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Review

PROTACs in Colorectal Cancer: A New Era in Targeted Protein Degradation Therapy

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Abstract

Colorectal cancer (CRC) is a leading cause of cancer-related mortality worldwide, with treatment challenges arising from late-stage diagnosis, therapy resistance, and the presence of undruggable targets. The advent of proteolysis-targeting chimeras (PROTACs) offers a novel therapeutic avenue by leveraging the ubiquitin-proteasome system (UPS) for targeted protein degradation. Unlike conventional inhibitors that act like temporary "off switches" for cancer-related proteins, PROTACs function as "disposal tags," marking harmful proteins for complete removal by the cell, enabling sustained oncogenic protein degradation. PROTACs address key drivers of CRC progression, including Kirsten rat sarcoma viral oncogene homolog (KRAS) , the Wnt/β-catenin pathway, bromodomain-containing protein 4 (BRD4), cyclin-dependent kinase 4/6 (CDK4/6), signal transducer and activator of transcription 3 (STAT3), and DNA repair regulators. This review explores the mechanistic foundation of PROTACs, their application in CRC therapy, and the ongoing advancements in optimizing their selectivity, bioavailability, and clinical translation. While challenges such as E3 ligase selection, intracellular delivery, and resistance mechanisms remain, recent innovations in linker chemistry, nanocarrier systems, and artificial intelligence (AI)-driven drug design are enhancing the clinical feasibility of PROTAC therapeutics. As research progresses, PROTAC-based therapies hold significant promise for overcoming current treatment limitations, paving the way for a new era of precision medicine in CRC management.

Keywords

PROTAC, Colorectal cancer, Protein degradation, Ubiquitin-proteasome system, Drug resistance

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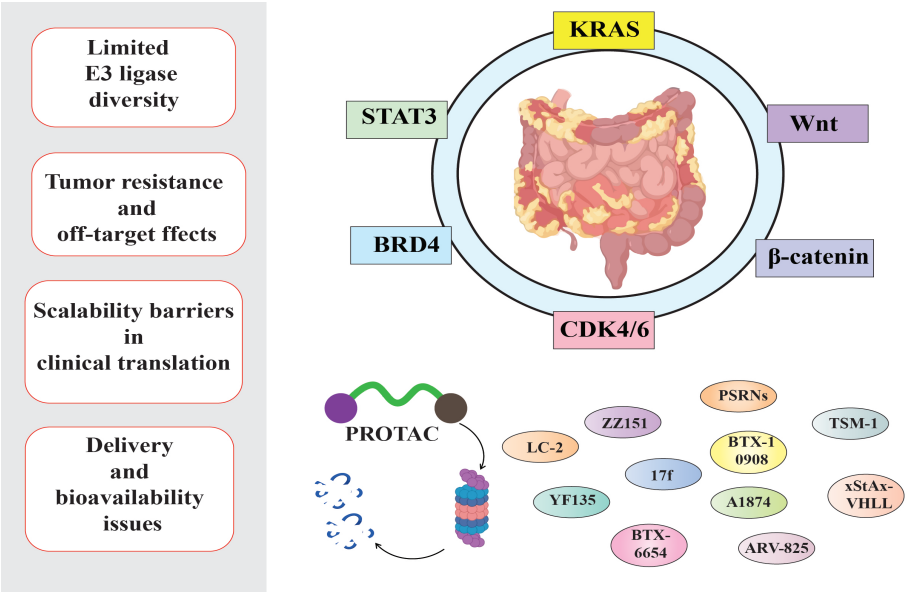
Graphical Abstract



1. Introduction

Colorectal cancer (CRC) is a major global health challenge, responsible for 1.93 million new cases and 935,000 deaths in 2020, accounting for 10% of all cancer cases (WHO, 2020) [1,2]. While CRC is most prevalent in developed regions like North America, Europe, and Oceania [3], its incidence is rising in low- and middle-income countries, reflecting a growing global burden [4-6]. CRC is often diagnosed at late stages due to its asymptomatic nature early on, reducing treatment effectiveness [7]. Early detection is challenged by limited access to reliable screening methods and the lack of specific symptoms. Symptoms like abdominal pain, weight loss, or blood in stool usually appear at advanced stages, complicating treatment and lowering survival rates. While screening tools like colonoscopy exist, their global use remains limited, especially in underserved populations [8].

CRC treatment includes surgery, chemotherapy, and radiation, with targeted therapies offering significant advancements [9]. While surgery is effective for localized CRC, metastasis to organs like the liver and lungs remains a major challenge. Chemotherapy, though beneficial, is limited by toxicity and resistance [10]. Targeted therapies, such as epidermal growth factor receptor (EGFR) monoclonal antibodies, show promise but are ineffective in patients with mutations like KRAS [11]. Resistance to both chemotherapy and targeted treatments highlights the need for novel therapeutic approaches.

The growing need for innovative therapeutic strategies in CRC has driven the exploration of PROTAC (Proteolysis targeting chimeras) technology. PROTACs represent a groundbreaking approach that induces targeted protein degradation through the ubiquitin-proteasome system. Unlike traditional small-molecule inhibitors that merely bind to and inhibit target proteins, PROTACs recruit cellular E3 ubiquitin ligases to tag disease-causing proteins for degradation. This mechanism enables the removal of proteins traditionally considered “undruggable,” such as transcription factors, scaffold proteins, and mutant enzymes lacking well-defined druggable binding sites [12].

The development of PROTAC technology has evolved through three generations, addressing key challenges in stability, specificity, and efficacy. First-generation PROTACs, based on peptide structures like nuclear factor kappa B inhibitor alpha(IκBα), proved the concept but faced limitations due to poor cell permeability and large size [13-16]. Second-generation PROTACs introduced small-molecule ligands, such as thalidomide derivatives to recruit cereblon (CRBN), significantly improving cell permeability and stability, though off-target effects and limited E3 ligase options remained challenges [17-21]. Third-generation PROTACs integrated advanced designs, including light-activated (photo-PROTACs) and phosphorylation-dependent PROTACs, providing spatiotemporal control over protein degradation. Nanotechnology-based delivery systems further enhanced tumor-specific distribution, while innovations in linker chemistry, alternative ligases (e.g., mouse double minute 2 (MDM2), ring finger protein 114 (RNF114)), and prodrug strategies continue to address remaining hurdles [22-27] (Table 1). This evolution positions PROTACs as a transformative platform for tackling previously untreatable targets in CRC.

Table 1. Overview of PROTAC generations: advancements, challenges, and key examples

Generation	Key features	Limitations	Examples
First-generation	Peptide-based PROTACs, concept validation	Poor cell permeability, large molecular size	IκBα-based PROTAC [13-16]
Second-generation	Small-molecule PROTACs, CRBN-recruiting ligands, improved stability and permeability	Off-target effects, limited E3 ligases	Thalidomide-based PROTACs [17-21]
Third-generation	Photo-PROTACs, phosphorylation-dependent PROTACs, tumor-specific delivery via nanotechnology, alternative E3 ligases (MDM2, RNF114)	Challenges in clinical translation, need for better bioavailability	Advanced linker-based PROTACs [22-27]

In CRC, PROTAC technology shows promise for targeting proteins involved in tumor progression and therapy resistance. For instance, PROTACs targeting BRD4, a key regulator of gene transcription, could enhance treatment efficacy by promoting its degradation [28,29]. Similarly, mutant KRAS, a common and resistant target in CRC, may be effectively addressed using PROTACs [30].

CRC is a significant global health burden, characterized by high morbidity and mortality. Current treatments are limited by drug resistance, emphasizing the need for new approaches. This article reviews PROTAC technology in CRC, focusing on its potential to target "undruggable" proteins and provide more effective, recent therapies.

2. Mechanism of Action and Catalytic Degradation

PROTACs exploit the ubiquitin-proteasome system to selectively degrade target proteins. These bifunctional molecules consist of two ligands connected by a linker: one ligand specifically binds to the protein of interest (POI), while the other recruits an E3 ubiquitin ligase. The process begins with the formation of a ternary complex, where the PROTAC simultaneously interacts with the POI and the E3 ligase, bringing them into close proximity. This proximity enables the E3 ligase to catalyze the transfer of ubiquitin molecules from the E2 ubiquitin-conjugating enzyme to lysine residues on the POI [31].

The ubiquitination process involves the activation of ubiquitin by the E1 enzyme, its transfer to the E2 enzyme, and its ligation to the POI by the E3 ligase. Multiple ubiquitin molecules are attached iteratively, forming a polyubiquitin chain on the POI. This polyubiquitin chain serves as a recognition signal for the 26S proteasome, a large proteolytic complex responsible for degrading polyubiquitinated proteins. The proteasome binds to the ubiquitin-tagged POI, unfolds it using ATP hydrolysis, and translocate it into its catalytic core, where proteolytic enzymes degrade the POI into small peptide fragments [31,32].

Unlike conventional inhibitors that block protein activity temporarily, PROTACs catalytically induce the permanent degradation of their target proteins. A single PROTAC molecule can engage in multiple cycles of degradation, as it dissociates from the ternary complex after ubiquitination and remains available to recruit additional POI molecules [33]. This catalytic efficiency, combined with the ability to completely eliminate disease-driving proteins, makes PROTACs a powerful tool for addressing previously "undruggable" targets (Figure 1).

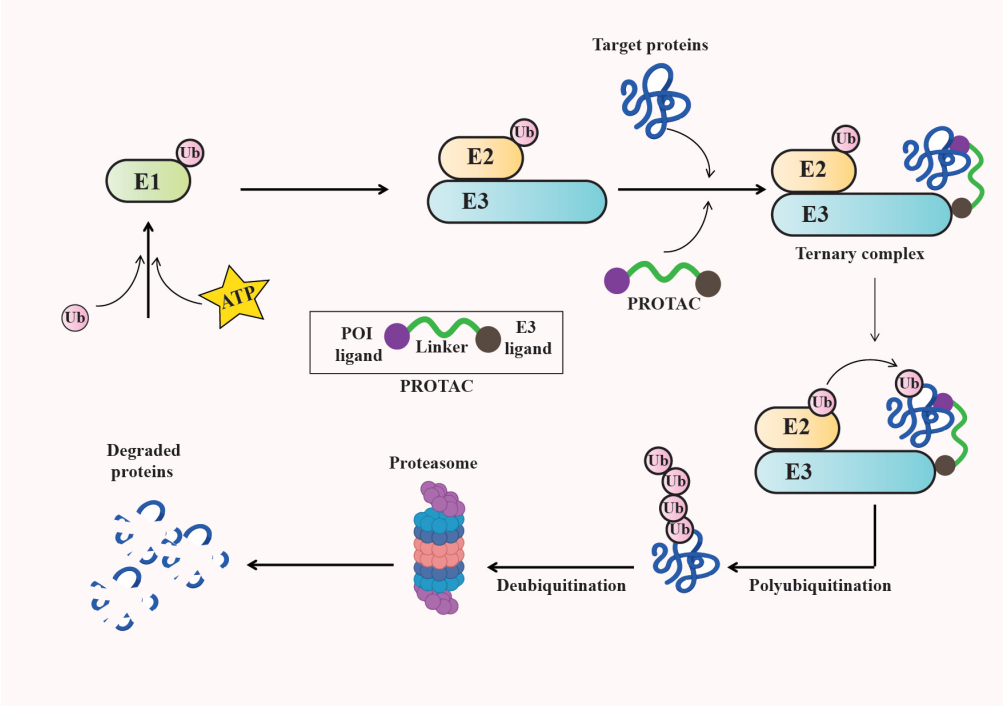


Figure 1. Schematic representation of proteolysis-targeting chimeras. This figure illustrates the ubiquitin-proteasome system-mediated degradation induced by PROTACs. PROTACs consist of a protein-of-interest (POI) ligand, a linker, and an E3 ligase ligand, enabling the formation of a ternary complex between the target protein and E3 ligase. This interaction promotes polyubiquitination of the target protein, marking it for proteasomal degradation. Following ubiquitination, the target protein is recognized and degraded by the proteasome into small peptides, while ubiquitin molecules are recycled. Unlike conventional inhibitors, PROTACs act catalytically, ensuring sustained target depletion with minimal drug exposure.

3. Clinical Advancements of PROTACs in Cancer Therapy

Despite promising preclinical efficacy, the clinical translation of PROTACs continues to face concerns regarding their safety, toxicity, and utility in human subjects. In the phase I trial of ARV-110, an androgen receptor (AR)-targeting PROTAC, for metastatic castration-resistant prostate cancer (mCRPC), preliminary results indicated a favorable safety profile, with a notable reduction in prostate-specific antigen (PSA) levels, suggesting potential antitumor activity. However, adverse events were observed, particularly in patients receiving ARV-110 alongside rosuvastatin, leading to significant elevations in aspartate aminotransferase (AST) and alanine aminotransferase (ALT) as well as renal impairment. These findings underscore the importance of monitoring for potential drug interactions and their impact on patient safety. Despite these challenges, the promising efficacy signals led to ARV-110's progression into phase II trials (NCT03888612) [34]. Compared to traditional androgen receptor inhibitors, such as enzalutamide, which function by competitive inhibition, PROTACs like ARV-110 achieve sustained degradation of the target protein. This catalytic degradation mechanism may lead to prolonged therapeutic effects and potentially reduce the risk of resistance observed in small-molecule inhibitors. However, PROTACs require functional E3 ligases for activity, and potential resistance mechanisms linked to E3 ligase downregulation must be further explored.

ARV-471, a PROTAC targeting estrogen receptors (ER) in metastatic breast cancer, demonstrated its ability to degrade both wild-type and mutant ERs, resulting in disease stabilization or partial remission in some patients. These promising results, coupled with a favorable safety profile and no severe treatment-related adverse events, led to the advancement of ARV-471 into phase II trials (NCT04072952). The clinical benefit rate (CBR) in early trials was 40%, reinforcing the potential of this compound as a therapeutic option for ER-positive breast cancer [35]. Traditional selective estrogen

receptor degraders (SERDs), such as fulvestrant, act by competitive inhibition of ER signaling, while PROTACs like ARV-471 promote complete degradation of ER proteins. This mechanism may offer advantages in overcoming resistance to endocrine therapy. However, delivery challenges remain a concern, particularly given the relatively larger molecular weight of PROTACs compared to small-molecule inhibitors.

ARV-766, designed for mCRPC, also showed encouraging results in its phase I trial. The treatment led to reductions in PSA levels, signaling potential antitumor activity. Mild gastrointestinal side effects, including nausea and diarrhea, were noted. Despite these, ARV-766 exhibited a favorable pharmacokinetic profile, making it a promising candidate for continued evaluation in phase II trials (NCT05067140) [36].

CC-94676, targeting the androgen receptor in advanced prostate cancer, showed promising effects in reducing testosterone and PSA levels. However, higher doses led to adverse events such as fatigue, dizziness, and elevated liver enzymes. Despite these challenges, the early signs of efficacy warranted continued investigation in phase II trials (NCT04428788), with an emphasis on monitoring liver function during treatment to mitigate potential risks [37].

Furthermore, the VERITAC-2 study is a pivotal phase 3 clinical trial evaluating ARV-471 in patients with ER+/HER2- advanced breast cancer, who have previously undergone therapy with CDK4/6 inhibitors and endocrine therapy. This randomized trial compares the efficacy and safety of ARV-471 (200 mg once daily) with fulvestrant, an established selective estrogen receptor degrader (SERD). Early phase results indicated that ARV-471 was well tolerated and demonstrated promising clinical activity, leading to its advancement into this phase 3 trial (NCT05654623), where its potential to be a superior alternative to fulvestrant will be further assessed [38].

Several other PROTACs are being explored in early-phase clinical trials, targeting a range of oncogenic proteins. Notably, ARV-766 (NCT05067140) and CC-94676 (NCT04428788) target the androgen receptor, while AC682 (NCT05080842) is aimed at degrading the estrogen receptor (ER) [37,39]. Key candidates also include DT2261 (NCT04886622) targeting B-cell lymphoma-extra large (BCL-xL), FHD-609 (NCT04965753) and CFT8634 (NCT05355753) targeting bromodomain-containing protein 9 (BRD9), and KT-474 (NCT04772885) and KT-413 (NCT05233033) degrading interleukin-1 receptor-associated kinase 4 (IRAK4) [40-43]. NX-2127 (NCT04830137) and NX-5948 (NCT05131022) target Bruton's tyrosine kinase (BTK), while CFT7455 (NCT04756726) addresses Ikaros family zinc finger proteins 1 and 3 (IKZF1/3), and KT-333 (NCT05225584) is designed to degrade STAT3 [44-47].

While PROTACs offer a novel therapeutic approach, they face challenges in comparison to traditional small-molecule inhibitors and monoclonal antibodies. Small-molecule inhibitors typically exhibit better oral bioavailability and lower molecular weight, which aids in drug delivery, while PROTACs require intracellular delivery and depend on E3 ligase activity for function. On the other hand, PROTACs offer advantages in targeting "undruggable" proteins and providing a sustained degradation effect, which can mitigate resistance mechanisms seen with conventional inhibitors. As the number of PROTACs in clinical trials grows, these studies will be crucial in assessing their therapeutic efficacy, safety profiles, and identifying the most suitable clinical applications for treating various cancers and other diseases.

4. Current Applications of PROTAC Technology in CRC

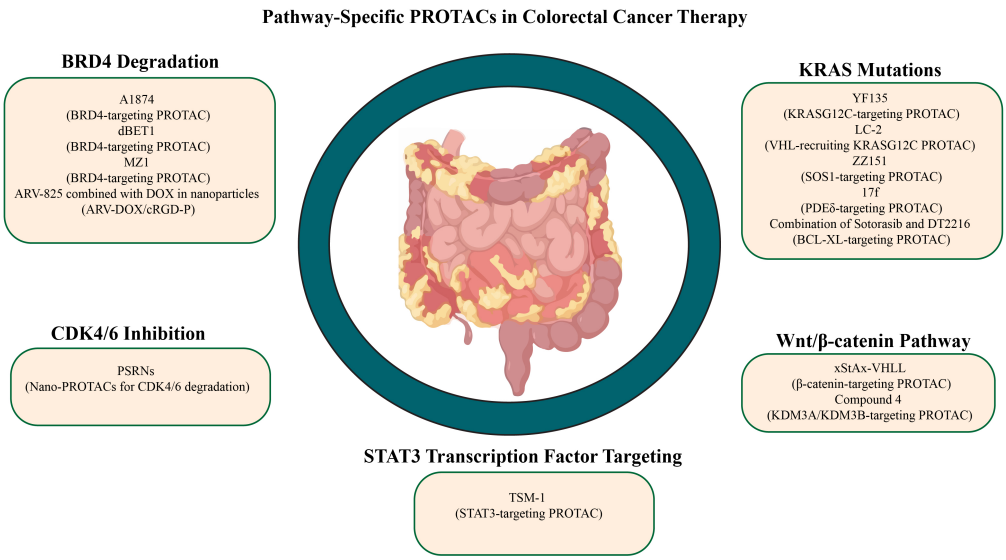


Figure 2. PROTAC mechanisms targeting key oncogenic pathways in CRC. This figure illustrates the major oncogenic pathways in CRC and their targeted degradation using PROTACs. PROTACs function by recruiting E3 ubiquitin ligases, leading to the ubiquitination and proteasomal degradation of oncogenic proteins. Specific PROTACs have been developed to degrade proteins involved in BRD4-mediated transcription, KRAS-driven signaling, Wnt/β-catenin activation, CDK4/6 cell cycle regulation, and STAT3 oncogenic signaling, all of which drive CRC progression. Proper labeling of target proteins and degradation mechanisms has been included for improved readability and clarity.

CRC remains a major challenge due to its resistance to conventional therapies. PROTAC technology offers a novel approach by selectively degrading oncogenic proteins through the ubiquitin-proteasome system. Unlike traditional inhibitors, PROTACs continuously eliminate target proteins, improving efficacy and reducing resistance [30]. Recent advances have refined PROTAC design, enhancing specificity, stability, and delivery. Efforts focus on key CRC drivers such as KRAS mutations, Wnt/β-catenin signaling, and BRD4 (Figure 2). The following sections explore how PROTACs are being developed to tackle these critical pathways.

4.1 Targeting KRAS Mutations

KRAS mutations, present in approximately 40% of CRC cases, drive tumor growth through activation of mitogen-activated protein kinase (MAPK)/extracellular signal-regulated kinase (ERK) and phosphoinositide 3-kinase (PI3K)/protein kinase B (AKT) pathways. Traditionally deemed "undruggable," PROTAC technology has introduced a novel approach by enabling the selective degradation of mutant KRAS proteins, overcoming limitations of conventional inhibitors.

Sotorasib, a $KRAS^{G12C}$ inhibitor, was developed as a targeted therapy for $KRAS^{G12C}$-mutated tumors, including CRC. Sotorasib effectively inhibits $KRAS^{G12C}$ signaling, suppressing downstream pathways like MAPK/ERK. Clinical trials have shown promising antitumor activity in $KRAS^{G12C}$-mutated CRC patients, particularly those who had failed previous therapies, making it a valuable therapeutic option for this challenging mutation [48]. Similarly, Adagrasib, another $KRAS^{G12C}$ inhibitor, selectively targets $KRAS^{G12C}$ in CRC. It has demonstrated potent antitumor effects in preclinical models and significant antitumor efficacy in clinical trials for $KRAS^{G12C}$-mutant CRC, including in advanced or metastatic cases [49,50].

In parallel, YF135, a reversible-covalent PROTAC developed by Yang et al., was designed to degrade $KRAS^{G12C}$ via von Hippel–Lindau (VHL)-mediated proteasomal degradation. YF135 effectively degrades $KRAS^{G12C}$ in preclinical models, attenuating downstream phosphorylated ERK (pERK) signaling and suppressing tumor growth in H358 and H23 cell lines [51]. Khan et al. demonstrated a synergistic approach by combining sotorasib with the BCL-xL-targeting PROTAC DT2216, which disrupted the BCL-xL/BIM interaction, enhanced apoptosis, and overcame resistance in $KRAS^{G12C}$-mutated tumors, showing superior antitumor efficacy in preclinical models [52]. Furthermore, LC-2 is a VHL-recruiting PROTAC developed to degrade $KRAS^{G12C}$. It covalently binds $KRAS^{G12C}$ using a MRTX849 warhead and recruits the VHL E3 ligase, leading to sustained degradation of $KRAS^{G12C}$ and suppression of MAPK signaling in both homozygous and heterozygous $KRAS^{G12C}$ cell lines [53].

In addition to direct KRAS degradation, PROTAC technology has been applied to target regulatory proteins involved in KRAS signaling. For instance, 17f degrades phosphodiesterase delta (PDEδ), a chaperone required for KRAS membrane localization, leading to functional inactivation of $KRAS^{G12D}$ and $KRAS^{G12V}$ mutants [54]. However, since PDEδ inhibition does not directly block KRAS activation, tumors may compensate through alternative membrane localization mechanisms.

To overcome this limitation, researchers have developed son of sevenless homolog 1 (SOS1)-targeting PROTACs, including ZZ151, BTX-6654, and BTX-10908, which block KRAS activation at an upstream level by degrading SOS1, a key guanine nucleotide exchange factor (GEF) [30,55,56]. ZZ151 is specifically optimized for $KRAS^{G12D}$ and $KRAS^{G12V}$ mutants, while BTX-6654 and BTX-10908 exhibit broader efficacy across multiple KRAS-driven cancers, including $KRAS^{G12C}$ and RTK-driven tumors. Compared to PDEδ degradation by 17f, SOS1-targeting PROTACs provide a more direct approach to KRAS inhibition, as they eliminate active KRAS formation rather than simply mislocalizing it. Additionally, since SOS1 degradation affects multiple KRAS mutations, these PROTACs may offer a broader therapeutic strategy for KRAS-mutant CRC.

While KRAS inhibitors such as sotorasib and adagrasib act by reversibly blocking the active site of $KRAS^{G12C}$, their efficacy is often compromised by acquired resistance due to secondary mutations or compensatory signaling [57]. In contrast, PROTACs facilitate complete degradation of KRAS, eliminating the protein rather than transiently inhibiting its function. This approach prevents reactivation through adaptive mechanisms and may provide a more sustained therapeutic response. Furthermore, inhibitors are typically mutation-specific (e.g., effective only against $KRAS^{G12C}$) [58], whereas certain PROTACs, such as ZZ151 and BTX-6654, target broader KRAS mutations by degrading upstream regulators like SOS1 [55], making them a potentially more versatile strategy for KRAS-mutant CRC.

These studies illustrate the potential of PROTAC technology in targeting KRAS mutations through innovative mechanisms, such as direct KRAS degradation, targeting regulatory proteins, and combination therapies. These approaches provide new opportunities to overcome resistance mechanisms and improve therapeutic efficacy in KRAS-mutant CRC.

4.2 Targeting the Wnt/β-catenin Pathway

4.2.1 Direct β-catenin-targeting PROTACs

The Wnt/β-catenin pathway is a key driver of CRC, often activated by mutations in adenomatous polyposis coli (APC) or catenin beta 1 (CTNNB1) [59]. This pathway regulates essential cellular processes, including proliferation and

differentiation, making it a crucial therapeutic target. However, direct inhibition of β-catenin has been challenging due to its intracellular localization and lack of accessible binding sites. PROTAC technology offers an innovative solution by selectively degrading β-catenin, effectively disrupting Wnt signaling.

Recent advances have highlighted the therapeutic potential of β-catenin-targeting PROTACs in CRC. Stapled α-helical peptide activator 1 (SAHPA1) and stabilized α-helix of the transcription factor Axin (xStAx) are designed for cellular penetration and selective Wnt signaling modulation. While SAHPA1 functions as an activator, xStAx inhibits β-catenin-TCF transcriptional activity [60]. Expanding on this approach, Liao et al. developed xStAx-VHLL, a β-catenin-targeting PROTAC engineered by linking xStAx to a von Hippel–Lindau (VHL) E3 ligase ligand. This bifunctional molecule promoted sustained β-catenin degradation in APC-mutant CRC cell lines and organoids, effectively suppressing Wnt-driven tumorigenesis. *In vivo* studies demonstrated that xStAx-VHLL significantly reduced tumor formation in BALB/C nude mice and decreased tumor burden in APCmin/+ mice. Furthermore, it downregulated key oncogenic mediators such as leucine-rich repeat-containing G-protein coupled receptor 5 (Lgr5), axis inhibition protein 2 (Axin2), Cyclin D1, and MYC proto-oncogene (MYC), impairing CRC proliferation. Notably, its efficacy in patient-derived CRC organoids underscores its therapeutic potential for targeting aberrant Wnt/β-catenin signaling [60,61]. These findings highlight the potential of β-catenin-targeting PROTACs as a promising approach for Wnt pathway inhibition in CRC.

4.2.2 Targeting upstream regulators of Wnt signaling

In addition to direct β-catenin degradation, PROTAC technology has been utilized to target upstream epigenetic regulators of Wnt signaling. Zaman et al. focused on targeting lysine demethylase 3A (KDM3A) and lysine demethylase 3B (KDM3B), key histone demethylases involved in CRC stem cell (CSC) function. These enzymes play a crucial role in epigenetic modulation of Wnt signaling, making them promising targets for PROTAC-based intervention [62].

Using CRBN-recruiting PROTACs, Zaman et al. achieved selective degradation of KDM3 proteins. Among the synthesized compounds, Compound 4 emerged as a potent degrader, effectively inhibiting Wnt signaling, eliminating CSCs, and significantly reducing tumor growth in CRC models [62]. These findings suggest that targeting epigenetic regulators of Wnt signaling through PROTACs could be a complementary strategy to direct β-catenin degradation, offering an alternative approach to suppress CRC progression.

Despite promising preclinical findings, the clinical translation of β-catenin-targeting PROTACs faces several challenges. One key concern is the potential toxicity associated with systemic β-catenin degradation, as this protein plays essential roles in normal tissue homeostasis. Additionally, optimizing PROTAC bioavailability and pharmacokinetics remains crucial for ensuring effective tumor targeting while minimizing off-target effects. Further studies are needed to evaluate their long-term safety and efficacy in clinical settings, as well as to determine patient subgroups that may benefit most from Wnt pathway inhibition through PROTAC-based strategies.

4.3 BRD4 Degradation

BRD4-targeting PROTACs have shown significant promise in CRC by selectively degrading BRD4 and disrupting transcriptional programs that support tumor growth. In preclinical models, BRD4-degrading PROTAC A1874 inhibited CRC cell proliferation, migration, and invasion while inducing apoptosis. It achieved this by downregulating oncogenes such as c-Myc, B-cell lymphoma 2 (BCL-2), and cyclin D1. Notably, A1874 retained cytotoxicity even in BRD4-knockout cells, suggesting additional mechanisms like tumor protein p53 (p53)stabilization and reactive oxygen species (ROS)production. *In vivo* studies further confirmed its ability to suppress tumor growth, highlighting its therapeutic potential [28]. In addition, Zhang et al. demonstrated that the BRD4 inhibitor AZD5153, in combination with the PARP (poly (ADP-ribose) polymerase) inhibitor BMN673, effectively suppressed CRC proliferation and induced apoptosis. This combination disrupted the G2/M checkpoint via Wee1 (WEE1 G2 checkpoint kinase) inhibition, resulting in synergistic anticancer effects *in vivo* [63]. Otto et al. compared BRD4 inhibition (via JQ1) with PROTAC-mediated degradation (via dBET1 and MZ1) in CRC models. Both approaches successfully reduced MYC expression and inhibited cell proliferation, but dBET1 was less effective in cereblon-deficient cells, emphasizing the importance of E3 ligase recruitment for PROTAC efficacy [29].

To overcome chemotherapy resistance, He et al. developed a nanoparticle system (ARV-DOX/cRGD-P) for co-delivering the BRD4 degrader ARV-825 and doxorubicin (DOX). This innovative system synergistically induced cell cycle arrest and apoptosis in DOX-resistant CRC cells. *In vivo*, it significantly inhibited tumor proliferation and angiogenesis, underscoring its potential for improving CRC treatment outcomes [64].

Unlike traditional BRD4 inhibitors, which reversibly block bromodomain binding, PROTACs induce complete degradation of BRD4, leading to more sustained suppression of oncogenic transcription. However, resistance mechanisms such as loss of cereblon or alternative E3 ligase downregulation may impact PROTAC efficacy. Additionally, BRD4 plays a role in normal transcriptional regulation, raising concerns about potential hematopoietic toxicity and off-target effects in non-tumor tissues. Further studies are needed to optimize PROTAC selectivity and minimize resistance, ensuring their clinical viability in CRC. These studies demonstrate the transformative potential of

BRD4-targeting PROTACs and inhibitors, offering new strategies to combat tumor progression, address resistance, and enhance therapeutic efficacy in CRC.

4.4 Targeting Cyclin-Dependent Kinases (CDK4/6)

Cyclin-dependent kinases (CDKs) play a crucial role in cell cycle regulation and have emerged as promising therapeutic targets in CRC. While small-molecule inhibitors such as palbociclib have shown clinical benefits, their efficacy is often limited by systemic toxicity and acquired resistance, highlighting the need for alternative therapeutic strategies. CDK9-targeting PROTACs have been developed to selectively degrade CDK9, suppressing its activity, downregulating Mcl-1 (myeloid cell leukemia-1), and inducing apoptosis in CRC models (95). Further optimization of linker composition enhanced CDK9 degradation, sensitizing CRC cells to the Bcl2 inhibitor Venetoclax. The concurrent degradation of CDK9 and Mcl-1 induced a potent apoptotic response, exhibiting synergistic effects in CRC and pancreatic cancer models [65].

Expanding on this approach, CDK4/6-targeting PROTACs offer another strategy for CRC treatment by selectively degrading these cell cycle regulators. These degraders arrest cell cycle progression at the G1 phase, suppress proliferation, and downregulate key effectors such as cyclin E and E2F (E2F transcription factors). Despite the advantages of CDK4/6 inhibition, traditional PROTACs face challenges such as systemic distribution and potential off-target effects, necessitating more precise delivery systems. Yang et al. introduced sequential responsive nano-PROTACs (PSRNs), which leverage pH- and enzyme-sensitive technology for enhanced tumor-specific delivery and degradation efficiency. Unlike conventional small-molecule PROTACs, which may be subject to rapid clearance, PSRNs utilize a nano-carrier system that ensures controlled release and selective activation in the tumor microenvironment, thereby minimizing systemic toxicity. In CRC xenograft models, CDK4/6-targeting PROTACs, including PSRNs, significantly reduced tumor growth, induced apoptosis, and potentiated immune checkpoint inhibitors like PD-1 (programmed cell death protein 1, α-PD-1) [66]. By improving pharmacokinetics and enhancing tumor accumulation, PSRNs offer a promising next-generation strategy for targeting CDK4/6, not only providing direct tumor suppression but also demonstrating potential synergy with immunotherapy.

Beyond their direct antiproliferative effects, CDK4/6-targeting PROTACs may enhance immunotherapy efficacy by modulating the tumor microenvironment. CDK4/6 inhibition has been shown to promote T-cell activation and reduce immunosuppressive signaling, potentially enhancing responses to immune checkpoint blockade. Additionally, PROTAC-mediated degradation of CDK4/6 may overcome resistance to conventional CDK inhibitors, restoring sensitivity to chemotherapy. Further investigations are needed to optimize these combination strategies and evaluate their clinical potential in CRC.

These findings underscore the advantages of nano-formulated PROTACs over conventional CDK-targeting approaches, particularly in enhancing degradation efficiency, selectivity, and immune modulation. CDK-targeting PROTACs as an effective therapeutic strategy, offering not only direct tumor suppression but also potential synergy with apoptotic regulators and immunotherapies.

4.5 Targeting STAT3 Transcription Factor

STAT3 (signal transducer and activator of transcription 3) -targeting PROTACs selectively degrade STAT3, disrupting key oncogenic signaling pathways in CRC. Jin et al. developed TSM-1, a PROTAC based on toosendanin (TSN), which targets STAT3 for degradation by recruiting an E3 ligase. TSM-1 demonstrated potent antitumor effects, reducing tumor growth in CRC models, including patient-derived xenografts (PDX) and organoids (PDO). In CRC xenograft models, TSM-1 led to reduced expression of STAT3 downstream effectors, inducing cell cycle arrest and apoptosis [67]. These findings highlight the effectiveness of STAT3-targeting PROTACs in CRC therapy, offering a novel approach to target STAT3-driven tumor progression.

While TSM-1 has demonstrated selective STAT3 degradation, further studies are needed to confirm its specificity, particularly its potential effects on other STAT family proteins. Additionally, systemic STAT3 degradation raises concerns about potential toxicity, as STAT3 plays key roles in immune homeostasis and normal tissue regeneration. Optimizing tumor-selective delivery and minimizing off-target effects will be critical for clinical translation, requiring further investigations into pharmacokinetics, bioavailability, and safety in human models.

4.6 Targeting DNA Repair and PARP-1 Degradation

Given the crucial role of DNA damage repair (DDR) pathways in tumor survival, targeting DNA repair proteins via PROTAC technology has emerged as a promising approach in CRC therapy. A novel PROTAC targeting PARP-1 was developed by conjugating the PARP-1 inhibitor olaparib to a CRBN ligand via an alkyl linker. This molecule effectively degraded PARP-1, leading to cell cycle arrest at the G1 phase and induction of apoptosis in CRC cells. Notably, this degradation mechanism differed from that of traditional PARP inhibitors, which typically induce G2/M arrest [68].

Recent studies suggest that the combination of PROTAC-based PARP-1 degradation with chemotherapy or radiotherapy can overcome resistance mechanisms in CRC cells, improving treatment efficacy and survival rates. The

synergistic effects of combining PARP-1 degradation with DNA-damaging agents further potentiate therapeutic outcomes, particularly in tumors with high mutation rates, such as CRC [69].

Additionally, PROTAC-mediated PARP-1 degradation significantly inhibited CRC cell migration and metastasis, although limitations such as poor metabolic stability and short half-life remain challenges for further clinical translation [68]. Targeting other members of the PARP family, such as PARP-2, may further enhance the therapeutic efficacy of PARP inhibitors in CRC, as they play overlapping roles in DNA repair processes [70].

4.7 Immunotherapy Enhancement via PD-L1 Targeting

Immune checkpoint blockade has revolutionized oncology, but PD-L1-targeting monoclonal antibodies have shown limited efficacy in several solid tumors, including CRC. To address this challenge, a PROTAC molecule (21a) targeting PD-L1 was synthesized by linking BMS-37 (a PD-L1-binding small molecule) to a CRBN ligand. This PROTAC demonstrated dose-dependent PD-L1 degradation in CRC models, leading to enhanced CD8+ T-cell infiltration and tumor suppression [71].

Preclinical studies revealed that PD-L1 degradation correlated with reduced mRNA expression, suggesting that this PROTAC not only degrades PD-L1 protein but also disrupts its transcriptional regulation. These findings highlight the potential of PD-L1-targeting PROTACs to enhance immune responses in CRC models resistant to conventional PD-L1 inhibitors [71]. Furthermore, combining PD-L1-targeting PROTACs with immune-modulating agents like TLR (Toll-like receptor) agonists has shown promise in amplifying immune responses and enhancing anti-tumor effects [72].

Unlike monoclonal antibodies that block PD-L1 at the cell surface, PROTACs facilitate complete degradation of PD-L1, preventing its recycling and potential re-expression [71, 73]. This mechanism may help overcome adaptive resistance observed with PD-L1 inhibitors, particularly in tumors with compensatory upregulation of immune checkpoints [73]. Additionally, PD-L1 degradation has been shown to enhance antigen presentation and immune cell activation [74], suggesting that PROTACs may exhibit greater durability of response compared to PD-L1 blockade alone. Combining PD-L1-targeting PROTACs with immune checkpoint inhibitors, chemotherapy, or small-molecule immunomodulators may further amplify anti-tumor immunity, warranting further clinical evaluation of these combination strategies.

Targeting other immune checkpoints, such as PD-1 and CTLA-4, in combination with PD-L1 degradation may provide a more comprehensive strategy to overcome immune evasion mechanisms in CRC. Recent studies have suggested that the use of PROTACs to target PD-L1 in combination with checkpoint inhibitors may offer synergistic effects, increasing the overall efficacy of immune checkpoint therapy in CRC (Table 2) [75,76].

Table 2. Current PROTAC compounds targeting oncogenic pathways with potential applications in CRC

PROTAC compound	Target protein	Mutation / Pathway targeted	Mechanism/Key Features	Ref
LC-2	KRAS	G12C	VHL-recruiting PROTAC; degrades KRASG12C, suppresses MAPK signaling	[53]
YF135	KRAS	G12C	Reversible-covalent PROTAC; degrades KRASG12C, inhibits pERK	[51]
17f	PDEδ	KRASG12D, KRASG12V	Disrupts KRAS membrane localization, suppresses MAPK/ERK signaling	[54]
ZZ151	SOS1	KRAS-related pathways	Degrades SOS1, blocks KRAS activation, effective in KRAS-mutant CRC	[30]
BTX-6654	SOS1	KRAS (Multiple)	CRBN-based degrader; suppresses pERK/pS6, synergizes with KRAS/MEK inhibitors	[55]
BTX-10908	SOS1	KRAS, RTK-driven cancers	CRBN-based degrader; reduces active RAS, inhibits pERK/pRSK/pS6	[56]
xStAx-VHLL	β-catenin	Wnt/β-catenin	Stapled peptide-based PROTAC; degrades β-catenin, suppresses Wnt signaling	[60]
Compound 4	KDM3A and KDM3B	Wnt/β-catenin	CRBN-recruiting degrader; eliminates CRC stem cells, inhibits Wnt	[62]
A1874	BRD4	Oncogenic transcription	Potently degrades BRD4, inhibits CRC proliferation and invasion	[28]
ARV-825	BRD4	Chemotherapy resistance	Enhances DOX efficacy, inhibits tumor proliferation	[64]
PSRNs	CDK4/6	Cell cycle regulation	Nano-PROTACs; degrade CDK4/6, enhance immune checkpoint therapy	[66]
TSM-1	STAT3	STAT3 oncogenic signaling	STAT3 degrader; induces apoptosis, suppresses tumor growth	[67]

4.8 Integration of PROTACs with Emerging Therapies

The integration of PROTAC technology with emerging cancer therapies, including radiotherapy, photodynamic therapy (PDT), immunotherapy, nanomedicine, and gene editing, represents a promising approach to enhancing treatment efficacy and minimizing off-target effects.

One notable advancement is the combination of PROTACs with radiotherapy, where radiation-responsive PROTAC prodrugs have been developed to enable precise, spatiotemporal protein degradation. These prodrugs remain inactive until exposed to X-ray radiation, at which point they selectively degrade target proteins in tumor cells, thereby enhancing the therapeutic effects of radiotherapy while reducing systemic toxicity [77] .

Similarly, the integration of PROTACs with PDT has demonstrated significant potential. A self-assembled nano-PROTAC system has been designed to co-deliver CDK4/6-targeting PROTACs alongside chlorin e6-based PDT agents. This carrier-free nanoparticle formulation facilitates precise targeting of cancer cells and enhances therapeutic efficacy. The synergistic effect of PDT-induced ROS and PROTAC-mediated protein degradation results in enhanced apoptosis and improved immune cell recruitment [78].

In the field of immunotherapy, PROTACs have been explored as a means to modulate the tumor microenvironment and enhance immune responses. PROTAC-based strategies targeting key immune checkpoints or tumor-associated proteins may improve the efficacy of immune checkpoint inhibitors and other immunotherapeutic agents. For instance, a PROTAC designed to degrade the anti-apoptotic protein MCL-1 has been shown to remodel the immunosuppressive tumor microenvironment and promote immune-mediated tumor clearance [79].

CAR T-cell therapy, which has shown remarkable success in hematological malignancies, faces significant hurdles in solid tumors like CRC due to an immunosuppressive tumor microenvironment. PROTACs can enhance CAR T-cell efficacy by selectively degrading immune checkpoint proteins such as PD-L1, thereby improving T-cell infiltration and function. Furthermore, PROTACs can target intracellular signaling molecules that drive tumor resistance, making cancer cells more susceptible to CAR T-cell attack. For example, degrading transcription factors or kinases involved in immune evasion could create a tumor microenvironment more favorable for CAR T-cell activity [80].

Nanomedicine has also played a crucial role in optimizing PROTAC applications by improving drug stability, solubility, and tumor-specific accumulation. Nano-PROTAC polymers encapsulate PROTAC molecules, preventing premature degradation and ensuring selective release within tumor tissues. These polymeric nanocarriers enhance pharmacokinetics and minimize systemic toxicity [81]. Additionally, antibody-PROTAC conjugates combine monoclonal antibody specificity with the potent degradation capability of PROTACs, allowing for highly selective protein degradation in cancer cells [82,83]. However, challenges such as immunogenicity, limited loading efficiency, and complex manufacturing must be addressed before their clinical translation .

A key aspect of targeted cancer therapy is the distinction between PROTACs and gene-editing technologies such as CRISPR-Cas9 and RNA interference (RNAi). Unlike CRISPR-Cas9, which induces permanent genetic modifications, PROTACs mediate transient and reversible protein degradation without altering the genome. This feature mitigates the risks associated with unintended genetic alterations and enhances the safety of *in vivo* applications. Additionally, CRISPR screens have helped identify new targets for PROTAC-based degradation, further expanding their potential in cancer treatment [82].

Overall, the integration of PROTACs with these emerging therapeutic strategies represents an exciting direction in oncology. By leveraging synergistic effects, these combination approaches offer the potential for more effective and less toxic treatment regimens.

5. Advances and Innovations in PROTAC Technology and Overcoming Challenges

The emergence and evolution of PROTAC technology have opened new horizons in targeted therapies, particularly in CRC. However, realizing this potential depends on overcoming current limitations, including challenges in design, delivery, resistance mechanisms, and scalability (Figure 3).

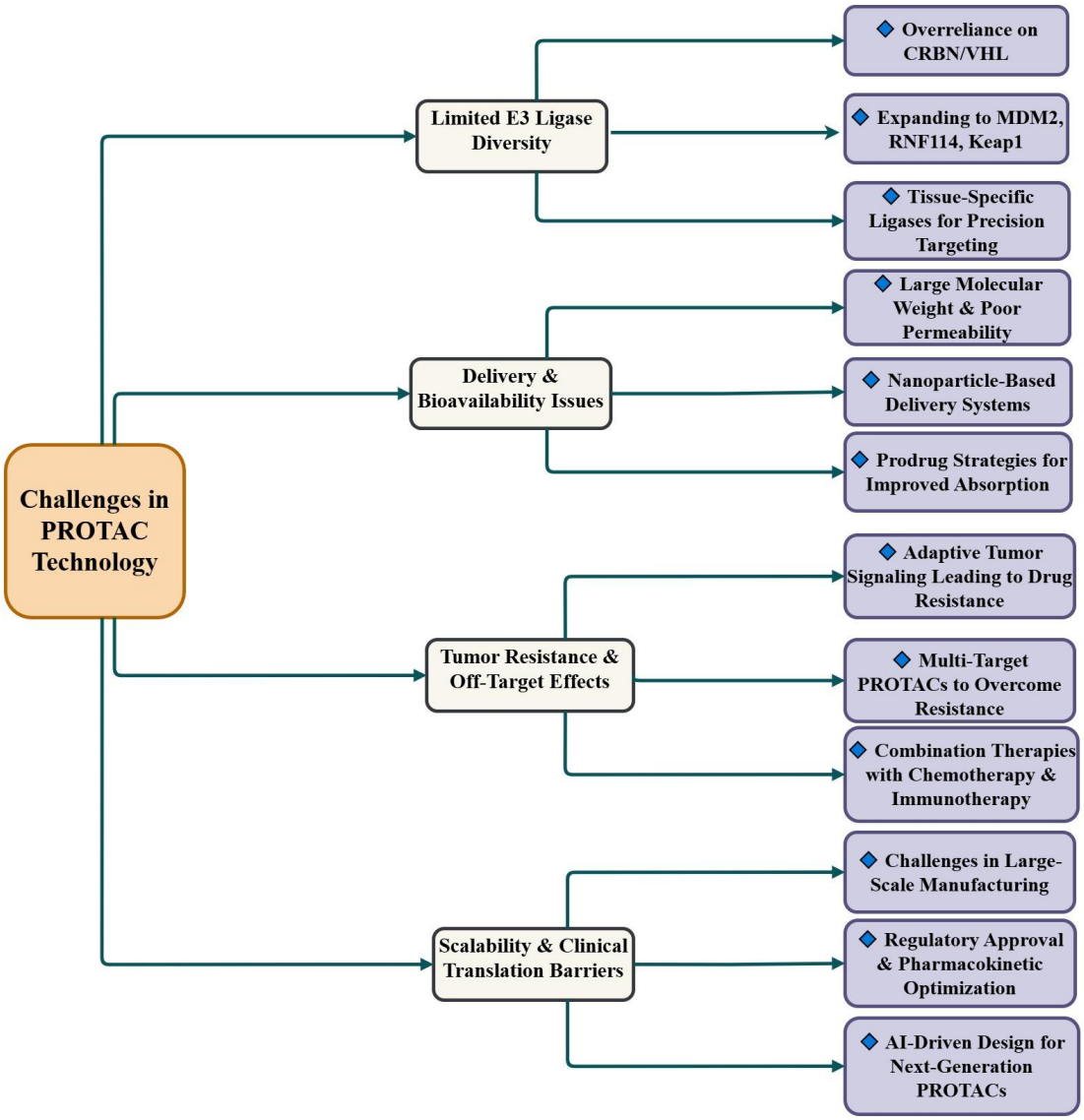


Figure 3. Challenges and Future Directions in PROTAC Technology for CRC. The figure outlines key obstacles in PROTAC development for CRC and potential strategies to overcome them. Major challenges include limited E3 ligase diversity, delivery and bioavailability issues, tumor resistance and off-target effects, and scalability barriers in clinical translation. Strategies such as expanding the E3 ligase repertoire, nanoparticle-based delivery, multi-target PROTACs, combination therapies, and AI-driven drug design are highlighted as promising directions for enhancing PROTAC efficacy and clinical applicability.

5.1 Expanding E3 Ligase Options and Selectivity

One of the main challenges in PROTAC technology is the overreliance on a limited set of E3 ligases, restricting the range of targetable proteins. Expanding the E3 ligase repertoire is essential for improving therapeutic selectivity and efficiency. CRBN- and VHL-based PROTACs dominate the current landscape [84], but recent studies have identified alternative ligases, such as MDM2 (mouse double minute 2) [85], DCAF16 (DDB1- and CUL4-associated factor 16) [86], RNF114 (ring finger protein 114) [87], and Keap1 (Kelch-like ECH-associated protein 1) [88]. These ligases have demonstrated potential for degrading a broader range of oncogenic targets.

MDM2 is a well-characterized E3 ligase that facilitates degradation by targeting tumor suppressors like p53 for ubiquitination and proteasomal degradation. Recent studies suggest that PROTACs utilizing MDM2 as a recruiter can efficiently degrade specific oncogenic proteins while maintaining a precise mechanism of action. Additionally, MDM2-based PROTACs may leverage the high expression of MDM2 in certain cancers to achieve enhanced tumor specificity, potentially improving therapeutic selectivity.[89,90]. DCAF16, in contrast, is part of the CUL4-DDB1 complex and is primarily involved in the degradation of nuclear proteins, including transcription factors. This feature makes DCAF16 a valuable tool for targeting proteins traditionally considered 'undruggable,' such as nuclear oncogenic factors. The ability of DCAF16 to degrade transcription regulators suggests that its incorporation into PROTAC design may provide new avenues for treating transcription-driven malignancies, including CRC [91,92]. Moreover, the development of tissue-specific E3 ligases is an emerging strategy to enhance tumor selectivity and reduce off-target effects in CRC therapy [85,93].

5.2 Improving Delivery, Bioavailability, and Patient Selection

Efficient delivery and bioavailability remain significant hurdles in PROTAC therapy due to poor solubility, limited cell permeability, and rapid clearance. Due to their large size and hydrophobic nature, PROTACs often suffer from low solubility, poor cell permeability, and rapid systemic clearance [94]. One approach to overcoming these limitations is the use of nanoparticle-based drug carriers, such as liposomes and polymeric nanoparticles, which enhance solubility, stability, and biodistribution [95-97]. Additionally, prodrug strategies involving chemical modifications of PROTACs have shown potential in improving tumor-specific activation while reducing systemic toxicity [98,99]. These advancements in drug delivery hold promise for optimizing PROTAC effectiveness in CRC treatment.

Preclinical studies have demonstrated that PROTACs effectively degrade target proteins and inhibit tumor growth in CRC models. However, clinical data on their efficacy across different CRC stages remain limited. An example of PROTAC's clinical potential is ARV-110 (bodegalutamide), which targets the androgen receptor and has demonstrated encouraging outcomes in Phase 1/2 trials for castration-resistant prostate cancer [100]. Compared to standard treatments such as chemotherapy and targeted therapies, PROTACs offer selective degradation of resistance-associated proteins, which may improve therapeutic outcomes. Nevertheless, further large-scale clinical trials are necessary to comprehensively assess the efficacy and safety of PROTACs in CRC patients at different disease stages.

5.3 Biomarker-based Patient Selection for PROTAC Therapy

A key factor for the clinical success of PROTAC-based therapies is the identification of predictive biomarkers to guide patient selection. Since PROTAC efficacy depends not only on target protein expression but also on the presence of functional E3 ligases and the efficiency of the ubiquitin-proteasome system, selecting patients based on these parameters could optimize therapeutic outcomes. For example, KRAS-targeting PROTACs may be most effective in $KRAS^{G12C}$-mutant CRC patients with high target protein stability and compatible E3 ligase expression (VHL or CRBN) [101]. Similarly, BRD4-targeting PROTACs may be more effective in tumors exhibiting high BRD4 dependency, as identified through transcriptomic and proteomic analyses [102]. Recent advances in multi-omics profiling and AI-driven biomarker discovery have enabled better stratification of patients who are likely to respond to PROTAC therapy [103]. Future clinical trials should incorporate biomarker-based selection criteria to enhance treatment precision and minimize off-target effects. This approach is critical for the successful translation of PROTACs into precision oncology.

5.4 Overcoming Resistance and Enhancing Combination Therapies

In addition to overcoming design and delivery challenges, ensuring the long-term efficacy and safety of PROTAC-based therapies remains a crucial aspect of their clinical translation. While preclinical studies have demonstrated sustained target degradation and therapeutic benefits, comprehensive evaluations of chronic toxicity and systemic off-target effects are still required. Recent advancements, including tumor-selective E3 ligases and prodrug strategies, offer promising approaches to mitigate long-term toxicities by enhancing tissue specificity and reducing systemic exposure [104]. Moreover, the development of multi-target PROTACs aims to prevent resistance mechanisms and maintain therapeutic efficacy over extended periods. Future research should focus on longitudinal clinical studies and pharmacokinetic profiling to ensure that PROTACs achieve both durability of response and minimal long-term adverse effects, facilitating their transition into widespread therapeutic use.

Tumor resistance and off-target effects pose additional challenges, as CRC cells can activate compensatory signaling pathways, reducing the efficacy of PROTAC therapy. Tumor heterogeneity and compensatory signaling networks can enable cancer cells to bypass PROTAC-induced protein degradation [105]. To counteract adaptive resistance, researchers have developed dual- and multi-target PROTACs, which simultaneously degrade multiple oncogenic proteins. For example, dual-target PROTACs degrading EGFR and MET have demonstrated superior efficacy in preclinical models by disrupting parallel signaling pathways and overcoming drug resistance [106,107]. Furthermore, combination therapies integrating PROTACs with chemotherapy or immunotherapy have shown promising synergistic effects in CRC treatment, particularly by enhancing the degradation of resistance-associated proteins such as PARP and β-catenin [108-110].

5.5 Scalability and Clinical Translation

These strategies provide new avenues to improve PROTAC durability and treatment response rates. Manufacturing scalability and clinical translation remain critical barriers that must be addressed to bring PROTACs into widespread therapeutic use. The complex synthesis of PROTAC molecules presents manufacturing challenges that limit large-scale production. Advances in synthetic chemistry and automated drug synthesis platforms are being explored to improve scalability and cost-effectiveness [111]. Additionally, regulatory agencies need to establish standardized frameworks for evaluating the safety, efficacy, and pharmacokinetics of PROTAC-based therapies [111]. While the synthesis of PROTACs is more complex and costly compared to conventional targeted therapies and immunotherapies, their catalytic mechanism may allow for sustained protein degradation with lower dosing, potentially improving long-term cost-effectiveness. Advances in AI-driven drug design and synthetic automation are expected to enhance scalability and affordability, further supporting their clinical viability.

Recent advancements in AI-driven drug discovery are also expected to accelerate PROTAC development. Computational methods, such as reinforcement learning (RL) models like PROTAC-INVENT, enable the design of optimized linkers and 3D molecular structures to enhance degradation efficiency [112]. AI-based predictive modeling has also been used to refine PROTAC binding affinities, allowing for the generation of more selective and potent molecules [113]. These advancements are critical for streamlining the transition of PROTACs from preclinical models to clinical application.

While PROTAC technology represents a transformative approach for CRC treatment, its clinical success hinges on overcoming four key challenges: limited E3 ligase diversity, delivery and bioavailability issues, tumor resistance, and scalability barriers. Expanding the use of alternative E3 ligases, such as MDM2 and DCAF16, offers a promising strategy to improve the diversity and specificity of PROTAC therapies. Future studies should further explore their compatibility with different oncogenic targets and assess their potential for clinical translation.

Expanding the E3 ligase toolbox, enhancing drug delivery strategies, developing multi-target PROTACs, and leveraging AI-driven optimization are pivotal steps toward realizing the full potential of PROTAC-based therapies. Continued research and innovation in these areas will be crucial in bringing PROTACs from experimental models into mainstream clinical practice, offering a revolutionary therapeutic strategy for CRC and beyond.

6. Conclusion

PROTAC technology has emerged as a transformative approach in CRC treatment, offering a novel mechanism to target and degrade disease-driving proteins. By addressing key oncogenic drivers such as KRAS, β-catenin, and BRD4, PROTACs have demonstrated significant potential in overcoming the limitations of traditional therapies, such as drug resistance and limited druggable targets. Their catalytic and selective mode of action positions PROTACs as a powerful tool in precision medicine, providing new hope for patients with advanced or treatment-resistant CRC.

Despite its promise, PROTAC technology faces notable challenges, including issues with delivery, E3 ligase diversity, and large-scale production. Addressing these limitations requires continued innovation in linker design, delivery systems, and the identification of novel E3 ligases. The integration of artificial intelligence and nanotechnology is already accelerating advancements in these areas.

As clinical trials for PROTAC-based therapies progress, their ability to combine with chemotherapy, immunotherapy, and radiation therapy could redefine the standard of care for CRC. Looking ahead, PROTACs are not only poised to revolutionize CRC treatment but also hold immense potential to shape the broader landscape of targeted cancer therapy, solidifying their role as a cornerstone of next-generation therapeutics.

Competing Interests

The author declares no competing interest.

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