Review

Progress in Anticancer Drug Development Targeting Ubiquitination-Related Factors

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Abstract: Ubiquitination is extensively involved in critical signaling pathways through monitoring protein stability, subcellular localization, and activity. Dysregulation of this process results in severe diseases including malignant cancers. To develop drugs targeting ubiquitination-related factors is a hotspot in research to realize better therapy of human diseases. Ubiquitination comprises three successive reactions mediated by Ub-activating enzyme E1, Ub-conjugating enzyme E2, and Ub ligase E3. As expected, multiple ubiquitination enzymes have been highlighted as targets for anticancer drug development due to their dominant effect on tumorigenesis and cancer progression. In this review, we discuss recent progresses in anticancer drug development targeting enzymatic machinery components.

Keywords: ubiquitination; cancer; drug target

1. Mechanisms of Ubiquitination

In the process of ubiquitination, ubiquitin (Ub) protein is covalently attached to substrate proteins either as a monomer (monoubiquitination) or as a polymer chain (polyubiquitination). Monoubiquitination simply adds a single Ub to one or multiple lysine (K) residues of substrates. Polyubiquitination modifies proteins with the C-terminal glycine residue of the Ub (Ub-G76), which is linked with one K residue of the proximal Ub via an isopeptide bond. All K residues in Ub, including K6, K11, K27, K29, K33, K48, and K63, can serve as a linkage site. Of note, in some particular cases, Ub can be conjugated to non-K residues, such as methionine-1 (M1), cysteine (C), serine (S), threonine (T), and tyrosine (Y) [1–4]. A poly-Ub chain is generally homogenous where all the Ub units are linked through the same residue sites. Of note, atypical types of poly-Ub chains are observed in eukaryotic cells [5,6], including mixed and branched poly-Ub chains. In mixed poly-Ub chains, the Ub units employ distinct residues for linkage [7], while branched poly-Ub chains contain a Ub unit providing more than one K residue concurrently for linkage formation (Figure 1) [1–4]. Upon ubiquitination, protein stability or activity is modified, and the linkage types largely decide the fate of substrates [8]. In general, mono-Ub, K6-, K11-, K29-, and K48-linked poly-Ub chains generally act as a "death label" for proteins and drive them for proteasome or lysosome-mediated degradation [9,10]. K63-linked poly-Ub chains usually regulate the activity and subcellular localization of substrate proteins [11–13]. Interestingly, the same Ub linkage could result in distinct outcomes. For instance, the K63-linked poly-Ub chain plays a role of a degradation inducer for octamer-binding transcription factor-4 (Oct4) in mouse embryonic stem cells [14–16]. The K11-linked poly-Ub chain does not serve as a "death label" for β-catenin but increases its stability in human colorectal cancer cells [17,18].

Ubiquitination is achieved by three types of enzymes, including the Ub activating enzyme E1, Ub binding enzyme E2, and Ub ligase E3. In this process, E1 produces the Ub–adenosine monophosphate (Ub–AMP) intermediate through ATP-dependent adenylation at Ub-G76. Next, the Ub–AMP attacks the E1 active C site via nucleophilic reaction. A thioester bond forms between the E1 and Ub-G76 accompanying AMP release [19]. Subsequently,

E2 mediates a transthiolation reaction to accept Ub at its active C site. At the final step, an E3 ligase simultaneously associates with the E2-Ub and a protein substrate, mediating isopeptide bond formation between the Ub and the substrate [8,20,21]. During this process, E2s largely decide the length and topological structure of Ub chains, while E3s usually specifically recognize substrates through protein–protein interactions [20,22]. In human cells, there are two E1s, 40 E2s, and over 600 E3s [23–25]. All E2s are characterized by a ~150 amino acid enzymatic UBC domain with the active site C. Those E2s only possessing the UBC domain in sequence are grouped as class I, while class II and III E2s additionally possess an extended C- and N-terminus, respectively. Class IV E2s contain extension regions at both ends. The extension regions usually regulate subcellular localization of E2s and mediate their interaction with other partners [25,26]. E3s can be divided into three types based on their sequences and Ub transferring mechanisms, including the really interesting new gene (RING)-type, homologous to the E6-AP COOH terminus (HECT)-type and RING between RING (RBR)-type E3s [27]. The RING-type E3s contain a characteristic RING or U-box domain with a similar RING finger fold in the structure. In the process of Ub transfer, the RING-type E3s directly hand over Ub from the E2s to the substrates [27], during which the RING domain, rather than the U-box, displays zinc ions (Zn^{2+}-dependent). To date, more than 500 RING-type E3s have been identified [27]. There are nearly 30 HECT-type E3s encoded in human cells [28]. In addition to the catalytic HECT domain, these E3s usually contain a variable N-terminal domain responsible for substrate recognition [29]. According to the sequences of the N terminus, HECT-type E3s can be further divided into three groups, including the WW domain-containing neuronal precursor cell-expressed developmentally downregulated 4 (Nedd4)/Nedd4-like E3s, HERC (HECT and RCC1-like)- and RLD (RCC1-Like domains)-containing E3s, and the HECT-type E3s without WW and RLD domains [30]. During ubiquitination, HECT E3s achieve Ub transfer through a two-step reaction. Firstly, Ub is transferred from E2 to the catalytic C site of E3 to form a HECT–Ub thioester intermediate. Next, the Ub is ligated to the substrates [27]. In human cells, there are 14 RBR-type E3s encoded, all of which are featured by two conserved Zn^{2+}-binding RING domains, RING1 and RING2 [31]. RBR-type E3s employ similar two-step reactions loading Ubs to substrates despite the absence of HECT domains, which attributes to the catalytic active site of C in RING2 [32].
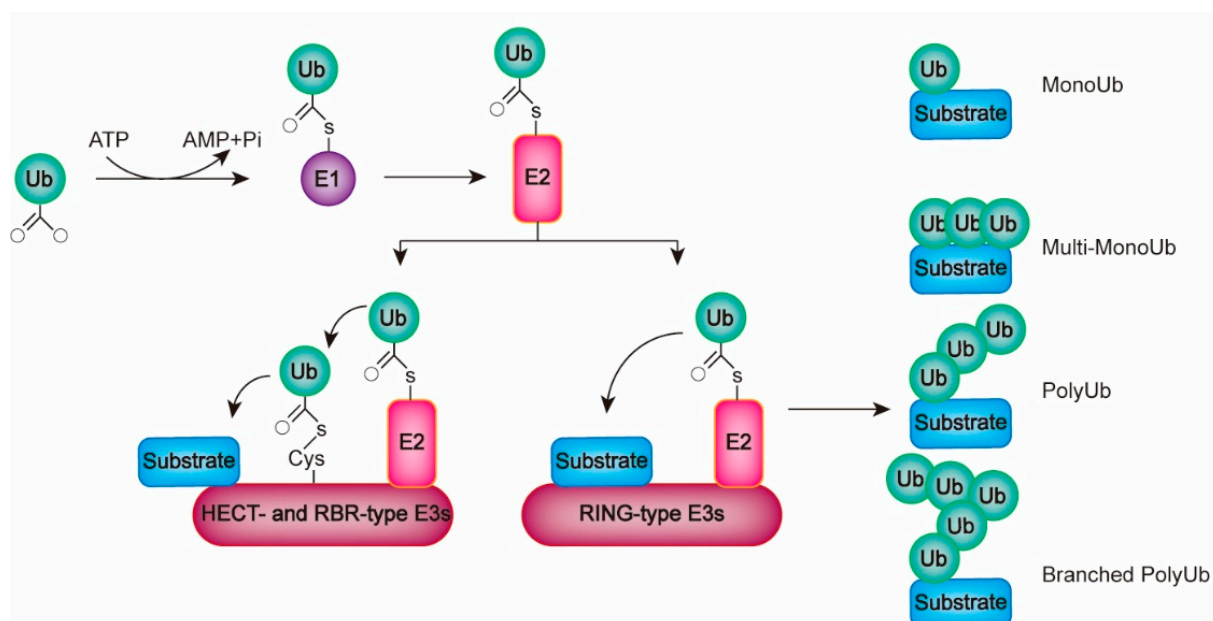

Figure 1. The ubiquitination machinery. Ubiquitination is achieved through the sequential activity of E1, E2, and E3. RING-type E3s can mediate a direct ligation of Ub from E2s to substrates, whereas HECT-/RBR-type E3s require two-step reactions. Typical types of Ub linkages include MonoUb, multi-MonoUb, poly-Ub, and branched poly-Ub.

Ubiquitination is widely involved in various biological processes, such as ribosome function [33], DNA replication [34,35], transcription [36], and inflammatory response [37]. Abnormal ubiquitination of key proteins could cause severe illnesses, such as metabolic disorder, inflammation, degenerative diseases, and malignant cancers [38]. Thus, targeting the ubiquitination process for drug development to achieve improved disease therapy, especially in the anticancer field, has become a research hotspot in recent years.

2. Cancer-Related Ubiquitination Factors

2.1. E1

The ubiquitin proteasome system (UPS) is an important process regulating protein homeostasis. Inhibition of E1 UAE can cause the accumulation of misfolded proteins in the endoplasmic reticulum, thereby destroying the homeostasis of the endoplasmic reticulum and allowing cells to enter the process of apoptosis [39,40]. This strategy appears effective to treat B-cell lymphoma and malignant hematological diseases (Table 1) [39,40]. Furthermore, UAE inhibition can stabilize some tumor suppressors, such as p53, thus delaying the progress of cancer development [41,42]. There is also evidence showing that this inhibition activates the NF-κB signaling pathway so as to suppress malignant tumor growth [43].

2.2. E2-Ubiquitin-Conjugating Enzyme 2C (E2-Ube2c)

Ube2c gene is located on chromosome 20q13.12 encoding a 179 amino acid E2 with a molecular weight of 19 kDa. It cooperates with the anaphase promoting complex/cyclome (APC/C) E3 complex to polyubiquitinate proteins for degradation [44,45]. The activity of Ube2c (Table 1) is involved in cell-cycle regulation and loss of genetic stability [46]. In cancer cells, Ube2c inhibits apoptosis and enhances tumor growth [47]. Ube2c overexpression has been detected in various cancers, such as hepatocellular carcinoma [48], esophageal cancer [49,50], and breast cancers [51,52]. In gastric cancer cells, Ube2c inhibition interrupts cell-cycle progression, while its elevation enhances cancer cell proliferation [47]. In rectal cancers, siRNA-mediated *Ube2c* depletion induces apoptosis and inhibits cell proliferation, further disturbing cancer growth and invasion [44].

2.3. E3s

2.3.1. Glycoprotein 78 (Gp78)

Gp78 is evolutionarily conserved and encodes a transmembrane glycoprotein possessing the leucine zipper motif and RING domain mediating E3 ligase activity [53,54]. Gp78 is localized on the endoplasmic reticulum membrane and interacts with endoplasmic reticulum-associated degradation (ERAD) E2s via the C terminus of its RING domain [55,56]. Gp78 promotes tumor metastasis and proliferation [57]. In sarcomas, Gp78 interacts with the transmembrane metastasis inhibitor KAI1 (also known as CD82), and inhibition of Gp78 can promote the accumulation of KAI1, lead to apoptosis, and reduce tumor metastasis (Table 1) [58].

2.3.2. Mouse Double Minute 2/Human Homolog of Mouse Double Minute 2 (MDM2/HDM2)

Tumor protein p53 (TP53) (also known as p53) is a tumor suppressor widely involved in critical signaling pathways, including autophagy, aging, differentiation, proliferation, DNA repair, and tumorigenesis [59–64]. p53 dysfunction is closely related to human cancers and neurodegenerative diseases [65,66]. Deletion in the *p53* gene aggravates deterioration of cancers [67–70]. RING-type E3 MDM2 binds to p53 through its N terminus to ubiquitinate p53 protein [71–73]. MDM2 mediates multiple monoubiquitination of p53 to promote its nuclear export to cytoplasm for proteasomal degradation [74]. MDM2 can also modify p53 via poly-Ub chain for degradation in the nucleus [75,76]. Furthermore, MDM2 binds to the transactivation domain of p53 and inhibits its transcriptional activity [77]. The activity of MDM2 in repressing p53 determines its oncogenetic effect. It has been shown that MDM2 displays an elevated expression in various human cancers, such as osteosarcoma,

neuroblastoma, lung cancer, colon cancer, breast cancer, and liver cancer, where it enhances p53 degradation, leading to poor survival and prognosis of patients (Table 1) [78–80]. In fact, in addition to MDM2, multiple RING-type E3s are involved in regulating p53 levels, including constitutive photomorphogenesis protein 1 (COP1), p53-induced protein with a RING-H2 domain (Pirh2), and co-chaperone carboxyl terminus Hsp70/90-interacting protein (CHIP). These E3s ubiquitinate p53 to inhibit its function and, thus, promote cancer development [81].

2.3.3. SCF^{Skp2} Complex

The RING-type E3 complex Skp1–Cul1–Skp2 (SCF^{Skp2}) is composed of multiple subunits including F-box protein S-phase kinase-associated protein 2 (Skp2), Cullin 1 (Cul1), Ring box 1 (Rbx1, also known as Roc1), and Skp1. Cul1 serves as a rigid scaffold to allow assembly of Rbx1 and Skp1 [82,83]. Rbx1 recruits E2 through its RING domain and constitutes the catalytic center with Cul1 to allow direct transfer of Ub to substrates [82]. Skp1 provides a docking site for Skp2. Skp2 specifically recognizes substrates via its F-box domain [84]. Skp2 (Table 1) is oncogenetic. Deficiency in Skp2 inhibits the development of breast cancer [85]. Several substrates have been identified to mediate its roles in tumorigenesis and malignancy. For instance, it ubiquitinates serine/threonine kinase Akt with K63-linked poly-Ub chain in the process of tumorigenesis. Cancers can also occur with enhanced degradation of forkhead box O1 (FOXO1) by Skp2 [86,87]. Transcriptional coactivator yes-associated protein (Yap) promotes tumor growth and metastasis [88]. Deletion of Yap can inhibit the development of breast cancer [89]. Skp2 can promote its activity through ubiquitination with K63-linked poly-Ub chain [90]. MutT homolog-1 (MTH1) is a nucleotide pyrophosphatase that oxidizes dNTPs to protect genomic DNA and prevents reactive oxygen species (ROS)-induced cytotoxicity in cancers [91,92]. In melanoma cells, MTH1 can be regulated by Skp2-mediated K63 polyubiquitination, which stabilizes MTH1 protecting DNA integrity [93].

2.3.4. Inhibitor of Apoptosis-Related Proteins (IAPs)

IAPs are RING-type E3s [94]. The human genome encodes five IAPs proteins in total, which are X-linked inhibitor of apoptosis (XIAP), cellular inhibitor of apoptosis proteins 1 and 2 (cIAP1/2), melanoma-inhibitor of apoptosis (ML-IAP), and inhibitor of apoptosis-like protein-2 (ILP2). In addition to catalytic C-terminal RING domains, their characteristic sequence is the baculoviral IAP repeat (BIR) responsible for protein–protein interaction [95–98]. IAPs are involved in regulating diverse biological processes, including apoptosis, immune response, cell cycle, and migration [99,100]. Many types of human cancers display overexpressed IAPs that enhance tumor growth. For instance, IAPs (Table 1) repress apoptosis of melanoma cells for uncontrollable growth [101]. In contrast, there is evidence showing a putative role of IAPs as a tumor suppressor since cIAP deficiency constitutively activates NF-κB signaling in malignant hematopoietic cancer cells [102].

2.3.5. WW Domain-Containing E3 Ubiquitin Protein Ligase 2 (Wwp2)

Wwp2 (also known as AIP-2, atrophin-1-interacting protein 2) is an HECT-type Nedd4 family E3 [103]. In addition to the HECT domain at the C terminus, Wwp2 contains a C2 domain at the N terminus and a tryptophan–tryptophan (WW) domain in the middle [104]. The WW region specifically recognizes phosphorylated PPxY motif-containing substrates [105]. One of the dominant substrates of Wwp2 is tumor suppressor phosphatase and tensin homolog (PTEN). PTEN is a lipid phosphatase [106]. It can inhibit tumor occurrence by repressing the PI3K/Akt pathway, and it plays an important role in cell survival and apoptosis regulation [107]. Mutations in PTEN can be observed in breast/prostate cancers and other human diseases [108–110]. Wwp2 can bind with the phosphatase domain of PTEN to promote its ubiquitination and degradation. In addition, another HECT-type E3 neural precursor cell expressed developmentally downregulated 4-1 (Nedd4-1) is involved in mediating PTEN polyubiquitination for degradation (Table 1) [104,110,111].

Table 1. Ubiquitination factors involved in cancer regulation.

Ubiquitination Factors	Cancer Types	References
UAE	B-cell lymphoma and malignant hematological diseases	[39,40,43]
Ube2c	Hepatocellular carcinoma, esophageal cancer, breast cancers, and gastric cancer	[47–52]
Gp78	Sarcomas	[58]
MDM2/HDM2	Osteosarcoma, neuroblastoma, lung cancer, colon cancer, breast cancer, and liver cancer	[78–80]
SCF^{Skp2} complex	Breast cancer and melanoma cells	[85–89]
IAPs	Melanoma cells and malignant hematopoietic cancer	[101,102]
Wwp2	Breast cancer and prostate cancer	[108–110]

3. Drug Development Targeting Ubiquitination-Related Factors

Since ubiquitination largely determines the stability and activity of proteins, it could be effective to develop drugs specifically targeting this process so as to achieve a better therapeutic effect. This has been become a hotspot in the field of disease therapy. These drugs can be derived from small molecules, peptides/proteins, or oligonucleotides [112]. The strategy to identify candidate targets for drug development requires combining computer-aided drug design methods and a high-throughput dataset of disease-related transcriptomes, drug responses, protein interactomes, and drug–target networks [113,114].

3.1. Proteinase Inhibitors

To date, three protease inhibitors have been approved by the Federal Drug Administration (FDA), bortezomib, carfilzomib, and ixazomib (Table 2). They are used to treat multiple myeloma [115–117]. Peptide borate inhibitor bortezomib blocks the chymotrypsin-like activity of the 26S proteasome to treat multiple myeloma patients [118–121]. Of note, use of bortezomib alone generally results in severe side-effects, which can be minimized through combining other drugs [122,123]. Bortezomib was also approved by FDA to treat mantle cell lymphoma [124]. Currently, use of bortezomib for other cancer types, such as autoimmune hemolysis and colon cancer, is under clinical trials [125,126].

Tetrapeptide epoxyketone carfilzomib selectively binds to the 26S proteasome to inhibit the activities of chymotrypsin-like protein, leading to accumulation of ubiquitinated substrates. In 2012, carfilzomib was approved by the FDA for clinical therapy of multiple myeloma [115,116,127–129]. Carfilzomib is currently at the stage of clinical trial for treatments of multiple cancers including neuroendocrine cancer, kidney cancer, lymphoma, acute myeloid, acute lymphoblastic leukemia, amyloidosis, and small-cell lung cancers [130].

Ixazomib (MLN2238, Ninlaro) is a boric acid derivative that inhibits chymotrypsin-like activity of 20S proteasome [130–132]. Compared with bortezomib, ixazomib displays a stronger antitumor effect [132]. Strikingly, treatment combining ixazomib and lenalidomide/dexamethasone can significantly increase the survival rate of myeloma patients [133]. Furthermore, ixazomib has completed a stage I clinical trial for glioblastoma, as well as a stage II clinical trial for malignant myeloid and lymphoid hematological cancers [130].

In addition to bortezomib, carfilzomib, and ixazomib, other protease inhibitors, such as marizomib, oprozomib, and delanzomib, are undergoing clinical trials for multiple myeloma and other cancers [115].

3.2. Drug Development Targeting the E1 Enzyme

Mammal genomes encode two E1s: UAE (also known as UBE1) and UBA6. Tak-243 (also known as MLN7243) is a small-molecule inhibitor specifically targeting UAE. Its application can reduce the overall mono- and polyubiquitination levels of cancer cells, leading to cancer cell death through an impaired cell-cycle process and accumulated DNA damage (Table 2) [134,135]. Tak-243 is currently undergoing clinical trials to treat refractory acute myeloid leukemia, refractory myelodysplastic syndrome, and chronic myelomonocytic leukemia [130].

3.3. Development of Drugs Targeting E3 Ligases

Generally, small0molecule drugs are designed using a lock-and-key mechanism to specifically target disease-related proteins. This strategy usually requires target proteins possessing a proper pocket region in structure as a binding site for small molecules. For those targets lacking unique pockets, two key strategies can be employed. First of all, proteolysis-targeting chimera (PROTAC) technology is a useful platform driving target proteins for degradation. The heterogeneous chimera is mainly composed of two important components, including one small-molecule ligand to specifically bind its target protein and one ligand to recruit an E3 to mediate ubiquitination of the captured protein for degradation [136–139]. Two examples designed using PROTAC with E3 cereblon (CRBN) as a ligand are Arv-110 and Arv-471 (Table 2) that are currently at the clinical trial stage. Arv-110 targets androgen receptor to treat metastatic castration-resistant prostate cancer (mCRPC), while Arv-471 targets estrogen receptor to treat breast cancer [130,138]. Although PROTAC technology is promising to develop drugs for human diseases, the sizes of molecules designed are always big. Moreover, choices of small-molecule ligands with high specificity in capturing E3 ligases are relatively limited. Another attractive strategy is represented by molecular glue degraders. They are small molecules that can modify molecular surface and, thus, enable novel interactions between targeted proteins and E3s, achieving ubiquitination-mediated protein degradation [140]. Compared with PROTAC, molecular glue degraders are smaller in size and easier to optimize their chemical properties. Several molecular glue degraders have been reported. CC-90009 recruits the CUL4–DDB1–CRBN–RBX1 (CRL4^{CRBN}) E3 complex to ubiquitinate G1-to-S phase transition 1 (GSPT1) for proteasomal degradation. It is currently undergoing a phase I/II clinical trial to treat leukemia [130,141]. Serdemetan (JNJ-26854165) serves as an HDM2 E3 ligase antagonist, which mainly prevents degradation of p53 by inhibiting the interaction of HDM2 with p53. Moreover, serdemetan is capable of inhibiting cholesterol transport. It is under clinical investigation for human cell lymphoma and multiple myoma (Table 2) [130,142,143].

3.4. MDM2 Inhibitors

E3 MDM2 interacts with tumor suppressor p53 to mediate its ubiquitination and proteasome degradation. Targeting the MDM2–p53 complex is an effective modality for cancer treatment [79,144]. A panel of small-molecule inhibitors of MDM2, including RG7112, RG7388, AMG-232, APG-115, BI-907828, CGM097, sirmadlin, milademetan, SAR405838, MK-8242, PRIMA1, and APR-246, is undergoing clinical trials investigating their therapeutic effects on cancers (Table 2) [145–147].

3.5. IAPs Inhibitors

RING-type E3 IAPs are involved in cancer development regulation through inhibiting apoptosis and may serve as potential target for cancer immunotherapy [148–150]. GDC-0152, LCL161, AT-406, AEG40826, TL-32711, and APG-1387 are drugs targeting IAPs at the clinical stages (Table 2) [151]. These small-molecule drugs enable the interaction of XIAP and cIAP1 to undergo proteasome dependent degradation. Their design is inspired by the natural compound IAP antagonist Smac/DIABLO domain [152]. GDC-0152 is the first IAP antagonist that has been put into clinical trials [153], which is used to treat solid cancers via intravenous injection. As the first oral Smac mimic inhibitor of apoptosis [154], the effects of Lcl161 in treating solid tumors, including small-cell lung cancer, breast cancer, myelofibrosis, and thrombocytosis, are now under clinical investigation [130].

3.6. SCF^{Skp2} Inhibitors

As discussed above, Skp2 is overexpressed in various cancers and promotes tumor occurrence and malignancy. Skp2 has been suggested as a promising target for anticancer drug development [155–158]. Currently, a panel of drugs targeting Skp2 is under clinical trials for treatment of acute lymphoblastic leukemia, prostate cancer, prostate adenocarci-

noma, and colon cancer. These promising drugs include curcumin, quercetin, lycopene, silibinin, epigalocatechin-3-gallate (EGCG), and vitamin D3 [130,159–163].

3.7. Nedd4-1 Inhibitors

Nedd4 family E3 Nedd4-1 is highly expressed in non-small-cell lung cancer (NSCLC), colon cancer, gastric cancer, and other cancers to promote cancer development [164,165]. To target Nedd4-1 is a potential avenue for the development of novel anticancer drugs [166–168]. Indole-3-carbinol (I3C) is derived from Cruciferae (Table 2). It possesses an indole carbinol structure and acts as an inhibitor against Nedd4-1, and it is currently at the clinical trial stage to treat human melanoma and breast cancer [130,169,170].

3.8. Hoil-1-Interacting Protein (HOIP) Inhibitors

RBR-type E3 HOIP is involved in regulating human immune response [171,172]. Bendamustine (Table 2), as an effective drug inhibiting HOIP, has been approved by the FDA and the European Medicines Agency (EMA) for the treatment of multiple myeloma, chronic leukemia, rituximab/refractory follicular, and low-grade lymphoma [173]. Furthermore, it is undergoing clinical trials for other human cancers, including ovarian cancer, metastatic HER2-negative breast cancer, and different types of lymphoma [130,174–176].

Table 2. Drugs targeting ubiquitination factors approved or in clinical trials.

Drugs	Mechanism and Application	References
Arv-110	As an inhibitor of PROTACs with E3 CRBN as a ligand, Arv-110 targets the androgen receptor to treat mCRPC.	[130,138]
Arv-471	As an inhibitor of PROTACs with E3 CRBN as a ligand, Arv-471 targets the estrogen receptor to treat breast cancer.	[130,138]
Bortezomib	1. Bortezomib blocks the chymotrypsin-like activity of the 26S proteasome to treat multiple myeloma patients. 2. Bortezomib is the first drug approved by the FDA for the treatment of multiple myeloma and myeloma.	[118–121]
Bendamustine	1. Bendamustine inhibits RBR-type E3 HOIP. 2. Bendamustine was approved by the FDA for clinical therapy of EMA for the treatment of multiple myeloma, chronic leukemia, rituximab/refractory follicular, and low-grade lymphoma.	[130,174–176]
Carfilzomib	1. Carfilzomib selectively binds to the 26S proteasome to inhibit the activities of chymotrypsin-like protein, leading to the accumulation of ubiquitinated substrates. 2. Carfilzomib was approved by the FDA for clinical therapy of multiple myeloma.	[115,116,127–129]
CC-90009	CC-90009 recruits the CRL4^{CRBN} E3 complex to ubiquitinate GSPT1 for proteasomal degradation.	[130,141]
Curcumin, quercetin, lycopene, silibinin, EGCG, and vitaminD3	These drugs promote apoptosis by downregulating Skp2 levels.	[130,159–163]
GDC-0152, LCL161, AT-406, AEG40826, TL-32711, and APG-1387	The drugs bind to the BIR3 domain of the IAP proteins through its N terminus, blocking caspase–IAP complex formation and promoting apoptosis.	[150–152]
Ixazomib	1. Ixazomib belongs to boric acid and inhibits chymotrypsin-like activity of 20S proteasome. 2. Ixazomib was approved by the FDA for clinical therapy of multiple myeloma.	[130–132]
I3C	I3C binds to the HECT domain of Nedd4-1 and inhibits cancer cell proliferation.	[130,169,170]
RG7112, RG7388, AMG-232, APG-115, BI-907828, CGM097, sirmadlin, milademetan, SAR405838, MK-8242, PRIMA1, and APR-246	These drugs inhibit the interaction of MDM2 with p53 so as to maintain p53 activity.	[79,144,145]
Serdemetan (JNJ-26854165)	1. Serdemetan prevents degradation of p53 by inhibiting the interaction of HDM2 with p53. 2. Serdemetan is capable of inhibiting cholesterol transport.	[130,142,143]
Tak-243 (MLN7243)	Tak-243 is the first UAE inhibitor based on a ubiquitination mechanism to enter the clinic.	[134,135]

4. Concluding Remarks and Perspectives

Ubiquitination-related factors are highly involved in regulating cancer development, providing them as promising "druggable" targets for cancer therapy. In spite of striking expectations, inhibitors or agonists against E1/E2/E3 components might possibly result in adverse effects on normal activities in cells since ubiquitination extensively monitors diverse fundamental biological processes. Thus, achieving high specificity in cancer cell targeting is critical to meet this challenge. Innovative solutions could be derived from multidisciplinary integration. For example, pH-response nanomaterials can serve as vectors mediating unique release of inhibitors/agonists against E1/E2/E3 in the cancer-specific pH environment. Furthermore, it will be of great importance to dissect the detailed mechanisms underlying the ubiquitination-related regulation of cancer onset and development. To date, increasing insights and techniques have been developed that would open a new arena for cancer therapy in the future.

Abbreviations

Ub	Ubiquitin
Ub-G76	C-terminal glycine residue of the Ub
M1	Methionine-1
Oct4	Octamer-binding transcription factor-4
E1	Ub activating enzyme
E2	Ub binding enzyme
E3	Ub ligase
C	Cysteine
RING	Really interesting new gene
HECT	Homologous to E6-AP COOH terminus
RBR	RING between RING
Nedd4	Neuronal precursor cell-expressed developmentally downregulated 4
HERC	HECT and RLD-containing
RLD	RCC1-like domains
UPS	Ubiquitin proteasome system
Ube2c	Ubiquitin-conjugating enzyme 2C
Gp78	Glycoprotein 78
ERAD	Endoplasmic reticulum-associated degradation
MDM2/HDM2	Mouse double minute 2/human homolog of mouse double minute 2
TP53	Tumor protein p53
COP1	Constitutive photomorphogenesis protein 1
Pirh2	P53-induced protein with a RING-H2 domain
CHIP	Co-chaperone carboxyl terminus Hsp70/90-interacting protein
Skp2	S-phase kinase-associated protein 2

Cul1	Cullin 1
Rbx1	Ring box 1
Skp1	S-phase kinase-associated protein 1
SCF^{Skp2} complex	The RING-type E3 complex Skp1–Cul1–Skp2
FOXO1	Forkhead box O1
Yap	Yes-associated protein
MTH1	MutT homolog-1
ROS	Oxygen species
IAPs	Inhibitor of apoptosis-related proteins
XIAP	X-linked inhibitor of apoptosis
cIAP1/2	Cellular inhibitor of apoptosis proteins 1 and 2
ML-IAP	Melanoma inhibitor of apoptosis
ILP2	Inhibitor of apoptosis-like protein 2
BIR	Baculoviral IAP repeat
Wwp2	WW domain-containing E3 Ubiquitin protein ligase 2
AIP-2	Atrophin-1-interacting protein 2
PTEN	Phosphatase and tensin homolog
Nedd4-1	Neural precursor cell expressed developmentally downregulated-4-1
FDA	Federal Drug Administration
PROTAC	Proteolysis-targeting chimera
CRBN	Cereblon
mCRPC	Metastatic castration resistant prostate cancer
CRL4^{CRBN} E3 complex	CUL4–DDB1–CRBN–RBX1 E3 complex
GSPT1	G1-to S phase transition 1
EGCG	Epigalocatechin-3-gallate
NSCLC	Non-small-cell lung cancer
I3C	Indole-3-carbinol
HOIP	Hoil-1-interacting protein
EMA	European Medicines Agency

References

1. Hochstrasser, M. Ubiquitin-dependent protein degradation. *Annu. Rev. Genet.* **1996**, *30*, 405–439. [CrossRef] [PubMed]
2. Peng, J.; Schwartz, D.; Elias, J.E.; Thoreen, C.C.; Cheng, D.; Marsischky, G.; Roelofs, J.; Finley, D.; Gygi, S.P. A proteomics approach to understanding protein ubiquitination. *Nat. Biotechnol.* **2003**, *21*, 921–926. [CrossRef] [PubMed]
3. Xu, P.; Peng, J. Characterization of polyubiquitin chain structure by middle-down mass spectrometry. *Anal. Chem.* **2008**, *80*, 3438–3444. [CrossRef] [PubMed]
4. Yau, R.; Rape, M. The increasing complexity of the ubiquitin code. *Nat. Cell Biol.* **2016**, *18*, 579–586. [CrossRef] [PubMed]
5. Wagner, S.A.; Beli, P.; Weinert, B.T.; Nielsen, M.L.; Cox, J.; Mann, M.; Choudhary, C. A proteome-wide, quantitative survey of in vivo ubiquitylation sites reveals widespread regulatory roles. *Mol. Cell Proteom.* **2011**, *10*, M111.013284. [CrossRef]
6. Xu, P.; Duong, D.M.; Seyfried, N.T.; Cheng, D.; Xie, Y.; Robert, J.; Rush, J.; Hochstrasser, M.; Finley, D.; Peng, J. Quantitative proteomics reveals the function of unconventional ubiquitin chains in proteasomal degradation. *Cell* **2009**, *137*, 133–145. [CrossRef]
7. Nakasone, M.A.; Livnat-Levanon, N.; Glickman, M.H.; Cohen, R.E.; Fushman, D. Mixed-linkage ubiquitin chains send mixed messages. *Structure* **2013**, *21*, 727–740. [CrossRef] [PubMed]
8. Pickart, C.M. Mechanisms underlying ubiquitination. *Annu. Rev. Biochem.* **2001**, *70*, 503–533. [CrossRef] [PubMed]
9. Pickart, C.M.; Fushman, D. Polyubiquitin chains: Polymeric protein signals. *Curr. Opin. Chem. Biol.* **2004**, *8*, 610–616. [CrossRef]
10. Livneh, I.; Kravtsova-Ivantsiv, Y.; Braten, O.; Kwon, Y.T.; Ciechanover, A. Monoubiquitination joins polyubiquitination as an esteemed proteasomal targeting signal. *Bioessays* **2017**, *39*, 1700027. [CrossRef]
11. Ea, C.K.; Deng, L.; Xia, Z.P.; Pineda, G.; Chen, Z.J. Activation of IKK by TNFalpha requires site-specific ubiquitination of RIP1 and polyubiquitin binding by NEMO. *Mol. Cell* **2006**, *22*, 245–257. [CrossRef] [PubMed]
12. Li, L.; Xin, H.; Xu, X.; Huang, M.; Zhang, X.; Chen, Y.; Zhang, S.; Fu, X.Y.; Chang, Z. CHIP mediates degradation of Smad proteins and potentially regulates Smad-induced transcription. *Mol. Cell Biol.* **2004**, *24*, 856–864. [CrossRef] [PubMed]
13. Kanayama, A.; Seth, R.B.; Sun, L.; Ea, C.K.; Hong, M.; Shaito, A.; Chiu, Y.H.; Deng, L.; Chen, Z.J. TAB2 and TAB3 activate the NF-kappaB pathway through binding to polyubiquitin chains. *Mol. Cell* **2004**, *15*, 535–548. [CrossRef]
14. Skaug, B.; Jiang, X.; Chen, Z.J. The role of ubiquitin in NF-kappaB regulatory pathways. *Annu. Rev. Biochem.* **2009**, *78*, 769–796. [CrossRef] [PubMed]
15. Zhao, S.; Ulrich, H.D. Distinct consequences of posttranslational modification by linear versus K63-linked polyubiquitin chains. *Proc. Natl. Acad. Sci. USA* **2010**, *107*, 7704–7709. [CrossRef] [PubMed]
16. Liao, B.; Jin, Y. Wwp2 mediates Oct4 ubiquitination and its own auto-ubiquitination in a dosage-dependent manner. *Cell Res.* **2010**, *20*, 332–344. [CrossRef]

17. Wang, J.; Zhang, Y.; Hou, J.; Qian, X.; Zhang, H.; Zhang, Z.; Li, M.; Wang, R.; Liao, K.; Wang, Y.; et al. Ube2s regulates Sox2 stability and mouse ES cell maintenance. *Cell Death Differ.* **2016**, *23*, 393–404. [CrossRef]

18. Li, Z.; Wang, Y.; Li, Y.; Yin, W.; Mo, L.; Qian, X.; Zhang, Y.; Wang, G.; Bu, F.; Zhang, Z.; et al. Ube2s stabilizes β-Catenin through K11-linked polyubiquitination to promote mesendoderm specification and colorectal cancer development. *Cell Death Dis.* **2018**, *9*, 456. [CrossRef]

19. Hann, Z.S.; Ji, C.; Olsen, S.K.; Lu, X.; Lux, M.C.; Tan, D.S.; Lima, C.D. Structural basis for adenylation and thioester bond formation in the ubiquitin E1. *Proc. Natl. Acad. Sci. USA* **2019**, *116*, 15475–15484. [CrossRef]

20. Nandi, D.; Tahiliani, P.; Kumar, A.; Chandu, D. The ubiquitin-proteasome system. *J. Biosci.* **2006**, *31*, 137–155. [CrossRef]

21. Ciechanover, A.; Heller, H.; Katz-Etzion, R.; Hershko, A. Activation of the heat-stable polypeptide of the ATP-dependent proteolytic system. *Proc. Natl. Acad. Sci. USA* **1981**, *78*, 761–765. [CrossRef] [PubMed]

22. Ye, Y.; Rape, M. Building ubiquitin chains: E2 enzymes at work. *Nat. Rev. Mol. Cell Biol.* **2009**, *10*, 755–764. [CrossRef]

23. Varshavsky, A. The ubiquitin system, an immense realm. *Annu. Rev. Biochem.* **2012**, *81*, 167–176. [CrossRef] [PubMed]

24. Metzger, M.B.; Hristova, V.A.; Weissman, A.M. HECT and RING finger families of E3 ubiquitin ligases at a glance. *J. Cell Sci.* **2012**, *125 Pt 3*, 531–537. [CrossRef]

25. Stewart, M.D.; Ritterhoff, T.; Klevit, R.E.; Brzovic, P.S. E2 enzymes: More than just middle men. *Cell Res.* **2016**, *26*, 423–440. [CrossRef] [PubMed]

26. Plafker, S.M.; Plafker, K.S.; Weissman, A.M.; Macara, I.G. Ubiquitin charging of human class III ubiquitin-conjugating enzymes triggers their nuclear import. *J. Cell Biol.* **2004**, *167*, 649–659. [CrossRef]

27. Morreale, F.E.; Walden, H. Types of Ubiquitin Ligases. *Cell* **2016**, *165*, 248–248.e1. [CrossRef]

28. Scheffner, M.; Staub, O. HECT E3s and human disease. *BMC Biochem.* **2007**, *8* (Suppl. S1), S6. [CrossRef]

29. Deshaies, R.J.; Joazeiro, C.A. RING domain E3 ubiquitin ligases. *Annu. Rev. Biochem.* **2009**, *78*, 399–434. [CrossRef] [PubMed]

30. Rotin, D.; Kumar, S. Physiological functions of the HECT family of ubiquitin ligases. *Nat. Rev. Mol. Cell Biol.* **2009**, *10*, 398–409. [CrossRef]

31. Marín, I.; Lucas, J.I.; Gradilla, A.C.; Ferrús, A. Parkin and relatives: The RBR family of ubiquitin ligases. *Physiol. Genom.* **2004**, *17*, 253–263. [CrossRef] [PubMed]

32. Dove, K.K.; Klevit, R.E. RING-Between-RING E3 Ligases: Emerging Themes amid the Variations. *J. Mol. Biol.* **2017**, *429*, 3363–3375. [CrossRef] [PubMed]

33. Spence, J.; Gali, R.R.; Dittmar, G.; Sherman, F.; Karin, M.; Finley, D. Cell cycle-regulated modification of the ribosome by a variant multiubiquitin chain. *Cell* **2000**, *102*, 67–76. [CrossRef] [PubMed]

34. Spence, J.; Sadis, S.; Haas, A.L.; Finley, D. A ubiquitin mutant with specific defects in DNA repair and multiubiquitination. *Mol. Cell Biol.* **1995**, *15*, 1265–1273. [CrossRef] [PubMed]

35. Hofmann, R.M.; Pickart, C.M. Noncanonical MMS2-encoded ubiquitin-conjugating enzyme functions in assembly of novel polyubiquitin chains for DNA repair. *Cell* **1999**, *96*, 645–653. [CrossRef] [PubMed]

36. Kaiser, P.; Flick, K.; Wittenberg, C.; Reed, S.I. Regulation of transcription by ubiquitination without proteolysis: Cdc34/SCF(Met30)-mediated inactivation of the transcription factor Met4. *Cell* **2000**, *102*, 303–314. [CrossRef] [PubMed]

37. Deng, L.; Wang, C.; Spencer, E.; Yang, L.; Braun, A.; You, J.; Slaughter, C.; Pickart, C.; Chen, Z.J. Activation of the IkappaB kinase complex by TRAF6 requires a dimeric ubiquitin-conjugating enzyme complex and a unique polyubiquitin chain. *Cell* **2000**, *103*, 351–361. [CrossRef] [PubMed]

38. Popovic, D.; Vucic, D.; Dikic, I. Ubiquitination in disease pathogenesis and treatment. *Nat. Med.* **2014**, *20*, 1242–1253. [CrossRef]

39. Best, S.; Hashiguchi, T.; Kittai, A.; Bruss, N.; Paiva, C.; Okada, C.; Liu, T.; Berger, A.; Danilov, A.V. Targeting ubiquitin-activating enzyme induces ER stress-mediated apoptosis in B-cell lymphoma cells. *Blood Adv.* **2019**, *3*, 51–62. [CrossRef]

40. Xu, G.W.; Ali, M.; Wood, T.E.; Wong, D.; Maclean, N.; Wang, X.; Gronda, M.; Skrtic, M.; Li, X.; Hurren, R.; et al. The ubiquitin-activating enzyme E1 as a therapeutic target for the treatment of leukemia and multiple myeloma. *Blood* **2010**, *115*, 2251–2259. [CrossRef]

41. Kitagaki, J.; Yang, Y.; Saavedra, J.E.; Colburn, N.H.; Keefer, L.K.; Perantoni, A.O. Nitric oxide prodrug JS-K inhibits ubiquitin E1 and kills tumor cells retaining wild-type p53. *Oncogene* **2009**, *28*, 619–624. [CrossRef] [PubMed]

42. Henningsen, K.M.; Manzini, V.; Magerhans, A.; Gerber, S.; Dobbelstein, M. MDM2-Driven Ubiquitination Rapidly Removes p53 from Its Cognate Promoters. *Biomolecules* **2021**, *12*, 22. [CrossRef] [PubMed]

43. Yang, Y.; Kitagaki, J.; Dai, R.M.; Tsai, Y.C.; Lorick, K.L.; Ludwig, R.L.; Pierre, S.A.; Jensen, J.P.; Davydov, I.V.; Oberoi, P.; et al. Inhibitors of ubiquitin-activating enzyme (E1), a new class of potential cancer therapeutics. *Cancer Res.* **2007**, *67*, 9472–9481. [CrossRef]

44. Zhang, Y.; Tian, S.; Li, X.; Ji, Y.; Wang, Z.; Liu, C. UBE2C promotes rectal carcinoma via miR-381. *Cancer Biol. Ther.* **2018**, *19*, 230–238. [CrossRef]

45. Townsley, F.M.; Aristarkhov, A.; Beck, S.; Hershko, A.; Ruderman, J.V. Dominant-negative cyclin-selective ubiquitin carrier protein E2-C/UbcH10 blocks cells in metaphase. *Proc. Natl. Acad. Sci. USA* **1997**, *94*, 2362–2367. [CrossRef] [PubMed]

46. Nicolau-Neto, P.; Palumbo, A.; De Martino, M.; Esposito, F.; de Almeida Simão, T.; Fusco, A.; Nasciutti, L.E.; Meireles Da Costa, N.; Ribeiro Pinto, L.F. UBE2C Is a Transcriptional Target of the Cell Cycle Regulator FOXM1. *Genes* **2018**, *9*, 188. [CrossRef] [PubMed]

47. Zhang, J.; Liu, X.; Yu, G.; Liu, L.; Wang, J.; Chen, X.; Bian, Y.; Ji, Y.; Zhou, X.; Chen, Y.; et al. UBE2C Is a Potential Biomarker of Intestinal-Type Gastric Cancer with Chromosomal Instability. *Front. Pharmacol.* **2018**, *9*, 847. [CrossRef]

48. Ieta, K.; Ojima, E.; Tanaka, F.; Nakamura, Y.; Haraguchi, N.; Mimori, K.; Inoue, H.; Kuwano, H.; Mori, M. Identification of overexpressed genes in hepatocellular carcinoma, with special reference to ubiquitin-conjugating enzyme E2C gene expression. *Int. J. Cancer* **2007**, *121*, 33–38. [CrossRef]

49. Matsumoto, A.; Ishibashi, Y.; Urashima, M.; Omura, N.; Nakada, K.; Nishikawa, K.; Shida, A.; Takada, K.; Kashiwagi, H.; Yanaga, K. High UBCH10 protein expression as a marker of poor prognosis in esophageal squamous cell carcinoma. *Anticancer Res.* **2014**, *34*, 955–961. [PubMed]

50. Li, L.; Li, X.; Wang, W.; Gao, T.; Shi, Z. UBE2C is involved in the functions of ECRG4 on esophageal squamous cell carcinoma. *Biomed. Pharmacother.* **2018**, *98*, 201–206. [CrossRef]

51. Qin, T.; Huang, G.; Chi, L.; Sui, S.; Song, C.; Li, N.; Sun, S.; Li, N.; Zhang, M.; Zhao, Z.; et al. Exceptionally high UBE2C expression is a unique phenomenon in basal-like type breast cancer and is regulated by BRCA1. *Biomed. Pharmacother.* **2017**, *95*, 649–655. [CrossRef] [PubMed]

52. Mo, C.H.; Gao, L.; Zhu, X.F.; Wei, K.L.; Zeng, J.J.; Chen, G.; Feng, Z.B. The clinicopathological significance of UBE2C in breast cancer: A study based on immunohistochemistry, microarray and RNA-sequencing data. *Cancer Cell Int.* **2017**, *17*, 83. [CrossRef] [PubMed]

53. Nabi, I.R.; Watanabe, H.; Raz, A. Identification of B16-F1 melanoma autocrine motility-like factor receptor. *Cancer Res.* **1990**, *50*, 409–414. [PubMed]

54. Shimizu, K.; Tani, M.; Watanabe, H.; Nagamachi, Y.; Niinaka, Y.; Shiroishi, T.; Ohwada, S.; Raz, A.; Yokota, J. The autocrine motility factor receptor gene encodes a novel type of seven transmembrane protein. *FEBS Lett.* **1999**, *456*, 295–300. [CrossRef] [PubMed]

55. Fang, S.; Ferrone, M.; Yang, C.; Jensen, J.P.; Tiwari, S.; Weissman, A.M. The tumor autocrine motility factor receptor, gp78, is a ubiquitin protein ligase implicated in degradation from the endoplasmic reticulum. *Proc. Natl. Acad. Sci. USA* **2001**, *98*, 14422–14427. [CrossRef] [PubMed]

56. Zhong, X.; Shen, Y.; Ballar, P.; Apostolou, A.; Agami, R.; Fang, S. AAA ATPase p97/valosin-containing protein interacts with gp78, a ubiquitin ligase for endoplasmic reticulum-associated degradation. *J. Biol. Chem.* **2004**, *279*, 45676–45684. [CrossRef]

57. Chiu, C.G.; St-Pierre, P.; Nabi, I.R.; Wiseman, S.M. Autocrine motility factor receptor: A clinical review. *Expert Rev. Anticancer Ther.* **2008**, *8*, 207–217. [CrossRef]

58. Tsai, Y.C.; Mendoza, A.; Mariano, J.M.; Zhou, M.; Kostova, Z.; Chen, B.; Veenstra, T.; Hewitt, S.M.; Helman, L.J.; Khanna, C.; et al. The ubiquitin ligase gp78 promotes sarcoma metastasis by targeting KAI1 for degradation. *Nat. Med.* **2007**, *13*, 1504–1509. [CrossRef]

59. Suzuki, N.; Johmura, Y.; Wang, T.W.; Migita, T.; Wu, W.; Noguchi, R.; Yamaguchi, K.; Furukawa, Y.; Nakamura, S.; Miyoshi, I.; et al. TP53/p53-FBXO22-TFEB controls basal autophagy to govern hormesis. *Autophagy* **2021**, *17*, 3776–3793. [CrossRef]

60. Beck, J.; Turnquist, C.; Horikawa, I.; Harris, C. Targeting cellular senescence in cancer and aging: Roles of p53 and its isoforms. *Carcinogenesis* **2020**, *41*, 1017–1029. [CrossRef]

61. Synoradzki, K.J.; Bartnik, E.; Czarnecka, A.M.; Fiedorowicz, M.; Firlej, W.; Brodziak, A.; Stasinska, A.; Rutkowski, P.; Grieb, P. TP53 in Biology and Treatment of Osteosarcoma. *Cancers* **2021**, *13*, 4284. [CrossRef] [PubMed]

62. Ren, Y.A.; Mullany, L.K.; Liu, Z.; Herron, A.J.; Wong, K.K.; Richards, J.S. Mutant p53 Promotes Epithelial Ovarian Cancer by Regulating Tumor Differentiation, Metastasis, and Responsiveness to Steroid Hormones. *Cancer Res.* **2016**, *76*, 2206–2218. [CrossRef] [PubMed]

63. Cho, S.; Kim, M.J.; Choi, Y.Y.; Yoo, S.S.; Lee, W.K.; Lee, E.J.; Jang, E.J.; Bae, E.Y.; Jin, G.; Jeon, H.S.; et al. Associations between polymorphisms in DNA repair genes and TP53 mutations in non-small cell lung cancer. *Lung Cancer* **2011**, *73*, 25–31. [CrossRef]

64. Stein, Y.; Rotter, V.; Aloni-Grinstein, R. Gain-of-Function Mutant p53: All the Roads Lead to Tumorigenesis. *Int. J. Mol. Sci.* **2019**, *20*, 6197. [CrossRef] [PubMed]

65. Baugh, E.H.; Ke, H.; Levine, A.J.; Bonneau, R.A.; Chan, C.S. Why are there hotspot mutations in the TP53 gene in human cancers? *Cell Death Differ.* **2018**, *25*, 154–160. [CrossRef] [PubMed]

66. Kanapathipillai, M. Treating p53 Mutant Aggregation-Associated Cancer. *Cancers* **2018**, *10*, 154. [CrossRef]

67. Yue, Z.; Zhou, Y.; Zhao, P.; Chen, Y.; Yuan, Y.; Jing, Y.; Wang, X. p53 Deletion promotes myeloma cells invasion by upregulating miR19a/CXCR5. *Leuk. Res.* **2017**, *60*, 115–122. [CrossRef]

68. Seifert, H.; Mohr, B.; Thiede, C.; Oelschlägel, U.; Schäkel, U.; Illmer, T.; Soucek, S.; Ehninger, G.; Schaich, M. The prognostic impact of 17p (p53) deletion in 2272 adults with acute myeloid leukemia. *Leukemia* **2009**, *23*, 656–663. [CrossRef]

69. Kadioglu, O.; Saeed, M.; Mahmoud, N.; Azawi, S.; Mrasek, K.; Liehr, T.; Efferth, T. Identification of potential novel drug resistance mechanisms by genomic and transcriptomic profiling of colon cancer cells with p53 deletion. *Arch. Toxicol.* **2021**, *95*, 959–974. [CrossRef]

70. Jia, Z.; He, J.; Cen, L.; Han, W.; Jiang, N.; Yang, J.; Zhou, M. P53 deletion is independently associated with increased age and decreased survival in a cohort of Chinese patients with diffuse large B-cell lymphoma. *Leuk. Lymphoma* **2012**, *53*, 2182–2185. [CrossRef]

71. Maki, C.G.; Huibregtse, J.M.; Howley, P.M. In vivo ubiquitination and proteasome-mediated degradation of p53(1). *Cancer Res.* **1996**, *56*, 2649–2654. [PubMed]

72. Haupt, Y.; Maya, R.; Kazaz, A.; Oren, M. Mdm2 promotes the rapid degradation of p53. *Nature* **1997**, *387*, 296–299. [CrossRef] [PubMed]

73. Honda, R.; Tanaka, H.; Yasuda, H. Oncoprotein MDM2 is a ubiquitin ligase E3 for tumor suppressor p53. *FEBS Lett.* **1997**, *420*, 25–27. [CrossRef] [PubMed]

74. Lai, Z.; Ferry, K.V.; Diamond, M.A.; Wee, K.E.; Kim, Y.B.; Ma, J.; Yang, T.; Benfield, P.A.; Copeland, R.A.; Auger, K.R. Human mdm2 mediates multiple mono-ubiquitination of p53 by a mechanism requiring enzyme isomerization. *J. Biol. Chem.* **2001**, *276*, 31357–31367. [CrossRef]

75. Lohrum, M.A.; Woods, D.B.; Ludwig, R.L.; Bálint, E.; Vousden, K.H. C-terminal ubiquitination of p53 contributes to nuclear export. *Mol. Cell Biol.* **2001**, *21*, 8521–8532. [CrossRef] [PubMed]

76. Li, M.; Brooks, C.L.; Wu-Baer, F.; Chen, D.; Baer, R.; Gu, W. Mono- versus polyubiquitination: Differential control of p53 fate by Mdm2. *Science* **2003**, *302*, 1972–1975. [CrossRef]

77. Kussie, P.H.; Gorina, S.; Marechal, V.; Elenbaas, B.; Moreau, J.; Levine, A.J.; Pavletich, N.P. Structure of the MDM2 oncoprotein bound to the p53 tumor suppressor transactivation domain. *Science* **1996**, *274*, 948–953. [CrossRef]

78. Oliner, J.D.; Saiki, A.Y.; Caenepeel, S. The Role of MDM2 Amplification and Overexpression in Tumorigenesis. *Cold Spring Harb. Perspect. Med.* **2016**, *6*, a026336. [CrossRef]

79. Zafar, A.; Wang, W.; Liu, G.; Xian, W.; McKeon, F.; Zhou, J.; Zhang, R. Targeting the p53-MDM2 pathway for neuroblastoma therapy: Rays of hope. *Cancer Lett.* **2021**, *496*, 16–29. [CrossRef]

80. Hou, H.; Sun, D.; Zhang, X. The role of MDM2 amplification and overexpression in therapeutic resistance of malignant tumors. *Cancer Cell Int.* **2019**, *19*, 216. [CrossRef]

81. Sane, S.; Rezvani, K. Essential Roles of E3 Ubiquitin Ligases in p53 Regulation. *Int. J. Mol. Sci.* **2017**, *18*, 442. [CrossRef] [PubMed]

82. Mason, B.; Laman, H. The FBXL family of F-box proteins: Variations on a theme. *Open Biol.* **2020**, *10*, 200319. [CrossRef]

83. Cardozo, T.; Pagano, M. The SCF ubiquitin ligase: Insights into a molecular machine. *Nat. Rev. Mol. Cell Biol.* **2004**, *5*, 739–751. [CrossRef]

84. Zheng, N.; Schulman, B.A.; Song, L.; Miller, J.J.; Jeffrey, P.D.; Wang, P.; Chu, C.; Koepp, D.M.; Elledge, S.J.; Pagano, M.; et al. Structure of the Cul1-Rbx1-Skp1-F boxSkp2 SCF ubiquitin ligase complex. *Nature* **2002**, *416*, 703–709. [CrossRef] [PubMed]

85. Chan, C.H.; Li, C.F.; Yang, W.L.; Gao, Y.; Lee, S.W.; Feng, Z.; Huang, H.Y.; Tsai, K.K.; Flores, L.G.; Shao, Y.; et al. The Skp2-SCF E3 ligase regulates Akt ubiquitination, glycolysis, herceptin sensitivity, and tumorigenesis. *Cell* **2012**, *149*, 1098–1111. [CrossRef] [PubMed]

86. Huang, H.; Regan, K.M.; Wang, F.; Wang, D.; Smith, D.I.; van Deursen, J.M.; Tindall, D.J. Skp2 inhibits FOXO1 in tumor suppression through ubiquitin-mediated degradation. *Proc. Natl. Acad. Sci. USA* **2005**, *102*, 1649–1654. [CrossRef] [PubMed]

87. Cai, Z.; Moten, A.; Peng, D.; Hsu, C.C.; Pan, B.S.; Manne, R.; Li, H.Y.; Lin, H.K. The Skp2 Pathway: A Critical Target for Cancer Therapy. *Semin. Cancer Biol.* **2020**, *67 (Pt 2)*, 16–33. [CrossRef] [PubMed]

88. Lamar, J.M.; Stern, P.; Liu, H.; Schindler, J.W.; Jiang, Z.G.; Hynes, R.O. The Hippo pathway target, YAP, promotes metastasis through its TEAD-interaction domain. *Proc. Natl. Acad. Sci. USA* **2012**, *109*, E2441–E2450. [CrossRef] [PubMed]

89. Chen, Q.; Zhang, N.; Gray, R.S.; Li, H.; Ewald, A.J.; Zahnow, C.A.; Pan, D. A temporal requirement for Hippo signaling in mammary gland differentiation, growth, and tumorigenesis. *Genes Dev.* **2014**, *28*, 432–437. [CrossRef]

90. Yao, F.; Zhou, Z.; Kim, J.; Hang, Q.; Xiao, Z.; Ton, B.N.; Chang, L.; Liu, N.; Zeng, L.; Wang, W.; et al. SKP2- and OTUD1-regulated non-proteolytic ubiquitination of YAP promotes YAP nuclear localization and activity. *Nat. Commun.* **2018**, *9*, 2269. [CrossRef]

91. Patel, A.; Burton, D.G.; Halvorsen, K.; Balkan, W.; Reiner, T.; Perez-Stable, C.; Cohen, A.; Munoz, A.; Giribaldi, M.G.; Singh, S.; et al. MutT Homolog 1 (MTH1) maintains multiple KRAS-driven pro-malignant pathways. *Oncogene* **2015**, *34*, 2586–2596. [CrossRef] [PubMed]

92. Sakumi, K.; Furuichi, M.; Tsuzuki, T.; Kakuma, T.; Kawabata, S.; Maki, H.; Sekiguchi, M. Cloning and expression of cDNA for a human enzyme that hydrolyzes 8-oxo-dGTP, a mutagenic substrate for DNA synthesis. *J. Biol. Chem.* **1993**, *268*, 23524–23530. [CrossRef] [PubMed]

93. Wang, J.Y.; Liu, G.Z.; Wilmott, J.S.; La, T.; Feng, Y.C.; Yari, H.; Yan, X.G.; Thorne, R.F.; Scolyer, R.A.; Zhang, X.D.; et al. Skp2-Mediated Stabilization of MTH1 Promotes Survival of Melanoma Cells upon Oxidative Stress. *Cancer Res.* **2017**, *77*, 6226–6239. [CrossRef] [PubMed]

94. Vaux, D.L.; Silke, J. IAPs, RINGs and ubiquitylation. *Nat. Rev. Mol. Cell Biol.* **2005**, *6*, 287–297. [CrossRef] [PubMed]

95. Deveraux, Q.L.; Reed, J.C. IAP family proteins—Suppressors of apoptosis. *Genes Dev.* **1999**, *13*, 239–252. [CrossRef]

96. Hinds, M.G.; Norton, R.S.; Vaux, D.L.; Day, C.L. Solution structure of a baculoviral inhibitor of apoptosis (IAP) repeat. *Nat. Struct. Biol.* **1999**, *6*, 648–651.

97. Eckelman, B.P.; Drag, M.; Snipas, S.J.; Salvesen, G.S. The mechanism of peptide-binding specificity of IAP BIR domains. *Cell Death Differ.* **2008**, *15*, 920–928. [CrossRef]

98. Dubrez, L.; Rajalingam, K. IAPs and cell migration. *Semin. Cell Dev. Biol.* **2015**, *39*, 124–131. [CrossRef]

99. Estornes, Y.; Bertrand, M.J. IAPs, regulators of innate immunity and inflammation. *Semin. Cell Dev. Biol.* **2015**, *39*, 106–114. [CrossRef]

100. Oberoi-Khanuja, T.K.; Murali, A.; Rajalingam, K. IAPs on the move: Role of inhibitors of apoptosis proteins in cell migration. *Cell Death Dis.* **2013**, *4*, e784. [CrossRef]

101. Liang, J.; Zhao, W.; Tong, P.; Li, P.; Zhao, Y.; Li, H.; Liang, J. Comprehensive molecular characterization of inhibitors of apoptosis proteins (IAPs) for therapeutic targeting in cancer. *BMC Med. Genom.* **2020**, *13*, 7. [CrossRef] [PubMed]

102. Lau, R.; Pratt, M.A. The opposing roles of cellular inhibitor of apoptosis proteins in cancer. *ISRN Oncol.* **2012**, *2012*, 928120. [CrossRef] [PubMed]

103. Zhang, R.; Zhang, J.; Luo, W.; Luo, Z.; Shi, S. WWP2 Is One Promising Novel Oncogene. *Pathol. Oncol. Res.* **2019**, *25*, 443–446. [CrossRef] [PubMed]

104. Bernassola, F.; Karin, M.; Ciechanover, A.; Melino, G. The HECT family of E3 ubiquitin ligases: Multiple players in cancer development. *Cancer Cell* **2008**, *14*, 10–21. [CrossRef] [PubMed]

105. Zou, W.; Chen, X.; Shim, J.H.; Huang, Z.; Brady, N.; Hu, D.; Drapp, R.; Sigrist, K.; Glimcher, L.H.; Jones, D. The E3 ubiquitin ligase Wwp2 regulates craniofacial development through mono-ubiquitylation of Goosecoid. *Nat. Cell Biol.* **2011**, *13*, 59–65. [CrossRef] [PubMed]

106. Myers, M.P.; Pass, I.; Batty, I.H.; Van der Kaay, J.; Stolarov, J.P.; Hemmings, B.A.; Wigler, M.H.; Downes, C.P.; Tonks, N.K. The lipid phosphatase activity of PTEN is critical for its tumor supressor function. *Proc. Natl. Acad. Sci. USA* **1998**, *95*, 13513–13518. [CrossRef] [PubMed]

107. Carnero, A.; Blanco-Aparicio, C.; Renner, O.; Link, W.; Leal, J.F. The PTEN/PI3K/AKT signalling pathway in cancer, therapeutic implications. *Curr. Cancer Drug Targets* **2008**, *8*, 187–198. [CrossRef]

108. Li, J.; Yen, C.; Liaw, D.; Podsypanina, K.; Bose, S.; Wang, S.I.; Puc, J.; Miliaresis, C.; Rodgers, L.; McCombie, R.; et al. PTEN, a putative protein tyrosine phosphatase gene mutated in human brain, breast, and prostate cancer. *Science* **1997**, *275*, 1943–1947. [CrossRef]

109. Steck, P.A.; Pershouse, M.A.; Jasser, S.A.; Yung, W.K.; Lin, H.; Ligon, A.H.; Langford, L.A.; Baumgard, M.L.; Hattier, T.; Davis, T.; et al. Identification of a candidate tumour suppressor gene, MMAC1, at chromosome 10q23.3 that is mutated in multiple advanced cancers. *Nat. Genet.* **1997**, *15*, 356–362. [CrossRef]

110. Maddika, S.; Kavela, S.; Rani, N.; Palicharla, V.R.; Pokorny, J.L.; Sarkaria, J.N.; Chen, J. WWP2 is an E3 ubiquitin ligase for PTEN. *Nat. Cell Biol.* **2011**, *13*, 728–733. [CrossRef]

111. Wang, X.; Trotman, L.C.; Koppie, T.; Alimonti, A.; Chen, Z.; Gao, Z.; Wang, J.; Erdjument-Bromage, H.; Tempst, P.; Cordon-Cardo, C.; et al. NEDD4-1 is a proto-oncogenic ubiquitin ligase for PTEN. *Cell* **2007**, *128*, 129–139. [CrossRef] [PubMed]

112. Ghidini, A.; Cléry, A.; Halloy, F.; Allain, F.H.T.; Hall, J. RNA-PROTACs: Degraders of RNA-Binding Proteins. *Angew Chem. Int. Ed. Engl.* **2021**, *60*, 3163–3169. [CrossRef] [PubMed]

113. Li, K.; Du, Y.; Li, L.; Wei, D.Q. Bioinformatics Approaches for Anti-cancer Drug Discovery. *Curr. Drug Targets* **2020**, *21*, 3–17. [CrossRef]

114. Berdigaliyev, N.; Aljofan, M. An overview of drug discovery and development. *Future Med. Chem.* **2020**, *12*, 939–947. [CrossRef] [PubMed]

115. Fricker, L.D. Proteasome Inhibitor Drugs. *Annu. Rev. Pharmacol. Toxicol.* **2020**, *60*, 457–476. [CrossRef]

116. Narayanan, S.; Cai, C.Y.; Assaraf, Y.G.; Guo, H.Q.; Cui, Q.; Wei, L.; Huang, J.J.; Ashby, C.R., Jr.; Chen, Z.S. Targeting the ubiquitin-proteasome pathway to overcome anti-cancer drug resistance. *Drug Resist. Updates* **2020**, *48*, 100663. [CrossRef]

117. Jayaweera, S.P.E.; Wanigasinghe Kanakanamge, S.P.; Rajalingam, D.; Silva, G.N. Carfilzomib: A Promising Proteasome Inhibitor for the Treatment of Relapsed and Refractory Multiple Myeloma. *Front. Oncol.* **2021**, *11*, 740796. [CrossRef]

118. Kane, R.C.; Bross, P.F.; Farrell, A.T.; Pazdur, R. Velcade: U.S. FDA approval for the treatment of multiple myeloma progressing on prior therapy. *Oncologist* **2003**, *8*, 508–513. [CrossRef]

119. Cohen, P.; Tcherpakov, M. Will the ubiquitin system furnish as many drug targets as protein kinases? *Cell* **2010**, *143*, 686–693. [CrossRef]

120. Kisselev, A.F.; Callard, A.; Goldberg, A.L. Importance of the different proteolytic sites of the proteasome and the efficacy of inhibitors varies with the protein substrate. *J. Biol. Chem.* **2006**, *281*, 8582–8590. [CrossRef]

121. Kane, R.C.; Farrell, A.T.; Sridhara, R.; Pazdur, R. United States Food and Drug Administration approval summary: Bortezomib for the treatment of progressive multiple myeloma after one prior therapy. *Clin. Cancer Res.* **2006**, *12*, 2955–2960. [CrossRef] [PubMed]

122. Dimopoulos, M.; Weisel, K.; Moreau, P.; Anderson, L.D., Jr.; White, D.; San-Miguel, J.; Sonneveld, P.; Engelhardt, M.; Jenner, M.; Corso, A.; et al. Pomalidomide, bortezomib, and dexamethasone for multiple myeloma previously treated with lenalidomide (OPTIMISMM): Outcomes by prior treatment at first relapse. *Leukemia* **2021**, *35*, 1722–1731. [CrossRef] [PubMed]

123. Yamamoto, S.; Egashira, N. Pathological Mechanisms of Bortezomib-Induced Peripheral Neuropathy. *Int. J. Mol. Sci.* **2021**, *22*, 888. [CrossRef] [PubMed]

124. Cheah, C.Y.; Seymour, J.F.; Wang, M.L. Mantle Cell Lymphoma. *J. Clin. Oncol.* **2016**, *34*, 1256–1269. [CrossRef]

125. Pasquale, R.; Giannotta, J.A.; Barcellini, W.; Fattizzo, B. Bortezomib in autoimmune hemolytic anemia and beyond. *Ther. Adv. Hematol.* **2021**, *12*, 20406207211046428. [CrossRef]

126. Härtel, H.; Theiß, J.; Abdelaziz, M.O.; Raftery, M.J.; Pecher, G.; Bogner, E. HCMV-Mediated Interference of Bortezomib-Induced Apoptosis in Colon Carcinoma Cell Line Caco-2. *Viruses* **2021**, *13*, 83. [CrossRef]

127. Kortuem, K.M.; Stewart, A.K. Carfilzomib. *Blood* **2013**, *121*, 893–897. [CrossRef]

128. Stewart, A.K.; Rajkumar, S.V.; Dimopoulos, M.A.; Masszi, T.; Špička, I.; Oriol, A.; Hájek, R.; Rosiñol, L.; Siegel, D.S.; Mihaylov, G.G.; et al. Carfilzomib, lenalidomide, and dexamethasone for relapsed multiple myeloma. *N. Engl. J. Med.* **2015**, *372*, 142–152. [CrossRef]

129. US FDA. Available online: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm (accessed on 25 October 2022).

130. Available online: https://clinicaltrials.gov (accessed on 25 October 2022).

131. Augello, G.; Modica, M.; Azzolina, A.; Puleio, R.; Cassata, G.; Emma, M.R.; Di Sano, C.; Cusimano, A.; Montalto, G.; Cervello, M. Preclinical evaluation of antitumor activity of the proteasome inhibitor MLN2238 (ixazomib) in hepatocellular carcinoma cells. *Cell Death Dis.* **2018**, *9*, 28. [CrossRef]

132. Kupperman, E.; Lee, E.C.; Cao, Y.; Bannerman, B.; Fitzgerald, M.; Berger, A.; Yu, J.; Yang, Y.; Hales, P.; Bruzzese, F.; et al. Evaluation of the proteasome inhibitor MLN9708 in preclinical models of human cancer. *Cancer Res.* **2010**, *70*, 1970–1980. [CrossRef]

133. Moreau, P.; Masszi, T.; Grzasko, N.; Bahlis, N.J.; Hansson, M.; Pour, L.; Sandhu, I.; Ganly, P.; Baker, B.W.; Jackson, S.R.; et al. Oral Ixazomib, Lenalidomide, and Dexamethasone for Multiple Myeloma. *N. Engl. J. Med.* **2016**, *374*, 1621–1634. [CrossRef] [PubMed]

134. Jin, J.; Li, X.; Gygi, S.P.; Harper, J.W. Dual E1 activation systems for ubiquitin differentially regulate E2 enzyme charging. *Nature* **2007**, *447*, 1135–1138. [CrossRef] [PubMed]

135. Hyer, M.L.; Milhollen, M.A.; Ciavarri, J.; Fleming, P.; Traore, T.; Sappal, D.; Huck, J.; Shi, J.; Gavin, J.; Brownell, J.; et al. A small-molecule inhibitor of the ubiquitin activating enzyme for cancer treatment. *Nat. Med.* **2018**, *24*, 186–193. [CrossRef] [PubMed]

136. Schneekloth, J.S., Jr.; Fonseca, F.N.; Koldobskiy, M.; Mandal, A.; Deshaies, R.; Sakamoto, K.; Crews, C.M. Chemical genetic control of protein levels: Selective in vivo targeted degradation. *J. Am. Chem. Soc.* **2004**, *126*, 3748–3754. [CrossRef] [PubMed]

137. Weng, G.; Shen, C.; Cao, D.; Gao, J.; Dong, X.; He, Q.; Yang, B.; Li, D.; Wu, J.; Hou, T. PROTAC-DB: An online database of PROTACs. *Nucleic Acids Res.* **2021**, *49*, D1381–D1387. [CrossRef]

138. Nalawansha, D.A.; Crews, C.M. PROTACs: An Emerging Therapeutic Modality in Precision Medicine. *Cell Chem. Biol.* **2020**, *27*, 998–1014. [CrossRef]

139. Sakamoto, K.M.; Kim, K.B.; Kumagai, A.; Mercurio, F.; Crews, C.M.; Deshaies, R.J. Protacs: Chimeric molecules that target proteins to the Skp1-Cullin-F box complex for ubiquitination and degradation. *Proc. Natl. Acad. Sci. USA* **2001**, *98*, 8554–8559. [CrossRef]

140. Schapira, M.; Calabrese, M.F.; Bullock, A.N.; Crews, C.M. Targeted protein degradation: Expanding the toolbox. *Nat. Rev. Drug Discov.* **2019**, *18*, 949–963. [CrossRef]

141. Surka, C.; Jin, L.; Mbong, N.; Lu, C.C.; Jang, I.S.; Rychak, E.; Mendy, D.; Clayton, T.; Tindall, E.; Hsu, C.; et al. CC-90009, a novel cereblon E3 ligase modulator, targets acute myeloid leukemia blasts and leukemia stem cells. *Blood* **2021**, *137*, 661–677. [CrossRef]

142. Jones, R.J.; Gu, D.; Bjorklund, C.C.; Kuiatse, I.; Remaley, A.T.; Bashir, T.; Vreys, V.; Orlowski, R.Z. The novel anticancer agent JNJ-26854165 induces cell death through inhibition of cholesterol transport and degradation of ABCA1. *J. Pharmacol. Exp. Ther.* **2013**, *346*, 381–392. [CrossRef]

143. Chargari, C.; Leteur, C.; Angevin, E.; Bashir, T.; Schoentjes, B.; Arts, J.; Janicot, M.; Bourhis, J.; Deutsch, E. Preclinical assessment of JNJ-26854165 (Serdemetan), a novel tryptamine compound with radiosensitizing activity in vitro and in tumor xenografts. *Cancer Lett.* **2011**, *312*, 209–218. [CrossRef]

144. Klein, A.M.; de Queiroz, R.M.; Venkatesh, D.; Prives, C. The roles and regulation of MDM2 and MDMX: It is not just about p53. *Genes Dev.* **2021**, *35*, 575–601. [CrossRef] [PubMed]

145. Konopleva, M.; Martinelli, G.; Daver, N.; Papayannidis, C.; Wei, A.; Higgins, B.; Ott, M.; Mascarenhas, J.; Andreeff, M. MDM2 inhibition: An important step forward in cancer therapy. *Leukemia* **2020**, *34*, 2858–2874. [CrossRef] [PubMed]

146. Fang, Y.; Liao, G.; Yu, B. Small-molecule MDM2/X inhibitors and PROTAC degraders for cancer therapy: Advances and perspectives. *Acta Pharm. Sin. B* **2020**, *10*, 1253–1278. [CrossRef] [PubMed]

147. LaPlante, G.; Zhang, W. Targeting the Ubiquitin-Proteasome System for Cancer Therapeutics by Small-Molecule Inhibitors. *Cancers* **2021**, *13*, 3079. [CrossRef]

148. Kumar, S.; Fairmichael, C.; Longley, D.B.; Turkington, R.C. The Multiple Roles of the IAP Super-family in cancer. *Pharmacol. Ther.* **2020**, *214*, 107610. [CrossRef]

149. Feltham, R.; Khan, N.; Silke, J. IAPS and ubiquitylation. *IUBMB Life* **2012**, *64*, 411–418. [CrossRef]

150. Michie, J.; Kearney, C.J.; Hawkins, E.D.; Silke, J.; Oliaro, J. The Immuno-Modulatory Effects of Inhibitor of Apoptosis Protein Antagonists in Cancer Immunotherapy. *Cells* **2020**, *9*, 207. [CrossRef]

151. Ye, P.; Chi, X.; Cha, J.H.; Luo, S.; Yang, G.; Yan, X.; Yang, W.H. Potential of E3 Ubiquitin Ligases in Cancer Immunity: Opportunities and Challenges. *Cells* **2021**, *10*, 3309. [CrossRef]

152. Cossu, F.; Milani, M.; Mastrangelo, E.; Lecis, D. Targeting the BIR Domains of Inhibitor of Apoptosis (IAP) Proteins in Cancer Treatment. *Comput. Struct. Biotechnol. J.* **2019**, *17*, 142–150. [CrossRef]

153. Flygare, J.A.; Beresini, M.; Budha, N.; Chan, H.; Chan, I.T.; Cheeti, S.; Cohen, F.; Deshayes, K.; Doerner, K.; Eckhardt, S.G.; et al. Discovery of a potent small-molecule antagonist of inhibitor of apoptosis (IAP) proteins and clinical candidate for the treatment of cancer (GDC-0152). *J. Med. Chem.* **2012**, *55*, 4101–4113. [CrossRef] [PubMed]

154. Infante, J.R.; Dees, E.C.; Olszanski, A.J.; Dhuria, S.V.; Sen, S.; Cameron, S.; Cohen, R.B. Phase I dose-escalation study of LCL161, an oral inhibitor of apoptosis proteins inhibitor, in patients with advanced solid tumors. *J. Clin. Oncol.* **2014**, *32*, 3103–3110. [CrossRef] [PubMed]

155. Wang, Z.; Fukushima, H.; Inuzuka, H.; Wan, L.; Liu, P.; Gao, D.; Sarkar, F.H.; Wei, W. Skp2 is a promising therapeutic target in breast cancer. *Front. Oncol.* **2012**, *1*, 57. [CrossRef]

156. Kitagawa, M.; Lee, S.H.; McCormick, F. Skp2 suppresses p53-dependent apoptosis by inhibiting p300. *Mol. Cell* **2008**, *29*, 217–231. [CrossRef] [PubMed]

157. Chan, C.H.; Morrow, J.K.; Li, C.F.; Gao, Y.; Jin, G.; Moten, A.; Stagg, L.J.; Ladbury, J.E.; Cai, Z.; Xu, D.; et al. Pharmacological inactivation of Skp2 SCF ubiquitin ligase restricts cancer stem cell traits and cancer progression. *Cell* **2013**, *154*, 556–568. [CrossRef]

158. Asmamaw, M.D.; Liu, Y.; Zheng, Y.C.; Shi, X.J.; Liu, H.M. Skp2 in the ubiquitin-proteasome system: A comprehensive review. *Med. Res. Rev.* **2020**, *40*, 1920–1949. [CrossRef]

159. Su, J.; Zhou, X.; Wang, L.; Yin, X.; Wang, Z. Curcumin inhibits cell growth and invasion and induces apoptosis through down-regulation of Skp2 in pancreatic cancer cells. *Am. J. Cancer Res.* **2016**, *6*, 1949–1962.

160. Huang, H.C.; Lin, C.L.; Lin, J.K. 1,2,3,4,6-penta-O-galloyl-β-D-glucose, quercetin, curcumin and lycopene induce cell-cycle arrest in MDA-MB-231 and BT474 cells through downregulation of Skp2 protein. *J. Agric. Food Chem.* **2011**, *59*, 6765–6775. [CrossRef]

161. Roy, S.; Kaur, M.; Agarwal, C.; Tecklenburg, M.; Sclafani, R.A.; Agarwal, R. p21 and p27 induction by silibinin is essential for its cell cycle arrest effect in prostate carcinoma cells. *Mol. Cancer Ther.* **2007**, *6*, 2696–2707. [CrossRef]

162. Huang, H.C.; Way, T.D.; Lin, C.L.; Lin, J.K. EGCG stabilizes p27kip1 in E2-stimulated MCF-7 cells through down-regulation of the Skp2 protein. *Endocrinology* **2008**, *149*, 5972–5983. [CrossRef]

163. Liu, W.; Asa, S.L.; Fantus, I.G.; Walfish, P.G.; Ezzat, S. Vitamin D arrests thyroid carcinoma cell growth and induces p27 dephosphorylation and accumulation through PTEN/akt-dependent and -independent pathways. *Am. J. Pathol.* **2002**, *160*, 511–519. [CrossRef] [PubMed]

164. Amodio, N.; Scrima, M.; Palaia, L.; Salman, A.N.; Quintiero, A.; Franco, R.; Botti, G.; Pirozzi, P.; Rocco, G.; De Rosa, N.; et al. Oncogenic role of the E3 ubiquitin ligase NEDD4-1, a PTEN negative regulator, in non-small-cell lung carcinomas. *Am. J. Pathol.* **2010**, *177*, 2622–2634. [CrossRef]

165. Eide, P.W.; Cekaite, L.; Danielsen, S.A.; Eilertsen, I.A.; Kjenseth, A.; Fykerud, T.A.; Ågesen, T.H.; Bruun, J.; Rivedal, E.; Lothe, R.A.; et al. NEDD4 is overexpressed in colorectal cancer and promotes colonic cell growth independently of the PI3K/PTEN/AKT pathway. *Cell Signal* **2013**, *25*, 12–18. [CrossRef] [PubMed]

166. Zeng, T.; Wang, Q.; Fu, J.; Lin, Q.; Bi, J.; Ding, W.; Qiao, Y.; Zhang, S.; Zhao, W.; Lin, H.; et al. Impeded Nedd4-1-mediated Ras degradation underlies Ras-driven tumorigenesis. *Cell Rep.* **2014**, *7*, 871–882. [CrossRef] [PubMed]

167. Lu, C.; Thoeni, C.; Connor, A.; Kawabe, H.; Gallinger, S.; Rotin, D. Intestinal knockout of Nedd4 enhances growth of Apc(min) tumors. *Oncogene* **2016**, *35*, 5839–5849. [CrossRef] [PubMed]

168. Ye, X.; Wang, L.; Shang, B.; Wang, Z.; Wei, W. NEDD4: A promising target for cancer therapy. *Curr. Cancer Drug Targets* **2014**, *14*, 549–556. [CrossRef] [PubMed]

169. Kundu, A.; Quirit, J.G.; Khouri, M.G.; Firestone, G.L. Inhibition of oncogenic BRAF activity by indole-3-carbinol disrupts microphthalmia-associated transcription factor expression and arrests melanoma cell proliferation. *Mol. Carcinog.* **2017**, *56*, 49–61. [CrossRef]

170. Quirit, J.G.; Lavrenov, S.N.; Poindexter, K.; Xu, J.; Kyauk, C.; Durkin, K.A.; Aronchik, I.; Tomasiak, T.; Solomatin, Y.A.; Preobrazhenskaya, M.N.; et al. Indole-3-carbinol (I3C) analogues are potent small molecule inhibitors of NEDD4-1 ubiquitin ligase activity that disrupt proliferation of human melanoma cells. *Biochem. Pharmacol.* **2017**, *127*, 13–27. [CrossRef]

171. Smit, J.J.; Monteferrario, D.; Noordermeer, S.M.; van Dijk, W.J.; van der Reijden, B.A.; Sixma, T.K. The E3 ligase HOIP specifies linear ubiquitin chain assembly through its RING-IBR-RING domain and the unique LDD extension. *Embo. J.* **2012**, *31*, 3833–3844. [CrossRef]

172. Iwai, K.; Fujita, H.; Sasaki, Y. Linear ubiquitin chains: NF-κB signalling, cell death and beyond. *Nat. Rev. Mol. Cell Biol.* **2014**, *15*, 503–508. [CrossRef] [PubMed]

173. Derenzini, E.; Zinzani, P.L.; Cheson, B.D. Bendamustine: Role and evidence in lymphoma therapy, an overview. *Leuk. Lymphoma* **2014**, *55*, 1471–1478. [CrossRef] [PubMed]

174. Damaj, G.; Gressin, R.; Bouabdallah, K.; Cartron, G.; Choufi, B.; Gyan, E.; Banos, A.; Jaccard, A.; Park, S.; Tournilhac, O.; et al. Results from a prospective, open-label, phase II trial of bendamustine in refractory or relapsed T-cell lymphomas: The BENTLY trial. *J. Clin. Oncol.* **2013**, *31*, 104–110. [CrossRef] [PubMed]

175. Santoro, A.; Mazza, R.; Pulsoni, A.; Re, A.; Bonfichi, M.; Zilioli, V.R.; Salvi, F.; Merli, F.; Anastasia, A.; Luminari, S.; et al. Bendamustine in Combination with Gemcitabine and Vinorelbine Is an Effective Regimen As Induction Chemotherapy before Autologous Stem-Cell Transplantation for Relapsed or Refractory Hodgkin Lymphoma: Final Results of a Multicenter Phase II Study. *J. Clin. Oncol.* **2016**, *34*, 3293–3299. [CrossRef] [PubMed]

176. Weidmann, E.; Kim, S.Z.; Rost, A.; Schuppert, H.; Seipelt, G.; Hoelzer, D.; Mitrou, P.S. Bendamustine is effective in relapsed or refractory aggressive non-Hodgkin's lymphoma. *Ann. Oncol.* **2002**, *13*, 1285–1289. [CrossRef]