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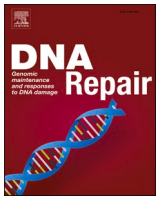

Multiple functions of PARP1 in the repair of DNA double strand breaks

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ABSTRACT

Poly(ADP-ribose) polymerase 1 (PARP1) is one of the most abundant nuclear proteins in human cells and plays critical roles in numerous cellular processes, including the response to DNA damage. PARP1 is activated by and rapidly localizes to both single- and double-strand breaks, where it catalyzes the addition of poly(ADP-ribose) chains onto itself and other chromatin- or repair-associated proteins. While the role of PARP in single-strand break repair is established, its functions at double-strand breaks (DSBs) are more complex, as it can promote or inhibit various steps in the multiple pathways that repair DSBs. In this review, we examine the DSB repair contributions of PARP1, as well as those of PARP2 and PARP3, which are also activated upon damage. We discuss their influence on chromatin regulation at break sites, their role in repair pathway selection, and finally, the regulation of repair mechanisms, including homologous recombination, non-homologous end-joining, and microhomology-mediated end-joining. Understanding these diverse and sometimes opposing roles is especially important in light of the clinical use of PARP inhibitors in cancers deficient in homologous recombination repair.

1. Introduction

Poly ADP-ribose polymerase (PARP) proteins directly contribute to a wide range of essential cellular processes, including DNA replication, transcription, chromatin remodeling, metabolism, programmed cell death, and the response to DNA damage [1-5]. Among the 17 PARP family members (PARP1–17), only PARP1, PARP2, and PARP3 are known to be activated by DNA breaks [2,6]. Of these, PARP1 is the most highly expressed, is responsible for the vast majority of cellular PARylation events, and is by far the most extensively studied [2,7].

PARP1 is a highly abundant nuclear protein that is conserved in single and multicellular eukaryotes, though it is notably absent from the model yeasts, *S. cerevisiae* and *S. pombe* [8]. Upon activation, PARP1 uses nicotinamide adenine dinucleotide (NAD+) to catalyze the addition of poly (ADP)-ribose (PAR) chains and branches, a negatively charged post-translational modification, onto a myriad of targets [10,3,5,9]. PARP1 recognizes and binds to DNA lesions within seconds following damage [11], where its binding to DNA breaks leads to activation, autoPARylation, and PARylation of chromatin, DNA damage and repair (DDR) proteins, or even nucleic acids [10,3,5,9].

Although the role of PARP in promoting single-strand break repair is well established, its functions at double-strand breaks (DSBs) are more intricate, in part because multiple repair pathways operate in parallel and in competition at these highly toxic lesions. Because unrepaired DSBs can lead to genome instability, cell death, or cancer [12], it is critical to understand how PARP contributes to their repair. This question is especially relevant given that PARP inhibitors are used as first-line maintenance therapies for homologous recombination (HR)-deficient cancers due to their synthetic lethality with HR loss [13-15]. Defining the precise role of PARP in DSB repair is therefore essential to fully understand the cellular consequences of PARP inhibitor treatment. This review summarizes current knowledge on the involvement of PARP proteins in DSB repair, with a primary focus on PARP1, while also addressing the functions of PARP2 and PARP3.

2. Structural and functional overview of PARP family members

2.1. Structure of PARP1, PARP2 and PARP3

PARP1, 2, and 3 (summarized in Fig. 1) share structural homology in two key regions: the WGR domain (named for conserved tryptophan-glycine-arginine residues), which mediates DNA binding and regulates catalytic activity; and the catalytic domain, composed of an alpha-helical domain (HD) and an ADP-ribosyl transferase (ART) fold [1,16,17,2]. The catalytic domain mediates NAD^+ binding and PAR catalysis, and is the target of PARP inhibitors, which act as competitive NAD^+

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analogs [15,18].

PARP1 is considerably larger than PARP2 and PARP3, due to a much longer N-terminal region that contains three zinc fingers (Zn1, Zn2, Zn3) and a BRCT (BRCA-C-terminus) domain [1,2]. The three zinc fingers bind DNA damage sites, with Zn3 specifically linking DNA binding with activation of the catalytic domain [1,19]. The BRCT domain is commonly referred to as the auto-modification domain, because both the domain and the flanking linker region contain sites for auto-PARylation. However, it also mediates protein-protein interactions and binds DNA [1,2,20]. Finally, PARP1 contains a caspase cleavage site, DEVD, which is cleaved during apoptosis and is often used as an apoptotic readout [1]. Meanwhile, the shorter N-terminal regions of PARP2 and PARP3 contribute to their DNA binding affinity [16].

2.2. Functional redundancy and divergence between PARP1, 2 and 3

Despite structural differences, PARP1 and PARP2 share significant sequence homology in their catalytic domain and can partially compensate for each other in certain contexts [21,22]. Loss of either gene leads to sensitivity to ionizing radiation, cell cycle arrest, and increased genomic instability in mice [23-25]. Yet, while neither gene alone is essential for viability, loss of both genes is embryonic lethal, indicating critical functional overlap [25]. This epistasis and the ability of PARP2 to partially compensate for the loss of PARP1 are particularly striking, given the functional dominance of PARP1, which accounts for up to 80–90 % of nuclear PARylation upon stress [2,26].

However, PARP1 and PARP2 exhibit important functional differences, including in their effect on SSB repair, class switch recombination, and T-lymphocyte development [22,26,27]. Notably, the combined loss of either PARP1 or PARP2 with the DNA repair kinase ATM (Ataxia-Telangiectasia Mutated) results in embryonic lethality [28], underscoring their non-redundant contributions to genome stability. These functional differences likely stem in part from divergences observed in their protein interactomes, which suggest they PARylate partially distinct sets of proteins [29-31].

PARP1 and PARP2 also display divergent kinetics at DSBs. At laser micro-irradiation sites in mouse embryonic fibroblasts (MEFs) and U2OS cells, PARP2 recruitment is slower but also persists longer compared to PARP1 [21,32]. Interestingly, PARP2 recruitment is also mildly impaired in the absence of PARP1, indicating that PARP1 and PARylation facilitate PARP2 accumulation at repair foci [21,32].

Although PARP1, PARP2, and PARP3 are all activated in response to DNA damage, PARP3 appears to play a more specialized role. One key difference lies in the protein activity: while PARP1 and PARP2 are both capable of PARylation, PARP3 is known to only mono (ADP)ribosylate (MARylation) [3]. PARP3 depletion delays repair of irradiated cells, but PARP3 null mice do not show radiosensitivity, and PARP1/PARP3 double knockout mice are viable, though they display increased sensitivity to radiation [33].

3. General roles of PARP and PARylation at DSBs

DNA DSBs exist as two major forms: double-ended DSBs (deDSBs), which arise from exogenous sources such as ionizing radiation or site-specific nucleases, and single-ended DSBs (seDSBs), which typically occur during DNA replication [34]. DeDSBs can be repaired by homologous recombination (HR), non-homologous end-joining (NHEJ), and, less frequently, by microhomology-mediated end joining (MMEJ) [12,35-38]. In contrast, seDSBs are mainly repaired by HR [34,39], as NHEJ would be toxic at these types of breaks and is actively repressed [40,41].

HR uses the sister chromatid as a template and thus is only active during S and G2 and widely considered the most accurate repair mechanism [42,43]. NHEJ is active during all interphase and is a relatively accurate process [42,44]. Finally, MMEJ is an inherently mutagenic pathway that can serve as a backup for both NHEJ and HR [45-52]. However, under physiological conditions, MMEJ mostly repairs breaks during mitosis, where it is the only active pathway [52-57].

3.1. PARylation as a DNA damage signal and protein recruitment platform

DNA-dependent PARylation functions as a signal amplification mechanism for the DNA damage response. The pathway consists of writers that catalyze PARylation (PARP proteins), erasers that remove PAR (e.g., PARG and ARH3), and readers that bind to PAR chains (e.g., XRCC1, BRCA2) [2,10]. Together, these PARylation-dePARylation events provide a dynamic spatiotemporal scaffold for protein recruitment and protein-protein interactions [10]. Notably, several common protein domains can bind PAR modifications, thereby promoting the recruitment of these proteins to PAR chains. These PAR-interacting domains include: PAR-binding zinc fingers (PBZ, found in APLF and CHFR), PAR-binding motifs (PBM, found in XRCC1, DNA ligase III, MRE11, ATM, DNA-PKcs, Ku70, and WRN), macrodomains (MacroH2A, PARG, ALC1, and some other PARPs), and BRCT domains (BARD1, NBS1, XRCC1, and DNA ligase IV) [1,10,58,59]. Additionally, the OB-folds of BRCA2 and the PIN domain of EXO1 bind PAR [1,58], while the FHA (Forkhead-associated) domains of NHEJ factors APTX and PNKP interact with *iso*-ADP-ribose, the linkage of PAR [58,59]. An

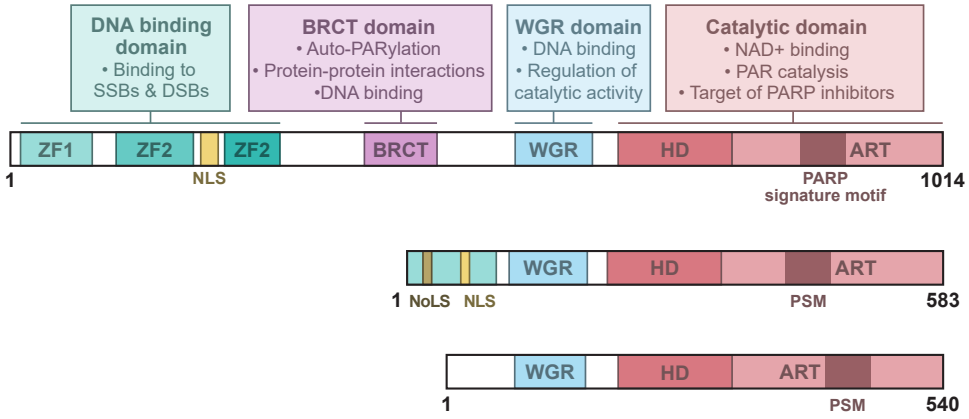

Fig. 1. Domains of PARP1, PARP2 and PARP3. PARP1, 2 and 3 have a catalytic domain that binds NAD+ and performs PAR catalysis, as well as a WGR domain that binds DNA and regulates catalytic activity. PARP1 also possesses three zinc-finger motifs that bind single- and double-strand breaks, and a BRCT domain that is the target of autoPARylation, mediates protein-protein interactions, and participates in DNA binding. The shorter N-terminus of PARP2 and PARP3 also promote DNA binding. *SSB: Single strand break; DSB: Double strand break; ZF: zinc finger; BRCT domain: BRCA1 C-terminal domain; WGR domain: tryptophan, glycine, arginine domain; HD: alpha-helical domain; ATR: ADP-ribosyl transferase fold; NLS: Nuclear localization signal; NoLS: nucleolar localization signal.*

exhaustive list of proteins that interact with PAR is described in the following references: [1,10,2,58]. Finally, on top of the DDR factors that bind PAR, another set of repair proteins are themselves PARylated, including Ku70, Ku80, DNA-PKcs, RPA, BRCA1, and Polθ [60-66]. Whether these PARylation events have functional relevance or are simply the collateral consequence of promiscuous PARP activity remains incompletely understood.

3.2. PARP influences DSB repair through chromatin regulation

DSB sensing and repair require extensive chromatin remodeling to enable recruitment of DDR factors and promote a permissive environment for repair to occur [67]. PARP contributes to these chromatin changes through histone PARylation, remodeling complex recruitment, and histone variant modulation (Fig. 2). A key cofactor in this process is Histone PARylation Factor 1 (HPF1), which partners with PARP1/2 to form a composite catalytic site [68,69]. On top of stimulating auto-PARylation and restricting PAR chains elongation, HPF1 redirects PARylation to serine residues, proposed to be a dominant modification upon DNA damage [70-74]. Serine ADP-ribosylation of histones promotes chromatin decompaction and recruitment of DDR proteins [75,76]. Consistently, *HPF1*-null cells show reduced recruitment of XRCC4, APLF, and BRCA1, and impaired activity of both HR and NHEJ [75].

A major function of PARP1 at sites of DNA damage is to mediate chromatin relaxation, thereby enabling access for DNA repair proteins. Early studies suggested that this decondensation can be driven by negatively charged PAR chains, which promote nucleosome disassembly [77]. PARP1 also transiently regulates the binding of linker histone H1 [78-81], and facilitates the eviction of nucleosomes around DSBs [76]. Additionally, recent evidence shows that PARylation of histone tails weakens nucleosome-nucleosome interactions, a key determinant of chromatin compaction [82]. Notably, PARP3 is also capable of MARylating histone H2B in the context of nicked DNA [83].

Importantly, chromatin relaxation is preceded by dynamic expansion and condensation events that are also regulated by PARylation [84]. The initial expansion of chromatin at DSBs is PARP-dependent [85-87], and possibly occurs via the transient recruitment of KDM4B, which reduces local H3K9 methylation [86,88]. This initial expansion is quickly followed by an extensive chromatin compaction that signals for repair. This compaction step is mediated by ATM, rather than PARylation, and involves the recruitment of two chromatin regulators, macroH2A1.2 and PRDM2 [84,86]. Notably, the two macroH2A1 isoforms have distinct functions in DNA repair: On one hand, macroH2A1.1, which binds PAR, promotes end-joining via NHEJ or MMEJ [86,89,90]. MacroH2A1.2, on the other hand, lacks the PAR-binding motif, and supports HR. One role of macroH2A1.2 is to recruit KDM5A, which demethylates H3K4me3 to support HR, although KDM5A is also recruited to DSBs via PAR binding [91].

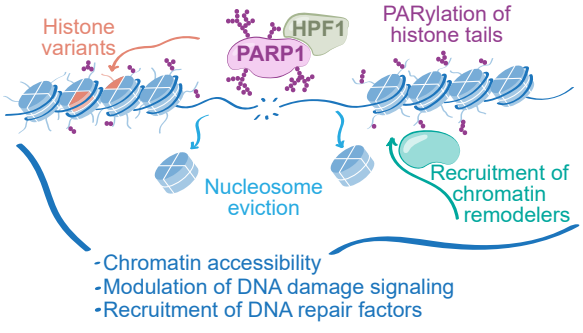

Fig. 2. PARP1 modulates chromatin at DNA breaks. In concert with its partner HPF1, PARP1 orchestrates multiple aspects of chromatin reorganization at sites of DNA damage. It PARylates histone tails, promotes nucleosome eviction, mediates histone variant changes, and recruits chromatin remodelers. Together, these activities promote chromatin accessibility, facilitate the spreading and activation of DNA damage signaling factors such as γH2AX, ATM, and RNF168, and ultimately drive the recruitment of diverse DNA repair proteins.

Beyond regulating chromatin accessibility, PARP also promotes the signaling pathways associated with DSBs. PARylation of histone H1.2 leads to its eviction from chromatin, which promotes ATM activation [80]. SAFB1 is transiently recruited to DSBs by PARP1/2, which enables efficient phosphorylation of γH2A.X [92]. PARP1 then promotes the recruitment and spreading of SMARCA5, which in turn reinforces the recruitment of RNF168 to DSBs [87].

PARP also mediates the recruitment of several chromatin remodeling factors to DSBs, including APLF, ALC1, and CHD2. APLF promotes NHEJ, primarily by serving as a scaffolding protein [93-95], but also by recruiting macroH2A1.1 to DNA lesions, a function that relies on its chromatin remodeling activity [96,97]. ALC1, a chromatin remodeler essential for the repair of damaged bases and nucleosome-buried abasic sites, also accumulates at DSBs via serine ADP-ribose-dependent recruitment [100,101,98,99]. However, ALC1 is dispensable for the cellular response to various genotoxic agents, including platinum and camptothecin, suggesting it is not required for DSB repair [102]. Finally, the chromatin remodeler CHD2 is recruited to breaks via its PAR-binding domain, and promotes chromatin changes that render NHEJ more efficient [103]. Notably, PARylation also contributes to DSB repair by indirectly promoting the recruitment of CHD3, CHD4, and CHD7 to damaged sites [104-106].

3.3. PARP impact on pathway choice via the regulation of deDSBs resection

DSB repair pathway choice is influenced by multiple factors, including the cell cycle stage, chromatin context, and local DNA sequence [107,108,42]. Resection of the break site represents a major branchpoint in determining repair pathway selection [109,110,43]. NHEJ is favored when the break site undergoes minimal resection, which is promoted by 53BP1, DNA-PK, and the shieldin complex [111,37,43]. Conversely, repair by HR and MMEJ depends on break resection [110,37,43]. Short range resection is mediated primarily by the MRN complex (MRE11, RAD50, and Nbs1) and CtIP and is sufficient for MMEJ to occur [112,113]. HR requires a second, more extensive resection step that allows strand invasion and template search and is mediated by either EXO1 or by DNA2 in complex with helicases BLM or WRN [43].

PARP1 is canonically regarded as a pro-resection factor. It competes with the central NHEJ component, DNA-PK (which is composed of the heterodimer Ku70/Ku80 (Ku) and the catalytic subunit, DNA-PKcs) [37,48-51] (Fig. 3A). This competition is cell cycle regulated: Ku predominates at DSBs in G1 and can outcompete PARP1, promoting NHEJ; in contrast, during S and G2, PARP1 can displace Ku from DNA ends, thereby enabling resection [114] (Fig. 3B). Beyond this competition, PARP1 also facilitates short-range resection by promoting the recruitment of key factors such as MRE11, NBS1, RAD50 and BRCA1 to damage sites [11,115,116]. Consistently, PARP1 enhances Cas9-mediated MMEJ in wildtype cells by bolstering resection at the break site [117]. Together, these studies support a model in which PARP1 stimulates short-range resection in S/G2, thereby promoting HR and MMEJ. Notably, PARP1 may also act as a barrier to extended long-range resection [118,60,65], which is discuss below.

Similarly, PARP2 promotes the resection of DSBs, although, intriguingly, it does so in a PARylation-independent manner, by limiting 53BP1 recruitment to break sites [119]. Accordingly, PARP2 depletion leads to decreased HR and increased NHEJ at DNA breaks induced by the endonuclease, I-Sce1 [119].

Meanwhile, PARP3 has context-dependent and somewhat paradoxical effects on resection. One study showed that it promotes resection during chromosomal translocations in murine cells [120]. In contrast, another study found that PARP3 limits resection by MARylating

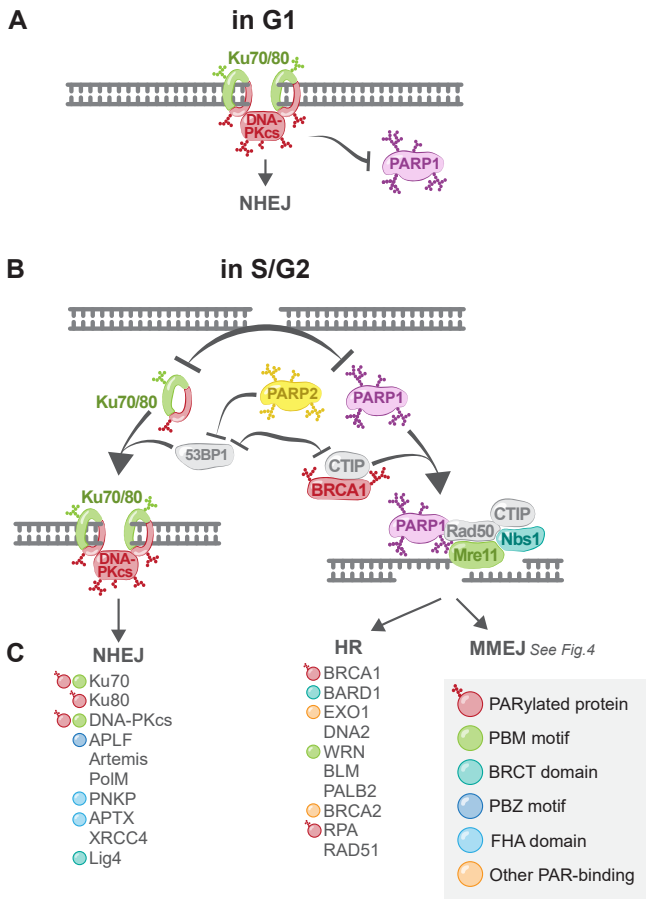

Fig. 3. PARP1 and PARP2 participate in DSB pathway choice regulation by modulating DNA end-resection. (A) In G1, DNA-PK prevents PARP1 from binding DSBs, thereby suppressing end resection and promoting NHEJ. (B) In S and G2, PARP1 and DNA-PK compete for access to DNA ends. While DNA-PK and associated factors inhibit resection to favor NHEJ, PARP1 and PARP2 promote resection, driving repair toward HR or MMEJ. PARP1 can displace DNA-PK from DSBs. It also facilitates the recruitment of the MRN complex, which performs short-range resection. Meanwhile, PARP2 inhibits 53BP1-mediated suppression of resection. (C) Downstream of end resection, PARPs regulate multiple repair processes by modulating various proteins, either through PARylation or via PAR-interacting domains, as indicated.

Ku70/Ku80 and by promoting the recruitment of Ku to laser-induced break sites [121]. Notably, loss of PARP3 did not promote HR activation, but instead led to larger deletion sizes at I-Sce1-mediated breaks, which is indicative of MMEJ repair [121]. Altogether, these data suggest that PARP3 could function to limit short-range resection, although this hypothesis remains to be tested.

4. Function of PARP in homologous recombination

4.1. PARP and the control of long-range resection

PARP and PARylation play multiple roles in regulating HR, particularly in the control of long-range resection. On one hand, both the PIN domain of EXO1 and the OB-folds of BRCA2 bind to PAR [122,123]. This facilitates the early recruitment of BRCA2, an essential step in recruiting EXO1 and initiating long-range resection [123]. In contrast, PARylation of BRCA1 inhibits long-range end-resection by limiting the recruitment of BRCA2 and EXO1 to DSBs [65]. This inhibitory function likely serves to prevent excessive resection. First, PARP inhibition results in elevated RPA and Rad51 foci [118]. Second, a BRCA1 PARylation hypomorphic mutant displays hyper-resection, resulting in elevated short- and long-tract gene conversion and heightened HR-mediated chromosome rearrangements [60,65]. A similar role in limiting recombinogenic HR has been proposed for PAR-mediated regulation of the BRCA1-RAP80 complex [124,125,60]. Consistently, *PARP1*-null human and murine cells have elevated levels of sister chromatid exchanges (SCEs) compared to wild-type cells [126,127,23], though this recombination increase may also reflect defects in single-strand break (SSB) repair. Indeed, cells lacking XRCC1 or TDP1, factors involved in base excision repair and TOP1 cleavage complex resolution, also exhibit elevated SCEs [128,129]. Thus, while PARylation may promote the initiation of long-range resection, its predominant role is likely to limit excessive resection and suppress recombinogenic HR.

4.2. PARP regulation of HR activity and efficiency

The role of PARP and PARylation in regulating HR activity remains unclear. Several studies report that PARP inhibition reduces and delays, but does not abolish, the recruitment of HR factors such as MRE11, NBS1, RAD50, EXO1, BRCA2, and BRCA1 to sites of laser-induced DNA damage [11,115,116,122,123]. These findings suggest that PARP1 facilitates the efficient early recruitment of HR factors but is not strictly essential. However, the impact of this delayed recruitment on HR efficiency is uncertain. Measurements of HR at I-Sce1-induced DSBs following PARP inhibition have yielded conflicting results, with studies reporting decreased, unchanged, or even increased HR activity [118,119,127,130,131,61]. Notably, observed reductions in HR have been attributed to PARPi-induced G2 arrest [131]. Together, these findings indicate that the influence of PARP1 on HR is context dependent. Although data on PARP3 are limited, some evidence suggests it may promote HR, as PARP3 depletion reduces HR efficiency in I-Sce1-based homology-directed repair assays and lowers sister chromatid exchange (SCE) levels following etoposide treatment [121].

4.3. Undefined role of PARP in HR at replication-induced DSBs

Although much of our current understanding of DSB repair derives from studies on double-ended DSBs (deDSBs), single-ended DSBs (seDSBs) are likely the predominant form of endogenous DSBs in unchallenged cells [34,35]. seDSBs are primarily repaired by HR, with MMEJ proposed to act as a backup pathway [45,132]. In contrast, NHEJ is actively suppressed at seDSBs, and its inhibition does not alter the repair outcome at these sites [133,40,41]. Importantly, HR repair of seDSBs differs mechanistically from that of deDSBs. For example, BRCA1 promotes resection at deDSBs, but this activity appears dispensable for seDSB repair [134].

The function of PARP in the regulation of HR at seDSBs remains unclear. A reason for this knowledge gap is the difficulty in disentangling the role of PARP in the repair of seDSBs by HR from its function at SSBs: Because seDSBs can originate from unrepaired single-strand breaks (SSBs) or replication fork collapse, inhibition of SSB repair or increased replication stress lead to an accumulation of seDSBs [135]. For instance, deletion of SSB repair factors such as XRCC1 leads to an increase in HR repair [129,133]. Similarly, because PARP1 plays a key function in SSB repair and at replication forks, its suppression is likely to affect HR outcome by increasing the prevalence of seDSBs [136-138]. Further complicating interpretation, studies using Cas9 nickase to induce SSBs demonstrate that nicks on the leading-strand typically result in seDSBs, while nicks on the lagging-strand DNA can produce either seDSBs or deDSBs [134,139]. Thus, it is likely that deDSB dynamics are involved during replication-induced breaks under certain circumstances.

Despite these complexities, HR reporter assays using nickase-induced SSBs have reported either no effect or increased HR activity upon PARP inhibition, suggesting that PARP1 is not essential for HR at nick-induced breaks [133,140]. In contrast, PARP inhibition following replication stress from hydroxyurea (HU) reduced Mre11 and RPA foci

formation and decreased HR-mediated gene conversions [138]. However, conflicting data exist regarding the effect of PARP inhibition on RAD51 foci formation in response to HU treatment [127,138,141,142,66]. Thus, further studies are needed to clarify the specific role of PARP1 in the repair of replication-stress associated DSBs.

5. Context-specific function of PARP in MMEJ

5.1. PARP1 promotes MMEJ in multiple contexts

MMEJ, also called alternative end-joining, is defined by the annealing of short microhomologies near the DNA break site, followed by fill-in synthesis to complete repair [45]. The core enzyme orchestrating synapsis and repair in this pathway is DNA polymerase theta (Polθ), encoded by the *POLQ* gene [143,144,46,47]. MMEJ was initially described as a backup pathway for NHEJ, identified by its contribution to end-joining activity in the absence of canonical NHEJ [34,45,49], though it is now recognized as a bona fide repair pathway that operates in both NHEJ-proficient and -deficient cells [34,113].

PARP1, along with XRCC1 and Ligase 3, were among the first factors identified as critical for MMEJ repair in mammalian cells [145-148,27,48,49]. Early studies using HeLa nuclear extracts showed that PARP1 mediates DNA synapsis at overhangs, independently of Ku70/80 and DNA-PKcs [48]. Subsequent work established that Ku competes with PARP1 for DNA binding *in vitro,* and that PARP inhibition impairs NHEJ-independent repair in plasmid end-joining assays [49-51]. Notably, the contribution of PARP1 to plasmid end-joining was observed in the absence of Lig4 or Ku80, but not in the absence of DNA-PKcs, suggesting that these dynamics only occur when certain NHEJ factors are perturbed.

The requirement for PARP1 in MMEJ repair has been further established in *A. thaliana*, as well as in mouse and human cell-free repair assays [145,146]. In addition, PARP1 promotes MMEJ-mediated chromosomal translocations in NHEJ- and HR-deficient MEFs [149]. It also promotes MMEJ during class switch recombination (CSR), as evidenced by reduced microhomology at recombination junctions in PARP1 deficient murine B-cells, although CSR-associated translocations remain unaffected [27]. Moreover, PARP inhibition or PARP1 knockdown abrogates MMEJ-dependent fusions of deprotected telomeres in *XRCC5*$^{-/-}$ (Ku80-deficient) MEFs [148,150,47]. PARP1 also promotes repair of telomere internal DSBs in MEFs, likely via MMEJ [151].

Mechanistically, PARP1 is proposed to promote DNA break synapsis and to facilitate the recruitment of MMEJ factors, such as the MRN complex for resection and XRCC1 for ligation [11,115,152,48] (Fig. 4A). Furthermore, PARP1 promotes Polθ localization to DNA damage sites [117,153,47]. Although Polθ undergoes PARylation [154], this modification is inhibitory, blocking its ability to bind DNA and perform fill-in synthesis. After Polθ is recruited by PARP1, its activation is proposed to depend on de-PARylation by poly(ADP-ribose) glycohydrolase (PARG) [10,154]. Consistently, inhibition of either PARP or PARG reduces MMEJ activity [117,154].

While the role of PARP3 in MMEJ has not been directly examined, indirect evidence suggests it may act as a suppressor. PARP3 has been shown to inhibit end-resection [121], a critical step in MMEJ. Consistent with this, PARP3-depleted cells exhibit increased deletion sizes at I-Sce1-induced breaks, a hallmark of MMEJ-mediated repair [121].

5.2. PARP1 is dispensable for MMEJ during mitosis

Importantly, it is now appreciated that MMEJ is a mitotic pathway, repairing DSBs that either are induced in mitosis, or induced in interphase but left unrepaired until mitosis [155,156,52,53,54]. Several studies have demonstrated that MMEJ activity is minimal during G1 in wildtype cells, likely because Ku outcompetes PARP1 [112,114] (Fig. 3**A**). Similarly, MMEJ is likely outcompeted by both NHEJ and HR during S and G2 [157,45,53]. In fact, even in HR-deficient cells, replication-induced DSBs are not repaired by MMEJ until mitosis onset [52].

However, most studies defining the role of PARP1 in MMEJ were conducted during interphase, often in the absence of competing

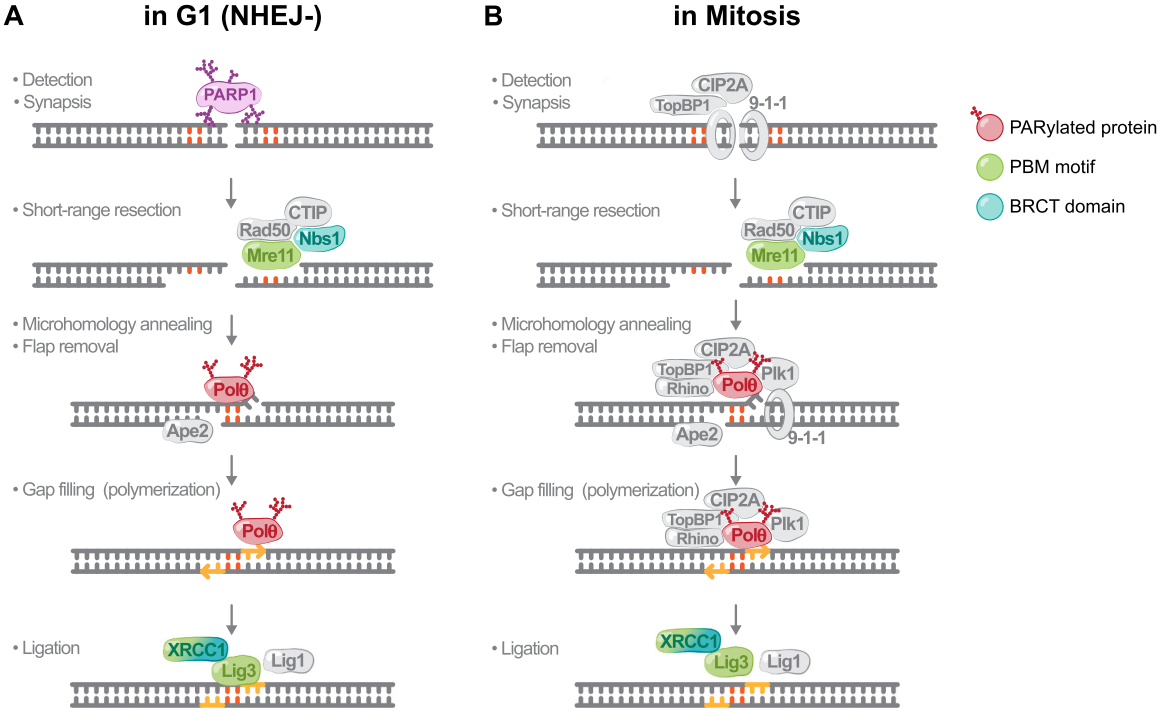

Fig. 4. The function of PARP1 in MMEJ is cell-cycle dependent. (A) During G1, PARP1 promotes DSB sensing and end-synapsis, facilitates the recruitment of the MRN complex, and promotes the recruitment of Polθ and XRCC1. (B) During mitosis, DNA sensing, synapsis, and recruitment of Polθ are mediated by the 9–1–1 complex, PLK1, Rhino, TOPBP1, and CIP2A.

canonical NHEJ factors, raising the question of whether PARP1-dependency remains relevant during mitosis. For example, studies that defined PARP1 as fundamental to MMEJ were conducted following DNA-PK suppression, when MMEJ is likely reactivated in G0/G1 [158,49,51]. Of note, PARP1-dependent MMEJ fusions of deprotected telomeres in Ku80-KO MEFs also occur in G1, as evidenced by the fact that both sister chromatids are engaged in the fusion [148,150,159]. While PARP1 promotes Polθ recruitment to laser micro-irradiation sites in interphase [117,153,47], two recent publications demonstrate that during mitosis, Polθ recruitment to DSBs is mediated by mitotic factors Rhino and Plk1 [53,54].

Indeed, recent evidence contradicts the prevalence of PARP1 in MMEJ. First, some NHEJ-independent end-joining mechanisms involving PARP1 do not require Polθ [158,160]. Additionally, PARP1 requirement for MMEJ was shown to be restricted to heterochromatin regions [161]. Moreover, a repair-seq screen, in which guide RNAs are linked to repair outcomes, suggested that PARP1 is not involved in MMEJ during mitosis. Guides targeting mitosis-specific MMEJ factors *TOPBP1* and the 9–1–1 complex suppressed MMEJ signatures similarly to *POLQ* guides, indicating that the MMEJ captured by this assay predominantly reflects the mitotic form. In contrast, *PARP1* guide RNAs had no effect on these repair outcomes [162]. Finally, in NHEJ deficient cells, recombination-activating gene (RAG)-induced G1 DSBs undergo repair by Polθ in the S-G2/M phase independently of PARP1 [155]. Importantly, neither DSB repair nor Polθ expression was detected in G1-arrested cells, further supporting that MMEJ is suppressed in G1.

Prompted by these discrepancies, our lab tested whether PARP1 is really required for MMEJ in cells with intact repair pathways. Using MMEJ reporters, we found that PARP1/2 inhibition or knockout fails to suppress Polθ-mediated MMEJ repair. Furthermore, unlike Polθ inhibition, PARP inhibition does not preclude the repair of DSBs during mitosis (Ortega et al., 2025 *Preprint: doi:* https://doi.org/10.1101/2025.06.09.658719).

Therefore, the role of PARP1 in MMEJ appears to be highly context-dependent: while it is required in G1, its proposed functions may be rendered redundant during mitosis (Fig. 4B). For example, in mitosis, Polθ recruitment to DSBs is mediated by Rhino/PLK1/TOPBP1, after damage sensing by the 9–1–1 complex, thus bypassing the need for PARP1 [163,53,54]. Similarly, synapsis could be facilitated by 9–1–1/TOPBP1/CIP2A [164-167]. It remains to be determined how XRCC1 is recruited independently of PARP1 during mitosis, or whether XRCC1 is dispensable in this context as well.

6. Modulatory roles of PARP in NHEJ

6.1. Regulation of NHEJ activity by PARP1-3

PARP1 is classically proposed to inhibit NHEJ, as it competes with DNA-PK to promote DSBs resection [48-51]. However, this competition appears to be regulated during the cell cycle. Single-molecule imaging experiments found that Ku dominates DSB binding in G1, effectively excluding PARP1. In contrast, in the S/G2 phases, both Ku and PARP1 can bind DSBs, with PARP1 capable of displacing Ku from the break [114].

Yet, in line with the recurring theme of context-specific PARP function, the relationship between PARP1 and NHEJ is more complex than initially proposed. In NHEJ reporter assays using I-Sce1-induced DSBs, PARP inhibition has been reported to either increase NHEJ activity or have no measurable effect [114,119,61], while PARP1 knockdown was shown to decrease NHEJ at the same reporter [103]. Consistently, neither PARP1/2 inhibition nor PARP1 knockdown alters the frequency of NHEJ-mediated fusions at deprotected telomeres, where NHEJ is activated without competition from other pathways [148,150].

PARP3, in contrast to PARP1 and 2, appears to promote NHEJ activity. It co-immunoprecipitates with several DDR proteins, including key NHEJ components DNA-PKcs, Ku70/80, and Lig4 [168]. PARP3 also mediates ATM-dependent phosphorylation of APLF, enhancing its retention to break sites and supporting Lig4-mediated ligation [95,169]. Additionally, PARP3 MARylates Ku70 and Ku80 and promotes Ku80 recruitment to laser-induced break sites, thereby limiting end-resection [121]. These findings suggest a direct role for PARP3 in stabilizing and promoting NHEJ. Consistently, PARP3 depletion reduces I-Sce1-mediated NHEJ repair efficiency [121]. Moreover, PARP3 promotes translocations in human cells, a process that is dependent on NHEJ [170,171].

6.2. PARylation of DNA-PK

Multiple lines of evidence indicate that PARP1 and DNA-PK interact: both Ku70 and DNA-PKcs contain PAR-binding motifs [10]; PARP1 co-purifies with Ku70, Ku80, and DNA-PKcs [62-64]; and the human interactome of PARP1 includes DNA-PK [29-31]. PARP1/DNA-PK binding was further confirmed by electron microscopy experiments that visualized the complex on DNA and showed PARP1 in contact with Ku [172].

This interaction leads to PARylation of all subunits of DNA-PK *in vitro*, which promotes PARP1 phosphorylation by DNA-PKcs in a DNA-dependent manner [61-63]. Yet, the significance of this PARylation for NHEJ activity remains unclear, as *in vitro* PARylation of DNA-PKcs and Ku have opposite effects. PARylation of Ku70/80 can impair its DNA binding, possibly facilitating access for HR machinery [64]. PARylation of DNA-PKcs, on the other hand, was shown to stimulate its autophosphorylation, which promotes NHEJ [62]. However, the same study showed that PARylation of DNA-PKcs also promotes phosphorylation of RPA *in vitro*, which is known to regulate replication stress [173]. Similarly, studies examining PARP inactivation and DNA-PK activity in cellular models yielded contradictory results. In HeLa cells following irradiation, PARP inhibition led to retained DNA-PKcs on DNA and sustained DNA-PK activation, further suggesting competition between PARP and NHEJ factors [61]. In contrast, PARPi treatment or PARP1 suppression in U2OS cells led to decreased Ku80 recruitment at micro-irradiation sites [118], suggesting here that PARP1 could promote rather than inhibit NHEJ.

Interestingly, although NHEJ is suppressed at seDBSs, Ku70/80 and DNA-PKcs are transiently recruited to these breaks, then rapidly removed: Ku70/80 by MRN and CtIP and DNA-PKcs via ATM-dependent phosphorylation [40,41]. While the precise role of DNA-PK recruitment at seDSBs remains unclear, it has been proposed to protect DNA ends from aberrant nuclease activity, regulate RPA or MRE11, decondense chromatin, or help orient MRE11 on the DNA break [41]. Therefore, one can speculate that PARylation of DNA-PK could serve to regulate its dynamic recruitment and removal at seDSBs. Supporting this idea, PARP1$^{-/-}$ chicken DT40 cells (which naturally lack PARP2) are hypersensitive to camptothecin, a topoisomerase I inhibitor that induces seDSBs. Strikingly, this sensitivity is rescued by disabling NHEJ, suggesting that PARP1 suppresses toxic NHEJ activity at replication-associated breaks and promotes HR-mediated repair [126].

6.3. Regulation of V(D)J and CSR

V(D)J recombination, essential for B- and T-lymphocyte receptor development, produces deDSBs that are primarily repaired by NHEJ [174]. DNA-PKcs deficiency abrogates V(D)J, leading to developmental arrest in murine B- and T-cells and resulting in severe combined immunodeficiency (SCID) in mice [175]. In contrast, PARP1 loss in mice does not prevent T- or B-cell maturation [176,177]. Loss of PARP2, though, leads to a reduction in thymocyte survival and perturbed T-cell receptor development, but cells develop nonetheless [176]. Notably, combined loss of PARP1 with B-cell-specific conditional deletion of PARP2 impairs B-cell development but does not fully block V(D)J recombination [178]. Together, these findings suggest that PARP1 and PARP2 function redundantly to support NHEJ during V(D)J

recombination, with PARP2 likely playing a more prominent role. However, neither protein is strictly required for this process.

Class switch recombination (CSR) functions to diversify the antibody repertoire in B cells and involves DSB intermediates that are repaired by NHEJ and MMEJ [179]. Both PARP1 and PARP2 are dispensable for CSR [27], and combined deletion does not fully block the process [178]. Nonetheless, PARP2-deficient cells exhibit elevated IgH/c-myc translocations during CSR compared to PARP1-null or WT cells, indicating a nonredundant role of PARP2 in suppressing CSR-associated genomic instability [27].

Together, these data support a model in which PARP1 and PARP2 are not essential for NHEJ but instead modulate its activity, likely in a dynamic and cell cycle–dependent manner, through regulation of DNA end-resection and PARylation of the DNA-PK components.

7. Conclusion

Decades of research have revealed the multifaceted and context-dependent roles of PARP in the repair of DNA double-strand breaks, including the promotion of repair through chromatin regulation and protein recruitment, as well as regulation of repair pathway choice and fidelity. Yet, many aspects of PARP function remain poorly defined.

Although PARP1 facilitates early resection and recruitment of HR factors at canonical DSBs, its function at seDSBs is far less clear. This uncertainty arises because PARP1 also plays a central role in single-strand break repair, which are a major source of seDSBs. Similarly, the mechanistic relevance of PARylation of repair proteins like Polθ, Ku, or BRCA1 at DSBs is still poorly understood. Finally, while PARP1 promotes MMEJ during G1 in the absence of NHEJ, it appears dispensable during mitosis, where other factors such as Rhino and Plk1 support MMEJ. Whether PARP1 plays other functions during mitosis, or if other PARP family members compensate in its absence, remain important open questions.

The wealth of knowledge gained on the role of PARP in DNA repair, alongside the unresolved mechanistic questions, have profound clinical implications. The observation that PARP inhibition is synthetic lethal with homologous recombination deficiency has enabled the development of targeted cancer therapies, with PARP inhibitors (PARPi) now standard of care for BRCA1/2-mutant tumors [13-15,18].

However, resistance to PARP inhibitors, whether intrinsic or acquired, remains a major clinical challenge. Overcoming this resistance requires a clear mechanistic understanding of how PARP inhibitors exert their cytotoxic effects in HR-deficient cells. Initially, this synthetic lethality was attributed to PARPi-induced failure to repair SSBs, resulting in the accumulation of seDSBs that cannot be repaired in the absence of HR [13,14]. However, we now appreciate that PARP inhibitors display other possible routes to lethality, including PARP trapping, increasing single-stranded DNA (ssDNA) gaps, and destabilizing the replication fork machinery [180-186].

Importantly, PARPi-mediated DNA lesions in HR-deficient cells are carried into mitosis, which appears to be a key determinant of PARPi response, as mitotic bypass suppresses PARPi toxicity [187]. Accordingly, PARP inhibition in POLQ and BRCA2 co-depleted cells leads to chromosome fragmentation [188]. Moreover, the sister-chromatid exchanges observed upon PARP inhibition are due to mitotic processing of under-replicated DNA and depend on POLQ rather than HR factors [188]. Altogether, these findings highlight mitotic MMEJ as a crucial repair pathway in HR-deficient cells and could further explain the synthetic lethal relationship between MMEJ and HR: HR-deficient cells rely on MMEJ to resolve mitotic DNA damage, enabling survival despite genomic instability, until MMEJ is lost as well.

Thus, PARP inhibitors function at the intersection of SSB repair, replication stress, and MMEJ-mediated mitotic repair. This provides a strong rationale for combination therapies that target multiple pathways. Inhibitors of ATR and POLQ, for example, show promise for enhancing PARPi efficacy and overcoming resistance [15,38]. However, successful development of such strategies will require a deeper mechanistic understanding of how PARP1 coordinates DSB repair in different chromatin, cell cycle, and replication contexts.

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Raquel Ortega: Writing – original draft. **Nausica Arnoult:** Writing – original draft, Visualization, Funding acquisition. **Benjamin G. Bitler:** Writing – review & editing, Funding acquisition.

Declaration of Generative AI and AI-assisted technologies in the writing process

During the preparation of this work the author(s) used ChatGPT in order to help improve the clarity of certain sentences. After using this tool/service, the author(s) reviewed and edited the content as needed and take(s) full responsibility for the content of the publication.

Declaration of Competing Interest

The authors declare no conflict of interest.

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