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Protein Ubiquitination in Tumor Initiation, Malignant Progression, and Targeted Therapy

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Abstract. Protein ubiquitination is a reversible post-translational modification that controls protein stability, subcellular localization, signaling complex assembly, and proteasome-dependent degradation. In cancer, altered ubiquitin signaling reshapes core oncogenic programs by regulating tumor suppressors, cell-cycle proteins, transcription factors, DNA damage response components, immune checkpoints, inflammatory mediators, and angiogenic regulators. Recent advances have clarified how ubiquitin chain topology, degron recognition, E3 ubiquitin ligase specificity, and deubiquitinase activity determine substrate fate rather than simply marking proteins for destruction. Dysregulated ubiquitination supports sustained proliferation, epithelial-mesenchymal plasticity, metastatic colonization, immune escape, therapy resistance, and tumor microenvironment remodeling. These mechanisms have also generated therapeutic opportunities. Proteasome inhibitors remain clinically relevant in selected hematologic malignancies, while E3 ligase modulators, deubiquitinase inhibitors, molecular glues, and proteolysis-targeting chimeras have expanded the druggable space to transcription factors, scaffolding proteins, mutant oncoproteins, and lineage-specific dependencies. This review summarizes recent progress in ubiquitination biology in cancer, with emphasis on enzymatic regulation, tumor-cell intrinsic malignant phenotypes, inflammatory and immune control, angiogenesis, and therapeutic strategies based on the ubiquitin-proteasome system and targeted protein degradation.

Keywords: Ubiquitination, Ubiquitin-proteasome system, E3 ubiquitin ligase, Deubiquitinase, Tumor microenvironment

1. Introduction

Ubiquitination is a covalent protein modification in which ubiquitin is attached to lysine residues, N-terminal amino groups, or occasionally non-lysine residues of substrate proteins. The modification is executed through an enzymatic cascade involving ubiquitin-activating enzymes, ubiquitin-conjugating enzymes, and ubiquitin ligases, while deubiquitinases remove or edit ubiquitin chains. Cancer cells use this reversible system to adjust protein abundance and signaling intensity with high temporal precision. Because tumor progression depends on continuous adaptation to genotoxic stress, immune pressure, hypoxia, nutrient limitation, and therapeutic intervention, altered

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ubiquitination provides a molecular route through which malignant cells remodel multiple cancer hallmarks at once [1].

The biological meaning of ubiquitination depends on chain architecture and substrate context. K48-linked chains classically promote proteasomal degradation, whereas K63-linked and linear chains often support signal transduction, DNA repair, trafficking, and immune pathway assembly. Mixed or branched chains, monoubiquitination, and ubiquitin-like modifications further expand the signaling vocabulary [2]. This expanded ubiquitin code explains why the same enzymatic system can destabilize tumor suppressors, stabilize oncogenic signaling complexes, silence antigen presentation, or promote inflammatory transcription. Protein fate and pathway output depend on how this regulatory language is written, edited, and read within a given cellular state.

Cancer research has placed E3 ubiquitin ligases and deubiquitinases at the center of this regulatory network because they provide substrate selectivity. E3 ligases such as MDM2, SCF complexes, APC/C, TRIM proteins, CRL family members, RNF proteins, KEAP1, FBXW7, and CBL family proteins participate in cell-cycle control, growth factor signaling, DNA damage responses, metabolic adaptation, and immune regulation. Deubiquitinases including USP7, USP8, USP14, USP22, USP48, USP51, and others can stabilize oncogenic proteins, alter checkpoint signaling, or modulate inflammatory pathways [3]. Their altered expression, mutation, or pathway rewiring contributes to malignant progression and provides druggable nodes for intervention.

Therapeutic development has accelerated this field. The ubiquitin-proteasome system has long been exploited through proteasome inhibitors in multiple myeloma and mantle cell lymphoma, but current strategies reach beyond global proteasome blockade. Molecular glues and proteolysis-targeting chimeras recruit E3 ligases to disease-relevant proteins and induce selective degradation. These approaches can remove proteins that lack conventional active sites and can eliminate scaffolding or transcriptional functions that inhibitors may not suppress. This review summarizes recent advances in ubiquitination-mediated cancer biology and therapeutic targeting.

2. Molecular basis of protein ubiquitination and its cancer-related biological effects

Protein ubiquitination operates as a dynamic regulatory system rather than a single degradation pathway. Substrate fate is determined by the enzyme cascade, degron exposure, chain linkage, chain length, subcellular localization, proteasome accessibility, and deubiquitinase-mediated chain editing. Tumor cells exploit this complexity to couple signal transduction with protein turnover. The same pathway can promote proliferation by degrading cell-cycle inhibitors, support metastasis by stabilizing epithelial-mesenchymal transition regulators, or increase immune escape by controlling checkpoint protein abundance and antigen presentation [4].

2.1. Enzymatic reaction systems and dynamic regulation of ubiquitination

The ubiquitination cascade begins with ATP-dependent activation of ubiquitin by an E1 enzyme, transfer to the catalytic cysteine of an E2 enzyme, and substrate-directed ligation mediated by an E3 ubiquitin ligase. RING ligases generally promote direct ubiquitin transfer from E2 to substrate, HECT ligases form a thioester intermediate before substrate transfer, and RBR ligases combine features of both mechanisms. The human genome encodes hundreds of E3 ligases, allowing extensive substrate selectivity across cell-cycle, DNA repair, immune, and metabolic pathways [5]. Degrons provide recognition signals, and their exposure can be controlled by phosphorylation, acetylation, conformational change, proteolytic cleavage, or ligand binding [6].

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The relationship among enzymatic writing, ubiquitin-signal recognition, and deubiquitinase-mediated erasure is illustrated schematically in Figure 1.

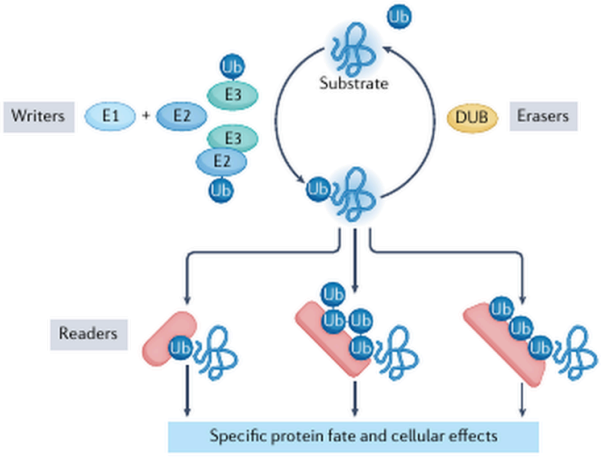


Figure 1. Core elements of the ubiquitin code and substrate-fate regulation [2]

Deubiquitinases counterbalance ligation by removing ubiquitin, trimming chains, or editing linkage composition. This editing can rescue substrates from proteasomal degradation, remodel signaling complexes, or terminate inflammatory pathway activation. In cancer, altered deubiquitinase activity can stabilize oncogenic transcription factors, DNA repair proteins, immune checkpoint regulators, or metabolic enzymes [7]. Because E3 ligases and deubiquitinases determine substrate selectivity and signal duration, their dysregulation often produces more specific oncogenic effects than broad changes in ubiquitin abundance.

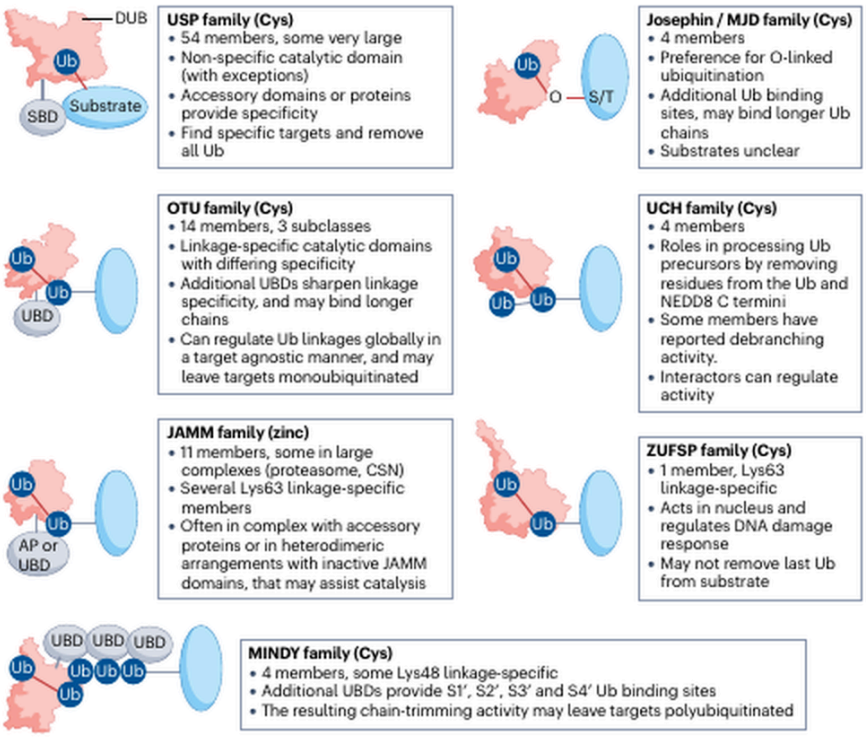


Figure 2. Structural classes and substrate-recognition features of deubiquitinases [8]

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The major DUB families and their modes of substrate engagement are shown in Figure 2, providing a structural framework for interpreting cancer-associated deubiquitination.

Ubiquitination is also shaped by the cellular compartment in which it occurs. Nuclear ubiquitination regulates chromatin-associated proteins, transcription factors, and DNA repair complexes, whereas cytoplasmic ubiquitination controls receptor signaling, kinase pathway duration, and protein quality control. Membrane-associated ubiquitination governs receptor internalization, endosomal sorting, and immune checkpoint trafficking. These spatial constraints are relevant to cancer because identical enzymes can produce distinct outcomes when recruited to different substrates or compartments. A substrate that is degraded after K48-linked polyubiquitination may instead participate in signaling when decorated with K63-linked or mixed chains, and the balance between these outcomes is frequently altered by oncogenic phosphorylation or stress-induced degron exposure [6].

2.2. Regulation of tumor cell proliferation by ubiquitination

Tumor proliferation requires persistent activation of growth-promoting pathways and disruption of cell-cycle checkpoints. Ubiquitination controls this process through degradation or stabilization of cyclins, cyclin-dependent kinase inhibitors, p53 pathway components, MYC, beta-catenin, mTOR signaling components, and receptor tyrosine kinases. E3 ligases can act as oncogenic drivers when they eliminate tumor suppressive proteins, but the same class of enzymes can suppress tumorigenesis when they degrade oncogenic substrates. FBXW7, for example, is commonly discussed as a tumor suppressive E3 ligase because it targets multiple growth-promoting proteins, while MDM2 promotes tumorigenesis through p53 degradation when the p53 regulatory axis remains intact [9].

Recent mechanistic studies illustrate how specific ubiquitination circuits sustain growth under therapeutic stress. RNF167 and the deubiquitinase STAMBPL1 modulate mTOR signaling and cancer progression, linking ubiquitin editing with nutrient-sensitive growth control [10]. Ubiquitination also intersects with DNA repair and replication stress. Altered degradation of repair factors can promote genomic instability while allowing cancer cells to survive genotoxic exposure. In this setting, ubiquitin signaling does not merely follow oncogenic transformation. It helps select tumor clones that tolerate replication errors, evade checkpoint arrest, and maintain proliferative signaling despite metabolic or therapeutic constraints.

Growth regulation by ubiquitination is closely connected with therapeutic resistance. Kinase inhibitors, endocrine therapy, radiation, and chemotherapy can impose selective pressure that changes degron phosphorylation, receptor turnover, and compensatory pathway stability. Cancer cells may stabilize alternative survival proteins through deubiquitinase induction or decrease degradation of drug-resistant signaling nodes. Conversely, restoration of substrate degradation can resensitize cells when the resistant phenotype depends on accumulation of a defined oncoprotein. This logic has supported degrader development against estrogen receptor, androgen receptor, BET proteins, CDK family members, and epigenetic regulators [11].

2.3. Regulation of tumor invasion and metastasis by ubiquitination

Metastasis requires epithelial-mesenchymal plasticity, extracellular matrix remodeling, altered adhesion, migration, intravasation, survival in circulation, and colonization of distant tissues. Ubiquitination regulates these processes by controlling the abundance and activity of EMT transcription factors, cytoskeletal regulators, adhesion molecules, receptor signaling proteins, and

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hypoxia-associated factors [4]. Substrate-specific degradation can suppress invasion when oncogenic EMT regulators are removed, whereas stabilization of Snail, Twist, ZEB family proteins, beta-catenin, or focal adhesion signaling components can promote dissemination.

The metastatic role of ubiquitination is strongly context-dependent because many E3 ligases and deubiquitinases regulate several substrates with opposing functions. Deubiquitinases may stabilize EMT drivers or cancer stemness regulators, while E3 ligases can either restrain or enhance invasion depending on substrate selection. USP51, for instance, has been reported to support colorectal cancer stemness and chemoresistance through a feed-forward relationship with HIF1A [12]. Ubiquitin-specific peptidase 22 has also been connected with metastatic metabolic adaptation in breast cancer through regulation of lipolysis-associated circuitry [13]. These examples indicate that metastatic progression often reflects coordinated ubiquitin-dependent remodeling of transcription, metabolism, and microenvironmental adaptation rather than a single substrate event.

3. Ubiquitination-mediated regulation of the tumor microenvironment and antitumor immunity

The tumor microenvironment is shaped by malignant cells, stromal cells, endothelial cells, extracellular matrix, and infiltrating immune populations. Ubiquitination regulates this ecosystem through inflammatory signaling, antigen presentation, immune checkpoint turnover, cytokine production, macrophage recruitment, T-cell function, and vascular remodeling. Because these processes are regulated by protein stability and signaling complex assembly, the ubiquitin system acts as a shared control layer between tumor-cell intrinsic oncogenic signaling and host immune responses [14].

3.1. Regulation of inflammatory signaling by ubiquitination

Inflammatory pathways are highly dependent on ubiquitin chain assembly and deubiquitinase-mediated editing. K63-linked and linear ubiquitin chains support signaling complex formation downstream of TNF receptors, Toll-like receptors, interleukin receptors, and pattern-recognition receptors. These chains recruit adaptors and kinases that activate NF-kappaB, MAPK, interferon, and inflammasome-related pathways. In cancer, persistent inflammatory signaling promotes survival, angiogenesis, invasion, immune suppression, and therapy resistance. A20, CYLD, TRAF family proteins, cIAPs, LUBAC components, and several USP family deubiquitinases regulate these pathways by controlling chain formation or removal [15].

Dysregulated inflammatory ubiquitination has consequences beyond cytokine abundance. It can determine whether cells undergo inflammatory death, apoptosis, necroptosis, pyroptosis, or survival after receptor stimulation [14]. This decision is relevant to tumor therapy because inflammatory cell death may enhance immune activation, whereas chronic low-grade inflammatory signaling can promote immune exclusion and tissue remodeling. Cancer cells and stromal cells may benefit from ubiquitin circuits that maintain inflammatory transcription without triggering lethal pathway activation.

3.2. Regulation of tumor immune responses by ubiquitination

Antitumor immunity depends on antigen processing, major histocompatibility complex expression, interferon signaling, immune checkpoint abundance, T-cell receptor signaling, and myeloid cell function. Ubiquitination regulates each of these processes. Tumor cells can reduce antigen

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presentation by altering ubiquitin-dependent trafficking or degradation of antigen-processing components, while deubiquitinases may stabilize PD-L1 and other immune regulators [16]. In colorectal cancer, EZH2 inhibition has been reported to enhance PD-L1 protein stability through USP22-mediated deubiquitination, showing how epigenetic treatment can intersect with ubiquitin-dependent checkpoint regulation [17].

Several recent studies have connected ubiquitin enzymes with immune evasion and immunotherapy response. In vivo CRISPR screens identified the E3 ligase COP1 as a regulator of macrophage infiltration and a potential cancer immunotherapy target [18]. USP8 inhibition reshaped an inflamed tumor microenvironment and potentiated immunotherapy in preclinical models [19]. USP2 inhibition enhanced phagocytosis by releasing CD47-restrained antitumor immune activity [20]. These data place ubiquitin regulators within strategies that modify immune recognition, myeloid suppression, and checkpoint responsiveness rather than targeting tumor proliferation alone.

A representative in vivo screening model linking COP1 activity to macrophage infiltration and immunotherapy response is summarized in Figure 3.

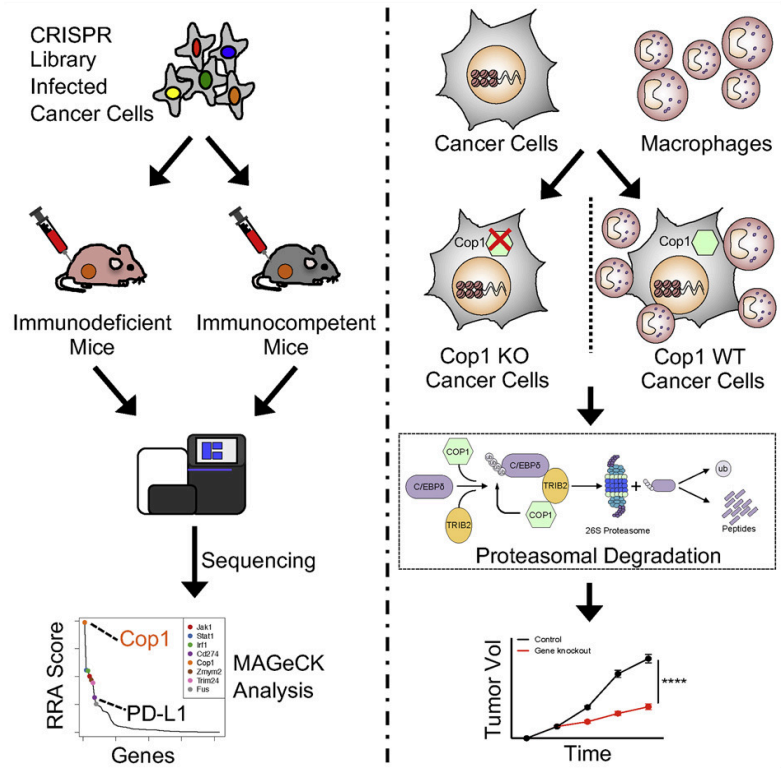


Figure 3. COP1-centered screening framework for tumor immune microenvironment regulation [18]

Ubiquitination also regulates lymphocyte-intrinsic signaling. T cells require controlled turnover of proximal receptor components, costimulatory proteins, inhibitory receptors, and transcriptional regulators to maintain cytotoxic function. Excessive ubiquitination of activating components can weaken T-cell receptor signaling, whereas defective degradation of inhibitory molecules can prolong exhaustion-associated states. CAR T-cell studies have shown that sequestration of the ubiquitin-modifying enzyme A20 can cause cell death in 4-1BB-encoding constructs, illustrating how engineered immunotherapies can be affected by ubiquitin pathway balance [15]. Therapeutic approaches directed at ubiquitination should account for tumor-cell effects and immune-cell effects simultaneously.

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3.3. Regulation of tumor angiogenesis by ubiquitination

Tumor angiogenesis is regulated by hypoxia-inducible transcription, VEGF pathway activation, endothelial cell survival, extracellular matrix remodeling, and inflammatory mediator release. Ubiquitination contributes to these processes through oxygen-sensitive degradation of HIF family proteins, regulation of VEGF receptor signaling, turnover of angiogenic transcription factors, and modification of inflammatory pathways that recruit proangiogenic myeloid cells. The VHL E3 ligase complex provides a central example. Under normoxia, hydroxylated HIF-alpha proteins are recognized and degraded by the VHL complex. Under hypoxia or VHL loss, HIF signaling persists and supports angiogenic and metabolic reprogramming.

Angiogenesis also depends on ubiquitin-regulated communication among tumor cells, endothelial cells, and immune cells. Inflammatory NF-kappaB signaling can increase proangiogenic cytokines, while ubiquitin-dependent receptor turnover determines the intensity of endothelial growth factor signaling. The relevance of this layer is particularly clear in tumors with hypoxia, acidosis, or therapy-induced stress, where altered proteostasis supports both vascular adaptation and immune escape. Although anti-VEGF therapy remains clinically established, targeting ubiquitin regulators that stabilize hypoxia and angiogenic signaling may provide additional opportunities when angiogenesis is coupled to immune suppression or drug resistance.

4. Cancer therapeutic strategies targeting ubiquitination regulation

The ubiquitin system has become a therapeutic platform because it controls protein abundance rather than merely enzyme activity. Drugs can inhibit the proteasome, modulate E3 ligase function, inhibit deubiquitinases, stabilize tumor suppressive degradation pathways, or redirect E3 ligases toward selected disease proteins. Each strategy has a distinct therapeutic window. Broad proteasome inhibition causes systemic proteotoxic stress, whereas targeted degradation depends on ligandable proteins, appropriate E3 ligase recruitment, ternary complex formation, and proteasome access [15].

4.1. Antitumor strategies targeting the ubiquitin-proteasome system

Proteasome inhibitors validate the ubiquitin-proteasome system as a cancer target. Bortezomib, carfilzomib, and ixazomib disrupt degradation of ubiquitinated proteins and create proteotoxic stress, particularly in plasma cell malignancies with high immunoglobulin production. Their activity is linked to endoplasmic reticulum stress, unfolded protein response activation, apoptosis, and altered NF-kappaB signaling. Recent reviews emphasize continuing relevance of proteasome inhibitors while also noting limitations including peripheral neuropathy, cytopenias, resistance, and narrower efficacy in many solid tumors [21-23].

Therapeutic refinement focuses on improving selectivity within the protein degradation machinery. Approaches include targeting proteasome subunits with distinct tissue dependence, combining proteasome inhibitors with immunomodulatory drugs or checkpoint blockade, and exploiting tumor states with high proteostasis burden. Neddylation inhibition also affects cullin-RING ligase activity and can modify cancer metabolism and stress responses [24]. These strategies show that global proteostasis disruption can remain useful, but toxicity and adaptive resistance encourage movement toward substrate-selective ubiquitin modulation.

The clinical performance of proteasome inhibition also demonstrates a general principle for ubiquitin-directed therapy. Tumor sensitivity depends on pathway dependency rather than pathway presence. Almost all cells require proteasomal degradation, but plasma cell neoplasms show marked

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vulnerability because secretory load and protein quality control are unusually high. The same concept applies to E3 ligase inhibitors, deubiquitinase inhibitors, and degraders. Patient selection should identify tumors in which a defined ubiquitin-regulated substrate or proteostasis state acts as a functional dependency instead of assuming that pathway modulation will be broadly active across histological types.

4.2. Antitumor strategies targeting E3 ubiquitin ligases

E3 ubiquitin ligases are attractive therapeutic targets because they specify substrate recognition. Inhibition of oncogenic E3 ligases may restore tumor suppressor stability, whereas activation or recruitment of tumor suppressive E3 ligases may eliminate oncogenic proteins. MDM2 inhibitors, KEAP1-NRF2 pathway modulators, cullin-RING ligase regulators, and TRIM family approaches illustrate the diversity of this strategy [25]. The difficulty lies in the structural and functional heterogeneity of E3 ligases. Many lack deep catalytic pockets, function through protein-protein interfaces, or require multiprotein assemblies that are difficult to modulate selectively.

Cancer therapy increasingly uses E3 ligases as recruited effectors rather than as conventional inhibitor targets. CRBN, VHL, DCAF15, DCAF16, RNF114, and other ligases have been explored as degradation platforms, but the available ligandable E3 ligase space remains limited [26, 27]. E3 ligase selection affects tissue distribution, neosubstrate risk, degradation kinetics, resistance mutations, and immunological effects. Deconvolution of ligase-substrate relationships and discovery of new E3 ligase ligands are needed to expand targeted degradation beyond the current CRBN- and VHL-dominated landscape.

Targeting E3 ligases also requires separation of catalytic function from scaffolding function. Some ligases regulate cancer pathways through ubiquitin transfer, whereas others assemble signaling complexes or recruit adaptors independently of catalytic activity. Inhibitors that disrupt one interface may not reproduce the biological effect of genetic depletion, and complete ligase loss may produce toxicity in normal tissues. Chemical strategies should be matched to the relevant mechanism, including catalytic inhibition, substrate-interface blockade, ligase stabilization, allosteric modulation, or heterobifunctional recruitment.

4.3. Antitumor strategies based on targeted protein degradation

Targeted protein degradation uses the ubiquitin-proteasome system to eliminate selected proteins. Proteolysis-targeting chimeras contain a ligand for the protein of interest, a linker, and an E3 ligase ligand. Molecular glues act through smaller chemical scaffolds that induce or stabilize interactions between a target protein and an E3 ligase. Both modalities can remove proteins whose scaffolding, transcriptional, or nonenzymatic functions are not fully suppressed by inhibitors [28]. Degrader activity depends on ternary complex geometry, ubiquitin acceptor accessibility, productive polyubiquitination, cellular permeability, pharmacokinetics, and tissue distribution.

The clinical translation of degraders has advanced rapidly. Protein degraders have entered trials in estrogen receptor-positive breast cancer, androgen receptor-driven prostate cancer, hematologic malignancies, and other tumor settings [29]. Vepdegestrant, an estrogen receptor PROTAC degrader, has progressed through late-stage clinical evaluation in advanced breast cancer, providing a concrete example of the transition from chemical biology to therapeutic testing [30]. Molecular glue design has also matured from serendipitous immunomodulatory drugs toward rational discovery of neosubstrate interactions. Remaining challenges include resistance through target mutation or E3 ligase pathway alteration, degradation of unintended neosubstrates, limited delivery to solid tumors,

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and uncertainty in predicting which proteins are most suitable for degradation. Future degrader development will require stronger integration of structural biology, chemoproteomics, proteome-wide selectivity profiling, and biomarker-guided clinical design.

5. Conclusions and outlook

Protein ubiquitination regulates tumor biology through coordinated control of protein degradation, signaling complex formation, transcriptional output, immune recognition, inflammatory pathway strength, and vascular adaptation. Recent work has replaced the simplified view of ubiquitination as a degradation tag with a more precise model in which chain topology, degrons, E3 ligase selection, deubiquitinase editing, and cellular context determine substrate fate. This model explains why ubiquitination can support either tumor suppression or malignant progression depending on the enzyme, substrate, and tissue state.

Several areas require closer mechanistic resolution. The substrate range of many E3 ligases remains incompletely mapped in cancer cells and immune cells. Deubiquitinase inhibitors need clearer selectivity profiles and stronger pharmacodynamic biomarkers. Ubiquitin-dependent immune regulation should be evaluated in models that preserve myeloid, lymphoid, endothelial, and stromal compartments. Angiogenic and inflammatory outputs should be studied together because hypoxia, cytokine signaling, and proteostasis stress often converge in the same tumor regions. These directions are experimental requirements rather than broad conceptual additions.

Therapeutic translation will depend on matching ubiquitin-directed drugs to defined tumor dependencies. Proteasome inhibitors will remain useful where proteotoxic stress is a dominant vulnerability. E3 ligase inhibitors and deubiquitinase inhibitors may benefit tumors driven by discrete stability defects. Targeted protein degradation may expand treatment options for transcription factors, scaffolding proteins, and mutant oncoproteins that resist occupancy-based pharmacology. Durable clinical benefit will require careful control of neosubstrate toxicity, resistance mechanisms, immune consequences, and patient selection. A substrate-resolved and context-specific understanding of ubiquitination will guide the next phase of cancer therapy development.

References

[1] Liu, F., Chen, J., Li, K., et al. (2024). Ubiquitination and deubiquitination in cancer: From mechanisms to novel therapeutic approaches. *Molecular Cancer*.
[2] Dikic, I., & Schulman, B. A. (2022). An expanded lexicon for the ubiquitin code. *Nature Reviews Molecular Cell Biology*.
[3] Ebadi, P., Stratton, C. M., & Olsen, S. K. (2025). E3 ubiquitin ligases in signaling, disease, and therapeutics. *Trends in Biochemical Sciences*.
[4] Han, S., Wang, R., Zhang, Y., et al. (2022). The role of ubiquitination and deubiquitination in tumor invasion and metastasis. *International Journal of Biological Sciences*.
[5] Cai, C., Tang, Y.-D., Zhai, J., & Zheng, C. (2022). The RING finger protein family in health and disease. *Signal Transduction and Targeted Therapy*.
[6] Zhang, Z., Mena, E. L., Timms, R. T., Koren, I., & Elledge, S. J. (2025). Degrons: Defining the rules of protein degradation. *Nature Reviews Molecular Cell Biology*.
[7] Ren, J., Yu, P., Liu, S., et al. (2023). Deubiquitylating enzymes in cancer and immunity. *Advanced Science*.
[8] Singh, N., & Singh, A. B. (2016). Deubiquitinases and cancer: A snapshot. *Critical Reviews in Oncology/Hematology*.
[9] Han, D., Wang, L., Jiang, S., & Yang, Q. (2023). The ubiquitin–proteasome system in breast cancer. *Trends in Molecular Medicine*.

DOI: 10.54254/2753-8818/2026.HZ38696

[10] Wang, D., Xu, C., Yang, W., et al. (2022). E3 ligase RNF167 and deubiquitinase STAMBPL1 modulate mTOR and cancer progression. *Molecular Cell*.
[11] Chirnomas, D., Hornberger, K. R., & Crews, C. M. (2023). Protein degraders enter the clinic — a new approach to cancer therapy. *Nature Reviews Clinical Oncology*.
[12] Mu, M., Zhang, Q., Li, J., et al. (2023). USP51 facilitates colorectal cancer stemness and chemoresistance by forming a positive feed-forward loop with HIF1A. *Cell Death and Differentiation*.
[13] Zhou, Y., Chu, P., Wang, Y., et al. (2024). Epinephrine promotes breast cancer metastasis through a ubiquitin-specific peptidase 22–mediated lipolysis circuit. *Science Advances*.
[14] Cockram, P. E., Kist, M., Prakash, S., Chen, S.-H., Wertz, I. E., & Vucic, D. (2021). Ubiquitination in the regulation of inflammatory cell death and cancer. *Cell Death and Differentiation*.
[15] Dou, Z., Bonacci, T. R., Shou, P., et al. (2024). 4-1BB-encoding CAR causes cell death via sequestration of the ubiquitin-modifying enzyme A20. *Cellular & Molecular Immunology*.
[16] Hsieh, H.-C., Ling, L.-L., & Wang, Y.-C. (2026). Post-translational modifications of immune checkpoints: Molecular mechanisms, tumor microenvironment remodeling, and therapeutic implications. *Journal of Biomedical Science*.
[17] Huang, J., Yin, Q., Wang, Y., et al. (2024). EZH2 inhibition enhances PD-L1 protein stability through USP22-mediated deubiquitination in colorectal cancer. *Advanced Science*.
[18] Wang, X., Tokheim, C., Gu, S. S., et al. (2021). In vivo CRISPR screens identify the E3 ligase Cop1 as a modulator of macrophage infiltration and cancer immunotherapy target. *Cell*.
[19] Xiong, W., Gao, X., Zhang, T., et al. (2022). USP8 inhibition reshapes an inflamed tumor microenvironment that potentiates the immunotherapy. *Nature Communications*.
[20] Dai, P., Sun, Y., Huang, Z., et al. (2025). USP2 inhibition unleashes CD47-restrained phagocytosis and enhances anti-tumor immunity. *Nature Communications*.
[21] Aliabadi, F., Sohrabi, B., Mostafavi, E., Pazoki-Toroudi, H., & Webster, T. J. (2021). Ubiquitin–proteasome system and the role of its inhibitors in cancer therapy. *Open Biology*.
[22] Spano, D., & Catara, G. (2023). Targeting the ubiquitin–proteasome system and recent advances in cancer therapy. *Cells*.
[23] Gazzaroli, G., Angeli, A., Giacomini, A., & Ronca, R. (2024). Proteasome inhibitors as anticancer agents. *Expert Opinion on Therapeutic Patents*.
[24] Zhou, Q., Lin, W., Wang, C., et al. (2022). Neddylation inhibition induces glutamine uptake and metabolism by targeting CRL3SPOP E3 ligase in cancer cells. *Nature Communications*.
[25] Suzuki, T., Takahashi, J., & Yamamoto, M. (2023). Molecular basis of the KEAP1-NRF2 signaling pathway. *Molecules and Cells*.
[26] Xiao, Y., Yuan, Y., Liu, Y., et al. (2024). Targeted protein degradation: Current and emerging approaches for E3 ligase deconvolution. *Journal of Medicinal Chemistry*.
[27] Ishida, T., & Ciulli, A. (2020). E3 ligase ligands for PROTACs: How they were found and how to discover new ones. *SLAS Discovery: Advancing the Science of Drug Discovery*.
[28] Hinterndorfer, M., Spiteri, V. A., Ciulli, A., & Winter, G. E. (2025). Targeted protein degradation for cancer therapy. *Nature Reviews Cancer*.
[29] Hamilton, E. P., Jeselsohn, R. M., Vahdat, L. T., & Hurvitz, S. A. (2025). PROteolysis TArgeting Chimera (PROTAC) estrogen receptor degraders for treatment of estrogen receptor–positive advanced breast cancer. *Targeted Oncology*.
[30] Campone, M., De Laurentiis, M., Jhaveri, K., et al. (2025). Vepdegestrant, a PROTAC estrogen receptor degrader, in advanced breast cancer. *The New England Journal of Medicine*.