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Advances in Proteolysis Targeting Chimeras

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Abstract: In recent years, proteolysis-targeting chimeras (PROTACs) have gained widespread attention as an emerging therapeutic approach. PROTACs are bifunctional molecules composed of a target protein-binding ligand, an E3 ubiquitin ligase ligand, and a linker connecting these ligands. By harnessing the cell's intrinsic ubiquitin-proteasome system (UPS), they promote the ubiquitination of specific target proteins, leading to their degradation and therapeutic effects. PROTACs show exceptional promise in targeting conventional "undruggable" targets compared to traditional small-molecule inhibitors. This review provides an overview of PROTACs, including their molecular mechanism of action, therapeutic benefits, development history, key design aspects, current research and development challenges, and future trends in next-generation PROTAC technology.

Keywords: PROTAC; Ubiquitin-proteasome system; Targeted therapy; Next-generation PROTAC

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1. Introduction

Cancer is a major disease that poses a serious threat to human health worldwide, with its incidence and death rates continuing to rise, adding a heavy burden to global health systems. According to the GLOBOCAN 2022 data released by the International Agency for Research on Cancer (IARC), there are approximately 20 million new cancer cases and 9.7 million deaths each year globally. Predictions suggest that by 2050, the number of new cases annually will exceed 35 million, marking an increasingly difficult challenge for cancer prevention and control [1].

Currently, common clinical treatments for cancer include surgery, radiotherapy, and chemotherapy. In molecular targeted therapy, small-molecule inhibitors are crucial because they specifically bind to oncogenic target proteins and block the proliferation and survival signaling pathways of tumor cells. However, these inhibitors face several limitations, such as the potential to cause target mutations leading to drug resistance, significant off-target toxicity, and the need for high doses over extended periods. These issues greatly restrict their clinical applications [2].

To address the issues above, proteolysis-targeting chimeras (PROTACs) have become a promising approach for anticancer drug discovery and development. PROTACs molecules are bifunctional compounds that bind to a target protein of interest (POI) on one end and recruit an E3 ubiquitin ligase(E3) on the other, leading to

ubiquitination of the POI and its degradation by the proteasome. Compared to traditional inhibitors, PROTACs offer potential benefits such as prolonged effects, the ability to target traditionally "undruggable" proteins, and the capacity to overcome drug resistance, opening new avenues for cancer therapy [3].

2. Mechanism of action and therapeutic benefits of PROTACs

2.1. Mechanism of action of PROTACs

Intracellularly, protein degradation and amino acid recycling mainly occur through two precisely regulated pathways: the lysosomal pathway and the ubiquitin-proteasome system (UPS) pathway. Of these two, UPS handles the degradation of most short-lived and misfolded proteins in the cell, and its dysfunction is closely linked to the development of many diseases, especially cancer [4]. Building on an in-depth understanding of the UPS mechanism, crews and his team first introduced the concept of PROTACs in 2001. These are heterobifunctional molecules composed of three key components: a ligand for binding POI, another ligand for recruiting E3 ligases, and a rationally designed linker covalently connecting them.

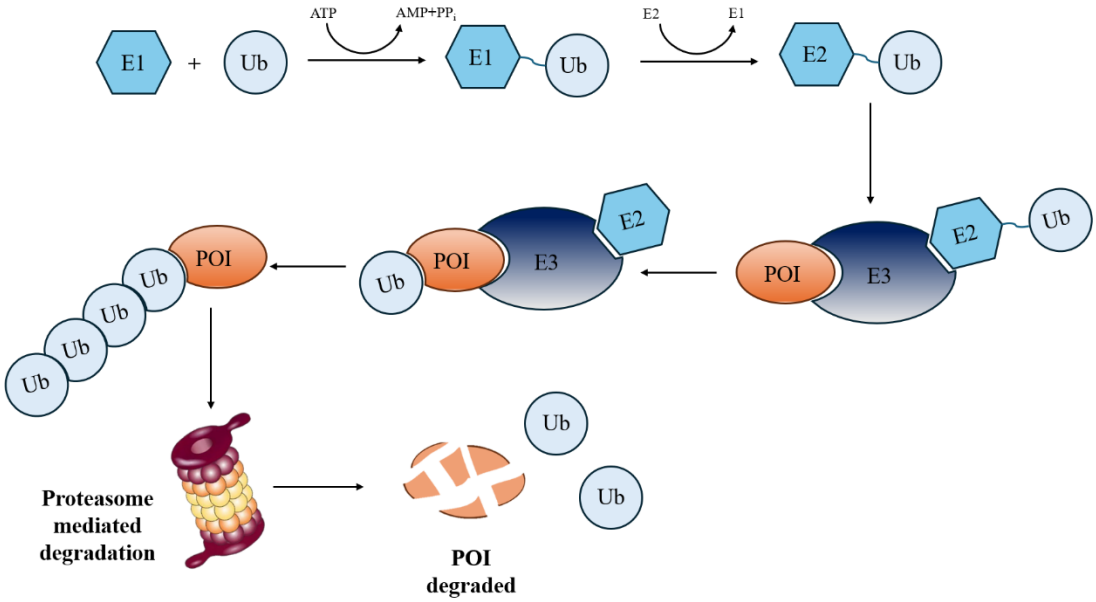

Figure 1. Schematic of the ubiquitination process.

The mechanism of action of PROTACs relies on the E1-E2-E3 enzymatic cascade in UPS (**Figure 1**). Specifically, first, ubiquitin (Ub) is activated by the ubiquitin-activating enzyme (E1) and transferred to the ubiquitin-conjugating enzyme (E2) with ATP supply. Then, in the formation of PROTACs in the "POI-PROTAC-E3 ligase" ternary complex, E3 catalyzes the transfer and covalent attachment of the E2-carrying Ub to the lysine residues of the POI. After multiple ubiquitination steps, the POI is tagged with a polyubiquitin chain, which is recognized by the 26S proteasome and degraded into short peptide fragments (**Figure 2**) [5]. Notably, PROTAC molecules only serve as a bridge in this process; they are not consumed and can be released and recycled after completing a degradation cycle, enabling efficient and sustainable removal of target proteins.

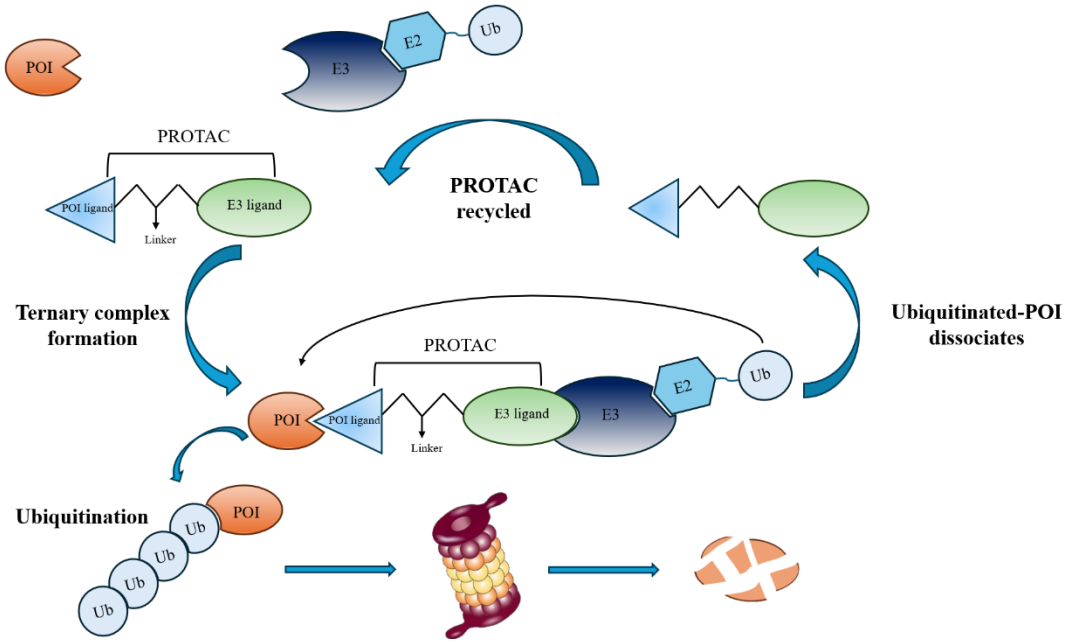

Figure 2. Schematic diagram of the PROTAC-mediated POI degradation process.

2.2. Therapeutic benefits of PROTACs

2.2.1. Targeting the "undruggable"

Small-molecule inhibitors typically work through an "occupancy-driven" mechanism, requiring high-affinity binding to active or allosteric sites to block protein function. This approach faces inherent limitations, contributing to over 80% of the human proteome being considered "undruggable" [6]. In contrast, PROTACs operate via an "event-driven" catalytic mechanism. They transiently bind to the target and recruit E3 ligases to induce its ubiquitination and subsequent proteasomal degradation, bypassing the need for traditional druggable pockets and thereby offering a novel strategy to target previously inaccessible proteins.

This advantage is powerfully illustrated by the targeting of B-cell lymphoma 6 (BCL6), a key oncogenic transcriptional repressor in diffuse large B-cell lymphoma (DLBCL) but long deemed "undruggable" due to its flat protein-protein interaction interfaces (PPI) [7–10]. PROTAC technology has enabled direct pharmacological intervention against BCL6, with multiple candidates now in clinical development. Bristol-Myers Squibb has advanced BMS-986458 into a Phase I/II combination trial for B-cell non-Hodgkin lymphoma (NHL), under the identifier NCT06090539 [11]. Concurrently, Arvinas has developed ARV-393, a next-generation BCL6 PROTAC that achieved a DC_{50} as low as 0.03 nM in preclinical models and entered a Phase I trial in 2024 (NCT06393738) [12–14]. These clinical advances demonstrate PROTACs' capacity to translate undruggable targets into therapeutic realities.

2.2.2. Overcoming drug resistance

Drug resistance, often mediated by target protein overexpression or mutations that impair inhibitor binding, remains a major challenge in targeted cancer therapy [15,16]. PROTACs offer a distinct solution by degrading the target protein entirely, making resistance mechanisms that rely on reduced binding affinity less effective.

This is exemplified in addressing resistance to the anaplastic lymphoma kinase (ALK) tyrosine kinase inhibitor (TKI) lorlatinib in non-small cell lung cancer (NSCLC), where compound mutations like G1202R/

L1196M frequently arise [17–19]. The PROTAC molecule WZH-17-002 was designed to address this. In a G1202R/L1196M mutant mouse model, WZH-17-002 treatment reduced tumor volume by 68% compared to lorlatinib and significantly delayed resistance development, demonstrating the potential of degradation-based strategies to overcome clinical resistance [20].

2.2.3. Enhancing therapeutic safety

The catalytic, "event-driven" mechanism of PROTACs enables sustained target degradation at low, sub-stoichiometric doses, reducing the off-target toxicity risks associated with the high, continuous exposure required by conventional occupancy-driven inhibitors [21]. This safety advantage is exemplified in targeting signal transducer and activator of transcription 3 (STAT3), a transcription factor implicated in tumor progression but historically difficult to drug due to a lack of suitable binding pockets [22]. The PROTAC molecule D11-PROTAC achieved over 90% STAT3 degradation at a low concentration (1.5 μM), effectively suppressing tumor cell proliferation and migration, thereby demonstrating the potential for high-efficacy therapy with an improved safety window [23].

3. Development history of PROTAC

Since its conceptual inception, PROTAC technology has evolved over two decades from a theoretical concept to a promising clinical anticancer platform. The field was pioneered in 2001 with the first peptide-based PROTAC [24]. A key advance came in 2008 with the first fully small-molecule PROTAC, which improved cell permeability [25]. The repertoire of E3 ligases expanded in 2010 with the introduction of inhibitor of apoptosis protein (IAP)-based PROTACs [26]. By 2015, the widespread adoption of highly potent von Hippel-Lindau (VHL)- and cereblon (CRBN)-based ligands significantly enhanced degradation efficiency and selectivity [27,28]. A major milestone was reached in 2019 when the first PROTAC drugs, ARV-110 and ARV-471, entered clinical trials for prostate and breast cancer, respectively, marking the technology's formal transition to clinical validation [29,30]. Subsequently, the field has rapidly diversified, with an increasing number of PROTAC candidates entering oncology trials and novel modalities including lysosome-targeting chimeras (LYTACs) and autophagy-targeting chimeras (AUTACs) emerging to expand the therapeutic potential of targeted protein degradation [31].

4. Key design elements of PROTACs

A typical PROTAC consists of three key parts: a warhead that targets POI, a ligand that recruits an E3 ligase, and a linker that connects them. The properties of each component critically influence the degradation efficiency, selectivity, and cellular activity of the PROTAC. The rational design of these modules and their synergistic interaction are essential for achieving effective targeted protein degradation and successful clinical translation.

4.1. Selection of POI ligands

The rational selection of POI ligands is crucial for successful PROTAC design. Most currently used POI ligands come from existing small-molecule inhibitors or modulators of target proteins, which are structurally optimized to serve as binding modules within the bifunctional structure of PROTACs [32]. During the design process, the binding affinity and selectivity between ligands and target proteins are critical—they not only determine whether PROTACs can effectively bind to target proteins but also greatly influence their off-target risks [33]. However, due

to the unique "event-driven" mechanism of PROTACs, the affinity requirement for POI ligands is not absolute—even ligands with moderate or low affinity can lead to highly efficient degradation. For instance, Zhou et al. developed PROTACs targeting $KRAS^{G12D}$ using a moderate-affinity analogue of MRTX1133 [34]. Despite reduced affinity, these molecules effectively degraded $KRAS^{G12D}$ in ASPC-1 cells (DC_{50} = 38.06 nM) and exhibited significant antitumor efficacy *in vivo*, demonstrating the utility of medium-affinity ligands in PROTAC design.

4.2. E3 ligase ligands

E3 ligase ligand is another essential component of PROTAC molecules, responsible for recruiting E3 and mediating the ubiquitination and proteasomal degradation of target proteins [35]. Currently, the most commonly used E3 ligases include CRBN, VHL, and MDM2, among others. Their selection requires careful consideration of factors such as tissue expression distribution, substrate specificity, and the specific therapeutic context [36].

When designing E3 ligase ligands, priority should be given to ensuring they have a high affinity for the target E3 ligase, which is essential for effective ternary complex formation. For example, thalidomide and its derivatives are widely used in the molecular design of PROTACS due to their potent and specific binding ability to CRBN [37]. Beyond binding affinity, the drug-like properties of the E3 ligand—such as good solubility, metabolic stability, and low cytotoxicity—are crucial for achieving a favorable pharmacokinetic profile and facilitating the clinical translation of PROTACs [38].

4.3. Selection of linker

The properties of the linker—including its length, hydrophilicity, flexibility, and attachment points on the ligands—can greatly affect the degradation efficiency of the PROTACs. For instance, Bond et al. demonstrated that shortening the linker in a BRD4-targeting PROTAC (ZXH-3-26) enhanced selectivity by restricting conformational freedom and reducing off-target binding to homologous BRD proteins [39]. Optimizing linker length through structure–activity relationship (SAR) studies is crucial: too short a linker may impair ternary complex formation, while excessively long linkers can introduce steric hindrance [40]. Emerging strategies, such as geometrically defined DNA linkers and linker-free designs, further expand the chemical space for PROTAC development [41,42].

4.4. Formation of ternary complexes

PROTACs mediate degradation by stabilizing a ternary complex between the POI and the E3 ligase. Complex stability is governed by the combined effects of POI and E3 ligand affinity, linker properties, and the resulting spatial orientation. The traditional development of PROTACs depends heavily on numerous time-consuming and inefficient trial-and-error "synthesis-test" cycles for POI ligands, E3 ligands, and linkers.

Computer-aided drug design (CADD) accelerates this process by enabling in silico modeling and optimization. Molecular docking and molecular dynamics (MD) simulations can predict ternary complex conformations and assess cooperativity—a key feature wherein the ternary complex exhibits enhanced stability relative to binary interactions. The "Method 4B" framework, for example, successfully predicted ternary structures and cooperativity trends for several PROTACs [43,44]. Energy-based methods such as MM/GBSA provide quantitative estimates of binding affinity and cooperativity factors, revealing how linker geometry influences PPI [45,46].

Therefore, CADD has transformed PROTAC development from an empirical trial-and-error approach to a more predictive and rational iterative optimization process. However, conventional force field-based computational

methods remain limited by their dependence on accurate initial conformations, high computational cost, and substantial resource demands [47].

Recent advances in artificial intelligence (AI) offer further improvements. For example, the PROTACable platform developed by Mslati et al., which integrates 3D structural modelling and deep learning techniques, employs an SE(3)-equivariance graph Transformer network, and is capable of using the spatial conformational relationships of POI, PROTAC, and E3 ligases as inputs for directly predicting the degradation activity of PROTAC, achieving an end-to-end automated assessment of the complex formation ability [48]. This method overcomes the limitations of the traditional multi-step computational process, significantly enhances prediction efficiency and reliability, and greatly supports the rational design of PROTACs.

5. Difficulties and challenges confronting PROTAC

Despite its transformative potential for drug discovery, the clinical translation of PROTAC technology faces several inherent challenges stemming from its structural properties, which significantly constrain its practical application. These limitations are primarily manifested in the following three aspects:

5.1. E3 Ligase dependency and off-target toxicity

The efficacy of PROTACs is contingent upon specific E3 ubiquitin ligases, which can lead to off-target toxicity. As noted by Vicente et al., while CRBN-based PROTACs are widely used due to the favorable binding affinity and physicochemical properties of their ligands, the varying expression levels of CRBN across different tissues and cell types can result in inconsistent degradation efficiency in off-target tissues [49]. This increases the risk of off-target effects and may even induce tissue-specific toxicity. Consequently, a key strategy for improving targeting specificity and reducing off-target toxicity is to prioritize E3 ligases that are highly expressed in diseased tissues but have low expression in normal tissues, and to actively develop novel, highly specific E3 ligase ligands.

5.2. Suboptimal drug-like properties

PROTACs are typically heterobifunctional molecules with molecular weights exceeding 700 Da, high lipophilicity, and large polar surface areas. These characteristics often cause them to deviate from the Rule of Five, thereby limiting their oral absorption, cell membrane permeability, and metabolic stability [50–52]. However, recent studies indicate that this challenge can be partially overcome through rational molecular optimization. For instance, research from institutions like Arvinas and AstraZeneca suggests that reducing the number of solvent-exposed hydrogen bond donors (eHBDs) can improve the membrane permeability of PROTACs, leading to better oral bioavailability.

5.3. Limited blood-brain barrier penetration

Owing to their large molecular size and polarity, PROTACs struggle to cross the blood-brain barrier (BBB) via passive diffusion, restricting their application in central nervous system (CNS) diseases. Nevertheless, this challenge has spurred the development of innovative delivery strategies. In 2025, the Wu Sijin group developed a transferrin receptor (TfR)-based DNA nanoflower delivery system capable of efficiently loading an Oligo-PROTAC and achieving highly efficient BBB crossing, significantly enhancing its distribution and degradation efficiency in brain tissue [53]. This strategy provides a novel and promising solution for applying PROTAC

technology to treat neurodegenerative diseases such as Alzheimer's and Parkinson's.

6. Future trends in next-generation PROTAC technology

Although structural modifications and optimized delivery strategies have partially mitigated limitations of PROTACs such as off-target toxicity, oral bioavailability, and BBB penetration, significant challenges remain in systematically improving their physicochemical properties to meet *in vivo* application requirements [54]. Consequently, research focus is gradually shifting towards smarter, next-generation PROTAC technology. These systems are designed to respond to exogenous or endogenous stimuli within specific tissues, enabling spatiotemporally controlled protein degradation, which promises to further enhance targeting precision and reduce systemic toxicity [55].

6.1. Click-release PROTAC (crPROTAC)

crPROTAC is a class of intelligent degradation systems designed for spatially controlled activation. They utilize bioorthogonal click chemistry as a molecular switch to release the active PROTAC specifically within target cells or tissues, thereby enhancing selectivity and minimizing systemic toxicity.

A representative strategy involves masking a PROTAC such as ARV-771 with a trans-cyclooctene (TCO) group. This inert prodrug circulates systemically until it encounters a tumor-targeting tetrazine peptide in the microenvironment, triggering a bioorthogonal reaction that releases the active degrader and enables precise BRD4 degradation [56,57]. An alternative strategy, ClickRNA-PROTAC, delivers mRNA encoding an E3 ligase fusion protein into tumor cells. The functional PROTAC is then assembled in situ through a bioorthogonal reaction between a transfected ligand and the expressed ligase, achieving highly specific target protein degradation [58].

6.2. Photo-activatable PROTAC

Photo-activatable PROTAC is a type of intelligent degradation approach that allows spatiotemporal control of protein degradation using external light exposure. The system remains biologically inactive after drug administration and is only activated under specific light wavelengths, thereby inducing target protein degradation within a defined space and time. This design significantly improves the accuracy and specificity of PROTAC molecules, while effectively reducing off-target toxicity and systemic side effects [59]. Currently, the main light-controlled PROTAC methods are mainly divided into two categories: photocaged PROTAC (pc-PROTAC) and photoswitchable PROTAC (ps-PROTAC).

6.2.1. pc-PROTAC

The pc-PROTAC strategy involves conjugating photolabile protecting groups to key functional sites of the PROTAC molecule—such as the E3 ligase ligand, rendering it inactive until exposure to specific light triggers cleavage and releases the active degrader.

Initial designs, developed independently by several groups around 2019–2020, primarily used ultraviolet A (UVA) light to activate PROTACs targeting proteins such as BRD4 and BTK [60–62]. However, UV light has limited tissue penetration and potential phototoxicity. To overcome this, visible light-activated pc-PROTACs were developed, offering reduced photodamage and improved spatial precision [63].

For deeper tissue applications, the first X-ray-activated PROTAC (RT-PROTAC) was reported in 2022 [64].

By incorporating an X-ray-sensitive photocage, PROTAC activity can be triggered locally within tumors upon irradiation. This approach not only achieves high tissue penetration and spatiotemporal control but also synergizes with clinical radiotherapy to inhibit tumor growth *in vivo*, highlighting its potential for combined cancer therapy [65].

6.2.2. ps-PROTAC

Unlike irreversible pc-PROTACs, ps-PROTACs incorporate a photoisomerizable linker that reversibly toggles between cis and trans configurations under different wavelengths of light. This allows dynamic, bidirectional control of ternary complex formation and protein degradation activity, enhancing precision and reducing off-target risks.

A representative example is the first agonist-based photoswitch NAMPT PROTAC developed by Sheng's group, which features an azobenzene-containing linker [66]. Under 450 nm light, the molecule adopts a trans configuration that promotes NAMPT degradation, lowering NAD^+ levels. Switching to 365 nm light isomerizes the linker to cis, restoring NAMPT activity and NAD^+ biosynthesis via its integrated agonist function [67,68]. This reversible system not only enables optical control of protein levels and metabolic output but also demonstrates light-regulated antitumor effects in a mouse model, highlighting its potential for spatially precise cancer therapy and pathway investigation.

6.3. Tumor microenvironment- activatable PROTAC

The tumor microenvironment (TME) exhibits endogenous features that differ markedly from those of normal tissues, including high levels of specific enzymes, increased concentrations of reducing substances, hypoxia, and elevated reactive oxygen species (ROS). These features provide a molecular foundation for developing tumor microenvironment-responsive PROTAC that can be selectively activated at the tumor site, thereby improving the accuracy of targeted protein degradation and minimizing systemic toxicity to healthy tissues. Currently, the four main strategies include enzyme-activatable PROTAC, glutathione-activatable PROTAC, hypoxia-activatable PROTAC, and reactive oxygen species-responsive PROTAC.

6.3.1. Enzyme- activatable PROTAC

Enzyme-activatable PROTAC achieves targeted activation by leveraging specific enzymes that are highly expressed in tumors. This class of molecules is in a pre-drug form and is enzymatically triggered to release PROTAC once inside the target tissue, leading to selective degradation of the POI, improved therapeutic precision, and fewer off-target effects.

For example, Liang et al. developed a prodrug molecule called Pro-PROTAC to specifically target cancer cells and enable controlled protein degradation [69]. This strategy was achieved by introducing trimethyl-locked quinone (TLQ) as a masking group in the PROTAC molecule targeting BRD4 at the hydroxyproline site of its VHL E3 ligase ligand. This group can be specifically reduced and undergo autocleavage by NAD(P)H quinone dehydrogenase 1 (NQO1), which is overexpressed in a wide range of tumor cells and at lower levels in normal tissues [70]. Thus, Pro-PROTAC remains "inert" in normal cells due to the loss of E3 ligase recruitment caused by the masking group, whereas in tumor cells, the removal of this group, catalyzed by NQO1, releases active PROTAC, which induces highly selective degradation of the oncogenic driver BRD4.

6.3.2. GSH- activatable PROTAC

The concentration of glutathione (GSH) is significantly higher in tumor cells than in the extracellular environment

and normal tissues, creating ideal conditions for the development of tumor-selectively activated prodrug-type PROTAC [71]. In the treatment of breast cancer (BC), for instance, PROTACs targeting oestrogen receptor α (ERα) have demonstrated significant therapeutic potential, but there is a risk of off-target toxicity due to non-specific protein degradation in normal tissues as well [72].

To address this issue, Zhou et al. developed a GSH-responsive ERα-targeting PROTAC [73]. The design involved creating a prodrug form of the PROTAC by introducing an *o*-nitrobenzenesulfonyl group at the hydroxyl moiety in the molecules of VHL ligand-based ERα PROTAC. This modification rendered the molecule inert under normal physiological conditions and allowed activation in the tumor cell-specific high GSH environment, enabling selective degradation of ERα. This strategy not only offers new ideas for the development of safer and personalized BC therapeutic regimens but also highlights the broad potential of microenvironment-activatable PROTAC in tumor therapy.

6.3.3. Hypoxia- activatable PROTAC

Hypoxia is a common pathological feature in solid tumors. The rapid growth of tumor cells escalates oxygen consumption, while aberrant tumor vasculature results in inadequate perfusion and the development of local hypoxic regions. This environment not only causes the overexpression of various pro-cancer proteins such as hypoxia-inducible factor (HIF), vascular endothelial growth factor receptor (VEGFR), and epidermal growth factor receptor (EGFR), but also further promotes drug resistance and malignant progression of the tumor [74,75].

Based on this mechanism, Cheng et al. designed and synthesized a novel class of hypoxia-activated PROTAC prodrugs (ha-PROTAC) by incorporating hypoxia-activated leaving groups (HALGs) into PROTACs targeting EGFR [76]. Experimental validation demonstrated that unmodified PROTACs could effectively degrade EGFR under both normoxic and hypoxic conditions, whereas ha-PROTAC was activated only under hyperoxic conditions, successfully achieving the goal of selectively degrading EGFR in hypoxic tumor regions.

6.3.4. ROS- activatable PROTAC

Elevated levels of ROS, particularly hydrogen peroxide (H_2O_2), constitute a common feature of the solid tumor microenvironment [77]. Exploiting this trait, Yao et al. developed an H_2O_2-responsive supramolecular system for tumor-selective PROTAC activation [78]. In pancreatic cancer cells, high H_2O_2 triggered the self-assembly of precursors into tetrazine-rich nanostructures, which subsequently released an active BRD4-targeting PROTAC via a bioorthogonal reaction. This system achieved more than 80% degradation of BRD proteins in cancer cells with minimal activity in normal cells, demonstrating high selectivity. In vivo, it effectively inhibited tumor growth in a pancreatic cancer mouse model without significant systemic toxicity, providing a key paradigm for ROS-dependent precision protein degradation.

6.4. Biomacromolecule-PROTAC conjugates

To enhance tumor selectivity, PROTACs have been conjugated to targeting biomolecules such as antibodies, folate, nucleic acid aptamers, and others. These conjugates specifically recognize receptors overexpressed on cancer cells, enabling receptor-mediated internalization and intracellular activation. This strategy improves tumor accumulation while minimizing off-target exposure.

6.4.1. Antibody-PROTAC conjugates

Antibody-PROTAC conjugates (APCs) merge the precise targeting of antibodies with the catalytic degradation of PROTACs, analogous to antibody-drug conjugates (ADCs) but replacing the cytotoxic payload with a PROTAC molecule [79]. For example, a cetuximab-based APC (CPRO) targeting mutant EGFR in NSCLC showed significantly enhanced cytotoxicity (10-30-fold lower IC_{50} than cetuximab alone), induced EGFR degradation, and inhibited tumor growth in 3D models, highlighting its potential to overcome kinase inhibitor resistance [80].

6.4.2. Folate-targeting PROTAC

Folate receptor α (FOLR1) is highly expressed on many malignant tumors but scarce in normal tissues, making it an ideal target [81]. Folate-PROTACs are designed with a cleavable linker that keeps the PROTAC inert in circulation. Upon FOLR1-mediated internalization into tumor cells, hydrolysis releases the active degrader, enabling tumor-selective protein degradation [82]. Conjugates like folate-ARV-771 and folate-MS432 effectively degraded targets in FOLR1-high cancer cells while sparing normal cells, demonstrating excellent tumor specificity [83].

6.4.3. Aptamer-PROTAC conjugates

Nucleic acid aptamers offer high-affinity recognition of cell-surface targets [84]. An aptamer-PROTAC conjugate termed dp53m was developed to selectively degrade the neoantigen p53-R175H mutant. dp53m potently inhibited the proliferation, migration, and 3D growth of p53-R175H mutant cancer cells and synergized with cisplatin, showcasing a promising strategy for precision degradation of undruggable oncoproteins [85,86].

7. Summary

Since its conceptualization, PROTAC technology has evolved into a groundbreaking therapeutic paradigm, moving beyond the limitations of occupancy-driven inhibition. By catalytically degrading target proteins via UPS, PROTACs offer a unique strategy to tackle “undruggable” targets, overcome drug resistance, and enhance therapeutic safety.

Despite its transformative potential, challenges remain for clinical translation, including molecular properties, ternary complex kinetics, and tissue-selective delivery. In response, next-generation strategies are focused on conferring spatial and temporal control. Conditionally activatable PROTACs enable precise external control over protein degradation. Tumor microenvironment-responsive PROTACs are designed to be selectively activated by pathological stimuli such as specific enzymes, redox imbalance, or hypoxia. Biomolecule-PROTAC conjugates leverage active targeting to enhance tumor specificity and reduce systemic exposure.

Driven by deepening mechanistic understanding, advanced computational design, and innovative delivery platforms, the PROTAC field is rapidly transitioning from preclinical validation to clinical investigation. These concerted efforts are poised to unlock novel, precision therapies for cancer and other diseases, fulfilling the promise of targeted protein degradation.

Disclosure statement

The authors declare no conflict of interest.

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