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Review

Poly-ADP ribosylation in DNA damage response and cancer therapy

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ABSTRACT

Poly(ADP-ribosyl)ation (aka PARylation) is a unique protein post-translational modification (PTM) first described over 50 years ago. PARylation regulates a number of biological processes including chromatin remodeling, the DNA damage response (DDR), transcription, apoptosis, and mitosis. The subsequent discovery of poly(ADP-ribose) polymerase-1 (PARP-1) catalyzing DNA-dependent PARylation spearheaded the field of DDR. The expanding knowledge about the poly ADP-ribose (PAR) recognition domains prompted the discovery of novel DDR factors and revealed crosstalk with other protein PTMs including phosphorylation, ubiquitination, methylation and acetylation. In this review, we highlight the current knowledge on PAR-regulated DDR, PAR recognition domain, and PARP inhibition in cancer therapy.

1. Introduction

Cell organisms are constantly subjected to genotoxic stress including endogenous reactive oxygen species derived from metabolism as well as exogenous ionizing radiation and ultraviolet sunlight [1,2]. It is estimated that cells can experience up to 10^5 DNA lesions per cell per day [2]. Unrepaired DNA damage lead to aberrant chromosome rearrangement, resulting in mitotic failure and deleterious gene mutations [3]. Throughout evolution, cells have developed robust DNA damage repair machineries to maintain genomic stability [4]. The DNA damage response (DDR) is a concerted process involving DNA damage detection, cell cycle checkpoint regulation, DDR factor recruitment, chromatin reorganization, and DNA processing and repair [5]. Poly (ADP-ribosyl)ation (PARylation) is a critical post-translational modification (PTM) that initiates and regulates DDR [6].

Poly(ADP-ribosyl)ation was first described over 50 years ago as a DNA-dependent reaction that consumes nicotinamide adenine dinucleotide (NAD^+) to synthesize poly(ADP-ribose) (PAR) chains [7]. ADP-ribosylation is catalyzed by poly(ADP-ribosyl)ation polymerases (PARPs) that covalently attach an ADP-ribose unit on glutamate, aspartate, arginine, lysine and serine residues on target protein using NAD^+ as a substrate [8–15].The enzymes can further catalyze formation of linear PAR chains through 2′-1″-*O*-glycosidic bonds or branched PAR chains via α(1‴−2″)-ADP-ribose linkages [16,17]. In humans, there are 17 protein members in the PARP family proteins [18,19]. According to the structure and functional domains, PARP family proteins are categorized as DNA-dependent PARPs (PARP-1, PARP-2 and PARP-3), Tankyrases (PAR-5a and PARP-5b), CCCH (Cys-Cys-Cys-Cys-His) Zinc Finger PARPs (PARP-8, PARP-12, PARP-13), PARPs with macro domain (PARP-9, PARP-14 and PARP-15) and unclassified PARPs (PARP-4, PARP-6, PARP-8, PARP-10, PARP-11, PARP-16). Based on the ADP-ribosyltransferase activity, PARPs can be divided into three groups. PARP-1, PARP-2, PARP-5a and PARP-5b contain catalytic His-Tyr-Glu triad and catalyze PARylation [20]. PARP-3, PARP-4, PARP-6, PARP-10, PARP-14, PARP-15, and PARP-16 are only capable of mono (ADP-ribosyl)ation (MARylation) [21]. PARP-9 and PARP-13 are inactive proteins since they lack NAD^+ binding residues [22].

In response to DNA damage, DNA-dependent PARPs, especially PARP-1, quickly recognize single strand break (SSB) and double strand break (DSB) DNA ends and start PAR synthesis. The substrates include PARPs themselves, nucleosomal and linker histones, and certain chromatin-associated proteins, which serves as a scaffold to mediate early recruitment of DDR factors and facilitates chromatin remodeling for DNA repair [23]. PARylation is a reversible PTM and undergoes rapid turnover [24]. The de-PARylation reaction is carried out by glycohyrdolases including PAR glycohydrolase (PARG), terminal ADP-ribose protein glycohydrolase 1 (TARG1), ADP-ribosylhydrolase 3 (ARH3), MacroD1 and MacroD2, and Nudix-Type Motif 9 and 16 (NUDT9, NUDT16) [25–29]. In this review, we will summarize the role of PARylation metabolism in DDR, describe the PAR recognition domain, and review current effort of PARP inhibition in cancer therapy.

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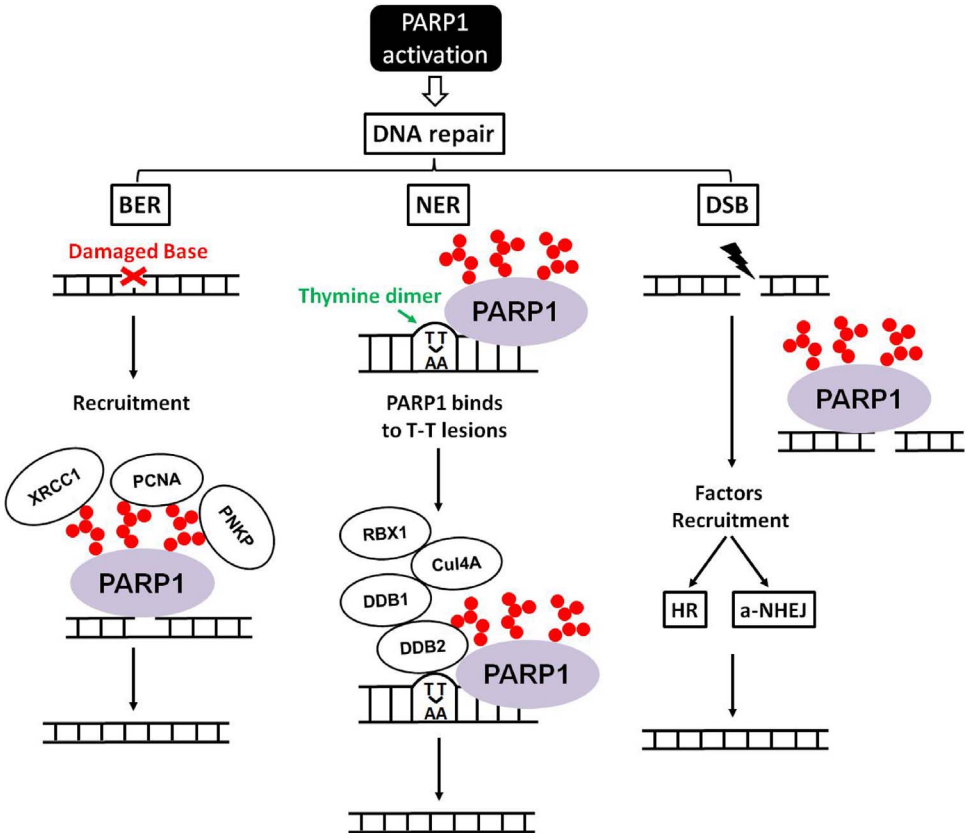


Fig. 1. PARP-1 activation and recruitment of DNA damage response factors in base excision repair (BER), nucleotide excision repair (NER) and double strand break (DSB) repair. XRCC1: X-ray repair cross-complementing protein 1; PCNA: proliferating cell nuclear antigen; DDB1: DNA damage-binding protein 1; DDB2: DNA damage-binding protein 2; cul4A: cullin-4A; RBX1: ring-box 1; HR: homologous recombination, a-NHEJ: alternative pathway of non-homologous end joining.

2. PARylation metabolism in DDR

PARP-1 and PARP-2 detect and bind DNA SSBs and DSBs using the N-terminal DNA binding domain [30]. It has been shown that PARP-1 is able to recognize both SSBs and DSBs within one second of their formation in cells [31]. DNA binding induces a conformation change to expose the enzymatic site of PARP-1, resulting in its activation and PARylation [32]. The PARylation reaction is robust and occurs immediately following DNA binding. The intranuclear PAR level can rise to 500 fold over baseline, consuming up to 90% of the cellular reservoir of NAD^+ [24,33]. PARP-1 activation at the sites of DNA damage results in the synthesis of PAR chains on PARP-1 and other protein substrates, which then recruit PAR-binding DNA repair components for SSB and DSB repair (Fig. 1). PAR chain at SSBs recruits XRCC1 (X-ray repair cross complementing protein 1), a pivotal scaffold protein for assembly and activation of DNA base excision repair machinery [34,35]. Recent studies from our group and others identified that the BRCT domain in XRCC1 is a strong PAR-binding domain that mediates the early recruitment of XRCC1 [36,37].

PAR at DSB lesions rapidly recruits meiotic recombination 11 (MRE11), an integral protein of the MRN (MRE11-RAD50-NBS1) complex and ataxia telangiectasia-mutated (ATM). These two key DDR factors detect DSB, halt cell cycle and activate downstream repair by homologous recombination (HR) or non-homologous end joining (NHEJ) [31,38]. HR, which mainly occurs in the S and G2 phases, requires the sister chromatid template for repair and is activated by 3′ nucleotide overhang from single-stranded DNA resection [39]. Although HR is grossly normal in PARP-1-inhibited cells [40], PARylation can facilitate HR by mediating the early recruitment of breast cancer susceptibility gene 1 and 2 (BRCA1 and BRCA2) [36,41]. The BRCT domain of BRCA1-associated RING domain protein 1 (BARD1), the functional partner of BRCA1, recognizes PARylation and mediates the recruitment of the BRCA1 complex to DSBs. BRCA2 uses its oligonucleotide/oligosaccharide-binding (OB) fold domain to bind PAR, leading to the recruitment of RAD51, a crucial recombinase for strand invasion in HR [41]. Additionally, PARP-1 activation at replication fork restarts the stalled fork for HR [42,43]. Lastly, we recently demonstrated that exonuclease 1 (EXO1) is recruited by PAR through its homologues of the PilT N-terminal (PIN) domain and mediates DNA end resection in HR [44].

NHEJ rejoins the two ends of DSB without the need for a homologous template. PARP-1 binding to DNA-dependent protein kinases (DNA-PKs) has been reported to maintain genomic integrity during V(D)J recombinations carried out by NHEJ [45]. Our data suggests that DNA ligase IV, a key component in NHEJ, can be recruited by PAR through interaction with its BRCT domain [46]. Furthermore, PARP-1 recruits chromodomain helicase DNA binding protein 2 (CHD2), thereby activating chromatin expansion and depositing histone variant H3.3 at DSB sites. Subsequently, PARP-1, CHD2 and H3.3 jointly recruit the assembly of NHEJ machineries [47]. In alternative NHEJ, PARP-1 directly interacts with DSB ends and activate PARylation, leading to recruitment of repair proteins of DNA ligase III/XRCC1 and poly nucleotide kinase-phosphatase (PNKP) [46,48].

PARylation induces remodeling of chromatin into an open conformation that is amendable for DNA repair. PAR chains on chromatin-associated PARP-1 acts as an aggregate of negative charge, repelling DNA, resulting in decondensation of chromatin [49]. Histone H2A, H2B, H3, and H4 can interact with PAR and cause the release of DNA from nucleosomal core particles [50,51]. Moreover, histones H1, H2A, H2B, H3 and H4 can undergo PARylation to serve as additional scaffolds for DDR factors to remodel nucleosome structures [52,53]. Furthermore, ADP-ribosylation on key lysine residues on histone tails including H3K27 and H4K16 may regulate histone methylation and acetylation [13,54]. Lastly, PAR-mediated recruitment of aprataxin-poly nucleotide kinase-like factor (APLF), a histone chaperon protein, facilitates relaxation of chromatin [55].

PARylation can regulate protein ubiquitination at DNA damage sites by recruiting ubiquitin E3 ligases including checkpoint with forkhead-

associated and RING finger (CHFR) and ring finger protein 146 (RNF146). CHFR recruitment by PAR catalyzes the first wave of ubiquitination at DNA damage sites, facilitating proteosomal degradation of DDR factors [56]. Similarly, RNF146 recruited by PAR ubiquitinates and targets PARP-1, XRCC1, DNA ligase III, and KU70 for proteosomal degradation [57].

PAR modifications at the DNA damage sites are highly dynamic. Genotoxic stress-induced PARylation on protein targets is rapidly degraded *in vivo* with half-life of 40 s to 6 min [24,58]. Accumulation of undigested PAR can trigger cell death through parthanatos, a form of programmed cell death [59]. The reported PAR degradation enzymes include PARG, ARH3, TARG1, MacroD1, MacroD2, NUDT9 and NUDT16. Many of these enzymes contain the macro domain that recognizes PAR and ADP-ribose [60]. The full length PARG isoform (110 kDa) localizes to the nucleus and is the major de-PARylation enzyme [61]. PARG cuts the ribose-ribose bond between the ADP-ribose units and is capable of both *endo*-glycohydrolytic and *exo*-glycohydrolytic cleavage [62,63]. However, PARG is incapable of removing the terminal ADP-ribose moiety attached to amino acid residue [63]. ARH3 performs the same enzymatic reaction as PARG but is reported to mainly cleave *O*-acetyl-ADP-ribose, a product of the NAD^+-dependent Sirtuin reaction [64]. ARH3 is also found to exert its activity on mitochondrial matrix-associated PAR and its PAR degradation activity in the nucleus is likely limited [26,65]. NUDT9 and NUDT16 hydrolyze the phosphodiester bond between ADP-ribose moiety and protein, resulting in a ribose-5′-phosphate (R5P) tags attached to the modified protein [66]. Their contribution to PAR homeostasis is currently unclear.

The removal of terminal ADP-ribose is proposed to be the rate-limiting step in PAR degradation, evident by the significantly longer half-life of protein MARylation compared to PARylation. Recently, TARG1, MacroD1 and MacroD2 were identified to be capable of digesting MARylation by cleaving glutamate-linked ADP-ribose [27,67]. Structural analysis reveals that TARG1 catalyzes the reaction by forming a covalent lysyl-ADP-ribose intermediate, subsequently resolved by a catalytic aspartic acid [27,68]. MacroD1 and D2 perform substrate-assisted catalysis using a positioned water molecule for hydrolysis of the glutamate-ADP-ribose bond [28,67]. Interestingly, theseenzymes have distinct subcellular localization. TARG1 predominately localizes to the nucleus [27]. MacroD1 localizes to mitochondria whereas MacroD2 has both nuclear and cytoplasmic localization [69].

There is accumulating evidence supporting the important role of de-PARylation in DDR. Both PARG and TARG1 are rapidly recruited to DNA damage sites by PARylation [27,70]. Interestingly, complete deletion of all isoforms of PARG in mice is embryonically lethal [71]. Additionally, PARG inhibition sensitizes cells to genotoxic stress and results in synthetic lethality with HR defect [72,73]. Furthermore, failure to remove ADP-ribose from the acceptor proteins leads to a neurodegenerative disorder characterized by lysosomal accumulation of the proteins with ribose-5-phosphate attached to the glutamic acid residue [74]. On the other hand, TARG1 truncation mutations are linked to an autosomal recessive neurodegenerative and seizure disorder [27]. TARG1 knockdown also sensitizes cells to DNA toxin such as methyl methanosulphonate [27]. Collectively, the data suggests that de-PARylation is an essential step in DDR while the detailed mechanism remains to be elucidated.

3. PAR recognition domain

PARylation mediates the fast recruitment of DDR factors to the sites of DNA damage through interactions with their PAR recognition domains. In the following, we will describe the known PAR-recognition domains, including the PAR-binding zinc finger (PBZ), the WWE domain, the BRCT domain, the FHA (forkhead-associated) domain, the OB-fold domain, the RRM (RNA recognition motif) domain, the PIN domain, and the GAR domain (Table 1). The growing numbers of the PAR recognition domains propelled the discovery in PARylation-regulated DDR, PARylation-induced PTMs and downstream signaling cascades [75]. Fig. 2 illustrates the interaction between various PAR recognition domains and PAR moieties. The PBZ-containing CHFR and the WWE domain-containing RNF146, deltex1, and TRIP12 mediate ubiquitanation of DDR factors. The macro domain-containing MacroH2a, MacroD1, MacroD2, TARG1, and PARG mediate degradation of PAR. The FHA, BRCT, OB fold, RRM, PIN and GAR domains are crucial in mediating the interactions between scaffold proteins and DNA processing proteins in DDR.

3.1. PAR-binding zinc finger (PBZ)

The PBZ domain is a small PAR-binding module found in two DDR factors, CHFR and APLF [76]. The domain has a consensus sequence of [K/R]xxCx[F/Y]GxxCxbbxxxxHxxx[F/Y]xH and contains putative C2H2 zinc-finger separated by a 6–8 amino acid spacer. The domain uses a central zinc ion surrounded by two cysteine and two histidine residues that specifically recognize the adenines in tandem ADP-ribose units [77,78]. CHFR is an ubiquitin E3 ligase that regulates PARP-1 displacement from DNA damage site [56]. APLF is an endonuclease that acts on auprinic-apyrimidinic site. It carries two PBZ domains, ZF1 and ZF2 with the zinc binding motif of $CX_5CX_6HX_5H$ [77]. Simultaneous interaction of both ZF1 and ZF2 with PAR mediate the high affinity recruitment to sites of DNA damage. Recently, we discovered a novel

Table 1
List of PAR Recognition Domains.

Domain	Length (residues)	PAR interaction	Proteins	Functions in DDR	Reference
PBZ	~ 30	Adenines in two tandem ADP-ribose units	CHFR, APLF, CTCF	Ubiquitination, DNA processing, Maintains DDR boundaries	[56,76–78,80]
WWE	80 – 100	isoADP-ribose	RNF146, PARP-7, PARP-11, PARP-14	Ubiquitination	[57,81–84]
Macro	130 – 190	Terminal ADP-ribose, pyrophosphate bond	MacroH2a, ALC1, PARP-9, PARP-14, PARP-15, MacroD1, MacroD2, TARG1, PARG	PAR degradation, chromatin remodeling	[27,28,63,85–88]
FHA	~ 80	Phosphate of isoADP-ribose	PNKP, APTX	Promotes BER and NHEJ	[46]
BRCT	~ 100	Phosphate of ADP-ribose	NBS1, BARD1, BRCA2, XRCC1, DNA Ligase IV	Promotes BER and DSB repair	[36,46]
OB fold	70 – 150	isoADP-ribose	hSSB1, BRCA2	Promotes DSB repair	[95–97]
RRM	~ 90	By structural similarity with nucleotides.	NONO, RBMX	Promotes DSB repair	[98,99,143]
PIN	130 – 150	By structural similarity with nucleotides.	EXO1, GEN1, SMG5	DNA end processing	[44]
GAR	variable	By structural similarity with nucleotides.	FUS/TLS, EWS/EWSR1, TAF15, SAFB1, SAF-A, hnRNPUL1/2	Chromatin remodeling, promotes DSB repair, regulates DDR factor gene expressions, R-loop removal	[100–105]

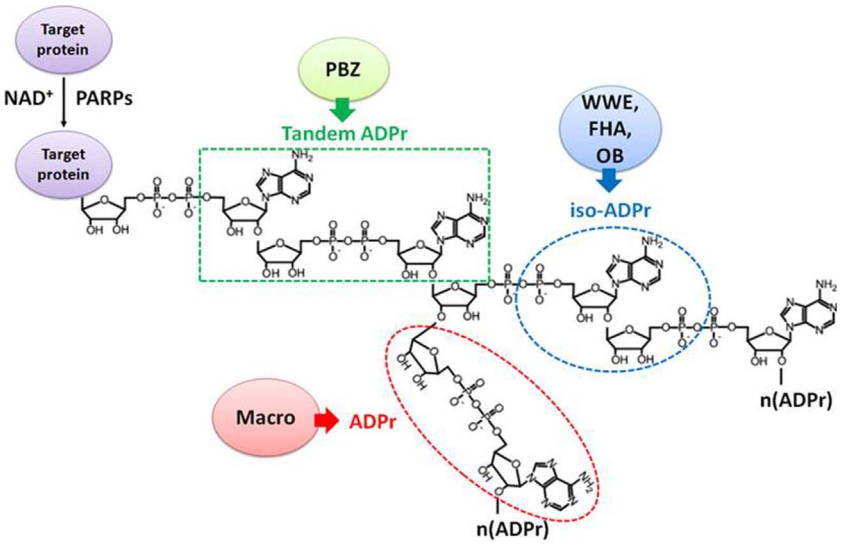


Fig. 2. Interactions between PAR recognition domains and PAR moieties. The PBZ domain interacts with the adenines in two tandem ADP-ribose units. The WWE, FHA and OB-fold domains interact with the *iso*-ADP-ribose unit. The Macro domain interacts with the terminal ADP ribose unit. PARP: poly ADP-ribose polymerase; NAD^+: nicotinamide adenine dinucleotide; ADPr: ADP-ribose; PBZ: PAR-binding zinc finger; FHA: forkhead-associated; OB: oligonucleotide/oligosaccharide-binding fold.

interaction of the CCCTC-binding factor (CTCF) with PAR. CTCF has been described as a chromatin barrier that separates euchromatin and heterochromatin. [79]. CTCF exhibits rapid PAR-dependent recruitment to sites of DNA damage [80]. CTCF contains eleven zinc finger and deletion of zinc finger 4–6 abolishes its interaction with PAR [80]. CTCF can possibly facilitate DNA repair by containing DDR to sites of DNA damage. CTCF knock-down sensitizes cells to ionizing radiation [80].

3.2. The WWE domain

The WWE domain consists of three conserved residues, tryptophan-tryptophan-glutamate that specifically recognize isoADP-ribose, which is the linker region between the two ADP-ribose units in PAR [81]. The WWE domains are found in two categories of proteins, ubiquitin E3 ligases (RNF146, deltex1, and TRIP12) and poly-ADP ribosyltransferases (PARP-7, PARP-11, PARP-12, PARP-13, and PARP-14) [20,82]. This domain is crucial for PAR-activated downstream ubiquitination in DDR. RNF146 (as known as Iduna) is recruited and activated by PAR [57]. It subsequently ubiquitinates PARP-1, XRCC1, DNA ligase III, and KU70 and targets these factors for proteosomal degradation [57]. RNF146 facilitates DNA repair and promotes cell survival after γ-irradiation [57,83]. Furthermore, RNF146 is found to promote WNT signaling by ubiquitinating Tankyrase-PARylated AXIN1/2 for proteosomal degradation [84].

3.3. The macro domain

The macro domain is an evolutionary conserved domain, first discovered in histone variant macroH2A [85,86]. The domain contains a 130 to 190 amino acid residues folded into a central β-sheet flanked by α-helices. It has a conserved diphosphate-binding loop that recognizes NAD metabolites including ADP-ribose and PAR [60,69]. Other macro domain-containing proteins include ALC1, PARP-9, PARP-14, PARP-15, MacroD1, MacroD2, MacroD3, TARG1 and PARG [20,60]. ALC1 is recruited by PARylation and catalyzes PARP-1-stimulated nucleosome sliding and chromatin remolding [87,88]. PARG catalyzes hydrolysis of PAR and is the major de-PARylation enzyme [63]. MacroD1, MacroD2 and TARG1 share a unique enzymatic function that removes terminal ADP-ribose from ADP-ribosylated proteins [27,28].

3.4. The BRCT domain and the FHA domain

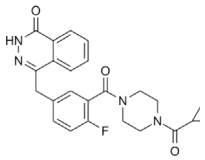
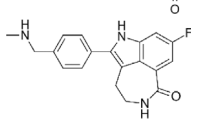
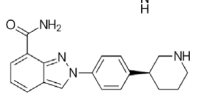
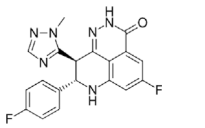
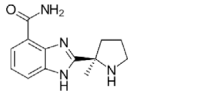
The BRCT domain and the FHA domain were first identified as motifs that recognize phosphorylated proteins. The BRCT domain binds phosho-serine moiety [89–91] and the FHA domain recognizes phosphor-threonine moiety [92,93]. These two domains facilitate assemblies of the protein complexes that regulate cell cycle and DDR [89,94]. Recently, we discovered that some BRCT domains can serve as ADP-ribose recognition motifs and mediate PAR-dependent recruitment of DNA DSB repair factors [36]. The BRCT domain of NBS1 recognizes PAR and rapidly recruits the MRN complex to DNA damage sites, leading to activation of the ATM signaling cascade in response to DNA DSBs. Moreover, the BRCA1/BARD1 complex is rapidly recruited via interaction of the BARD1 BRCT domain and PAR, promoting homologous recombination. The BRCT domain in DNA Ligase IV interacts with PAR to mediate its recruitment to sites of DNA damage and thereby facilitates NHEJ. We also discovered that the FHA domains in PNKP and APTX can recognize isoADP-ribose, the linker unit in PAR, with high affinity (Kd = 0.24 μM and 0.37 μM, respectively) [46]. Mutations of the FHA domains abolish the rapid recruitment of PNKP and APTX to DNA damage sites. Altogether, the dual phosphorylation and PARylation recognition property enables both the early recruitment and stabilization of the BRCT and FHA domain-containing DDR factors at sites of DNA damage.

3.5. The OB fold domain, RRM domain, PIN domain and GAR domain

PAR and oligonucleotide are structurally similar since both contain phosphodiester backbone and ribose rings with adenine base. The OB fold domain, RRM domain, PIN domain and RGG box were originally discovered as RNA binding motif. Recently, these domains were identified as PAR-binding modules. The OB fold domain is 70–150 amino acid domain that consists of a β barrel capped by an α helix [95,96]. The OB fold domain was first identified in bacterial and yeast as an domain that interacts with oligonucleotide and oligosaccharide [95]. Recently, we discovered that the OB fold domain recognizes isoADP-ribose. The OB fold domain in human single strand break (hSSB1) recognizes isoADP-ribose and mediates the fast recruitment of hSSB1 to sites of DNA damage. Screening of other OB fold domain-containing protein reveals high affinity interaction of MEIOB (meiosis specific with OB domain), CTC1 (CST telomere replication complex component 1), hSSB2 and BRCA2 with PAR [41,97].

The RRM domain has approximately 90 amino acid residues and consists of four anti-parallel β sheet interconnected by two α helices. The RRM domain is the most abundant RNA-binding motif in eukaryotic cells [98]. The RRM domain-containing proteins regulate post-transcriptional RNA processing. Recently, the RRM domain at the N-terminus of NONO was identified to bind PAR with high affinity [99]. NONO is recruited to sites of DNA damage through interaction with PAR and contributes to NHEJ.

Table 2
List of PARP inhibitors.

Compound Company	MW (g/mol)	Structure	Ki (nM)	IC_{50} (nM)	Status in clinical development	Reference
Olaparib (AZD2281) AstraZeneca	435.08		n/a	PARP-1: 5 PARP-2: 1	FDA approved for advanced ovarian cancer with gBRCAmut with ≥ 3 prior lines of chemotherapy	[116,144]
Rucaparib (CO-338) Clovis	421.36		PARP-1: 1.4 PARP-2: n/a	PARP-1: 0.8 PARP-2: 0.5	FDA approved for advanced ovarian cancer with gBRCAmut or sBRCAmut with ≥ 2 lines of chemotherapy	[145,146]
Niraparib (MK-4827) Tesaro	320.39		n/a	PARP-1: 3.8 PARP-2: 2.1	FDA approved for recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who have complete or partial response to platinum chemotherapy	[147]
Talazoparib (BMN-673) Pfizer	380.35		PARP-1: 1.2 PARP-2: 0.85	PARP-1: 0.57 PARP-2: n/a	In Phase III study as monotherapy in patients with locally advanced or metastatic breast cancer with gBRCAmut	[148]
Veliparib (ABT-888) Abbvie	244.29		PARP-1: 5.2 PARP-2: 2.9	n/a	In Phase III studies as combination therapy with chemotherapy in patients with breast and ovarian cancer with gBRCAmut or sBRCAmut and lung cancer	[149]

Abbreviations: MW: molecular weight, gBRCAmut: germline BRCA mutations, sBRCAmut: somatic BRCA mutations, FDA: United States Food and Drug Administration, n/a: not available.

The PIN domain has nuclease activity that cleaves specific sequence of ssDNA/ssRNA. We identified that the PIN domain of EXO1 is a PAR recognition domain [44]. The PAR-mediated fast recruitment of EXO1 facilities early DNA end resection. Further screening revealed that the PIN domains of GEN1 and SMG5 can interact with PAR.

GAR (glycine-arginine-rich) domain consists of a sequence enriched in arginine and glycine. It is also termed RGG (arginine-glycine-glycine) box. This positively charged motif renders its affinity to RNA and more recently to PAR [31]. The GAR domain in MRE11 mediates the rapid recruitment to sites of DNA damag. RGG region in the RNA-binding proteins including FUS/TLS, EWS/EWSR1, TAF15, SAFB1, SAF-A, and hnRNPUL1/2 were found to mediate PAR-dependent recruitment of multi-protein complex at sites of DNA damage [100–105]. SAF-A is a mRNA biogenesis factor that facilitates R-loop removal from the DNA damage site [105].

3.6. PAR-binding motif (PBM)

PBM was the first PAR-interacting domain described [106]. It consists of ~20 amino acids with a putative sequence of [HKR]-X-X-[AIQVY-KR-KR-AILV-FILPV] [107,108]. PBM consists of a short degenerated peptide sequence and is unlikely to form a folded structure [18]. Its mode of interaction with PAR is unclear and there lacks structural data on this motif [21]. There are several evidences suggesting that PBM is not a distinct PAR binding domain. First, the putative PBM in XRCC1 resides in the BRCT domain. The entire BRCT domain is required for its affinity with PAR, rather than the short PBM [46]. Furthermore, many of the PBM-containing proteins, including DNA ligase3, hnRNP family proteins, and MRE11 contain the BRCT domain, RRM domain or GAR domains that are high affinity PAR-binding domains [107]. Collectively, the data suggests the specific PAR interactions occur with the other PAR binding domains described above but not PBM.

4. PARP inhibition in cancer therapy

PARP-1 and PARP-2 are the major PARylation enzymes activated in response to genotoxic stress. PARP-1/2 were proposed to be effective targets for cancer treatment given their pivotal roles in DDR [109,110]. In 1979, it was first demonstrated that PARylation inhibition with nicotinamide analog sensitizes cancer cells to cytotoxic insults [111]. Subsequently, a number of PARP inhibitors were developed to target the catalytic NAD^+-binding pocket in PARP-1 and PARP-2 (Table 2). In 2005, Farmer et al. and Bryant et al. showed that PARP inhibition specifically kill BRCA1 and BRCA2 mutant cells, demonstrating synthetic lethality of PARP inhibition with HR defect [112,113]. The mechanism for PARP inhibitors-selective killing of HR defect cells was originally proposed to inhibit PARylation and cause persistent DNA SSBs, leading to formation of DSBs at replication fork and fork collapse [113]. The mode of action has been revised to reflect the emerging evidence that inhibitor-inactivated PARP-1 is trapped on the DNA [114]. Trapped PARP-1–DNA complexes are cytotoxic by causing replication fork collapse through direct collision and by obstructing the direct interaction of DDR factors with the broken DNA [114,115] (Fig. 3). In addition, loss of PARylation impairs early recruitment of both BRCA1 and BRCA2 to DNA lesions, suggesting that the PARylation directly contributes to HR [36,41].

The specific activity of PARP inhibitors on cells with HR defects led to clinical trials to target cancers associated with BRCA1 and BRCA2 mutations. In 2014, the United States Food and Drug Administration (FDA) approved the first PARP inhibitor, olaparib monotherapy in patients with germline BRCA1/2 mutated, advanced stage ovarian cancer treated with three more lines of chemotherapy [116]. In Table 2, we list

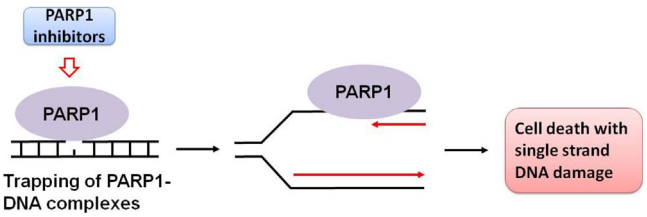


Fig. 3. Synthetic lethality of PARP inhibition in cancer cells with homologous recombination (HR) defect.

the selected PARP inhibitors that are approved or in late stage of clinical development. In addition to olaparib, there were two other PARP inhibitors recently approved by the FDA. Rucaparib was approved to treat patients with BRCA mutations-associated advanced ovarian cancer in December 2016. Niraparib was approved to treat patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer in March 2017. Among the PARP inhibitors in clinic and in development, talazoparib appears to be the most potent molecule to inhibit and trap PARP-1/2 [117]. Active investigations are underway to test the clinical efficacy of these molecules in solid tumors including breast, castration-resistant prostate and pancreatic cancers with germline BRCA1/2 mutations [118].

Besides germline BRCA1/2 mutations, the cells with other types of HR defects confer similar sensitivity to PARP inhibitors. These include cells with somatic BRCA1/2 mutation, BRCA1/2 promoter hypermethylation or mutations in genes essential for HR including *ATM*, *ATR*, *PALB2*, and the *FANC* gene family [119,120]. Furthermore, the genomic instability including loss of heterozygosity, telomeric allelic imbalance and large-scale state transitions due to HR defect can be detected as mutational "scar" by cancer genomic analysis [121,122]. This HR defect with mutational "scar" phenotype is also termed "BRCAness" since the cells with germline BRCA1/2 mutations exhibit the same genetic aberrations [123]. Using this approach, it was demonstrated that the recurrent ovarian cancer patients without germline BRCA1/2 mutations but with the biomarker of BRCAness scar have longer progression free survival when treated with niraparib [124]. Moreover, the emergence of liquid biopsy to analyze the cancer genomics in blood circulating tumor cells and circulating DNA can further improve the screening of cancer patients for PARP inhibitor therapies [125]. Besides using PARP inhibitor as monotherapy, there are several ongoing clinical trials that explore the use of PARP inhibitors in combination with platinum, taxane or alkylating chemotherapy, radiotherapy, and other inhibitors targeting cell cycle regulation and the PI3 K/AKT/mTOR (phosphoinositide 3-kinase/AKT/mammalian target of rapamycin) pathway [118,126]. Taken together, these advances will expand the use of PARP inhibitors in the clinical setting.

Resistance to PARP inhibitor is an emerging clinical problem. The resistance originates from the genetic heterogeneity within a tumor, or acquired resistance following PARP inhibitor therapy. There have been several reported mechanisms of drug resistance from PARP inhibitor. They include increased drug efflux, partial HR deficiency, recovery of HR defect, and activation of compensatory signaling pathways. P-glycoprotein (Pgp) is a member in the ATP binding cassette (ABC) transporter family that transports molecules [127]. Overexpressoin of the Pgp transporter causes resistance to PARP inhibitor and addition of the Pgp inhibitor overcomes the PARP inhibitor resistance [128,129]. BRCA1 loss of function mutations causes HR defect and induces tumorigenesis. There are several hypomorphic mutations of BRCA1 that result in incomplete inactivation of HR [130–132]. BRCA1-c61G RING-inactivating mutation induces loss of tumor suppression but retains ability to form RAD51 foci upon irradiation [130]. Furthermore, BRCA1^{185delAG} mutation, a detectable germline mutation, generates the BRCA1 mutant lacking the RING domain [131]. This RING-lacking BRCA1 is not completely functional in HR but remains capable of facilitating RAD51 foci formation at the DNA damage site [131]. Furthermore, Similarly, it was reported that mutation in BRCA1 exon 11 generates a splice variant lacking exon 11, BRCA1-Δ11 isoform [132]. This mutant can partially compensate for full-length BRCA1. Tumor cells carrying these BRCA1 mutants are resistant to PARP inhibitors [132].

Recovery of HR defect renders cancer cells resistant to PARP inhibitor therapy. Reactivation of functional BRCA1 gene by the loss of promoter hypermethylation restores HR deficiency [133]. In addition, secondary mutations in BRCA2 can cause genetic reversion of BRCA2 loss of function mutation. For example, c.6174delT in BRCA2 mutant is a truncated protein from the frameshift mutation [134]. A secondary mutation in the BRCA2 mutant allele results in intragenic deletion of c.6174delT mutation, thereby restoring the open reading frame (ORF) and the HR deficiency [134]. Similar ORF-restoring mutations have been detected in the PARP inhibitor-resistant breast cancer cell line HCC1428 [135]. 53BP1 is an important regulator of DSB repair response. Loss of 53BP1 partially recovers HR defect by promoting ATM-dependent processing of broken DNA ends to produce the recombinogenic single-stranded DNA [136]. Loss of 53BP-1 causes PARP inhibitor in BRCA-1 mutated mouse mammary tumors and in ATM-deficient breast cancer cells [136,137]. The PARP inhibitor resistance in BRCA1 mutant ovarian carcinoma cells has also been observed by restoration of the HR defect by a microRNA, miR-622 targeting the Ku complex [138]. Activations of signaling pathways that facilitate DDR contribute to PARP inhibitor resistance. Inhibitions of ATR, mTOR and NF-kB pathways have been shown to be effective in overcoming PARP inhibitor resistance [139–142].

5. Perspectives and conclusions

Among the PARylation-regulated biology, DDR is the first one described and is one of the most studied processes. The advance in this field led to the successful development of PARP inhibitors for cancer therapy. The better characterization of the PAR recognition domains adds layers of complexities onto the DDR process. Many of the DDR factors contain multiple domains that mediate simultaneous interactions with DNA, RNA and proteins PTMs. Further research is needed to uncover the intricate cross talks mediated by these interactions. Furthermore, details of ADP-ribose unit removal from the PAR chain complex remain elusive. There also lacks detailed understanding of how PAR catabolism regulates DDR. Inhibition of de-PARylation enzymes with potent, cell permeable inhibitors may present an opportunity for efficacious cancer therapy targeting PAR metabolism.

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