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Advances in the Application of PROTAC Technology in Cancer Therapy

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Abstract. Traditional small-molecule anticancer inhibitors primarily block single protein activities and are vulnerable to mutation-mediated drug resistance. Proteolysis-targeting chimera (PROTAC) technology induces the ubiquitin-proteasome-dependent clearance of oncogenic proteins and provides a promising new strategy for precision cancer therapy. This paper summarizes the molecular basis, degradation mechanism, design principles, and translational progress of PROTAC degraders in cancer treatment. PROTACs consist of a target ligand, an E3 ubiquitin ligase ligand and a connecting linker, and they exert unique event-driven antitumor effects by inducing ternary complex formation and target ubiquitination. Representative ER, AR, BTK, BCL-xL, and BRD4 degraders have shown promising preclinical or clinical activity, especially in drug-resistant tumors. Current challenges include poor oral pharmacokinetic properties, incomplete tumor selectivity, uncertain long-term safety, and emerging resistance mechanisms related to ubiquitin signaling. Optimized ligand-linker design, tumor-selective E3 ligases, prodrug strategies and biomarker-guided clinical trials are expected to greatly promote the clinical development of PROTAC-based anticancer therapies.

Keywords: PROTAC, targeted protein degradation, ubiquitin-proteasome system, cancer therapy, drug resistance

1. Introduction

Malignant tumors remain a major global health burden because of their molecular heterogeneity, metastatic potential and frequent development of therapeutic resistance. Over the past two decades, targeted therapies, including kinase inhibitors, endocrine therapies, monoclonal antibodies and immune checkpoint inhibitors, have improved outcomes for selected patient populations. Nevertheless, conventional targeted agents still face intrinsic limitations. Many oncogenic proteins lack deep, druggable pockets; many inhibitors block only one enzymatic or binding activity while leaving scaffolding or transcriptional functions intact; and prolonged treatment frequently selects for target mutations, bypass signaling, target amplification or drug-tolerant cellular states [1-3].

Proteolysis-targeting chimera (PROTAC) technology offers a mechanistically distinct solution to these limitations. A PROTAC is a heterobifunctional small molecule composed of a ligand for the protein of interest, a linker and a ligand for an E3 ubiquitin ligase. By bringing the target protein into

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proximity with the E3 ligase, PROTACs promote ternary complex formation, ubiquitination and subsequent 26S proteasome-mediated degradation. Therefore, PROTACs operate through an event-driven pharmacological mode rather than an occupancy-driven inhibition mode [1, 4, 5]. A redesigned schematic of this process is shown below (See Figure 1).

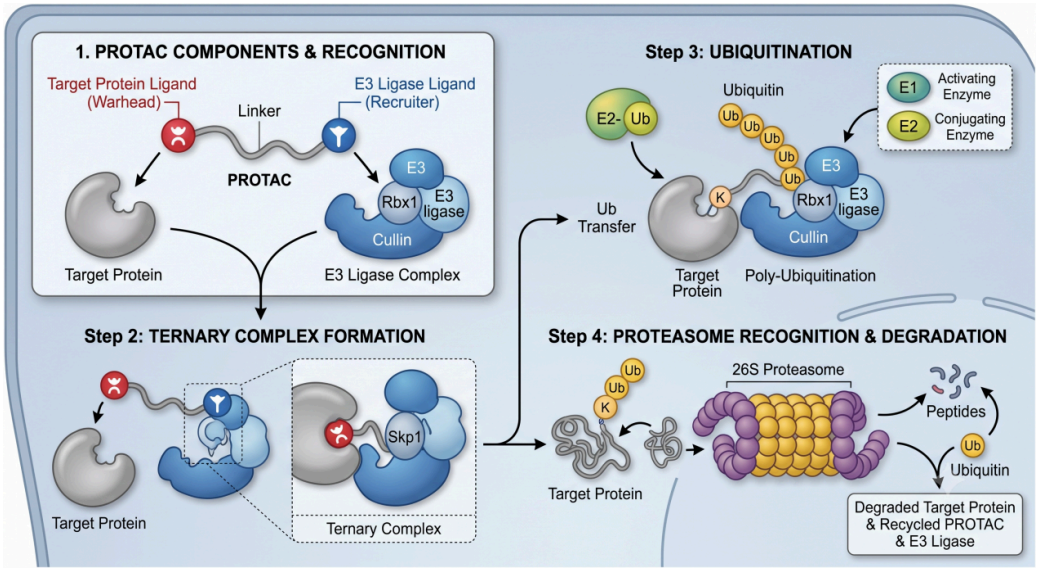

Figure 1. Redesigned schematic of PROTAC-mediated target protein degradation

A PROTAC molecule binds the protein of interest and recruits an E3 ubiquitin ligase to form a ternary complex. The target protein is then polyubiquitinated and degraded by the 26S proteasome, while the PROTAC molecule and E3 ligase can be recycled for additional degradation cycles. This figure was redrawn and reorganized to illustrate the mechanism rather than directly reproduce a published image.

2. Basic composition and degradation mechanism of PROTAC

The degradation activity of a PROTAC depends on three interrelated molecular elements: the target ligand, the E3 ligase ligand and the linker. The target ligand determines initial recognition of the protein of interest, whereas the E3 ligase ligand recruits a ubiquitin ligase such as CRBN or VHL. The linker is not merely a chemical spacer; it determines the geometry, flexibility and cooperativity of the ternary complex. Productive ternary complex formation allows the E2-E3 ubiquitination machinery to transfer ubiquitin chains to accessible lysine residues on the target protein, which is then recognized and degraded by the proteasome [1, 3, 4].

Compared with conventional inhibitors, PROTACs may eliminate the entire target protein and thereby remove enzymatic, scaffolding, transcriptional and protein-protein interaction functions simultaneously. This property is highly relevant for oncogenic regulators such as nuclear receptors, BET proteins and transcription factors. In principle, after one degradation event, a PROTAC molecule can dissociate and participate in additional cycles of degradation, enabling sub-stoichiometric pharmacological effects. However, degradation efficiency is influenced by target abundance, E3 expression, ternary complex stability, lysine accessibility, cell permeability and intracellular drug exposure [3-5].

A key feature of PROTAC pharmacology is that stronger binary binding does not always translate into better degradation. The stability and cooperativity of the ternary complex are often more

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predictive of degradation potency than isolated ligand affinity. In addition, excessive PROTAC concentrations can produce the hook effect, in which binary complexes predominate and productive ternary complex formation decreases. Therefore, evaluation of PROTAC candidates should include DC50, Dmax, degradation kinetics, selectivity, cytotoxicity, ternary complex cooperativity and pharmacokinetic/pharmacodynamic relationships [1, 4, 5].

3. Core optimization factors for PROTAC molecular design

Target ligand selection is the starting point of PROTAC design. For targets with known inhibitors, such as AR, ER, BTK, BRD4 and BCL-xL, established ligands can be converted into degradation warheads if they contain suitable exit vectors for linker attachment. For targets lacking classical binding sites, fragment screening, covalent ligand discovery, peptide-based binders and structure-guided approaches may expand targetability. This broadens the degradable proteome beyond the boundaries of classical small-molecule inhibition [2, 4].

E3 ligase selection is equally important. Although more than 600 human E3 ligases exist, current PROTAC development relies heavily on a limited number of ligases, especially CRBN and VHL. This narrow E3 toolbox restricts tissue selectivity and may constrain the range of degradable targets. Expanding the E3 ligase repertoire, especially toward tumor-enriched or tissue-selective ligases, is therefore a major direction for next-generation degrader development [6].

Linker optimization integrates medicinal chemistry with structural biology. Linkers that are too short may cause steric hindrance, whereas overly long or flexible linkers may weaken productive ternary complex formation and reduce cell permeability. Modern PROTAC optimization increasingly relies on structural modeling, proteomics and iterative cellular testing rather than simple assembly of two ligands with an arbitrary linker [5, 6].

4. Preclinical and clinical applications of PROTACs in solid tumors

Several PROTAC degraders have moved from chemical biology tools toward clinical oncology candidates, and their development has provided proof of concept for targeted protein degradation as a therapeutic modality in solid tumors [7].

4.1. Breast cancer

Estrogen receptor-positive breast cancer is one of the most advanced areas of PROTAC translation. ER signaling drives tumor growth in a large subset of breast cancers, but endocrine therapy resistance frequently emerges through ESR1 mutations, ER pathway reactivation and adaptive survival signaling. Vepdegestrant (ARV-471) is an oral ER-targeting PROTAC designed to degrade both wild-type ER and clinically relevant mutant ER proteins [8].

Preclinical studies demonstrated that vepdegestrant induces robust ER degradation and antitumor activity in ER-positive breast cancer models, including endocrine-resistant models. Clinical investigation further supports the concept that ER degradation may provide therapeutic benefit in ER-positive/HER2-negative advanced breast cancer, particularly in molecularly selected patients with ESR1-mutant disease [8, 9]. These findings show that PROTACs may be most effective when patient selection is guided by target dependence and resistance biomarkers.

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4.2. Prostate cancer

The androgen receptor is a central driver of prostate cancer, especially metastatic castration-resistant prostate cancer. Resistance to AR pathway inhibitors can arise through AR amplification, ligand-binding domain mutations, splice variants and bypass signaling. AR degraders are designed to reduce total AR protein levels, potentially suppressing both ligand-dependent signaling and non-enzymatic AR functions. Bavdegalutamide (ARV-110) is a representative AR PROTAC that has shown AR degradation and antitumor activity in preclinical models [10].

The development of AR PROTACs illustrates both the promise and complexity of targeted degradation in solid tumors. Although degradation may overcome certain mutation-mediated resistance mechanisms, clinical activity depends on AR mutation spectrum, intratumoral drug exposure, coverage of splice variants and patient selection. These issues highlight the need for integrated biomarker strategies in future AR degrader trials [7, 10].

4.3. Lung cancer and other solid tumors

In lung cancer and other solid tumors, PROTAC research has focused on targets such as EGFR, ALK, the KRAS signaling axis, BRD4, CDKs, STAT3 and BCL-xL. For kinase targets with established inhibitors, degradation may provide a strategy to address resistance caused by mutant proteins or non-catalytic functions. For transcriptional and epigenetic regulators, protein elimination may more completely suppress oncogenic programs than functional inhibition alone [3, 5].

BCL-xL degradation is an important example of how PROTAC design may improve the therapeutic window. Classical BCL-xL inhibitors are limited by platelet toxicity. VHL-recruiting BCL-xL degraders attempt to exploit lower VHL expression in platelets, thereby preserving antitumor activity while reducing thrombocytopenia risk. This strategy demonstrates that E3 ligase biology can be used not only to induce degradation but also to shape tissue selectivity [6, 7].

5. Applications of PROTACs in hematological malignancies

Hematological malignancies provide favorable conditions for PROTAC application because malignant cells are relatively accessible to systemic drugs and often depend strongly on specific oncogenic signaling proteins. BTK degraders are being explored for B-cell malignancies, particularly in the context of resistance to covalent BTK inhibitors. By eliminating BTK protein rather than merely blocking its kinase activity, BTK PROTACs may bypass resistance caused by binding-site mutations [11].

Other targets in hematological malignancies include BCL-2 family proteins, IKZF1/3, STAT3 and BRD4. Some CRBN-recruiting degraders may also influence immune regulatory networks through degradation of immunomodulatory substrates. Overall, hematological tumor studies suggest that PROTACs may be most effective in diseases with clear target dependence, measurable pharmacodynamic biomarkers and strong intracellular target accessibility [11]. Notably, compared with traditional small-molecule inhibitors, PROTACs exert sustained antitumor effects by inducing complete target protein depletion, which can effectively inhibit the proliferation and invasion of hematological tumor cells. Moreover, their unique catalytic degradation mechanism enables low-dose administration, which effectively reduces the risk of off-target toxicity and improves the safety of clinical medication for blood tumor treatment.

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6. PROTACs for tumor resistance intervention and combination therapy

Drug resistance remains a major rationale for developing PROTAC-based anticancer therapeutics. Target mutations, protein overexpression and bypass pathway activation can limit the durability of conventional inhibitors. Because PROTACs remove the whole oncoprotein, they may suppress both catalytic and non-catalytic functions and thereby overcome selected resistance mechanisms. ER and AR degraders provide early examples of this strategy in endocrine-resistant breast cancer and castration-resistant prostate cancer [8-10, 12].

PROTACs may also be combined with existing anticancer modalities. ER degraders have been investigated together with CDK4/6 and PI3K/mTOR pathway inhibitors, while degraders targeting STAT3, PD-L1-related pathways or epigenetic regulators may reshape tumor immune microenvironments and enhance immunotherapy responses. However, rational combinations require careful toxicity assessment, pharmacodynamic monitoring and biomarker-guided patient selection [8, 12].

7. Next-generation modified PROTAC platforms

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8. Clinical translation limitations and future outlook

Several obstacles still limit the broad clinical application of PROTACs. First, many PROTAC molecules fall outside conventional drug-like chemical space, leading to poor oral absorption, uneven tissue distribution and uncertain intracellular exposure. Second, tissue selectivity cannot be fully guaranteed; degradation of target proteins in normal tissues may cause unexpected on-target toxicity. Third, tumor cells may develop resistance through E3 ligase downregulation, altered ubiquitin-proteasome activity, target mutation or drug efflux. Fourth, standardized clinical endpoints for target degradation remain underdeveloped, and many trials still rely mainly on tumor shrinkage rather than degradation-depth biomarkers [5, 12, 13].

Future research should focus on four directions. First, new linkers, low-polarity scaffolds and optimized E3 recruiters should be developed to improve pharmacokinetic performance. Second, multi-omics approaches should be used to identify biomarkers predicting degradation sensitivity,

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resistance and toxicity. Third, tumor-targeted delivery systems and prodrug strategies should be translated into clinically testable platforms. Fourth, randomized clinical trials should evaluate rational combinations of PROTACs with endocrine therapy, immunotherapy, chemotherapy and targeted inhibitors while incorporating pharmacodynamic biomarkers [12-15].

9. Conclusions

PROTAC technology represents a transformative approach in cancer therapy by shifting the therapeutic strategy from functional inhibition to targeted protein elimination. By recruiting E3 ubiquitin ligases to oncogenic proteins, PROTACs can trigger ubiquitination and proteasomal degradation, potentially overcoming limitations of conventional targeted therapy. ER, AR, BTK, BRD4, BCL-xL and STAT3 degraders illustrate the broad applicability of this platform in solid tumors and hematological malignancies. Nevertheless, clinical translation remains constrained by drug-like property limitations, tissue-selective toxicity, resistance mechanisms and incomplete biomarker systems. Continued advances in medicinal chemistry, E3 ligase discovery, structural biology, proteomics and tumor-specific delivery are expected to accelerate the development of safer and more effective PROTAC-based anticancer therapies.

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