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## Poly adenosine diphosphate-ribosylation, a promising target for colorectal cancer treatment

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### Abstract

The development of colorectal cancer (CRC) can result from changes in a variety of cellular systems within the tumor microenvironment. Particularly, it is primarily associated with genomic instability that is the gradual accumulation of genetic and epigenetic changes consisting of a characteristic set of mutations crucial for pathways in CRC progression. Based on this background, the potential to focus on poly [adenosine diphosphate (ADP)-ribose] polymerase (PARP)-1 and poly-ADP ribosylation (PARylation) as the main causes of malignant formation of CRC may be considered. One of the important functions of PARP-1 and PARylation is its deoxyribonucleic acid (DNA) repair function, which plays a pivotal role in the DNA damage response and prevention of DNA damage maintaining the redox homeostasis involved in the regulation of oxidation and superoxide. PARP-1 and PARylation can also alter epigenetic markers and chromatin structure involved in transcriptional regulation for the oncogenes or tumor suppressor genes by remodeling histone and chromatin enzymes. Given the high importance of these processes in CRC, it can be considered that PARP-1 and PARylation are at the forefront of the pathological changes required for CRC progression. Therefore, this review addresses the current molecular biological features for understanding the multifactorial function of PARP-1 and PARylation in CRC related to the aforementioned roles; furthermore, it presents a summary of recent approaches with PARP-1 inhibition in non-clinical and clinical studies targeting CRC. This understanding could help embrace the importance of targeting PARP-1 and PARylation in the treatment of CRC, which may present the potential to identify various research topics that can be challenged both non-clinically and clinically.

**Key Words:** Colorectal cancer; Poly adenosine diphosphate-ribose polymerase-1; Poly adenosine diphosphate-ribose; Poly-adenosine diphosphate ribosylation

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**Core Tip:** The main focus is on highlighting the pivotal role of poly adenosine diphosphate-ribose polymerase-1 (PARP-1) and poly-adenosine diphosphate ribosylation (PARylation) in regulating deoxyribonucleic acid damage response, redox homeostasis, chromosomal instability, and transcriptional activity under the common denominator of overcoming the genomic instability in colorectal cancer (CRC). The importance of targeting PARP-1 and PARylation in the treatment of CRC will be emphasized because the level of understanding of pathological changes leading to malignant transformation of CRC by PARP-1 and PARylation may increase.

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## INTRODUCTION

Colorectal cancer (CRC) is a type of cancer that begins with a malignant transformation in the colon or rectum and usually begins as benign clumps of cells called polyps from the lining of the large intestine[1]. CRC proceeds gradually through three connected stages. The first is the initiation of altering the molecular signals of normal cells that are still classified as precancerous. The next step is the promotion in which an increase in abnormal signaling is induced. The final step is progression wherein the phenotypes change, transformed cells are discovered, and a CRC can be diagnosed[2]. Then, changes in various cellular systems within the tumor microenvironment can make it possible to lead a favorable direction for adaptation even with excessive cancer cell growth[1,2]. Recent studies reporting on the details of this malignant transformation have revealed that the following molecular biological and genetic changes play an important role in the development and progression of CRC[3]. The formation of CRC is predominantly associated with genomic instability caused by the gradual accumulation of genetic and epigenetic changes leading to a transformation of normal colon epithelium into colon adenocarcinoma[3,4]. The phenomena representing genomic instability, such as chromosomal and microsatellite instability, have been studied, and they are reportedly associated with defects in mitosis, telomere stability, and the deoxyribonucleic acid (DNA) damage response. Thus, allowing for the accumulation of a characteristic set of mutations crucial for activating critical pathways in CRC development[4,5]. Reactive oxygen species (ROS) are continuously produced in aerobic organisms both endogenously and through involvement in various physiological and pathological processes in the cancer cells[6]. The oxidative stress caused by ROS may play an important role in regulating genetic alterations, and mutations in genetic material can contribute to CRC cell growth, survival, and metastasis[7]. Advances in molecular biology over the past few years have increased our knowledge of the oncogenic mechanisms involved in CRC development, and oncogenes have been shown to have a major role in cancer cell proliferation, angiogenesis, and metastasis[8]. These oncogenic activities can also form an interconnected network that includes the phosphorylation of proteins related to carcinogenic transcription factors, thus leading to malignant transformation of CRC[4,5,9]. Mutations in the tumor suppressor gene, which counteracts this action, also markedly contribute to the sustained survival of CRC[4].

In recent studies, checkpoint inhibitors were expected to be potential treatments for CRC patients with high genomic instability[10]. However, the proportion of patients to whom they could be applied was low, thus showing poor overall prognosis and limited treatment options; this is particularly exemplified by deficient mismatch repair associated with rat sarcoma viral oncogene homolog (RAS) mutations[11]. Thus, finding alternative and effective treatments for patients with CRC is an urgent unmet clinical need, and the roles of various proteins that occupy a key position in genomic alterations to DNA damage responses are emerging as a new target for CRC treatment. Recent genome-wide studies have identified distinct subpopulations of CRC that possess unstable genomic properties due to mutations in their DNA repair genes[4]. Although the major mechanistic role of these mutations on DNA damage response genes in CRC has not yet been elucidated and data on clinical effects are reportedly

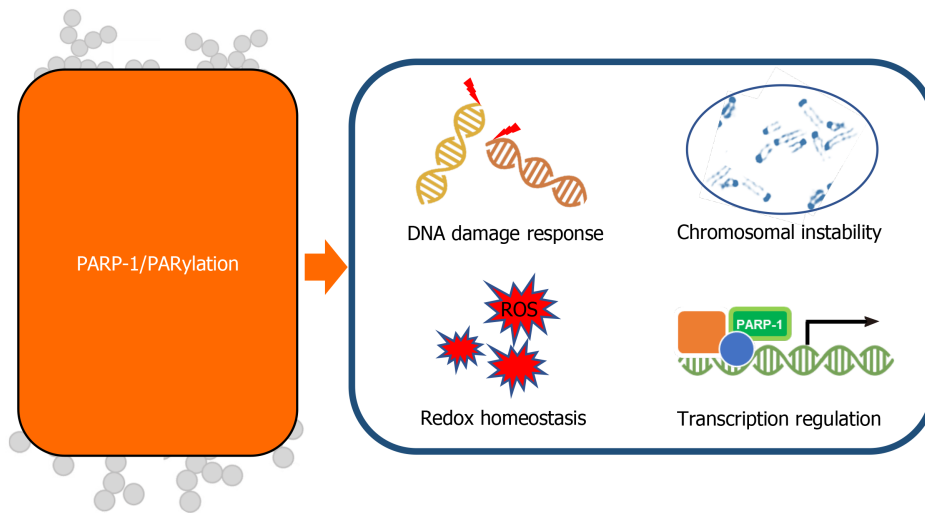
insufficient, widespread recognition of the clinical need for targeting DNA damage responses offered a great opportunity to arouse interest in poly [adenosine diphosphate (ADP)-ribose] polymerase (PARP)-1[12]. PARP-1 is a nuclear enzyme of cellular homeostasis that modifies nuclear proteins by poly ADP-ribosylation (PARylation), and one of its important functions is to induce a response to DNA damage[12,13]. The pivotal role of PARP-1 in regulating the DNA repair process has led to clinical investigations that potentially target this important enzyme in ovarian and pancreatic cancer patients with breast cancer susceptibility gene (BRCA) mutations[14]. However, finding the optimal biomarkers that can be used to explore their applicability for CRC remains a challenging task. In addition to the representative functions of PARP-1 involved in overcoming genetic instability, cancer-specific phenomena elicited for CRC survival can be interestingly explained by the molecular biological processes in which PARP-1 participates[14,15]. Because PARP-1 and PARylation are known to have a wide range of essential functions for cellular homeostasis, the following roles are also attracting attention toward the tumor microenvironment[13,15]. PARP-1 can regulate mitochondrial activity by occupying a prominent position characterized by the regulation of mitochondrial peroxide and oxidation[16]. Further, PARP-1 may directly participate as a transcription regulator being a member of the transcription family, and PARylation can regulate gene expression or protein activation by remodeling histone and chromatin enzymes through direct and indirect pathways (Figure 1)[17,18]. In other words, the widespread functions essential for cellular homeostasis in the tumor microenvironment that PARP-1 and PARylation can lead to malignant transformation of CRC, and these are more likely to adapt better even under inferior conditions unfavorable for survival[13-18].

Therefore, this review summarizes the current knowledge on the molecular biological and biochemical process of PARylation to understand the multifactorial functions of PARP-1 that enable the proliferation and survival of CRC. Further, cases from clinical studies involving patients with CRC targeting PARP-1 were listed, and treatment outcomes are also discussed.

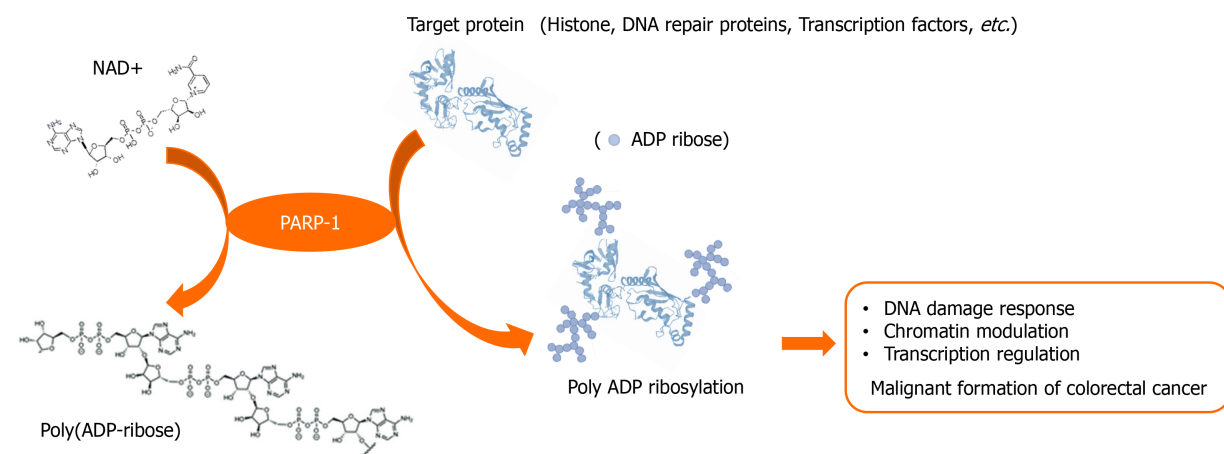
## PARP-1 AND PARYLATION

PARP-1 is a member of the recently well-studied PARP family and forms a domain containing approximately 106 molecules[19,20]. PARP-1 catalyzes the polymerization of ADP-ribose from the donor nicotinamide adenine dinucleotide (NAD<sup>+</sup>) on the target protein to form a linear or branched poly ADP-ribose (PAR) polymer through a biochemical action called PARylation[21]. PARP-1 forms a structure in which the N-terminal double zinc finger DNA binding domain, nuclear localization signal, central auto-transformation domain, and C-terminal catalytic domain are well conserved[22]. The functional aspect is characterized by having a composition advantageous for interaction with other molecules, particularly with DNA structures. The N-terminal DNA-binding domain has three zinc fingers and a specific sequence for localization in the nucleus, and two homologous zinc finger proteins are characterized by the zinc finger motif[23]. Auto-modifying domains include the BRCA1 C-terminal motif and are involved in the interaction with intracellular proteins or nuclear proteins or both. The C-terminal catalytic domain comprises six  $\beta$ -strands and one  $\alpha$ -helical motif that functionally binds to NAD<sup>+</sup>[19,23]. The PARP signature (NAD<sup>+</sup> binding site) motif is composed of an acceptor for adenosine and donor of nicotinamide wherein ADP-ribose from NAD<sup>+</sup> are transferred to target proteins to PAR synthesis (Figure 2)[23,24].

PARP-1 is a princeps enzyme that can mediate PAR synthesis and attach it to acceptor proteins[21]. Various molecular and biological functions essential for cancer cell survival are associated with PARylation, and more than 90% of PARylation depends on the regulatory function of PARP-1[13]. PARylation proceeds according to an integrated and dynamic biochemical process, and the hypothesis that the synthetic method is determined by two potential pathways has recently been established[13,22]. PARP-1 catalyzes the transfer of ADP-ribose units from NAD<sup>+</sup> to form a branched-chain, PAR, which is negatively charged to specific amino acid residues, such as aspartate, arginine, serine, lysine, and glutamate, on PARP-1 itself and other acceptor proteins[13,22]. The PAR synthesis is based on the attaching of ADP-ribose to the 2'-OH end of the growing chain at the terminus adjacent to the PARylation target, depending on the reaction mechanism of PARP-1[13,21,22]. It may appear as if it is self-applicable only to the auto-modification of PARP-1; however, at certain stages of the extension reaction, reactive intermediates during PARylation may also be transferred to other acceptor molecules in their vicinity[13,21,22]. Besides, PAR may be



**Figure 1 Multifactorial role of poly adenosine diphosphate-ribose polymerase-1 and poly-adenosine diphosphate ribosylation in cancer development.** Poly adenosine diphosphate-ribose polymerase-1 (PARP-1) can occupy a position as an important regulator of deoxyribonucleic acid damage response, redox homeostasis, chromosomal instability, and transcription, which are required for the dysfunctional regulation for a crucial role in tumorigenesis. Therefore, a crucial process for malignant transformation of colorectal cancer can be attributed to the involvement of PARP-1 and Poly-adenosine diphosphate ribosylation. PARP-1: Poly adenosine diphosphate-ribose polymerase-1.



**Figure 2 Poly adenosine diphosphate-riboseylation in cancer.** Poly adenosine diphosphate-ribose polymerase-1 (PARP-1) branched poly adenosine diphosphate (ADP)-ribose polymers following the cleavage of nicotinamide adenine dinucleotide+ to ADP-ribose. PARP-1 enables interactions by catalyzing the covalent attachment of poly ADP-ribose polymers on acceptor proteins, such as histones, deoxyribonucleic acid repair proteins, transcription factors, and chromatin modulators. This enzymology reaction is known as poly ADP-riboseylation on target proteins, and this process may be important for the malignant transformation of colorectal cancer. ADP: Adenosine diphosphate; PARP-1: Poly adenosine diphosphate-ribose polymerase-1.

synthesized by sequentially adding the following ADP-ribose residues to the 2'-OH end of the ADP-ribose moiety[21]. Particularly because the substrate properties for PARP-1 are reduced in the extension reaction, the NAD<sup>+</sup> analog is an ideal modification to modify most PAR acceptor sites by short ADP-ribose oligomers[21, 25]. The ability of PARP-1 to link long, negatively charged PAR polymers to a variety of acceptor proteins by PARYlation suggests that their role as a modulator in favor of survival signals in cancer cells may accompany potential molecular biological and biochemical changes[20,26]. The PAR binding on acceptor proteins can form deterministic structures through intramolecular interactions; these structures may have non-covalent, attractive interactions with other molecules[21]. Thus, PARYlation can modulate protein activity by functioning as a site-specific covalent modification, protein binding matrix, or steric block[26,27]. Recent studies have increased our understanding of the role of PARYlation in various molecular and cellular processes, including DNA damage response, chromatin modification, and transcription regulation[15,20]. It has also been demonstrated that the molecular and cellular aspects of PARYlation can play a potential role in many pathophysiological outcomes,



including carcinogenesis and overcoming genomic instability[25]. In particular, carcinogenesis is a multi-step process involving abnormalities such as genomic maintenance, cell cycle regulation, proliferation, and differentiation and is closely related to initiation, promotion, and progression of cancer followed by all subsequent processes leading to advanced stages involving metastasis[2]. Since PARP-1 and PARylation have been investigated as promising regulators of all these processes, it may be considered a major target for the inhibition of malignant transformation[16-20]. Therefore, it is essential to understand the multifactorial role of PARP-1 and PARylation in the broader framework of CRC development.

## MULTIFACTORIAL ROLE OF PARP-1 AND PARYLATION IN MALIGNANT TRANSFORMATION OF CRC

### *DNA damage response and defense mechanisms*

DNA damage refers to a single or double-strand break resulting from physical or chemical changes to DNA that can affect the interpretation and transmission of genetic information[28]. This leads to an unbeneficial environment for normal cell survival. However, DNA damage is well recognized as a critical factor in cancer development and progression[29]. A reason for endogenous DNA damage in CRC is the induction of replication stress by oncogenes[30,31]. Mutations or overexpression of proto-oncogenes can transform them into oncogenes that induce sustained cell growth and carcinogenesis[32]. The oncogenic cell cycle is usually associated with the induction of replication stress, which is also defined as irregular replication fork progression and DNA synthesis[31]. Another cause of endogenous DNA damage in CRC is an increase in ROS[7]. ROS is derived from the incomplete reduction of oxygen, a by-product of energy metabolism. And it can affect cellular function by reacting with biomolecules, including nucleic acids and proteins[6]. Consequently, damage to the nucleotide sequence causes aneuploidy by inducing DNA strand breaks and genomic instability, which is a critical contributor to induce colon carcinogenesis following gene mutations [33]. The aforementioned process supports the hypothesis that it may be related to the development and progression of CRC; however, unregulated replication stress and/or increased oxidative stress focused on sustained ROS production can have a devastating effect on the survival of cancer cells[7,31,33]. Therefore, it is necessary to activate the protective mechanism constantly.

CRC can exert a function characterized by initiating various reactions to protect the genome in response to DNA damage and ensuring cancer cell survival[4,33]. The DNA damage response pathway in CRC is characterized by a complex network of multiple effectors that promote DNA replication and cell proliferation, and genomic alterations to the DNA damage response pathway may appear[4,12]. Under such a tumor microenvironment, the roles of PARP-1 and PARylation on DNA damage responses can be considered as important factors in overcoming genomic instability[14,15]. PARP-1 functionally interacts with the DNA single-strand break (SSB) repair factor named X-ray repair cross-complementing protein 1 (XRCC1) which plays an important role in the SSB repair signaling pathway, thus facilitating the recruitment and assembly of the SSB repair machinery[17,34]. Recent studies have shown that PARylation is induced directly on the BRCA1 C-terminal domain of XRCC1 and mediates the early recruitment of XRCC1 targeting DNA lesions[35]. To deal with a double-strand break, CRC can employ DNA repair mechanisms including non-homologous end joining (NHEJ) and homologous recombination (HR)[36,37]. However, cancers that arise from BRCA1 germline mutations are deficient in HR DNA repair and are vulnerable to DNA damage[38]. If DNA lesions are detected in BRCA1-mutated cancers, PARP-1 and PARylation may play a pioneering role in constructing a platform for recruiting NHEJ repair factors, such as DNA-dependent protein kinases [37]. Further, CRC cells can activate the function of an antioxidant program to protect the cells from irreversible oxidative damage by excessive ROS accumulation [39]. The antioxidant program can be driven by defense through enzymatic antioxidants, including the detoxification of secondary metabolites and the direct removal of the electrophiles themselves[40]. Of course, PARP-1 and PARylation remove the negative aspects of oxidative stress and exert their key roles in areas of positive utilization related to cancer cell growth or oncogene expression[15,41]. Antioxidant enzymes are dependent on the activation of the transcriptional action of nuclear factor erythroid-related factor 2 (NRF2), a basic leucine zipper protein, and NRF2 is involved in maintaining intracellular homeostasis in response to physiological changes between intracellular redox actions[42]. The dissociation of NRF2 and Kelch-like ECH-related

protein 1 is promoted as the production of intracellular ROS increases to levels that threaten the survival of CRC cells[43]. It can enhance a wide range of downstream cellular defense processes regulated by NRF2, such as glutamate-cysteine ligase and glutathione S-transferase[42]. Recent studies have revealed molecular cooperation between NRF2 and PARP-1 in the transcription of antioxidant genes[41]. Evidence that PARylation is directly involved in this cooperative process is not yet available; however, the relevance of PARylation in the mechanism of action of Sirtuin 6 related to the transcriptional activity of NRF2 is well demonstrated[41,44]. In particular, PARP-1 can act by directly binding to the antioxidant response element or the promoter of a small Maf heterodimer; therefore, PARylation can be anticipated to play a direct or indirect role in NRF2 activity[41]. Furthermore, counteracting mechanism with PARP-1 and PARylation is denoted by its interaction with the protein kinase B (AKT) pathway. Phosphatidylinositol 3 phosphorylates AKT to induce an active form and acts as a redox sensor in cancer cells[7]. Active AKT contributes to hydrogen peroxide accumulation by stimulating oxidative metabolism and inhibition of class O of forkhead box-dependent catalase; however, PARP-1 and PARylation can inhibit the mammalian target of rapamycin complex 1 signaling pathway, thus resulting in downregulation of AKT activity[7,45]. At this point, it can be emphasized that PARP-1 and PARylation can directly participate in DNA repair and can maintain redox homeostasis to prevent DNA damage by regulating the oxidation state caused by the rapid growth of CRC.

### **Chromosomal instability**

Chromosomal instability is defined as a defect that involves the loss or rearrangement of chromosomes during cell division and has been well demonstrated as the cause of genetic mutations leading to the stressful tumor microenvironment that supports the rapid growth of cancer[46]. It is a common feature that accompanies most solid tumors and can be classified as numerical or structural chromosomal instability[46,47]. Various molecular characterizations of genomic changes make it possible to elucidate the role of chromosomal instability in cancer; furthermore, these could provide important information related to the mechanisms of tumorigenesis and genetic anomalies[46,47]. Since chromosomal instability is associated with cancer progression, increased invasiveness, poor prognosis, and resistance to anticancer mechanisms, some investigations could work on elucidating therapeutic benefits by targeting chromosomal instability in cancers[46,48]. For one, the pathway that regulates chromosome segregation during mitosis and the one involved in the response mechanism to taxane were found to be similar in CRC characterized by chromosomal instability[47]. This is a promising discovery that metastatic CRC is made inherently resistant to anticancer mechanisms by a taxane, and thereafter, various studies have supported that PARP-1 and PARylation play key roles in such resistance[14,16]. An important implication in recent studies is that the role of PARP-1 and PARylation in chromosomal instability can be emphasized in the chromatic structure change and regulation of epigenetic genes and mitosis[19,25].

Regulation of chromatin structure by PARP-1 may involve direct binding to histones as well as non-histone proteins or chromatin-related proteins or the alteration of nucleosomal structure through PARylation[19,27]. It has been demonstrated that environmental stimulation for the development of cancer can induce PARP-1- and PARylation-dependent nucleosome loosening, leading to histone removal and opening of chromatin structures[49,50]. Activation of PARP-1 promotes chromatin decondensation in response to signaling pathways for cancer cell growth and differentiation[49]. Chromatin decondensation could be induced by competitive displacement of histone H1 in the nucleosomes by PARP-1 and ADP-ribosylation on histone H1[51]. The induction of negatively charged PARylation on histone proteins can reportedly lead to repulsion with DNA, thus leading to chromatin decondensation[52]. Then, PARP-1 activity on chromatin can target a wide range of domains, and at the nucleosomal level, it recognizes specific structural features and binds directly to the nucleosomes[19,53]. The histone cores of the nucleosomes, such as H2A, H2B, H3, and H4, and the linker histone H1 are well-known direct targets of PARP-1, and such a function of action can be considered as a proof to induce localized decondensation of chromatin[25,51]. Recent studies indicated that PARP-1 binds to mononucleosomes and interacts with trinucleosomes, which is consistent with its role as a chromatin architectural protein[18,54]. Thereby, the reduction in affinity for surrounding proteins caused by PARP-1 and PARylation may help protect the linker DNA from nuclease digestion; in this context, its role in the facilitation of the reassembly of free histones into nucleosomes may suggest that PARP-1 and PARylation also act as a chaperone for histone protection under chromosomal instability[18,51,54]. Studies on CRC have

demonstrated a role of PARylation in the regulation of chromatin relaxation by histone proteins H1, H2A, and H2B[14,54].

PARylation of histones leading to open chromatin morphology is well known as another function that enables epigenetic regulation[19,55]. Histones can undergo covalent modifications from conserved lysine or arginine residues by enzymes called histone acetyltransferases or methyltransferases, which are related to the regulation of oncogene expression[56]. A link between PARylation and acetylation may exist *via* the positive transcriptional control of histone acetyltransferases by PARP-1, such as that of E1A binding protein P300 and cyclic adenosine monophosphate response element-binding protein (CBP), together with the recently identified covalent PARylation on P300 and CBP[57]. PARylation also has an important role in the maintenance of histone H3 at lysine 4 as it impinges on its demethylation process through the covalent modification of the demethylase lysine demethylase 5B[18]. Undergoing such epigenetic variations with PARylation is a key event necessary for activation of nuclear factor-kappa B-dependent genes in CRC and recruiting of key proteins involved in the DNA damage response[15,58]. Further, approximately hundreds to thousands of genes are considered to be abnormally methylated in the CRC genome, and this epigenetic change may be an important part of the pathogenesis of CRC[59]. When abnormally methylated genes are detected in normal mucous membranes, they are classified into a group with a high risk of developing CRC because abnormal methylation is equally detected in adenocarcinomas as well as in adenomas[4,58,59]. Thus, methylation is considered to play an important role in the progression of CRC[4, 58]. Some cases of abnormally methylated genes in CRC include integrin subunit alpha 4, O<sup>6</sup>-methylguanine DNA methyltransferase (MGMT), sodium-coupled monocarboxylate transporter 1, human mutL homolog 1 (MLH1), and amyloid-beta precursor protein-binding family A member 1. In particular, it has been suggested that abnormal methylation of DNA repair genes, such as MGMT and MLH1, in colorectal adenoma may promote progression to adenocarcinoma[60]. There have been some reports on the regulation of MGMT or MLH1 functions by covalent or non-covalent PARylation in ovarian cancer or glioblastoma; however, only the indirect effects of PARP-1 and PARylation were investigated in CRC, and there is still no study demonstrating a direct correlation between such genes and PARylation[12,58,61,62].

CRC is genetically classified into microsatellite instability and chromosomal instability, and chromosomal instability accounts for about 85% of sporadic CRCs[63]. Since the main feature of chromosomal instability is aneuploidy, it was predicted that it could be caused by structural changes in chromosomes and abnormal mitosis[64]. A variety of genetic changes that contribute to chromosomal instability remain to be elucidated, but the main cause of the high aneuploidy because of an increase in the total chromosome number is reportedly a trait that can be shared with the occurrence of mitotic defects[65]. Potential defects in various genes that participate in many mitotic processes for CRC development can lead to uneven separation of chromosomes and have been investigated to their involvement in the aneuploidy and carcinogenesis of CRC[47]. These include chromosomal condensation, centrosome replication, microtubule dynamics, and checkpoints for proper progression of the cell cycle[46,47]. For example, centromere protein A is a centromere-specific histone-H3-like variant essential for centromere structure and function, which play a critical role in the assembly of protein complexes that perform the function of identical chromosomal separation in the CRC[66]. In addition, aurora kinases can be overexpressed in CRC, resulting in a transgenic activity[67]. Checkpoint gene budding uninhibited by benomyl (BUB)s are mutated in CRC, and exogenous expression of mutant BUBs confers abnormal spindle checkpoints[68]. The checkpoint with forkhead-associated and ring finger domains (CHFR) is a mitotic checkpoint and tumor-suppressor gene, its loss contributes to carcinogenesis of CRC[69]. Although there are still no reports demonstrating genetic benefits for cancer survival by the regulation of CRC-specific mitotic defects by PARP-1 and PARylation, the existing theory offers a chance to focus on the possibility that the function of PARP-1 and PARylation is related to the regulation of mitotic checkpoint genes, which are involved in the mitotic defect of CRC. PARP-1 is accumulated in the centrosome chromatin until metaphase during mitosis and dissociates from anaphase after interacting with centromere proteins A and B and BUB mitotic checkpoint proteins[15,68,70]. It has also been found to interact with aurora kinases to inhibit DNA damage-induced activity and reduce histone H3 serine 10 phosphorylation[71]. Furthermore, another mitotic checkpoint, known as the antephase checkpoint, precedes the spindle assembly checkpoint and occurs in the initial prophase[72]. The antephase checkpoint responds to microtubule toxicity or DNA damage and causes chromosomal decondensation and delayed mitosis[72]. CHFR has a role in the ubiquitination of polo-like kinase 1 as an E3 ubiquitin ligase,

and it can be stabilized by PARylation. The key function of CHFR is to ensure intact anaphase checkpoints, and it has been demonstrated that PARylation increases interaction with CHFR to control prophase checkpoints in stressful environments during mitosis[70,73,74]. It is likely for listed genes to be potential candidates to be targeted for demonstrating the association of mitosis defects with PARP-1 and PARylation in identifying the malignancy of CRC [60,63-66,68,69,71-74].

### **Modulation of tumor suppressor gene and oncogene expression**

The sequential acquisition of genetic and epigenetic changes in CRC has been well defined recently through widespread genetic studies[4,31,33,47]. These studies presented clear evidence that the initiation and progression of CRC depend on the mutation of tumor suppressor genes or abnormal expression of oncogenes in stages followed by invasive and metastatic CRC[4,31,33,47]. Somatic mutations in the adenomatous polyposis coli (*APC*) gene are observed in slightly over 80% of all sporadic CRC. Similarly, mutations in the DNA mismatch repair genes, such as *mutS* homolog 2, *mutL* homolog 1, and *PMS2*, are found in the majority of the remaining 20% of sporadic CRC[47,75]. Many kinds of genes have been recently identified, and they have a causal relationship with the formation of CRC in the later stages of neoplastic transformation. Representative examples include Kirsten ras (*KRAS*) oncogenic activation and mutant inactivation of several tumor suppressor genes, including deleted pancreatic cancer locus 4 and *p53*[76,77]. Among the changes in various genes in CRC, studies on *APC*, *p53*, and *KRAS* were the recently focused. *APC* is a key component of the  $\beta$ -catenin disruption complex involved in the degradation and inhibition of the Wnt/ $\beta$ -catenin signaling pathway; therefore, a mutation in *APC* induces the stabilization and accumulation of  $\beta$ -catenin in the tumor microenvironment, thus this mutation is in charge of the earliest process in the development of CRC[78,79]. *p53* is a tumor suppressor gene that encodes a transcription factor that regulates the transcription of countless genes involved in various processes, such as DNA repair, cell cycle arrest, death, and metabolism[80]. The *p53* mutation is associated with the progression of sporadic CRC and leads to adenoma-to-carcinoma transition as the loss of function contributes to the propagation of damaged DNA to daughter cells[4,77]. *KRAS* is a membrane-bound protein with intrinsic guanosine triphosphatase (GTPase) activity and belongs to a family of RAS genes involved in signaling pathways that regulate cell proliferation, differentiation, and survival[76]. *KRAS* mutations impair the intrinsic GTPase activity of *KRAS*, causing the accumulation of *KRAS* protein in the state of GTPase binding activity, resulting in constitutive activation of downstream proliferative signaling pathways[76]. Following this context, since the current understanding of PARP1-induced PARylation can be emphasized owing to its potential involvement in transcriptional regulation by interaction with PARylated proteins, it is necessary to give an eye to the function of PARP-1 and PARylation concerning the gene regulation of *APC*, *p53*, and *KRAS* in CRC.

Defects of the function of the *APC* tumor suppressor gene are associated with familial and sporadic CRC, resulting in the accumulation of  $\beta$ -catenin and activation of T-cell factor 4 and lymphoid enhancer factor[81,82]. PARP-1 interacts with the T-cell factor 4 in CRC to act as a bridge for the complex interaction of T-cell factor 4 with  $\beta$ -catenin[83]. Through this function, PARP-1 increases the transcriptional activation of T-cell factor 4 and lymphoid enhancer factor with  $\beta$ -catenin[50,83]. mRNA and protein expression level of PARP-1 is reportedly elevated in the clinical biopsy of familial adenomatous polyposis and sporadic CRC, suggesting that they may be a possible cause of PARP-1 regulatory transcriptional activation in CRC[84]. It has also been demonstrated that PARP-1-mediated transcription up-regulation with T-cell factor 4 and lymphoid enhancer factor may be increased in sporadic CRC compared to normal tissues[50,82,83]. A direct correlation of PARylation with T-cell factor 4 or lymphatic system enhancer has not yet been established; however, it is possible to deduce that transcriptional regulation of PARP-1 is carried out in conjunction with PARylation based on the evidence for PAR accumulation in the nucleus of CRC cells[27]. That is, PARP-1 can positively regulate the transcriptional activity of T-cell factor 4 and lymphoid enhancer factor in CRC, and it can be inferred that *APC* may be more active in CRC when PARP-1 and PARylation are actively involved[27,81-83]. PARP-1 also has a unique function that allows direct regulation of sequence-specific transcription factors, and it can form a complex that allows down-regulation of all transcription processes involving *p53*[50,85]. The formation of a transcription inhibitory complex is made possible by direct covalent binding of PAR to *p53* to induce *p53* stabilization[14, 50,85]. PARylation of *p53* first leads to recruitment of histone deacetylases; this transcriptional inhibitory complex can upregulate cancer-related genes and phenotypes by raising the level of expression of hypoxia-inducing factor-1 $\alpha$  and vascular



endothelial growth factor, which is related to malignant transformation of CRC[14,85]. It has been suggested that PARP-1 interacts with the G4 motif region of the KRAS promoter under the tumor microenvironment subjected to oxidative stress, such as increased ROS levels[86-88]. As aforementioned, oxidative stress caused by ROS can play an important role in the regulation of genetic changes and can be considered a common feature in most solid cancers, particularly contributing to the growth, survival, and metastasis of CRC[6,7,88]. Under such a condition, it has been proved that PARP-1 is recruited to the KRAS promoter G4 structure after which it undergoes auto-PARylation[88]. The results revealed the mobilization of the transcription factors, heterogeneous nuclear ribonucleoprotein A1 (HNRNPA1), and the protooncogene (MYC)-associated zinc finger protein, as well as the formation of a transcription pre-initiation complex[88,89]. It may be characterized by favoring recruitment to the promoter of cationic transcription factors required for KRAS transcription, such as HNRNPA1 and MYC-associated zinc finger protein, because of the strong anionic properties of PAR[88].

## NON-CLINICAL AND CLINICAL STUDIES ON CRC TREATMENT

The first-generation PARP1 inhibitor, a nicotinamide analog, was found to have a cytotoxic effect on tumor cells when combined with genotoxic stress agents; however, it was not applicable for *in vivo* experiments because they had to be used in millimolar concentrations for *in vitro* studies[90]. More effective second-generation PARP-1 inhibitors were developed based on quinazoline analogs, some of which have become the basis for further development of more effective PARP-1 inhibitors, and they applied to the investigations targeting most cancer types[90]. However, non-clinical studies on inhibiting PARP-1 in CRC are still in their infancy, and regarding anticancer effects targeting CRC through a method of inhibiting PARP-1, results of only small-scale studies conducted mainly using a few small molecules, such as PJ34, NU1085, and AG14361, are available[91-94]. The phenanthridine PJ34 treatment reportedly decreased the viability of CRC cells by G2/M cell cycle arrest and subsequent clustering of additional centroids[91]. Previous studies have shown that NU1085, a family of benzimidazole PARP-1 inhibitors, exhibited potent anticancer effects in a panel of CRC cell lines at low concentrations regardless of the status of p53[92]. AG14361, binding to the catalytic domain of PARP-1, inhibited the growth of CRC even at extremely low concentrations, and its combination with irinotecan impeded the growth of human CRC in the xenograft model by 2-to 3-fold without body-weight loss[93,94]. Recently, five PARP inhibitors, olaparib, niraparib, veliparib, rucaparib, and talazoparib, are drawing attention[95-100]. Olaparib is an oral PARP inhibitor first approved for the treatment of advanced ovarian cancer; however, today, it is also being applied to patients with other cancer types with BRCA mutations[96]. Niraparib is an oral medicine for the highly selective inhibitor of PARP-1 and-2 used for the treatment of women with advanced ovarian cancer regardless of BRCA mutation or HR deficiency status[100]. Veliparib, an oral inhibitor of PARP-1 and-2, is also being studied for its applicability to treating many types of cancer with BRCA mutations, as well as advanced ovarian cancer[97]. Rucaparib is an oral, small-molecule inhibitor of PARP-1, -2, and -3[98]. Talazoparib is an orally bioavailable PARP inhibitor with the potential antineoplastic activity that targets cancer with BRCA mutations or with deficiencies in DNA damage repair[99]. The five mentioned PARP-1 inhibitors reportedly have anticancer effects, primarily under the characteristics of the tumor microenvironment associated with genetic changes. CRC cells with short hairpin RNA depletion of ataxia telangiectasia mutated protein kinase are sensitive to olaparib, and the depletion of p53 enhances this sensitivity[101]. The combination of niraparib or rucaparib with the topoisomerase I inhibitor irinotecan obtained results showing enhanced anticancer efficacy targeting CRC cells regardless of microsatellite status [102,103]. Veliparib could be more sensitive to CRC cells undergoing mutations in mismatch repair or mutS Homolog 3 genes, and talazoparib could increase antitumor effects through the formation of DNA a double-strand break in CRC cell lines and xenograft animal models with wild-type BRCA genes[104,105].

According to the outcomes in previous clinical trials, the lack of anticancer activity in PARP-1 inhibitors mainly targeting CRC has led to little interest in further clinical development. This is because a clinical trial for talazoparib involving patients with breast cancer including CRC with HR pathway gene mutation is ongoing; however, no tumor response targeting CRC has been noted so far[106]. The exact indications were defined as non-breast tumors, such as the pancreas, uterine, testicular, parotid

**Table 1** The ongoing clinical trials of poly adenosine diphosphate-ribose polymerase-1 inhibitor for the treatment of colorectal cancer

Drug	Trial ID	Target Indication	Outcome measurement	Arm
Olaparib	NCT04456699	Unresectable or metastatic CRC patients who have not progressed following first-line therapy of FOLFOX with bevacizumab	Primary: PFS (up to 6 yr); Secondary: OS, ORR, DOR, AE (up to 6 yr)	(1) Olaparib; (2) Olaparib + Bevacizumab; (3) 5-FU + Bevacizumab; Triple-arms
Olaparib	NCT04166435	O6-MGMT hypermethylated CRC patients	Primary: ORR (up to 2 yr); Secondary: AE, PFS, OS (up to 2 yr)	Temozolomide + Olaparib; Single-arm
Niraparib	NCT03983993	Patients with metastatic CRC	Primary: Clinical benefit rate (CR + PR + SD, up to 5 yr); Secondary: ORR, DOR, PFS, OS (up to 5 yr)	Niraparib + Panitumumab; Single-arm
Rucaparib	NCT03337087	Treating patients with metastatic CRC up to third-line of prior therapy	Primary: MTD, DLT, ORR (SD, CR, PR; up to 3 yr); Secondary: DCR, PFS, OS, AE (up to 3 yr)	liposomal irinotecan + 5-FU + rucaparib; Single-arm

FOLFOX: Leucovorin + 5-FU + Oxaliplatin; PFS: Progression-free survival; OS: Overall survival; ORR: Objective response rate; DOR: Duration of response; AE: Adverse events; CR: Complete response; PR: Partial response; SD: Stable disease; DLT: Dose-limiting toxicity; MTD: Maximum tolerated dose; DCR: Disease control rate; MGMT: Methylguanine deoxyribonucleic acid methyltransferase.

salivary, and CRC[106]. And, a placebo-controlled phase 2 study evaluated the efficacy and tolerability of veliparib in combination with 5-fluorouracil, leucovorin, and irinotecan (FOLFIRI) compared to placebo plus FOLFIRI in patients with refractory and metastatic CRC[107]. Although there were no unexpected safety issues, it solely showed similar efficacy between the two groups[107]. However, the feasibility of its applicability to CRC treatment is being investigated in recent clinical trials in combination with existing anticancer drugs. The ongoing cases of clinical trials involving combination with PARP-1 inhibitors are as follows (Table 1): (1) In patients with histologically confirmed metastatic or unresectable CRC who have not recovered following first-line therapy of 5-fluorouracil, leucovorin, and oxaliplatin with bevacizumab, the efficacy and safety of olaparib monotherapy or in combination with bevacizumab has been evaluated in comparison with bevacizumab with 5-fluorouracil [108]; (2) The efficacy of temozolomide in combination with olaparib has been evaluated in patients with MGMT promoter hypermethylated advanced CRC[109]; (3) The adverse effects and activity of the combination of niraparib with an epidermal growth factor receptor inhibitor, panitumumab, has been evaluated in previously treated patients with RAS wild-type, microsatellite stable, and microsatellite instable metastatic CRC[110]; and (4) Phase I/II study for the investigation of side effects and best dose of liposomal irinotecan and rucaparib when given together with 5-fluorouracil and to see how well they work in treating patients with metastatic CRC [111]. The bright side is that the cases of clinical trials using PARP-1 inhibitors for CRC treatment is still only at the beginning stage, which can be counted with a finger, and it is anticipated that clinical trials that take into account the aforementioned various functions of PARP-1 and PARylation in CRC have not been initiated in earnest. This is because obvious challenges still exist to clear up scattered tasks, such as finding optimal biomarkers to screen applicable and appropriate patients with CRC.

## CONCLUSION

The pathogenic roles of PARP-1-driven PARylation contributing to CRC are being actively considered in various processes required for CRC development, such as DNA damage response, transcriptional regulation, and overcoming chromosomal instability. In particular, further understanding the genetic characteristics of CRC related to the aforementioned functions for achieving significant clinical benefits by targeting PARP-1 is necessary. Therefore, it is essential to continue the discovery of optimal biomarkers that can be appropriately applied to the treatment of CRC and the pathogenetic investigations to overcome the predicted toxicity or resistance. If a clearer scientific background is supported, it is strongly inferred that the feasibility of clinical trials targeting PARP and PARylation for CRC treatment could increase.

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