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PARP in colorectal cancer: Molecular mechanisms, immunity, clinical trials, and drug combinations

Minireview

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The changes in cell homeostasis in the tumor microenvironment may affect the development of colorectal cancer (CRC). Genomic instability is an important factor. Persistent genomic instability leads to epigenetic changes, and mutations are a major factor in the progression of CRC. Based on these mechanisms, it is reasonable to link poly (ADP-ribose) polymerase (PARP) with the treatment of CRC. PARP is mainly involved in DNA repair, which has an essential role in the DNA damage response and prevention of DNA damage, and maintains oxidation and superoxide redox homeostasis in the intracellular environment of the tumor. This article reviews the latest research progress on PARP and PARP inhibitors (PARPi) in CRC. It mainly includes molecular mechanisms, immunity, clinical trials, and combination strategies of CRC. The research of PARPi in CRC has broad prospects, and the combinations with other drugs are the main research direction in the future.

Key words: PARP, colorectal cancer, DNA damage; immunity, clinical trial

DNA damage response (DDR) is a very conservative mechanism in cells to resist DNA damage (DD) induced by external and internal factors, including DNA recognition and repair. It is a network composed of multiple signal transduction pathways to monitor and transmit damage signals and form an appropriate response mechanism. Poly (ADP-ribose) (PAR) is the major signaling molecule of DDR, an instantaneous post-translational stress modification (PTM) sensor and promoter of DNA repair (DR). PAR polymerases (PARP), also called ARTD (Diphtheria toxin-like ADP-ribosyl transferase) family, are involved in the encoding of PAR [1]. The PARP enzyme family consists of 17 family members. Nicotinamide adenine dinucleotide (NAD+) is cleaved into ADP-ribose and nicotinamide by the ADP-ribosyl transferase (ART) enzyme, and the cleaved product of the former is linked to the serine, glutamic, aspartic, arginine, lysine, or cysteine residues or DNA/RNA terminus of the protein [2]. ARTs mostly modify their target with an ADP-ribose fragment, referred to as mono-(ADP-ribosyl)-ation (MARylation). However, ARTs are also capable of extending protein binding units to form longer PAR polymers [3]. In particular, PARP-1 was shown to have a key role in DR and genome integrity. PAPR-1 catalyzes the composition of a PAR strand comprising approximately 200 ADP-ribose units, with each strand 20–25 units apart. Following DD, PARP-1 produces a matrix-like structure that binds DR proteins together. In addition, PARP-1 promotes covalent and non-covalent poly-(ADP-ribosyl)-ation (PARylation) of a variety of proteins to regulate their function (Figure 1A) [4]. PARP-1 is an important sensor of DD and is involved in several important cellular functions, including chromatin remodeling, replication, immunity, and cell death [5]. PARP-1 has a key function in DR and genome maintenance, including the base excision repair, and two double-strand break (DSB) repair pathways [6]. The studies revealed that PARP-1 has a key function in the development of tumors, including glioblastoma, small cell lung cancer, and glioblastoma. Abnormal PARP-1 contributes to the occurrence of tumors, and PARP-1 is a promising new anticancer target [7].

Colorectal cancer (CRC) remains among the most prevalent gastrointestinal tumors worldwide. CRC is fourth most common in the United States after breast, lung, and prostate cancer, and second only to lung cancer in death rates [8]. In China, CRC is among the top five cancers and is an important cause of cancer-related deaths [9].

The progression of CRC is strongly related to tumor genes, including PARP-1 and Programmed cell death 1 ligand 1 (PD-L1) [10, 11]. PARP has a key function in the pathogenesis of colon cancer, and PARPi are also effective in the treatment of tumors. This article reviews the research progress of PARP and PARPi in colorectal cancer.

The biological functions of PARP

The basic functions of PAPR. PARP regulates a variety of nuclear-related features, including DR, DNA replication, chromatin dynamics, and mitotic processes. It is intensely triggered in DDR and is involved in most PAR formation after genotoxic stress [12]. PARP-1 is one of the most abundant PARP enzymes, contributing about 85% of PARylation activity. PARP-1 activation results in autocytosis and PARylation of target proteins, recruiting DDR proteins to the damage (Figure 1B) [13]. The involvement of PARP-1 can be found in most DDR pathways. When DNA single strand breaks, PARP-1 is able to recruit XRCC1, which underlies the formation and initiation of the underlying resection restoration mechanism and the consequent restoration of small damages induced by oxidation or alkylation [14]. In addition, PARP-1 is thought to be involved in homologous recombination repair (HRR) of DSB, because components of the HRR mechanism, such as ataxic mutation, are quickly recruited to the site of DD in a dependent PAR manner [15]. Along with its involvement in the DDR, PARP-1 is also involved in chromosome remodeling, and transcriptional regulation [16]. In addition, PARP-1 is involved in diverse processes of

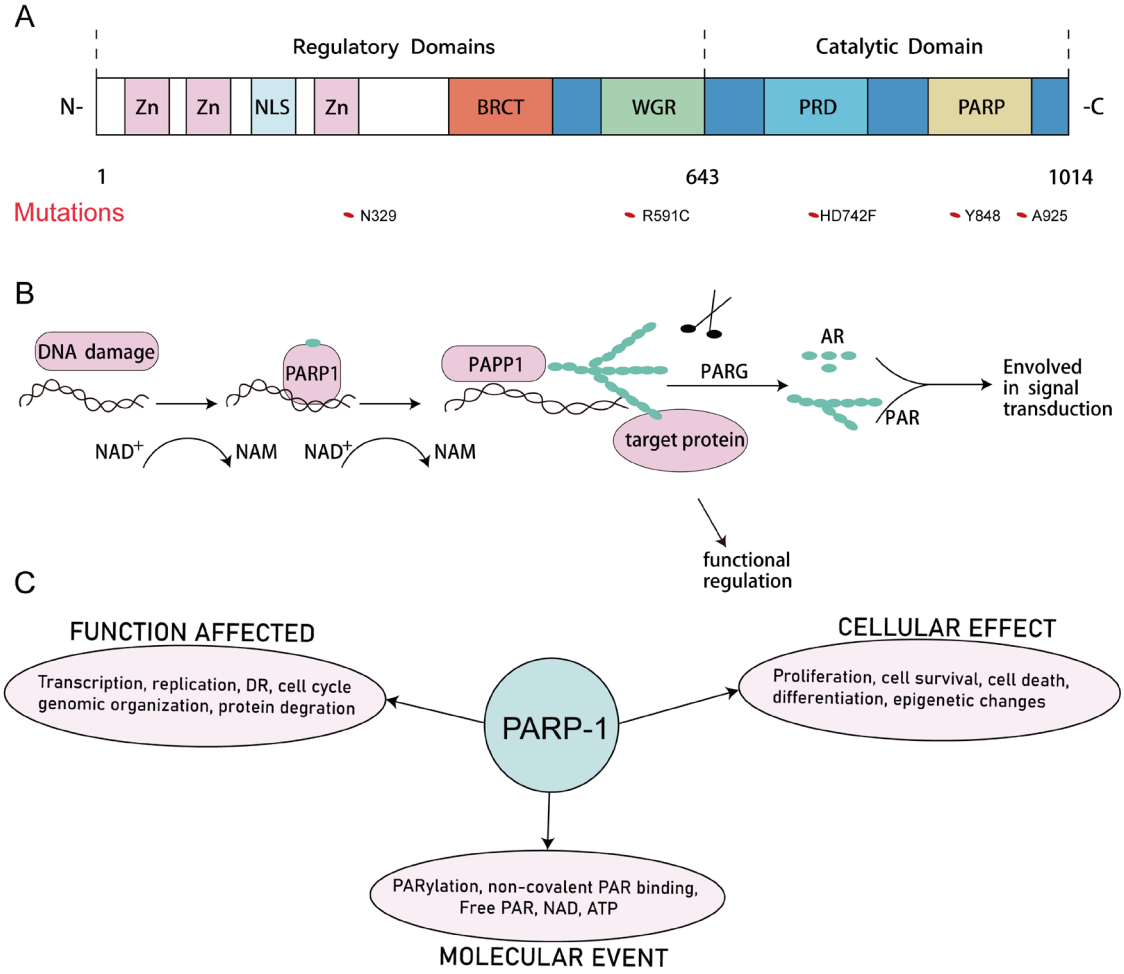

Figure 1. A) The two main domains of the PARP-1 protein are the regulatory domain and the catalytic domain, respectively. Zn: Zing fingers; NLS: Nuclear localization signal. BRCT: Breast cancer suppressor protein 1 domain; WGR: Trp-Gly-Arg sequence. PRD: PARP regulatory domain. N: Amino terminus; C: Carboxyl terminus. Numbers represent amino acids. B) PARP-1 recruits DNA damage response proteins. Abbreviations: NAD+-Nicotinamide adenine dinucleotide; NAM-Nicotinamide; PAR-poly (ADP-ribose); AR-ADP-ribose; PARG-Poly(ADP-ribose) glycohydrolase C) The role of PARP-1 in the cellular processes.

cell death, such as apoptosis and autophagy [14]. As shown in Figure 1C, we provided the role of PARP-1 in cellular processes.

PARP-1 and BRCA gene mutation. PARP-1 of the PARP family is closely related to the expression of the tumor suppressor gene BRCA in colorectal cancer [10, 17]. The BRCA allele is regarded as a tumor suppressor gene because it is mutated during tumorigenesis. BRCA proteins repair DSB through a process known as HRR, a DR mechanism that directs DSB repair through homologous DNA sequences [18]. When BRCA1 and BRCA2 cause HRR defects, the non-conserved state of DR dominates, such as non-homologous end joining (NHEJ). The above approach allows the fusion of broken DNA ends of DSB without using homologous sequences to instruct restoration, and they can delete inserted DNA sequences by fusing DNA regions near sites with short sequence homology in the DSB. Thus, priority application of non-conservative restoration processes in the presence of HRR deficiency would normally result in DNA alterations, including deletion of genetic material. This outcome will promote the progression of cancer [19]. PARP-1 is activated by recognizing structurally damaged DNA fragments and is considered to be a receptor of DD, contributing to the binding of repair proteins to repair DD [5]. PARPi were constructed based on DDR of PARP. PARPi captures PARP proteins onto single strand DNA-binding protein (SSB). If the inhibitor binds to the PARP functional threshold and the PARP protein stays in the DNA for a long enough time, it can be met by the DNA duplication mechanism, which may cause the replication fork to stop, resulting in the breakdown and the production of DSB. In HRR-deficient tumors, using classic NHEJ results in mistake-prone fixes with multiple cycles of DNA duplication, potentially leading to irresistible genomic instability and tumor cell death [20].

Common PARP-associated pathways. PAPR is involved in the regulation of various tumor signaling pathways, such as the PI3K/Akt pathway. In endometrial cancer, suppression of the PI3K/Akt pathway increases the efficacy of PARPi in PTEN mutant cell lines [21]. The downstream PI3K gene AKT is activated in response to exposure to PARPi, and these results limit the efficacy of PARPi in cancer therapy [22]. However, PARPi activate the PI3K/Akt pathway, thereby reducing the side effects of chemotherapeutic drugs by protecting mitochondrial integrity [23]. The second major signaling pathway linked to PAPR is the NF-κB. In colon cancer, PARP-1 can influence the activation of TLR4-related signal transduction by modulating NF-κB activity, resulting in NF-κB mobilization and ensuing nuclear preservation. In addition, inhibition of PARP expression further controls NF-κB activity through the PI3K/Akt signaling pathway [24]. PARP also promotes pancreatic cancer cell proliferation and gemcitabine chemotherapy resistance by activating the NF-κB pathway [25]. PARP protein also plays an important role in the Wnt signaling pathway. Overactivation of Wnt signaling drives PARPi resistance, while suppression of the Wnt pathway decreased DR ability and dramatically suppressed cancer development *in vivo* [26]. PARPi increase the cytotoxicity of cisplatin to cervical cancer cells by inhibiting the Wnt pathway and further components, such as c-Myc, cyclin D1, and MMPs [27].

Biomarkers associated with PARPi treatment. PARPi are suitable for the treatment of a wide range of tumors [28–32], but not all tumors respond well after treatment. Therefore, we should identify the tumor population suitable for drug therapy, predict the efficacy of drugs for different patients, and follow up the tumor progression of patients during treatment to adjust the drug dose. BRCA proteins repair DSB through a process called HRR, a type of DR that uses homologous DNA sequences to instruct DSB repair. BRCA mutations, which can be detected in blood samples, are the most reliable and viable biomarkers for selecting patients for PARPi treatment [32]. Rad51 is localized in the nucleus and is a specific cell feature of HR malfunction, which can predict the efficacy of tumor therapy. Overexpression of aurora A, which is able to reduce the induction of Rad51, is involved in the sensitivity of cancer cells to PARPi [33]. H2AX histone is an essential HR-related marker, creating a site for the assembly of DR and chromatin remodeling factors on DSB foci. ATM phosphorylates H2AX histones to create γH2AX and serves as a cell cycle filter. The pathway is deficient in a group of elements, such as ATM, CHK, and CDK1 complex, and leads to synthetic lethality with PARPi [32, 34]. The investigators found that abnormalities in the PI3K/AKT pathway were related to HRR. Suppression of the PI3K/AKT pathway activity can reduce BRCA expression and lead to PARPi inhibition [35]. PARP-1 is the main active component of PARP protein. Although no biomarkers related to PARP-1 have been detected as genetic biomarkers, genes related to PARP-1 act as a prognostic marker [36]. For instance, CDK5 knockdown correlates with the synthetic lethality of PARP-1 suppressors. It was shown that in BRCA mutant cells, REV7 lies downstream of 53BP1 and induces the DSB repair pathway, while deletion of 53BP1 or REV7 imparts PARPi resistance [37]. Biomarkers associated with PARPi therapy can predict the efficacy of PARPi and guide cancer treatment.

Introduction to PARPi. Olaparib is an oral PARPi that has shown clinical benefit in trials of mutated BRCA-positive HER2-negative breast cancer metastases. Olaparib has also been shown to be effective in unresectable and metastatic Mismatch Repair (MMR) type Microsatellite stable (MSS) CRC, and the combination of olaparib and 5-FU may facilitate non-metastatic MMR deficiency (dMMR)/microsatellite instability (MSI) CRC [38, 39]. Rucaparib is a minor component of PARPi with strong activity towards PARP. Rucaparib is also authorized in the US and EU as maintenance therapy for adult patients with relapsed or recurrent tumors that have responded fully or partially to platinum-based chemotherapy [40]. SN38 topoisomerase 1 inhibitor damages DNA by inducing SSB, which, if not repaired,

result in DSB [41]. Niraparib enhances the effects of SN38 on DSB and Rad51 recruitment and is more sensitive to ATM mutations in colon cancer cells. Niraparib also induces the G2/M arrest of CRC cells to regulate tumor progression. Niraparib enhances the effects of SN38 on double strand break and Rad51 recruitment and is more sensitive to ATM mutations in colon cancer cells. Niraparib also induces the G2/M arrest of CRC cells to regulate tumor progression [42]. As with other PARPi, talazoparib has shown *in vitro* antitumor activity only in cancers with homologous recombination defects. However, its advantages lie in the fact that effective antitumor responses can still be observed at lower concentrations [43]. The most relevant mechanisms of action for Veliparib are the inhibition of PARP-1/2 and the "PARP capture" process by which PARPi exert their cytotoxic effects in HR proficient cells [44]. One of the main mechanisms of effect is sensitization to DD therapy, including chemotherapy and radiation. Veliparib impairs SSB and DSB repair to enhance the effects of graded radiation [45]. Pamiparib, an inhibitor of PARP-1 and PARP-2, is being developed for the treatment of various cancers. Pamiparib has been shown to be more effective than Olaparib in BRCA1-mutated breast cancer and has excellent anti-proliferative activity in cancer cells with BRCA1/2 mutations or HR pathway deficiency [46]. Fuzuloparib is a small molecule oral PARPi for the treatment of solid tumors. Fuzuloparib was recently approved in China for the treatment of BRCA mutation-associated recurrent advanced ovarian, fallopian tube, and primary peritoneal cancers [47]. We summarized the common PARPi information (Table 1).

Immune regulation of PARP and PARPi

PARPi combined with immune checkpoints enhances the immune response. Immuno-checkpoint inhibitors, including anti-PD1/PD-L1 and anti-CTLA-4, have been clearly observed for therapeutic effects in tumors and have been approved for various cancer types [49]. CTLA-4 attenuates the acquisition of T cell effector function and inhibits the antitumor immune response [50, 51]. PARPi enhances the efficacy of CTLA-4 antibody checkpoint inhibitors through IFN-γ [52]. Veliparib is a PARPi that enhances the efficacy of CTLA-4 blockade and contributes to tumor clearance [52]. PARPi can increase the inhibitory feature of Treg cells by promoting the expression levels of CTLA-4 [53]. PD-L1, as a ligand of PD-1 on the tumor surface, is the basis for the critical association of the PD-1/PD-L1 pathway with tumors. Blockade of the PD-1/PD-L1 pathway enhances the therapeutic effect of PARPi [54]. Jiao et al. showed that PARPi inhibited T cell activation and increased tumor cell killing by upregulating PD-L1 expression mainly by inhibiting GSK3β [55]. Further study of the mechanism found that PARPi directly targets the DDR protein PARP to promote the expression of PD-L1 [56]. In addition, PARPi can promote the expression of PD-L1 by inducing CHK1 phosphorylation, and inhibition of PD-L1 can restore the suppression function of PARPi on CD8+ T cells [57].

PARPi activates the cGAS-STING and ATM-ATR-CHK1 pathway. Tumor-derived DNA can be absorbed and labeled by host antigen presenting cells (APC), thereby activating the cGAS-STING pathway and inducing inflammation and anti-tumor immunity [58]. cGAS is the main cellular solute sensor of dsDNA. cGAS binds to dsDNA to change its conformation and promote the production of cGAMP, which acts as a second messenger to activate STING and stimulate its translocation from the endoplasmic reticulum (ER) to perinuclear structures, thereby activating anti-tumor immune responses [59]. Interestingly, PARPi can promote dsDNA accumulation, thereby activating the cGAS-STING-TBK1-IRF3 innate immune pathway to induce antitumor immune responses [54]. PARPi generates fragments of cytoplasmic chromatin with micronucleus characteristics that activate downstream type I IFN signaling and CCL5 secretion in non-small cell lung cancer [60], and PARPi activates STING-TBK1-IRF3 intrinsic immune and enhances chemokine expression to induce activation of cytotoxic T lymphocytes (e.g., CXCL10 and CCL5) [56]. PARPi could significantly promote the invasion of CD4+ T and CD8+ T cells in a BRCA-deficient model by enhancing the STING signaling, and PARPi enhance the expression of PD-L1 by activating the cGAS-STING pathway in tumor cells [61]. CD8+ T cells treated with Olaparib decreased the expression of IC receptors PD-1 related to T cell suppression and depletion and created greater levels of IFN-γ [62]. A similar study also reported that PARPi can interact with TNF-α and IFN-γ in BRCA1 mutated tumors, indicating

Table 1. The information of common PARPi.

PARPi	Molecular weight (g/mol)	Molecular formula	IC50 (nM) Dias et al. [48]	Targets	Pub Chem Compound ID number
Olaparib	434.50	$C_{24}H_{23}FN_4O_3$	1	PARP-1/2/3/4	23725625
Rucaparib	323.40	$C_{19}H_{18}FN_3O$	1	PARP-1/2/3/4	9931954
Niraparib	320.40	$C_{19}H_{20}N_4O$	4	PARP-1/2	24958200
Talazoparib	380.40	$C_{19}H_{14}F_2N_6O$	0.6	PARP-1/2	135565082
Veliparib	244.29	$C_{13}H_{16}N_4O$	2	PARP-1/2/3	11960529
Pamiparib	298.31	$C_{16}H_{15}FN_4O$	0.83	PARP-1/2	135565554
Fluzoparib	472.40	$C_{22}H_{16}F_4N_6O_2$	1.5	PARP-1/2	56649297

that the increase of effector cytokines in the cancer environment could increase cancer cell death after targeted therapy [52]. PARPi promotes the production of IFN-γ and proinflammatory cytokines by upregulating STING, leading to the enhancement of CD4+ and CD8+ T cells in tumors [63].

Protein kinases ataxia telangiectasia mutated (ATM) and ataxia telangiectasia and Rad3-related (ATR) are both important molecules in the DDR signaling pathway, where ATM is directly activated by DNA DSB, while ATR is activated by RPA-coated single strand DNA, and the activation of ATM and ATR leads to subsequent activation of CHK1 [64, 65]. ATM-ATR pathway initiates DNA repair through transcriptional and post-transcriptional regulation of DR proteins and recruitment of repair factors to damaged DNA to activate DR proteins [66]. Studies have reported that DSB promotes PD-L1 expression in an ATM-ATR-CHK1-dependent manner, and BRCA2 depletion promotes the upregulation of PD-L1 after DSB. In addition, DSB activation of STAT1/STAT3 phosphorylation and IRF1 is required for DSB-dependent upregulation of PD-L1 [67]. Martincuks et al. showed that PARPi promoted STAT3 activity in cancer-related immune cells to inhibit tumor progression, and PARPi-treated immune cells reduce the production of IFN-γ, as well as increased expression of the immunosuppressive cytokine IL-10 [68]. The related mechanisms of PARPi regulating immunity are shown in Figure 2.

PARP protein and PARPi in CRC. CRC is the main contributor to tumor deaths worldwide. Despite significant advances in molecular and immunotherapeutic approaches, the prognosis of patients with advanced CRC remains a significant challenge. Recent studies have suggested that immune checkpoint inhibitors (ICI) are a potential therapy with high genomic instability in CRC. However, checkpoint inhibitors are less effective and have a poor prognosis in CRC patients with RAS mutation-associated mismatch repair defects [69]. Therefore, it is a pressing clinical challenge to identify alternative, effective treatments for CRC patients, and various proteins that occupy key positions in genomic alterations in DDR are being investigated for CRC therapy. PARP's critical role in regulating DR has led to extensive clinical studies [70]. In CRC, PARP is involved not only in overcoming genetic instability but also in molecular biological processes. In summary, PARP proteins lead to the malignant transformation of CRC, which is critical for cell homeostasis in the tumor microenvironment [71–73].

Mechanism of PARP protein and PARPi in CRC. Changes in various cell homeostasis in the tumor microenvironment can influence the development of CRC. Genomic instability is an important factor. Persistent genomic instability leads to epigenetic changes and mutations are a major factor in the progression of CRC. On the basis of these mechanisms, PARP and PARylation are considered to be the main factors contributing to the malignant formation of CRC. The most important function of PARP and PARylation is the repair of DNA, which has an essential function in the DD reaction and prevention of DD and maintains oxidation and

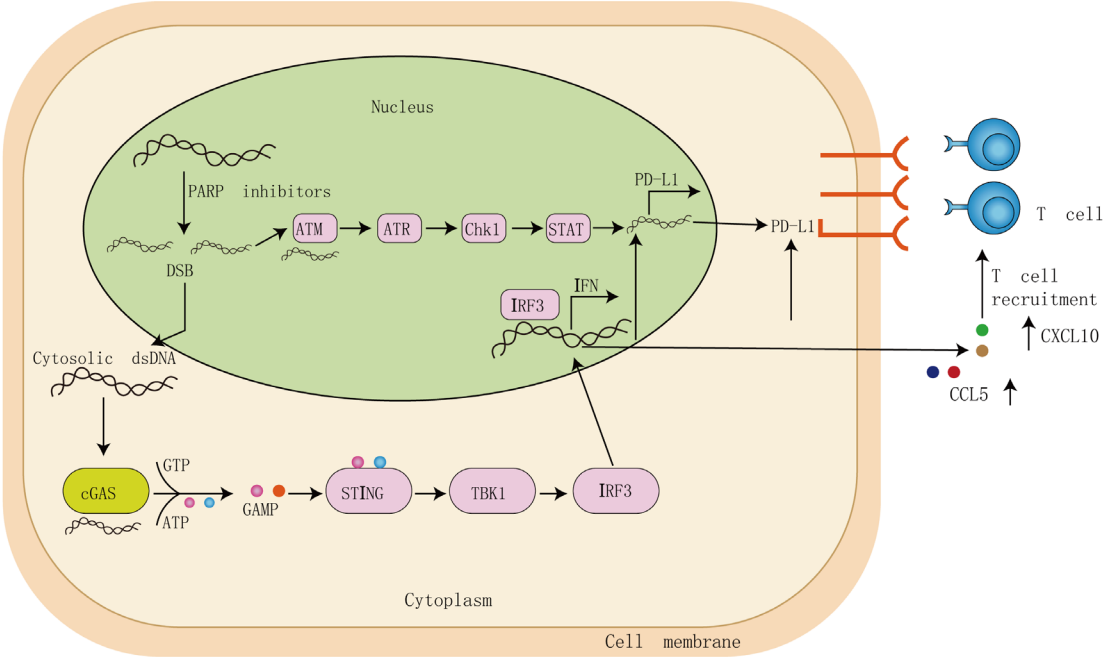

Figure 2. Related mechanisms of PARPi regulation of immunity. PARPi-induced DNA breaks produce fragments of cellular solute dsDNA that activate type 1 interferon (IFN) responses via the circular GMP-AMP synthase (cGAS)-STING pathway. These results upregulate chemokines responsible for T cell recruitment, and programmed death ligand 1 (PD-L1) is upregulated and may lead to T cell depletion. In addition, PARPi-induced double-strand breaks can upregulate PD-L1 expression by enhancing anti-tumor immunity or the ATM-ATR-Chk1 pathway.

superoxide redox homeostasis in the intracellular environment of tumor cells. PARP alters epigenetic and chromatin structures regulated by oncogenic or tumor suppressor gene transcription through histone and chromatin remodeling. Considering the heightened role of the development in CRC, it could be argued that the related mechanisms of PARP involvement in cancer are an important method to study the progression of CRC [74].

The cell cycle is a strongly controlled progression that promotes cell proliferation and abnormalities in the cell cycle are seen in all types of tumors. There is growing evidence that the cell cycle regulates a variety of cellular processes beyond the enhancement of cell division. Current research suggests that targeting cell cycle constituents could be an important anti-tumor strategy [75]. Rucaparib promotes the death of MSI CRC cells. Flow cytometry showed an increased S-phase arrest and late cell apoptosis in MSS CRC cells, and increased G2/M phase arrest and total cell apoptosis and early cell apoptosis in MSI CRC cells. These effects may depend on the expression of p21, p53, and PTEN. In mice, the combination of irinotecan was observed to significantly reduce tumor size by regulating Ki-67, RPS6KB1, and caspase 3 [28]. Similar results were observed in MMR defective CRC. In MMR deficient tumor cells, olaparib decreased the survival rate of clone formation, induced the accumulation of DD, and reduced adhesion and migration. The combination of olaparib and 5-FU enhanced the G2/M phase block, apoptosis, and polyploidy in CRC cells [38]. Zhang et al. find that GSK3 inhibitors make CRC cells more sensitive to PARPi treatment. The combination of PARPi and GSK3 inhibitors significantly inhibited tumor cell growth, leading to the G2/M cell cycle arrest and promoting apoptosis. However, in tumor growth in HCT-15 and RKO xenograft mouse models, treatment with PARPi did not inhibit tumor size in mice [76]. The binding of melanopsin and olaparib induces high copying pressure and DSB in CRC, resulting in tumor cell death after the G2 phase block. The same structure was observed *in vivo* tumor xenografts, and olaparib alone did not inhibit CRC cell proliferation [77]. In addition, bromodomain-containing protein 4 (BRD4) downregulates the proliferation of CRC cells, making them more sensitive to the anticancer effects of PARPi [78].

The mutation rate of TP53 is about 55–60% in non-highly mutated CRC, second only to APC, while the mutation percentage of TP53 was reduced to around 20% in CRC with high genetic instability.

In addition, TP53 mutations are associated with poor prognosis in CRC, and the TP53 mutation rate increases to 80% in patients with advanced CRC with metastasis [79]. The research reveals that TP53 has an essential function in the development of CRC. It has been reported that TP53 tumor suppressor factors are involved in the treatment of CRC with PARPi. This was addressed by using AZD2461, a PARP 1/2/3 inhibitor well tolerated in CRC patients, against CRC with diverse TP53 states. The AZD2461 reduces cell growth of TP53 wild-type and TP53–/– CRC cells by increasing ROS and DD [80]. A preclinical study of CRC cell lines revealed that TP53 proteins increase the likelihood of PARPi responses in MSS CRC cells. Inhibition of Rad51 transcription response to DSB in DNA by TP53 protein [81]. PARPi induce RNA-Processing endoribonuclease (RMRP) expression by C/EBPβ, and RMRP promotes tumor resistance to PARPi by blocking TP53 activation [82]. ATM (Ataxia telangiectasia-mutated gene) and homologous binding, such as BRCA, undergo somatic mutations in more than 20% of CRC. Interestingly, ATM-deficient HCT116 CRC cells are susceptible to olaparib, and TP53 deficiency increased this susceptibility [83]. Further studies of the mechanism by which PARPi is used to treat CRC found that the therapeutic dose delivered to xenograft CRC does not cause significant toxicity to the surrounding mouse organs. In addition, PARPi therapy can be used as a targeted therapy for cancers with TP53 pathway mutations [84]. In conclusion, PARPi sensitivity is closely related to TP53 wild-type status in CRC cell lines, where PARPi mainly regulates transcriptional activity downstream of TP53.

KRAS mutations are present in about 45% of CRC and related to tolerance to EGFR-targeted treatment. KRAS-mutated cancer is related to a worse prognosis in CRC patients [85]. KRAS mutations reduced PARPi-induced STING signaling and interferon response in CRC cancer cells. MEK inhibitors promote PARPi-induced innate immune activation in KRAS mutant cells by enhancing DD of cellular solute dsDNA with STING proteins. Promotion of MAPK signaling in KRAS wild-type mitigated PARPi-induced STING and IFN signaling [11]. The effect of bevacizumab+olaparib combination therapy in KRAS mutant was studied *in vivo*. Combination treatment successfully inhibited cancer progression in KRAS-mutated CRC. Further mechanistic studies showed that tumor hypoxia and deprivation HRR were detected with vessel regression under bevacizumab treatment. Therefore, under hypoxia, olaparib can block the cell cycle in the G2/M phase, enhance DD, and significantly promote cell apoptosis in KRAS mutant CRC [86].

Cancer stem cells (CSC) are cancer cells that can self-renew and differentiate, initiate tumor growth, and proliferate unregulated, leading to abnormal growth that makes them resistant to therapies that target rapidly replicating cells [87]. It is essential to investigate the related mechanisms of CSC in CRC. CSC preferentially repair chemotherapy-induced DNA breaks, and this mechanism of action encourages us to study drug inhibitors from the DD pathway. CSC preferentially repair chemotherapy-induced DNA breaks, and this mechanism of action encourages us to study drug inhibitors from the DD pathway. PARPi increases the sensitivity of CSC to chemotherapy and decreases CSC activity, self-renewal, and DDR after chemotherapy. PARPi monotherapy ineffective in killing CSC, but PARPi in combination with chemotherapy inhibits cancer progression *in vivo* [88]. Niraparib enhances the effects of SN38 on double strand breaking and

Rad51 recruitment, and the combination of niraparib and SN38 can regulate CSC growth [42]. Lunasin induces CSC apoptosis through PARP [89]. PARP-1 was upregulated in pancreatic, liver, and colon cancer, and PARP-1 upregulation is more pronounced in CSC-characteristic cell populations. PARP-1 reduced the formation of 3D tumor balls in CRC cells. Further research suggests that PARP-1 is engaged in a common mechanism of drug resistance in gastrointestinal tumor CSC [90]. Nicotinamide phosphoribosyl transferase (NAMPT) expression is associated with high levels of CSC in colon tumors. NAMPT promotes the activation of CSC-related pathways through PARP-1 and SIRT-1 in colorectal cancer tumors. Furthermore, NAMPT regulates CSC pathways related to SIRT-1 and PARP-1 [91].

PARPi also regulates CRC cell growth through other mechanisms. To clarify the function of PARP-1 in CRC, azoxymethane (AOM)/dextran sodium sulfate (DSS)/dextran sodium sulfate (DSS) was performed on PARP-1–/– and wild-type PARP-1 CRC cells. Induced CRC cell development was long. Microscopically examined mice reveal significantly more tumors in the wild type than in PARP-1–/–. These results provide evidence for increasing alkylation-induced DNA strand break formation in PARP-1–/– cells [92]. In CRC CT26 cell model, PARPi significantly upregulated IRF3 phosphorylation level and STING expression [54]. Upregulation of PARP-1 bound protein (PARPBP) expression was found in oxaliplatin-resistant CRC. Further studies showed that a member of the driver protein family 18 B (KIF18b) promotes the PARPBP, thereby maintaining oxaliplatin resistance in CRC. DNMT3b methylated PARPBP promoter from SP1 inhibits transcription in CRC cells by exploring the PARPBP gene promoter. Enhanced KIF18b diminishes DNMT3b recruitment to the PARPBP promoter through direct engagement with SP1 in CRC-resistant cells [93]. PARPi radiosensitizer V600E and WT genes in RKO, and can inhibit cell growth. Olaparib has little impact on patient survival if used alone, but combination therapy leads to a dramatic improvement in radiosensitivity [93]. Treatment of CRC cells with mTOR complex (mTORC) suppressors and olaparib promoted γ-H2AX and 53BP1, inhibited BRCA1 and Rad51, reduced phosphorylation of ATR/Chk1, and induced necrotic apoptosis. Moreover, mTORC inhibitors consume MCL-1 in xenografts to inhibit HRR and enhance sensitivity to olaparib [94]. In CRC, non-SMC condensing I complex Subunit D2 (NCAPD2) inhibited autophagy through the PARP-1/SIRT1 axis [95]. In addition, olaparib can also regulate the growth of CRC cells by inhibiting ARG-1, iNOS, and COX-2 [96]. Further *in vivo* validation of PARPi-related mechanisms. The combination of PARPi and chemotherapy inhibits tumor growth and increases survival [97]. The relevant mechanism of PARPi involved in CRC treatment was revealed in Table 2.

Immune mechanism of PARP protein and PARPi in CRC. In KRAS mutant cancers, MEK inhibitors suppress the KRAS pathway transduction, triggering, and amplifying PARPi-promoted DD, cell solute DSB generation, STING pathway activation, and CD8+ T cell recruitment. In addition, the combination of PARPi, anti-PD-L1, and MEK inhibitors significantly inhibited tumor growth in KRAS tumor models with immunocompetent mutations [11]. Jamal et al. also showed that the combination of anti-PD-1/PD-L1 and PARPi drugs also inhibited the growth of CRC cells [100]. A novel combination of HS-173 (PI3K inhibitor) and niraparib induces immunogenic cell death. Some CRC patients benefit significantly from combined immunoradiotherapy. PARPi and PI3K inhibitor are revealed as new combinations that synergistically potentiate the toxicity and increase immunogenic cell death in CRC. These inhibitors are collectively encapsulated in polymer micelles to offset solubility restrictions while minimizing off-target toxicity. Combining these micelles with X-ray and anti-CTLA-4 immunotherapy in CRC mice can inhibit tumor growth and increase tumor immune cell infiltration to improve efficacy [98]. Veliparib is an effective radiosensitizer in CRC. Dose-dependent expression of MHC-1 and PD-L1 on the tumor surface. In the CRC tumor model, concomitant veliparib and radiotherapy dramatically extend anti-PD-1-mediated cancer progression retardation and survival *in vivo*. In addition, these effects were more pronounced in MC38 tumor models with microsatellite instability mutations. The

Table 2. Effect of PARPi in CRC.

PARPi	Effects of PARPi	Mechanism	Reference
Talazoparib	Inhibited proliferation	Impaired G2/M phase; TP53-mediated suppression of RAD51	[78, 81]
Olaparib	Enhanced anti-PD-1 immunotherapy and chemosensitivity; inhibited proliferation and metastasis; promoted apoptosis	Targeting MDSC function; impaired G2/M phase; reduced CSC viability and self-renewal	[38, 86, 88, 90, 96]
Rucaparib	Inhibited proliferation and promoted apoptosis	Impaired G2/M and S phase	[28]
Simmiparib	Inhibited proliferation and promoted apoptosis	Impaired G2/M phase	[76]
Niraparib	Induced immunogenic cell death	TP53-mediated suppression of RAD51	[81, 98]
123I-MAPi	Inhibited proliferation and promoted apoptosis	Correlating p53 Status	[84]
AZD2461	Inhibited proliferation	Increased ROS	[80]
Veliparib	Increased the radiosensitivity	–	[99]

Note: "–"-not reported in literature

combination of veripanib and ionizing radiation regulates the depletion of CD8+ T cells [99].

Olaparib blocks CRC oncogenesis by modulating the inhibitory function of myeloid-derived suppressor cells (MDSCs). T cell function and cytotoxicity in the tumor are evaluated by granase-B/IFN-γ. The decrease of PARP protein induced by lipopolysaccharide (LPS) promoted the expression of IL-6, TNF-α, and iNOS. Olaparib inhibited TNF-α and MCP-1 and significantly reduced tumor load. Compared with high-dose olaparib, low-dose olaparib has a better antitumor effect because only low-dose olaparib increases CD3+ T cells, while the increase in high-dose olaparib is mostly attributed to CD8+ T cells [96]. Gene expression of pro-inflammatory cytokines (IL-1β and IL-6), CXCR2, and COX-2 were downregulated in PARP-1–/– mice. Further study of immune infiltration revealed a decrease in the number of monocytes in PARP-1–/– animals by confocal microscopy. HMGB1, a pro-inflammatory cytokine secreted by activated macrophages and natural killer cells, is downregulated in PARP-1–/–, further suggesting that PARP is involved in innate immune responses [92]. CXCL16 is expressed by activating PARP and Caspase-3 mediated apoptosis pathways [101]. Combination treatment with everolimus and olaparib leads to necrotic apoptosis in CRC. Necrotic apoptosis of cancer cells releases injury-related molecular mechanisms that induce a strong immune response and lead to the activation of CD8+ T cells, NK T cells, and other immune cells [94].

Poly-(ADP-ribose)-glycohydrolase (PARG) not only has a key function in the modulation of PARP but also regulates the expression of downstream genes by combining with PARP. The expression of PARP and NF-κB in hepatic metastasis of colon cancer in the PARG silencing group was lower than that in the negative group. What is more, IL-10 and TGF-β levels were upregulated in PARG-silenced mice. The research shows that PARG knockdown could downregulate the levels of PARP and NF-κB, inhibit the secretion of IL-10 and TGF-α, and ultimately affect the proliferation and differentiation of DC and T cells [24].

Clinical trials of PARPi in CRC. PARPi has shown good results in studies of CRC at the cellular and animal levels. Next, we analyzed the clinical trial results of PARPi. The phase 2 olaparib study enrolled 33 patients, 20 with MSS and 13 with MSI-H. Participating patients accepted more than one cycle of olaparib for 28 days. The results showed that the main adverse effects experienced by patients included nausea (48%), fatigue (36%), and vomiting (33%) and that patients had a median progress free survival (PFS) of 1.84 months. There was no statistically significant difference in median PFS or overall survival (OS) in the MSS group compared to the MSI-H group [102]. This phase I study (NCT00535353) evaluated the efficacy and resistance of olaparib in conjunction with irinotecan. Pharmacokinetic samples of olaparib, irinotecan, and SN-38 were collected during the first cycle. Eleven of 25 patients received olaparib and irinotecan continuously every 3 weeks (group A) and 14 patients received olaparib and irinotecan intermittently every 2 weeks (group B). The results revealed that intermittent olaparib administration was better tolerated. The best response was disease stabilization in 9 patients, 2 in group A and 7 in group B [103]. The phase 2 CRC study (NCT01051596) of veripanib was conducted. The primary objective was to study disease control rates (DCR) in patients with metastatic CRC who had failed all standard therapies after 2 cycles of veripanib plus temozolomide. The results showed that the patients were well tolerated. The primary endpoint was successfully achieved with 24% DCR and 2 confirmed partial responses. PFS and OS were 1.8 and 6.6 months, respectively [104]. The researchers present a schematic and design approach to the CRC phase 3 trial (NCT04456699), which assesses the efficacy and security of a folfox plus bevacizumab regimen in CRC with unresectable or metastatic CRC that has not advanced after induction, compared with olaparib plus bevacizumab versus 5-fluorouracil plus bevacizumab. We look forward to the publication of the researchers' findings [105]. Next, we summarized the ongoing PARPi clinical trial in CRC (Table 3; www.clinicaltrials.gov, last update).

Table 3. Ongoing clinical trials of PARPi in CRC.

Compound	Sponsor	Status	Clinical phase	Estimated Enrollment	Identifier	Estimated completion date	Locations
Olaparib	Grupo Espanol Multidisciplinario del Cancer Digestivo	Not yet recruiting	Phase 2	40	NCT05201612	December, 2024	Spain
Olaparib	National Cancer Institute (NCI)	Recruiting	Phase 1; Phase 2	384	NCT02484404	December 30, 2024	United States
AZD5305	AstraZeneca	Recruiting	Phase 1; Phase 2	715	NCT04644068	July 29, 2025	United States
Rucaparib	Academic and Community Cancer Research United	Active, not recruiting	Phase 1; Phase 2	110	NCT03337087	July 1, 2026	United States
PARPi	Peking University	Recruiting	Not Applicable	400	NCT04584008	September 2022	China
Talazoparib	Pfizer	Active, not recruiting	Phase 1	75	NCT04672460	November 20, 2022	United States
Rucaparib	Clovis Oncology, Inc.	Active, not recruiting	Phase 2	220	NCT04171700	June 2022	United States

Resistance to PARPi in CRC. PARPi is approved for clinical use in solid tumors; however, in most patients, resistance to PARPi develops, resulting in treatment failure. Here we describe the mechanisms of resistance to PARPi. To confirm the resistance of CRC KRAS mutations to PARPi, we compared the role of PARPi and anti-PD-L1 combinations in mouse CRC models with KRAS-mutated states (CT26: (KRAS G12D) and MC38 (wild type)). The results revealed that drug therapy enhanced cancer development in MC38 tumors. However, CT26 did not react to olaparib alone or in combination with anti-PD-L1 [11]. PARP inhibitors target PARP proteins, so the alteration of the PARP protein itself might lead to resistance. Pettitt et al. screened five PARP-1 mutation sites associated with talazoparib resistance, including p.329N, p.742-743HD, p.848delY, p.A925, and p.R591C (Figure 1A). PARP-1 trapping assays showed that the N329Q and HD742F mutant proteins were not trapped by PARPi, whereas the PARP-1 portion of the 848delY mutant protein was trapped, explaining the PARPi resistance phenotypes associated with these mutations. A925 mutation directly disrupts the catalytic activity of PARP-1, and R591C mutation affects the WGR domain at the domain contact point, and the R591C mutation can eliminate capture leading to drug resistance [106]. The presence of CSC is also a major cause of drug resistance, showing mechanisms of resistance to DD, such as PARP-1 [90]. Rad51 recombinase, a key effector of HR, is recruited by BRCA2 to DNA breaks and forms homopolymeric filaments that invade homologous chromatids and uses them as repair templates. In particular, BRCA-deficient tumors have shown that inhibition of Rad51 increases the sensitivity of PARPi [107]. Niraparib enhances the effects of SN38 on double-strand breaking and Rad51 recruitment, and the combination of Niraparib and SN38 can regulate CSC growth [42]. PARP-1 is upregulated in colon tumor cells, and the upregulation of PARP-1 is more pronounced in CSC-characteristic cell populations. PARP-1 reduced the formation of 3D tumor balls in CRC cells. Further studies have revealed that PARP-1 is engaged in a common mechanism of drug resistance in gastrointestinal tumor CSC [90]. NAMPT promotes the activation of CSC-related pathways through PARP-1 and SIRT-1 in colorectal cancer tumors. In addition, NAMPT regulates cancer stem cell pathways associated with SIRT-1 and PARP-1 [91]. Tumor cells become resistant to PARPi, and chromatin remodeling helps enhance this development. Therefore, targeting PARP-1-mediated chromatin remodeling may be beneficial, which may reverse drug resistance [4]. PARPi therapy for CRC can be used in combination with other drugs to enhance the effect.

Combination strategies. PARPi has synergistic effects with other bioactive molecules in treatment and helps to overcome drug resistance. PARP/PI3K dual inhibitors, which can target both PARP and PI3K, have been considered a promising therapeutic strategy for triple-negative breast cancer (TNBC). Compared with PARPi, PARP/PI3K dual inhibitor has excellent anti-proliferation properties on TNBC cells. In addition, PARP/PI3K dual inhibitors showed good metabolic stability and high safety [108]. Both PARP and histone deacetylase (HDAC) are important antitumor targets. In recent years, studies have shown that HDAC inhibitors and PARP inhibitors have synergistic effects in cancer treatment [109]. Interestingly, CUDC-907, a dual inhibitor of HDAC-PI3K, also has synergistic effects with olaparib in cancer therapy [110]. PARP-1 can repair DNA damage induced by Topo inhibitors. The combination of PARPi and Topo inhibitors showed excellent anti-tumor proliferation ability and good metabolic characteristics. Inhibition of both Topo and PARP-1 also overcame resistance and improved treatment outcomes [111]. The research of PARPi in tumors has broad prospects, and the combinations with other drugs are the main research direction in the future.

Chemotherapeutic agents. PARP proteins interact with a variety of chemotherapeutic drugs, such as oxaliplatin, doxorubicin, gemcitabine, irinotecan, and 5-fluorouracil [28, 90, 112]. These chemotherapeutic agents mainly inhibit RNA, DNA, and protein synthesis and regulate CRC. In addition, PARPi makes CRC CSC sensitive to chemotherapy and reduces the activity, self-renewal, and DD repair of CRC CSC treated with chemotherapy [88]. Studies on the combination of PARPi and chemotherapeutic drugs in CRC are summarized in Table 4.

Immune checkpoint inhibitors. ICI, such as anti-PD1/PD-L1, have been clearly observed for therapeutic effects in tumors and have been approved for various cancer types [49]. The combination of PARPi and ICI PD-1 against MSI high and MSS tumors showed the potential sensitization effect of anti-PD-1 therapy on MSS tumors [96]. In another study, the researchers found similar results in the PD-1/PD-L1 axis [54]. The efficacy of ICI in combination with PARPi is summarized in Table 4.

DNA damage. ATM protein kinase has a key function in the DDR. Deletion or inactivation of two versions of the ATM

Table 4. PARPi in combination with other drugs for CRC.

PARPi	Combination strategy	Refs.
Rucaparib	Irinotecan	[28]
AZD2281	5-fluorouracil and oxaliplatin and leucovorin	[88]
Olaparib	Doxorubicin and gemcitabine	[90]
Olaparib	Oxaliplatin	[112]
Olaparib	Immune checkpoint inhibitor, anti-PD-L1 antibody	[49, 96]
Talazoparib	Immune checkpoint inhibitor, anti-PD-L1 antibody	[54]
Olaparib	ATM inhibitor, KU55933	[84]
Olaparib	DNA damage, Alkannin	[77]
Simmiparib	GSK3 inhibitors, LY2090314	[76]
Olaparib	MEK inhibitor, trametinib and anti-PD-L1 antibody	[11]
Olaparib	mTOR complex inhibitor, AZD2014 or everolimus	[94]
Niraparib	PI3K inhibitor, HS-173	[98]
Talazoparib	BRD4 Inhibitor, AZD5153	[78]
Olaparib	VEGF inhibitor, bevacizumab	[86]

gene causes ataxia capillaris, and sequencing of the tumor shows that ATM is changed in a number of human tumors, including colorectal, lung, prostate, and breast cancers [83]. Alkannin inhibits anti-tumor growth through a variety of mechanisms, including the redox cycle that produces ROS and consumes antioxidants. They also inhibit thioredoxin reductase 1 (TrxR1)-induced ROS accumulation and DNA chain breaks induced by DNA topoisomerase I [77]. PARPi is more effective in combination with other DNA-damage inhibitors, as shown in Table 4.

Kinase inhibitor. Glycogen synthase kinase (GSK3) is a serine/threonine protein kinase that modulates a variety of pathways. In terms of anti-tumor mechanisms, it is considered to be a promising tumor inhibitor owing to its modulatory role in the Wnt/β-catenin pathway [76]. MEK inhibition promotes PARPi-induced STING signaling and IFN responses *in vitro* [11]. We summarized the efficacy of PARPi and related kinase inhibitor combinations in CRC in Table 4.

Signaling pathways inhibitors. Phosphoinositol 3 kinase (PI3K)/AKT pathway inhibitors have been revealed to inhibit DDR tumors and enhance the antitumor sensitivity of PARPi, synergically enhancing toxicity and inducing immunogenic cell death in CRC models [98]. The mTOR pathway inhibitors inhibit phosphorylation and cap-dependent translation of 4EBP1, thereby reducing related protein synthesis in cancer cells [94]. The research results of PARPi and signaling pathway inhibitors are summarized in Table 4.

Other drugs. BRD4 plays an important function in the progress of many cancers and is regarded as a potential tumor therapeutic target. BRD4 inhibitors inhibit the development of CRC by inhibiting Wee1 *in vitro* and *in vivo* and make PARPi more sensitive to the therapeutic effects of CRC [78]. Bevacizumab is a humanized monoclonal antibody that suppresses vascular endothelial growth factor and has been authorized for the therapy of metastatic CRC. Bevacizumab combined with chemotherapy significantly increased OS and PFS in metastatic CRC patients [86]. The results of the combination of PARPi and other drug inhibitors in CRC are summarized in Table 4.

In conclusion, as a key protein of DDR, PARP protein is related to cell modification, transcription, and other physiological functions. PARP has a vital function in various cancers, such as regulating cell cycle, apoptosis, and drug resistance in cancer cells. PARP-1, the most studied PARP, mainly regulates tumor growth through the cell cycle in CRC. PARP protein is also closely associated with TP53 and KRAS mutations. PARPi regulates the immune microenvironment of tumors, including checkpoint inhibitors, immune cells, and cytokines. In many experiments, the single therapy of PARPi failed to achieve good efficacy due to cytotoxicity. However, PARPi has a strong synergistic effect with other drug combinations and has achieved good therapeutic effects in CRC cells, animals, and clinically. The development of PARPi and other drug combinations is the main direction for the future.

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