation of targeted proteins involves a tightly coordinated process where ubiquitin is covalently attached to the substrate protein through the sequential action of three enzymes. Ubiquitin is a small protein comprising 76 amino acids found in all eukaryotic cells [5]. The energy derived from ATP hydrolysis initiates the activation of ubiquitin activating enzyme (E1) allowing the formation of thioester bond between E1 and ubiquitin. This is followed by transfer of ubiquitin from E1 to ubiquitin-conjugating enzyme (E2), forming a thioester bond similar to that of E1. The third final step involves the covalent attachment of ubiquitin to lysine residues of target protein, catalyzed by ubiquitin ligase (E3) [6]. The 26S proteasome complex comprises a core 20S proteasome and one or two units of the regulatory 19S proteasome (Figure 1). Once a target protein has been modified with a polyubiquitin chain, it is recognized by the 19S proteosome which removes the polyubiquitin chain and the protein is then unfolded and translocated into the 20S proteasome where it is degraded into short peptides [7]. While polyubiquitination has been associated with protein clearance through proteasomal degradation, mono-ubiquitination, which involves the

addition of a single ubiquitin moiety to the substrate protein, is shown to affect a range of cellular processes including kinase activity, epigenetic regulation, protein translocation, and DNA damage signaling [8][9].

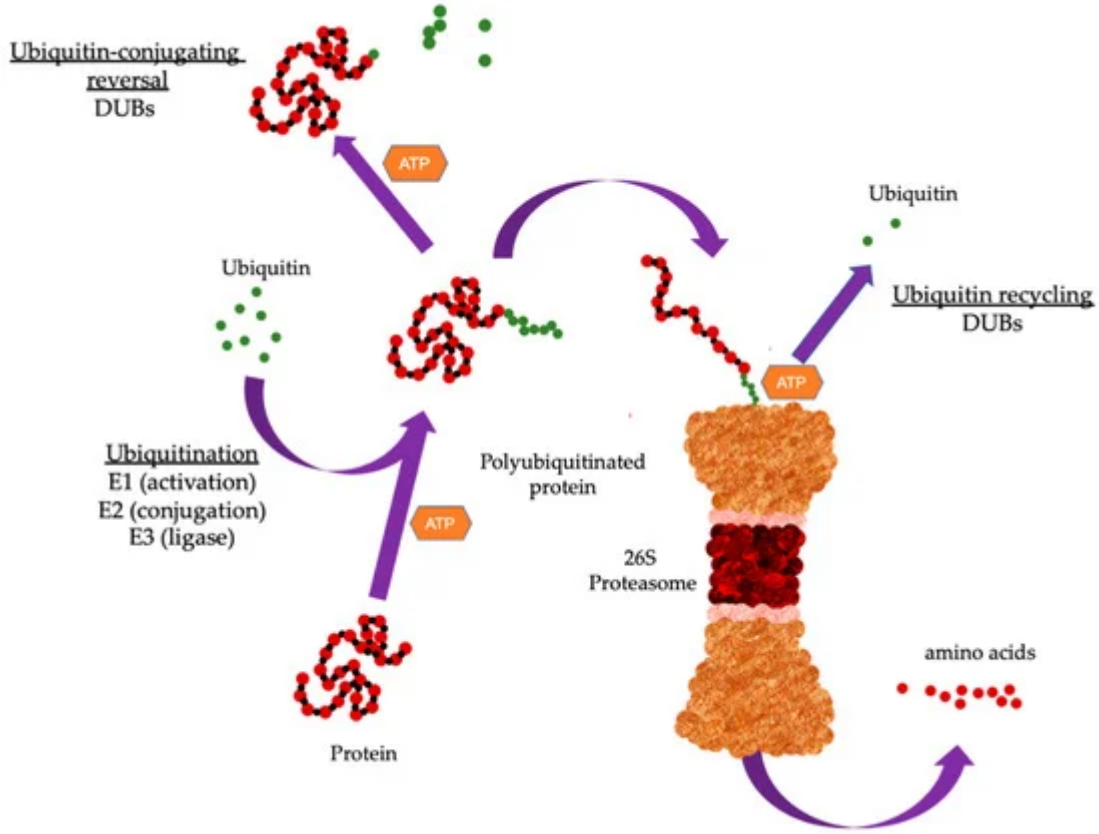

Figure 1. Overview of the ubiquitin proteasome system (UPS). The UPS cascade. Substrate protein is ubiquitinated through the sequential action of three enzymes. E1 binds to activated ubiquitin and is transferred to the ubiquitin-conjugating enzyme (E2). The E2 carries the activated ubiquitin to ubiquitin ligase (E3), which then facilitates the transfer of ubiquitin from E2 to a lysine residue in the target protein. Proteins can be modified with a single mono-ubiquitin molecule, or with ubiquitin chains of different lengths and linkage types. Substrate proteins modified with specific chains are recognized and subsequently degraded by the 26S proteasome. Deubiquitinating enzymes (DUBs) remove ubiquitin from substrate proteins by removing mono-ubiquitination or by trimming or removing the ubiquitin chain. Typically, poly-ubiquitination has been associated with protein clearance through proteasomal degradation while mono-ubiquitination which involves the addition of a single ubiquitin moiety to the substrate protein affects cellular processes.

Ubiquitin contains seven important lysine residues which can be ubiquitinated (K6, K11, K27, K33, K48, and K63) and can form polyubiquitin chains. The two best characterized ubiquitin linkages are K48 and K63 where K48 polyubiquitination targets proteins for degradation by the 26S proteasome complex [10] and K63 participates in DNA damage signaling and recruits DNA repair proteins to damage sites [11]. Protein ubiquitination can be reversed through the removal of ubiquitin from target proteins by deubiquitinating enzymes (DUBs), and this rescues protein

destined for degradation. DUBs have also been implicated in the maturation, recycling, and editing of ubiquitin [12][13][14]. Further, chain configuration and linkage can endow ubiquitin with additional roles through the formation of more complex topologies with unknown activities [15]. Dysregulation or abnormal UPS function is frequently seen in various human malignancies and this identifies the aberrant components of the UPS as potential drug targets [16][17]. This review endeavors to present recent literature on the functional roles of UPS in human cancers. We cover how the dysregulation of UPS components may function either as an oncogene or tumor suppressor and affects cellular signaling in tumors. Further, we present current small inhibitors against the UPS and highlight issues that has severely restricted its development.

Increasing evidence demonstrate ubiquitin enzymes are important in carcinogenesis. Though there are numerous cancer-related studies on these enzymes, a large majority primarily focuses on E3 ligases. Studies on E1-activating enzymes have been largely used to identify potential targets in UPS inhibition in cancer while studies on E2-conjugated enzymes revealed their involvement in cell cycle progression, DNA repair, and regulation of oncogenic signaling pathways during tumorigenesis [18][19]. Further E2 enzymes are often found upregulated and highly correlated with poor prognosis in various malignancies including the pancreas, lung, breast, skin, and thyroid [20]. Currently, eight E1s, > 40 E2s, and > 600 E3s have been identified in the human proteome [21].

2. Dysregulation of UPS in cancer

2.1. E2 enzymes

The ubiquitin-conjugating E2 family comprises > 40 members, and modulates protein stability and ubiquitination through the conjugation of ubiquitin to target proteins [22]. E2-conjugating enzymes are also found dysregulated in cancers and reported to be potent mediators contributing towards multiple tumorigenic processes including migration/invasion, proliferation, drug resistance, radiation resistance, cell cycle, apoptosis, and stimulation of oncogenic pathways. Examples of dysregulated E2 enzymes in cancer are summarized in Table 1

Table 1. Summary of the functions of E2 and E3 enzymes in human cancers described in this review.

Family	Name	Role	Cancer Type	Function	Test Model	Reference
E2	UBE2C	Oncogene	Gastric	Chromosomal stability, Proliferation, Migration, Invasion	In vitro, In vivo	[23]
		Oncogene	Colon	Cell cycle, Proloferation	In vitro	[24]
		Oncogene	Colorectal	Proliferation, Invasion	In vitro	[25]

Family	Name	Role	Cancer Type	Function	Test Model	Reference
		Oncogene	Thyroid	Proliferation	In vitro	[26]
		Oncogene	Breast	Proliferation, Drug resistance, Radiation resistance	In vitro	[27]
		Oncogene	Liver	Proliferation, Drug resistance, Migration, Invasion	In vitro	[28]
		Oncogene	Non-small cell lung	Drug resistance	In vitro	[29]
	UBE2Q1	Oncogene	Colorectal	Proliferation		[30]
		Oncogene	Liver	p53 signaling, Cell cycle	In vitro	[31]
		Oncogene	Breast	p53 signaling	In vitro	[32]
	UBE2S	Oncogene	Endometrial	SOX6/β-catenin signaling, Proliferation	In vitro	[33]
		Oncogene	Lung adenocarcinoma	Proliferation, p53 signaling, Apoptosis	In vitro	[34]
		Oncogene	Liver	p53 signaling, Cell cycle	In vitro	[35]
E3	FBW7	Tumor suppressor	Burkitt's lymphoma	c-Myc signaling	In vitro	[36][37]
		Tumor suppressor	Chronic myelogenous leukemia	c-Myc signaling	In vitro, In vivo	[38]
		Lipogenesis	Lung, Melanoma, Thyroid, Cervical	mTORC2/SREBP1 signaling	In vitro	[39]
		Tumor suppressor	T cell leukemia	Notch signaling	In vitro, In vivo	[40]
		Tumor suppressor	Colorectal	c-Myc signaling, Cell cycle	In vitro	[41]
		Tumor	Esophageal	c-Myc signaling	In	[42]

Family	Name	Role	Cancer Type	Function	Test Model	Reference
		suppressor	squamous cell		vitro	
		Tumor suppressor	Colorectal, Cervical, Ovarian, Non-small cell lung	Apoptosis (via Mcl1)	In vitro	[43]
	MDM2	Oncogene	Neuroblastoma	p53 signaling	In vitro, In vivo	[44]
		Oncogene	Cervical	Cell cycle, Apoptosis	In vitro	[45]
		Oncogene	Liver	Metastasis, Drug response	In vitro, In vivo	[46]
	Cdc20	Oncogene	Breast	Metastasis, Drug response	In vitro	[47]
	Cdh1	Tumor suppressor	Breast	Src signaling	In vitro	[48]
	β-TRCP	Tumor suppressor	Breast, Prostate	MTSS1 signaling	In vitro	[49]
		Oncogene	Lung	FOXN2	In vitro, In vivo	[50]
[55]		Tumor suppressor	Papillary thyroid	VEGFR2 signaling	In vitro, In vivo	[51]
	E6AP	Oncogene	Prostate	Radiation response	In vitro	[52]
		Oncogene	Prostate	p27 signaling	In vitro, In vivo	[53]
		Oncogene	Prostate	Metastasis	In vitro, In vivo	[54]

tin chains into four s are the sting new E3 ligases including mples of

y are still unknown [56][57]. USPs are, by far, the largest class of DUBs, com- prising ~60 human proteases with most containing several domains apart from the catalytic domain. Conserved sequences among these proteases are restricted to the catalytic domain which is designated by the catalytic motif containing Cys, His, and Asp (or Asn) residues. Conserved catalytic domains are thought to be important for substrate specificity, catalytic activity regulation, and mediating protein–protein interaction to each USP. Dysregulated DUBs in cancer are hence potential drug targets. The challenge in the development of drugs is the difficulty in designing a specific inhibitor for a single DUB. 3D crystallography structures of catalytic domains of USP2, USP7, USP8, and USP14 reveal a

remarkable structural conservation of their active site shared among these enzymes, thus providing evidence that the development of inhibitors may prove to be challenging [58][59][60]. Further, the crystal structures show that the catalytic domains are in inactive conformation prior ubiquitin binding suggesting an alternative target for intervention. Apart from deubiquitination, DUBs have been shown to modulate cellular processes in human malignancies including DNA damage response, oncogenic signaling cascades, drug resistance, apoptosis, cell cycle, immunomodulation, and invasion/migration. Examples of dysregulated DUBs in cancer are summarised in Table 2.

Table 2. Summary of the functions of DUB enzymes described in this review.

Name	Role	Cancer Type	Function	Test model	Reference
BAP1	Tumor suppressor	Lung, Osteosarcoma, Colon	DNA double-strand repair	In vitro	[61][62][63]
	Tumor suppressor	Renal	Ferroptosis signaling	In vitro	[64]
USP7	Oncogene	Lung	p53 signaling	In vitro, in vivo	[65]
	Oncogene	Cervical	Self-renewal; Foxp3 signaling	In vitro	[66]
	Oncogene	Non-small cell lung	Immune Response; Foxp3 signaling	In vitro	[67]
USP22	Oncogene	Lung	Cell Cycle	In vitro	[68]
	Oncogene	Lung adenocarcinoma	EGFR-TKI resistance	In vitro, in vivo	[69]
	Oncogene	Colon	CCNB1 signaling	In vitro, in vivo	[70]
	Oncogene	Glioblastoma	KDM1A signaling	In vitro, in vivo	[71]
UCHL1	Oncogene	Breast	Drug resistance; Invasion/migration	In vitro	[72]
Ataxin 3	Oncogene	Breast, Osteosarcoma, Cervical, Colorectal	DNA	In vitro	[73]
	Oncogene	Testicular	mTOR/Akt signaling	In vitro	[74]
PSMD11	Oncogene	Cervical. Osteosarcoma	DNA damage response	In vitro	[75]

	Oncogene	Lung, Prostate, Colorectal, Breast, Cervix	Cell cycle	In vitro	[76]
	Oncogene	Liver	E2F1 signaling	In vitro, in vivo	[77]
A20	Tumor suppressor	Colorectal	Apoptosis signaling	In vitro	[78]
	Tumor suppressor	Diffuse large B-cell lymphoma	NF-kβ signaling	In vitro	[79]
	Tumor suppressor	Sarcoma	NF-kβ signaling	In vitro	[80]

3. UPS Inhibitors in Cancer therapy

The progress in targeting the UPS has been slow and this delay has been attributed to the following reasons. First, most components of the ubiquitin system do not possess a well-defined catalytic pocket to allow binding of small inhibitors. Second, the ubiquitination process relies on the dynamic rearrangement of multiple protein–protein interactions that traditionally have been challenging to disrupt with small molecule inhibitors. Third, components of the UPS are shown to possess both oncogenic and tumor suppressor properties due to the complexity of their regulatory cellular processes. Despite these challenges, components of the UPS have been considered as attractive targets for cancer treatment. In the following sections, we introduce some inhibitors against components of the UPS that have been tested in preclinical and clinical studies as summarized in Table 3.

Table 3. Summary of UPS inhibitors which are FDA-approved and/or tested in clinical trials described in this review.

Inhibitor	Target	Cancer Type	Clinical Trial	Reference
Bortezomib	Proteasomal inhibitor	Multiple myeloma, Mantle cell lymphoma, Leukemia, Neuroblastoma, Head and Neck, Thyroid, Hepatocellular	FDA approved	www.clinicaltrials.gov [81][82][83][84][85][86][87][88]
Carfilzomib	Proteasomal inhibitor	Multiple myeloma, Lymphoma, Relapsed and/or refractory multiple myeloma, Leukemia, Lung, Thyroid, Refractory renal cell carcinoma	FDA approved	www.clinicaltrials.gov [52][89][90][91][92][88]
Ixazomib	Proteasomal inhibitor	Multiple myeloma, Relapsed and/or refractory multiple myeloma, Lymphoma,	FDA approved	www.clinicaltrials.gov [93]

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Inhibitor	Target	Cancer Type	Clinical Trial	Reference
		Leukemia, Breast, Glioblastoma, Renal cell carcinoma, Hodgkin and T cell lymphoma		
Delanzomib	Proteasomal inhibitor	Non-Hodgkin's lymphoma	Phase I	www.clinicaltrials.gov
Marizomib	Proteasomal inhibitor	Multiple myeloma, Advanced solid tumors	Phase I/II	www.clinicaltrials.gov
Oprozomib	Proteasomal inhibitor	Multiple myeloma, Glioma, Pancreatic, Lung, Melanoma, Lymphoma, Glipblastoma	Phase I/II/III	www.clinicaltrials.gov
MLN4924	NAE and UBA1(E1)	Advanced malignant solid tumors, Melanoma, Hepatocellular, B cell lymphoma, Hematologic malignancies, Acute myelocytic leukemia	Phase I/II/III	www.clinicaltrials.gov
TAK981	SAE (E1)	B cell lymphoma, colorectal, non-Hodgkin's, Advcnced/metasiatic solid tumors	Phase I/II	www.clinicaltrials.gov
TAS4464	NAE (E1)	Multiple myeloma, non-Hodgkin lymphoma	Phase I/II	www.clinicaltrials.gov
SAR-405838	MDM2 (E2)	Solid tumors	Phase I	www.clinicaltrials.gov [87][94]
CGM-097	MDM2 (E2)	Advanced p53 wildtype solid tumors	Phase I	www.clinicaltrials.gov [95][96]
DS-3032b	MDM2 (E2)	Acute myelocytic leukemia	Phase I/II	www.clinicaltrials.gov [97][98]
Debio1143 (AT-406)	cIAP1/2 (E3)	Acute myeloid leukemia	Phase I	www.clinicaltrials.gov [99]
LC-161	IAP (E3)	Advanced solid tumors	Phase I	www.clinicaltrials.gov [100]
Birinapant	IAP (E3)	Solid tumors	Phase I/II	www.clinicaltrials.gov [101]
Pimozide	USP1	Glioma, Non-small cell lung cancer	FDA approced for Tourette's	[102][103]

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Inhibitor	Target	Cancer Type	Clinical Trial	Reference
			syndrome; Preclinical	
Mitoxantrone	USP11	Metastatic crastrate -resistant prostate, Acute myeloid leukemia, Advanced breast cancer, non-Hodgkin's lymphoma, Primary liver	FDA approved	[104][105][106][107][108][109][110][111][112]

components. This shows that there is an untapped potential for the devel-opment of drugs against other components of the UPS. Thus, ubiquitin activating steps, E2, E3 and DUBs can be exploited for inhibition [113][114]. Unfortunately, most of these inhibitors show good efficacy in culture models but less so in animal models and clinical trials [115][116][117]. Traditionally, the ubiquitin activating steps and degrading proteasome have the greatest potential due to presence of well-defined active pockets that lend to issues of substrate specificity. The other UPS components however do not possess defined pockets for targeting with small inhibitors. Hence, delay in the development of successful UPS inhibitors can be attributed to the lack of knowledge of target protein structures and identifiable activity pockets for inhibitor binding. Advances in technology such as computer-aided design, mass spectrophotometry and high throughput screening may aid in the identification of suitable candidates. Further, the occurrence of oncogenic signaling together with aberrant UPS activity may affect the success of future UPS inhibitors. Nevertheless, a greater effort is required to elucidate the functions of aberrant UPS at both preclinical and clinical levels to better understand their roles in human malignancies to develop alternative paradigms for therapeutic intervention.

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