Journal of Zhejiang University-SCIENCE B (Biomedicine & Biotechnology) in press
www.jzus.zju.edu.cn; www.springer.com/journal/11585
E-mail: jzus_b@zju.edu.cn

Review

https://doi.org/10.1631/jzus.B2400146

Future of PARP inhibitors in cancer treatment: overcoming resistance and enhancing efficacy with combination therapies

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Abstract: Poly(ADP-ribose) polymerase (PARP) is a family of proteins that play a crucial role in diverse cellular processes, including DNA repair, cell death, and changes in chromatin structure. PARP inhibitors (PARPi) have been recognised as notable agents in the realm of anticancer therapeutics owing to their capacity to specifically impact DNA repair pathways, thereby inducing targeted death of cancerous cells, particularly in cancers with homologous recombination deficiencies (HRD). These inhibitors have been approved for the treatment of several cancers, such as ovarian, breast, and pancreatic cancers. Despite their promising therapeutic attributes, developing resistance to PARPi presents a formidable obstacle, curtailing their overall efficacy. This article presents a comprehensive description of the potential mechanisms related to PARPi resistance, an in-depth study of potential strategies to overcome resistance, and an assessment of the therapeutic potential of the PARPi in combination with alternative therapies.

Key words: Poly(ADP-ribose) polymerase (PARP); PARP inhibitor (PARPi); Cancer; PARPi resistance; PARPi modulation; Cancer alternative therapies

1 Introduction

Poly(ADP-ribose) polymerase (PARP) is a group of 17 proteins involved in various cellular mechanisms such as apoptosis, response to stress, DNA repair, and remodelling of chromatin (Zhao et al., 2019). The first PARP family members were identified in 1963 in a study of enzymes thought to be DNA-dependently activated by nicotinamide mononucleotides (NMN) and involved in polyA production (Chambon et al., 1963). Subse-

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Received Mar. 13, 2024; Revision accepted Aug. 28, 2024;
Crosschecked xxx. xx, 20xx; Published online xxx. xx, 20xx

quent research trials showed that the deriving molecule does not have polyA properties since it contains the ATP adenylate part, ribose sugar, and NMN phosphate components. Therefore, it was hypothesized that this enzyme exhibits the transglycosidase function by forming a polymer of ADP ribose by catalyzing the polymerization of the intermediate of nicotinamide adenine dinucleotide (NAD) while simultaneously forming a ribose-ribose bond and removing the nicotinamide residues.

The best-known and most characteristic member of the PARP family is PARP1, which was originally recognized by its role in the identification and repair of single-strand breaks (SSB) in DNA molecules (Heeke et al., 2018). A study by Beck et al. (2014) proposed that PARP1 can be involved in playing a role in alternative DNA repair mechanisms, including DNA mismatching repair, standard and alternative non-homologous end conjugation, repair of excised nucleotides, and homologous recombination (HR). The PARP2 gene encodes a protein similar to poly (ADP-ribosyl) transferase 2, which has a catalytic domain that can catalyze the poly (ADP-ribosyl) mechanism. This protein consists of a catalytic domain, which is similar to the catalytic domain of poly (ADP-ribosyl) transferase (PART), but lacks the DNA binding domain at the N-terminal, which initiates the catalytic domain of the C-terminal of PART. This protein may also contain some residues in the region of the N-terminal, which may exhibit strong DNA-binding characteristics and can be involved in targeting the protein to the nucleus and/or nucleolus. Two alternative spliced transcriptional variants have been found encoding different isoforms (Liu et al., 2022). The function of PARP3 proteins is to modify basic proteins through polyADP ribosylation, which is necessary for various mechanisms such as genome stability, DNA repair, and control of programmed cell death.

PARP inhibitors (PARPi) are a new group of anti-cancerous agents that compete with NAD+ residues to occupy the catalytic functional sites of PARP enzymes. Inhibition of PARP activity was first demonstrated in 1971, when the HeLa cell line was treated with nicotinamide and thymidine residues (Preiss et al., 1971). Further studies identified that benzamide molecules can also inhibit PARP function through competition with NAD+. However, these residues were found clinically unsuitable because of their low specificity and potency. Generally, PARP1 is considered to be the main molecule targeted by PARPi because it is much more abundant than PARP2 or PARP3. However, because of the structural analogy of NAD joining domains of a few members of the PARP protein family, some PARPi may also inhibit other PARPs such as PARP2 and PARP3. Some other off-target effects are also observed in kinases (Antolin et al., 2020). PARPi are efficient in treating tumors lacking HR repair. In particular, PARPi have been found to attack the cancerous cells with significant HR gene mutations associated with breast cancer 1 and 2 (BRCA1 and BRCA2) (Tuli et al., 2019). Many PARPi have been authorized for the therapy of various cancers such as breast, pancreatic, and BRCA-mutated ovarian cancer. Additionally, many clinical trials have recently been filed with clinicaltrials.gov with PARPi as anticancer therapy for lung cancer, pancreatic cancer, BRCA1/2-mutant resistant germline or systemic breast cancer, pancreatic carcinoma, and ovarian carcinoma. In this review, we discussed the relationship between PARP and DNA repair, various mechanisms of PARPi, their clinical significance and therapeutic role against various cancers, PARPi resistance, and their modulation by alternative therapies.

2 Relationship between PARP and DNA repair pathways

2.1 The role of PARP1 in single strand break repair (SSBR)

PARP1 plays a significant role in single strand break (SSB) repair (Laspata et al., 2024). SSBs are also formed as intermediates in the base excision repair (BER) mechanism; some studies have shown that PARP may be considered essential for BER (Chaudhari et al., 2021). However, there is conflicting evidence about the susceptibility to agents that cause base damage in PARP1-inhibited cells and PARP1-deficient cells (Saville and Sobol, 2022). One study showed that PARP does not need to repair base disruption but restores SSB induced by H_2O_2 (Hirota et al., 2022). There is also some evidence that there may be PARP1-independent and PARP1-dependent SSBR mechanisms. One study suggested that PARP1 is needed in the G stage of the cell

cycle for SSBR rather than in the S phase, but PARPi inhibit SSBR at each stage of the cellular cycle (Li et al., 2022). Furthermore, a DNA break can be detected immediately by sensing DNA damage at the conserved N-terminal and PARP binding domain (Moor et al., 2020). Eventually, PARP1 induces the post-translational polymerization of ADP ribose subunits (PAR) from the NAD+ molecule to the chosen protein molecules by forming covalent binding to an acidic residue (Bian et al., 2019). The activation of PARP1 allows automatic PARylation of PARP1 by glutamate, serine, and tyrosine residues in the auto-modifying PARP1 domain. Auto-PARylation can initiate PARP1 and cause further PARylation of histone protein and related chromatin-linked protein subunits (Ray Chaudhuri and Nussenzweig, 2017). Overall, this auto- and hetero-modification recruits additional molecules, such as XRCC1, to the site of DNA damage, thereby promoting efficient DNA repair (Fig. 1).

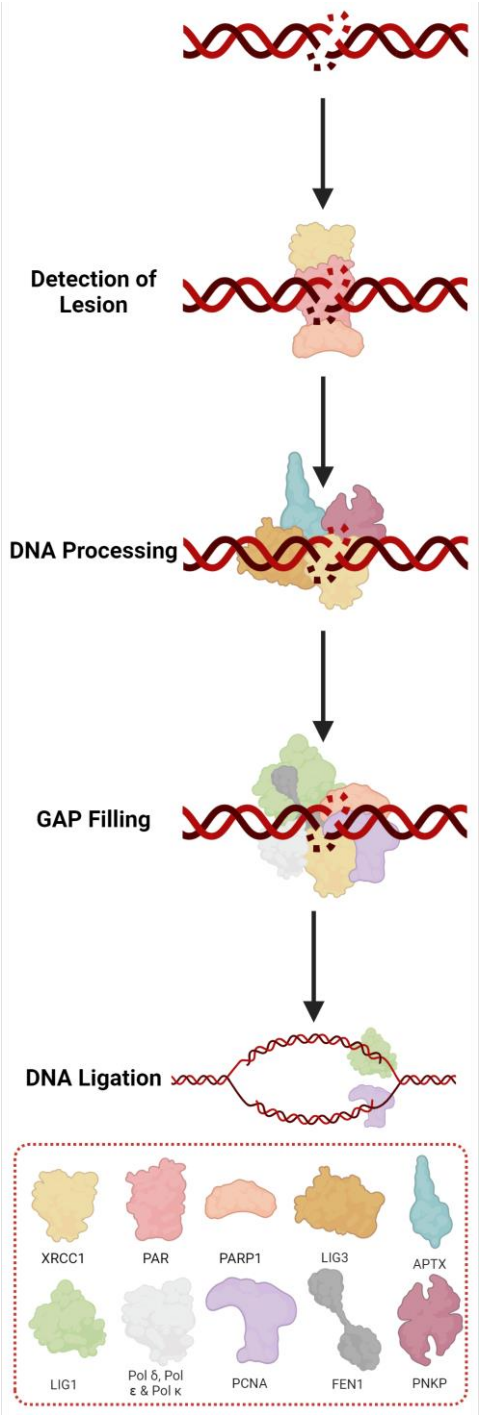

Fig. 1 A schematic representation of the role of PARP1 proteins in SSBR through the base excision repair pathway. Detection of SSBs is a crucial step for the subsequent recruitment of XRCC1, which serves as a platform for bringing in PNKP, aprataxin (APTX), and DNA ligase 3 (LIG3) to manage the SSB. Following this initial stage is the gap-filling process, conducted by DNA polymerase δ (Pol δ), Pol ε, and Pol β, with the additional requirement of PARP1 to enhance the 5′ flap endonuclease activity of FEN1. Ultimately, the DNA molecules are joined together by LIG1. Created in BioRender.com

PARP2 and PARP3 play significant roles in the repair of DNA, and some of these roles have a partial redundancy with PARP1. To demonstrate functional redundancy, a study was conducted by Harrision et al.

(2020). Mice lacking PARP2 exhibited post-replication instability of the genome, and those with double mutations of PARP2 and PARP3 exhibited embryonic lethality. Further, the role of PARP2 in SSBR has also been identified and overlaps with that of PARP1 when XRCC1 is involved (Hanzlikova et al., 2017). Cells lacking PARP3 also exhibit genomic instability and slow down SSB repair, but are non-radiosensitive (Azarm and Smith, 2020). PARPs 1, 2, and 3 have a similar structure and have been found to be switched on in similar pathways by local destabilization of the catalysis domain through DNA-dependent catalytic stimulation.

2.2 DNA Double-Strand Break Repair (DSBR) pathways

Targeted treatments, for example, with PARPi, are more specific than routine treatments like radiation therapy or chemotherapy, have fewer off-target side effects, and may lead to more satisfactory outcomes for patients suffering from cancer. As introduced earlier, PARPi have been shown to target tumor cells with defective HR pathways because of mutations in either BRCA1 or BRCA2 cancer but are less toxic to normal body cells having functional HR. The two main DNA DSBR pathways are explained briefly below (Fig. 2).

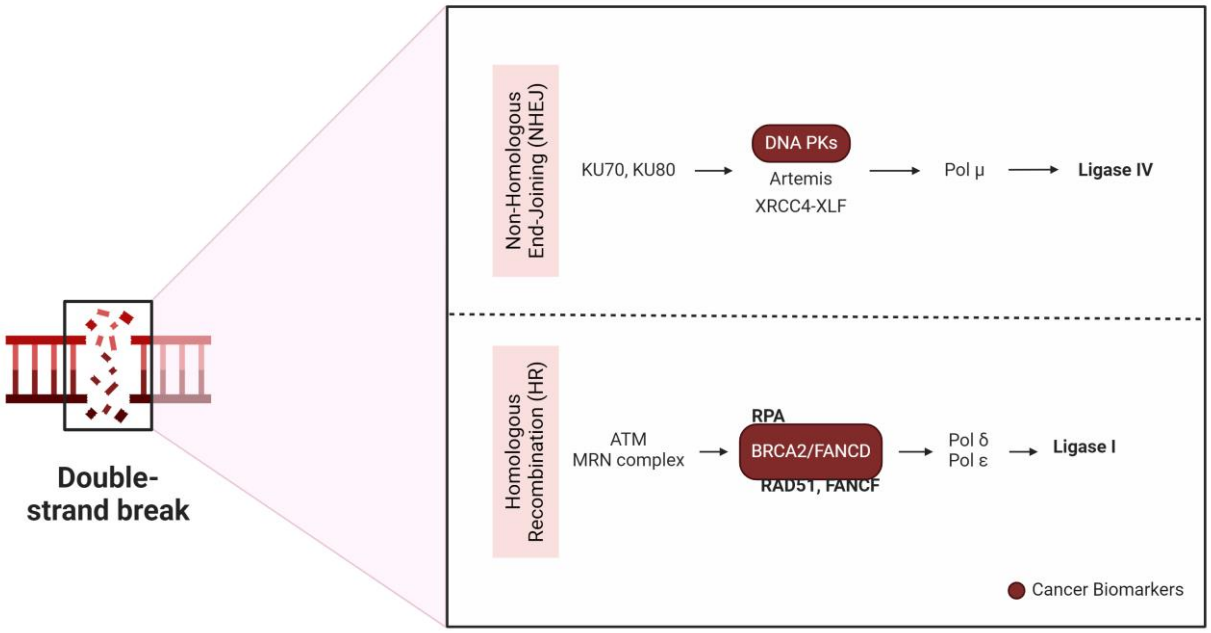

Fig. 2: Double Strand Break Repair Pathways. Homologous Recombination (HR) repair is initiated by the MRN protein complex, which acts as a sensor for DSBs and recruit's ATM kinase to the site. The MRN complex excises nucleic acid, creating a 3' overhang of ssDNA. This overhang binds to the RPA heterotrimer, which Rad51 subsequently replaces to form a helical strand of nuxclear protein. The strand then locates homologous DNA sequences and initiates DNA formation. Non-homologous End Joining (NHEJ), on the other hand, is initiated by the Ku heterodimer, which consists of Ku70 and 80 protein subunits, which acts as a scaffolding and activates DNA-based protein kinase (DNA-PKs). In conjunction with known enzyme proteins, the DNA PKs complex fills gaps or cuts DNA, and the XRCC4-XLF, together with ligase, then recombines the ends. Created in BioRender.com

2.2.1 Homologous Recombination (HR) repair pathway

The HR pathway is one of the lowest lapse-producing pathways of DSBR but, because of the need for a template sister chromatid, this pathway is limited to the G2 and S phases of the cell cycle. HR is a complicated pathway that requires a large amount of protein. The group of MRN proteins includes MRE11, Rad50, and Nbs1, which play many functions in response to DNA damage. The best-known function of the MRN protein complex is to act as a sensor for DSBs and, upon detection of DSBs, starts HR (Mccarthy-Leo et al., 2022). Further, the

MRN group of proteins is immediately directed toward the DSB site, promoting ataxia telangiectasia mutated (ATM) kinase recruitment and full activation, and initiating the upcoming ATM-initiated phosphorylation of every individual of the MRN group of proteins. This action further facilitates MRN protein engagement and activates the downstream ATM-based signaling pathway (Shibata and Jeggo, 2021). This MRN protein group, in conjugation with CtIP, starts the degradation of the nucleic acid, excising the DNA from 5' to 3', creating a 3' overhang of ssDNA (Mccarthy-Leo, et al., 2022). The excision of terminal chains is subsequently initiated by another group of exonuclease proteins, like Exo1. The resulting 3'-end binds with high affinity to the Replication Protein A (RPA) heterotrimer, mediates the elimination of secondary structures and protects part of the ssDNA. Rad51 then undergoes BRCA1/2 initiated RPA replacement to form a helical strand of nuclear protein on the ssDNA (Constantinou, 2019). This helical strand of protein localizes homologous DNA sequences and carries out strand entry to develop the Holliday linkage intermediate. The penetrating strand 3' end is then used to initiate DNA formation and expand the homologous region combination. The resulting complex DNA structures (Holliday junctions) are fixed by a BTR complex composed mainly of RMI1, RMI12, topoisomerase IIIα, and Bloom syndrome helicase (BLM). Holliday junction breaks indicate completion of HR activity and efficient dsDNA cleavage recovery.

2.2.2 Non-homologous End Joining (NHEJ) pathway

Unlike HR, NHEJ does not need a homologous DNA template for DSBR; instead, in NHEJ, the DNA ends are directly joined. In addition, this mechanism is active at every stage of the cell cycle. Because of the absence of a guiding DNA strand, NHEJ is recognized to be a relatively error prone DSBR pathway and is linked to increased deletions and insertions of nucleotides. Therefore, it has a higher probability of developing genomic mutations (Sheng et al., 2018). The NHEJ pathway is activated by joining Ku heterodimers (consisting of Ku70 and 80 protein subunits) to DSBs (Sishc and Davis, 2017). Then, these Ku heterodimers function as mobilizing, scaffolding, and activating DNA-based protein kinases (DNA-PKs) at the lesion site to form a catalytically active complex. Breaking the bridge across DNA-PKs allows DNA to be cut or gaps filled with many known enzyme proteins. The IV/XRCC4 ligase complex then recombines at the end of the DNA (Kumari, 2023).

2.2.3 Alternative Non-Homologous End Joining (Alt-NHEJ) pathway

The alternative non-homologous end-joining (Alt-NHEJ) repair mechanism, also referred to as the microhomology-mediated end-joining (MMEJ) pathway, needs a spectrum of 2 to 20 nucleotides with sequence similarity at the DNA ends of DSBs to initiate repair (Caracciolo et al., 2021). Initially, the recognition of DNA breaks is carried out by PARP1, which triggers activation of DNA End Resection through the MRN/CtiP complex, exposing the microhomology sequence at the repair site. Subsequently, the DNA ends are connected and aligned using short microhomologies, while the non-homologous 3' tails are eliminated by XPF-ERCC1 nucleases (Caracciolo, et al., 2021). The resulting gaps in the DNA strands are then filled through PolQ-mediated DNA synthesis (Caracciolo et al., 2020), after which the DSBs are ultimately repaired by the DNA Ligase III/XRCC1 complex. In situations where DNA Ligase III is not as efficient, DNA Ligase I may step in to facilitate the final step of ligation of the DNA ends.

Recent experimental findings highlight the significance of Alt-NHEJ as an alternative pathway in instances where C-NHEJ or HR malfunction during the various stages of DNA repair processes. These stages include (a) detection of DSBs through competition between PARP1 and Ku for DNA ends; (b) filling of gaps facilitated by PolQ, which inhibits HR by directly interacting with RAD51 and removes RPA from resected DSBs; and (c) ligation of DNA, which occurs due to the exclusive activities of DNA ligase IV from C-NHEJ and DNA ligase III from Alt-NHEJ (Caracciolo, et al., 2021). Conversely, functional HR or NHEJ actively inhibits the error-prone Alt-NHEJ repair process. Additionally, a Fanconi Anemia (FA) pathway deficiency may indirectly reduce Alt-NHEJ by promoting Ku-dependent C-NHEJ (Kee and D'andrea, 2010). In conclusion, these observations demonstrate the collaborative efforts of multiple mechanisms to prevent the potentially harmful effects of abnormal activation of Alt-NHEJ on genomic stability.

In addition to serving as a backup pathway, Alt-NHEJ has been shown to play a physiological role in double-strand breaks caused by ionizing radiation or in the metabolism of mitochondrial DNA (mtDNA), given that DNA Ligase III is the primary DNA ligase in mitochondria.

Alt-NHEJ can lead to inaccurate repair, promoting genomic instability through various mechanisms. These include the lack of a DNA template strand like in HR, leading to the inability to restore the original DNA sequence, PolQ-mediated gap filling causing erroneous nucleotide insertions, and generation of large deletions by the endonuclease/exonuclease complex to expose microhomologies. Additionally, the N-terminal zinc finger domain DNA of ligase III facilitates the joining of unrelated DNA molecules, promoting translocations through high flexibility and distinct DNA binding domain features, allowing simultaneous binding of two different DNAs for intermolecular ligations (Caracciolo, et al., 2021).

3 Synthetic lethality of PARPi mechanisms

PARPi are a group of anti-cancerous agents that compete with NAD+ residues to occupy catalytic functional sites of PARP enzymes. PARPi inhibition activity was first demonstrated in 1971 when the HeLa cell line was treated with nicotinamide and thymidine residues (Preiss, et al., 1971). Then, further studies identified that benzamide molecules can inhibit PARP function through competition with NAD+. However, these residues were found to be clinically unsuitable because of less specificity and low potency (Valabrega et al., 2021). Generally, PARP1 is recognized as the main molecule targeted by PARPi. However, because of the structural analogy of NAD joining domains of a few members of the PARP protein family, some PARPi may also inhibit other PARPs such as PARP2 and PARP3. Some other off-target effects are also observed in kinases (Antolin, et al., 2020). PARPi efficiently treat tumors lacking HR repair in synthetic lethal interactions. In 2005, a synthetic lethality mechanism was first reported among PARPi i and in BRCA mutated or depleted cells, and it was predicted that repression of PARP1 function resulted initially in disruption of replication forks, followed by repair of this replication by an HR-dependent pathway. Because HR activity is impaired in BRCA1/2 mutant tumor cells, folded replication forks cannot be resynthesized, and cell death occurs.

4 PARPi mechanisms

4.1 Inhibition of SSBR

PARP1 proteins have been shown to play an important role in SSBR. Initially, it was thought that PARPi could impair the SSBR of DNA and cause damage by accumulating in the cells (Curtin and Szabo, 2020). Later studies found that synthetic lethality caused by PARPi is associated with SSBR impairment (Sizemore et al., 2018). However, little is known about the initiation by PARPi of the aggregation of single-strand breaks (SSBs) in DNA molecules (Han et al., 2020). Furthermore, small-interfering RNA (siRNA) initiates XRCC1 depletion, which is an important protein in response to SSBR, and depletion of XRCC1 increases the susceptibility to two kinds of PARPi, Veliparib and Olaparib (Xia et al., 2021). This is consistent with the finding that genetic inhibition of PARP shows remarkably little cytotoxicity compared to the use of PARPi, whereas similar cytotoxicity would be expected if the process of PARPi toxicity is caused by SSBR inhibition (Murai et al., 2012). These findings suggest that PARPi susceptibility may be initiated by mechanisms other than SSBR inhibition.

4.2 Stalling of replication fork and PARP inhibition

Mediation of PARP activity at the point where the replication fork is stopped is necessary for the resumption of replication through MRE-11 proteins (Koppensteiner et al., 2014). Furthermore, DSBs can occur in DNA after the replication fork encounters DNA damage or breakage. Based on these results, it is predicted that PARPi can cause the death of tumor cells because blocked replication forks do not restart in cells that are deficient in HR, which is supported by the evidence that PARPi causes synthetic lethality only in cells which are

deficient in HR or stabilization of replication forks (Li, et al., 2022). PARPi also work through the PARP trapping mechanism, which is also associated with stalling of the replication fork and is considered a well-established theory. This suggested pathway also provides new insights into why inhibition of PARP function is considerably more toxic to cells than genetic deletion of PARP1 by siRNA (Xia, et al., 2021). The earlier PARP trap theory suggested that PARPi attached competitively to the PARP1 NAD^+ binding motif, leading to the uptake of PARP1 into DNA because PARP1 cannot be automatically PARylated (Hu et al., 2022). This theory was supported by powerful evidence that DNA-PARP1 complexes pre-exposed to PARPi have a reduced capability to dissociate after auto-modification induction of PARP1 by the NAD^+ domain. That is why it is proposed that PARPi cause the trapping of PARPs to a small extent (Hopkins et al., 2015).

PARP1 is involved in SSBR of DNA, and it suggested that trapping of PARP1 leads to DNA damage that will not be bypassed by the replication fork, which leads to DSBs in DNA during the S-phase of the cell cycle (Hanzlikova and Caldecott, 2019). The only methods that can be adopted to repair DSBs are HR or NHEJ repair methods. As mentioned previously, an HR repair mechanism is required to repair error-free DSBs that need an active BRCA1/2 protein (Vos et al., 2018). However, in cancers lacking HR, for example, BRCA1/2 mutant cancers, inhibition of PARP results in the formation of DSBs that may be reformed only by the NHEJ repair mechanism. NHEJ repair imitates the direct recombination of DNA damage without the need for homologous templates. This direct reconnection raises the frequency of catastrophic genome instability, which can lead to the death of the cells (Svetec Miklenić and Svetec, 2021). In addition, folded replication forks induced by PARPi cannot be reformed by the NHEJ repair mechanism, which results in the death of cancerous cells deficient in HR (Fig. 3a) (Faraoni and Graziani, 2018).

4.3 Activation of NHEJ repair mechanism

Many studies have shown that an integrated lethal correlation between BRCA1 and PARP inhibition is associated with increased activity of NHEJ in cancerous cell lines HR. This over-expression of NHEJ upregulates the survival of catastrophic genome vulnerability and the ultimate death of cells (George et al., 2017). The NHEJ repair pathway was first suspected after the discovery that PARPi therapy increased phosphorylation of DNA-PKs subunits, thereby enhancing the function of NHEJ (Fig. 3b) (Patel et al., 2011). Studies supporting this hypothesis showed that the poly(ADP-ribose) anionic framework (pADPr) formed by direct activation of PARP1 interacts with Ku 70 and 80 to stop the activity of the NHEJ pathway (Wang et al., 2006; Fattah et al., 2010). Therefore, inhibition of PARP1 function abolished this downregulation and increased NHEJ activity. In addition, Veliparib treatment has been found to increase NHEJ function in ovarian cancer cells lacking BRCA (Hjortkjær et al., 2018).

4.4 Impaired Okazaki fragment processing and speed of replication fork

Recent findings indicate that the inhibition of FEN1 and LIG1 leads to PARP1 accumulation, facilitating XRCC1-mediated processing. Evidence supports that PARPi therapy enhances replication fork progression by 1.4-fold, implicating PARP1 in the response to unligated Okazaki fragments (Fig. 3c, d) (Maya-Mendoza et al., 2018). This observation suggests that PARPi toxicity may stem from DSBs associated with accelerated replication. Recent studies indicate that increased replication speed may lead to an accumulation of replication-associated ssDNA gaps (Cong et al., 2021). It is posited that these cytotoxic ssDNA gaps arise from PARP1 involvement in processing Okazaki fragments or resolving stalled replication forks, with inhibition of PARP leading to short single-stranded gaps. Although this hypothesis is not widely acknowledged, it is supported by substantial evidence. This includes the notable increase in ssDNA gaps post-PARPi treatment in BRCA-deficient tumor cell lines relative to BRCA-wild type. Additionally, a marked reduction in ssDNA gaps was noted in PARPi-resistant cell models, indicating that PARPi sensitivity is linked to the extent of ssDNA gaps induced by treatment (Cong, et al., 2021).

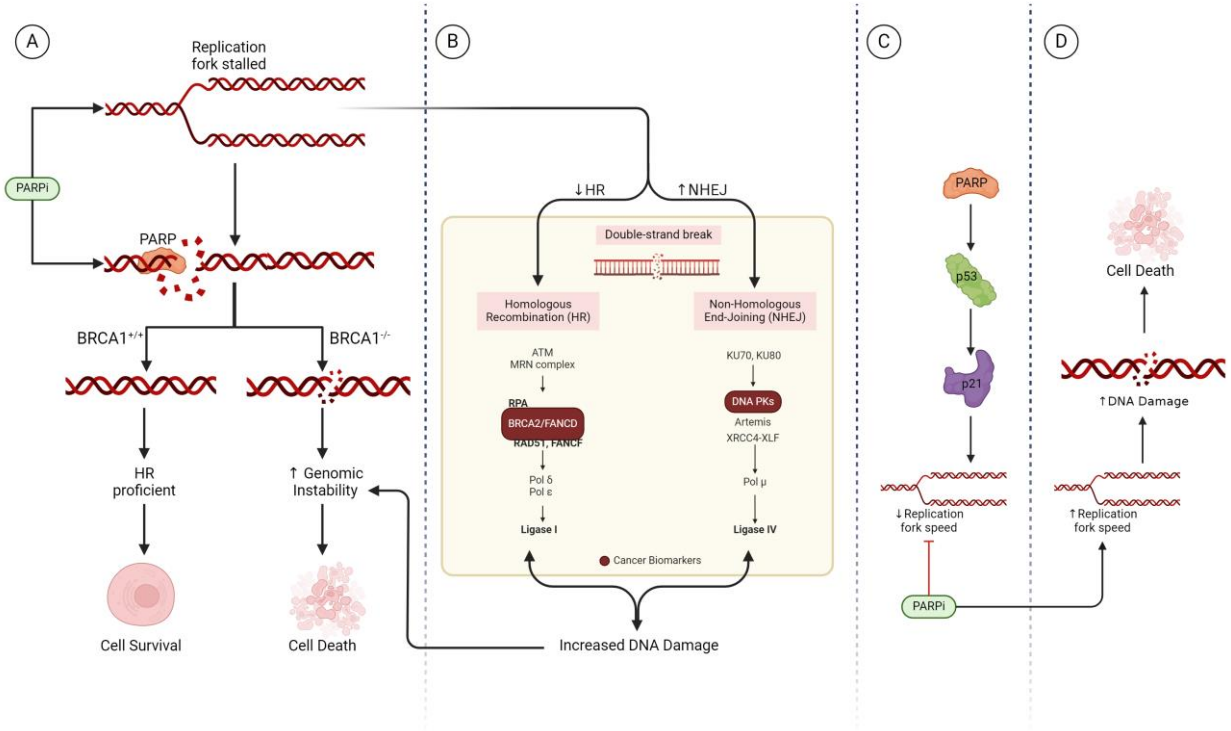

Fig. 3 Mechanisms of action of PARP inhibitors. (a) PARP arrives at the DNA breakage site and starts the process of repairing by recruiting other repair factors. However, in the presence of a PARP inhibitor (green), PARP is trapped at the breakage site, leading to inhibition of the replication process. As a result, the cell can initiate a double-strand break (DSB). Cells with BRCA1+/+ carry out the HR and restore genomic integrity in contrast to BRCA1-/- cells. (b) Down-regulation of homologous recombination repair and upregulation of non-homologous end joining activity (c, d) modulation of replication fork speed by PARP inhibitor. Created in BioRender.com

5 List of clinically approved PARPi

A number of PARPi are currently approved for therapy of various cancers such as prostate, BRCA1/2-mutated breast cancer, pancreatic, and ovarian cancer. The considerably low mutation rate of BRCA1/2 cancers limits its use to treatment of 10–15% of ovarian and breast carcinomas, 4.0 to 7.0% of pancreatic carcinomas, and a lower percentage of prostatic cancers (Oh et al., 2019). However, the latest research suggests that PARPi has been used on a wider scale for treating several cancers. PARPi approved for treating various types of cancers are listed in Table 1.

Table 1. List of FDA and EMA approved PARP inhibitors used as therapeutic agents against various types of cancers

PARP inhibitor	Indications	Approving authority	Approval Year	References
Olaparib	Regenerating ovarian carcinoma, tumor of the fallopian tube, and primary peritoneal carcinoma	FDA+EMA	2017	(Friedlander, et al., 2018; Poveda et al., 2021)
	HER2-negative breast tumor	FDA	2018	(Robson, et al., 2017)
	HER2-negative breast tumor	EMA	2019	(Robson, et al., 2017)
	For treatment of progressed pancreatic carcinoma	FDA	2019	(Golan, et al., 2019)
	Also approved as 1st line treatment for progressed ovarian carcinoma, tumor of	FDA+EMA	2018-2019	(Moore et al., 2019)

	the fallopian tube, and primary peritoneal carcinoma			
Olaparib+ Bevacizumab	1st line therapy of progressed ovarian carcinoma, tumor of the fallopian tube, and primary peritoneal carcinoma	FDA	2020	(Ray-Coquard, et al., 2019)
Olaparib	For the treatment of metastatic prostate carcinoma	FDA	2020	(De Bono et al., 2020)
Rucaparib	Advanced ovarian cancer	FDA	2016	(Oza et al., 2017)
	Advanced ovarian cancer	EMA	2018	(Oza, et al., 2017)
	Reoccurring ovarian carcinoma, tumor of the fallopian tube, and primary peritoneal carcinoma	FDA+EMA	2018-2019	(Coleman et al., 2017)
	For the treatment of metastatic prostate carcinoma	FDA	2020	(Abida et al., 2019)
Niraparib	Reoccurring ovarian carcinoma, tumor of the fallopian tube, and primary peritoneal carcinoma	FDA+EMA	2017	(Mirza et al., 2016)
	Early Breast Cancer	EMA	2017	(Gonçalves et al., 2020)
	Reoccurring primary peritoneal, ovarian, and fallopian tube cancers	FDA	2019	(Moore, et al., 2019)
	For treatment of progressed ovarian cancer and primary peritoneal cancer	FDA+EMA	2020	(Gonçalves, et al., 2020)
Talazoparib	Progressed or HER2-negative metastatic breast cancer	FDA+EMA	2018	(Ettl et al., 2018)
	Early breast cancer	EMA	2019	(Gonçalves, et al., 2020)
Veliparib	BRCAm advanced TNBC and ovarian cancer	FDA	2020	(Somlo et al., 2017)
	Early Breast Cancer	EMA	Phase III	(Gonçalves, et al., 2020)
Pamiparib	Early Breast Cancer	EMA	Phase II	(Gonçalves, et al., 2020)

FDA: Food and Drug Administration; EMA: European Medicines Agency

6 Mechanisms of PARPi resistance

6.1 Restoration of HR activity

Among the best-known mechanisms of resistance against PARPi is the recovery of HR potential. DSBs can be efficiently restored by restoring the HR ability, enabling cancerous cells to survive. This is due mainly to back mutation or inhibition of NHEJ activity.

6.1.1 Reversion mutations

The most common way to restore HR is to reactivate BRCA1/2 by secondary mutation. These back mutations are recognized in individuals identified with BRCA1/2 germ cell mutation and mutation in somatic cells in breast and ovarian cancers (Shroff et al., 2018). In severe ovarian cancer studies, BRCA-back mutations in independent DNA were found in 18.0% and 13.0% of platinum-resistant and refractory cancers, respectively. In addition, the existence of BRCA1/2 reverse mutations have been shown to reduce the duration of the PFS rate by therapy with Rucaparib from 9 to 1.8 months (Lin et al., 2019). That study provided the first evidence that an intra-genic deletion of BRCA-1 or 2 mutations contributes to establishing PARPi-resistance against cancers. A study by Gornstein et al. (2018) of women aged 55 years diagnosed with progressed breast cancer showed a better response to Olaparib PARPi because of the V1283fs*2 mutation in BRCA2 cancer. After treatment for about 10 months, the patients' primary cancer became resistant to Olaparib. Thus, functional BRCA2 isoforms have previously been designed to induce resistance to PARPi in susceptible cell models by regaining effective HR (Fig. 4a).

6.1.2 Repression of NHEJ

Studies have suggested that abnormal HR caused by mutations in BRCA1 may be reinitiated by the co-destruction of genes regulating NHEJ (Noordermeer and Van Attikum, 2019). Furthermore, a decrease in the level of 53BP1 protein, which is engaged in the mobilization of NHEJ, restores BRCA1 lacking HR and reduces allergic reactions to PARPi (Callen et al., 2020). A decrease in Shieldin expression has been observed in many types of breast cancers with acquired PARPi resistance. In addition, after DSBs, REV7 protein is known to localize to the injury site, suppress the process of NHEJ, and increase HR (De Krijger et al., 2021). ShRNA-mediated inhibitory activity of the REV7 gene has been found to stop the NHEJ pathway and thus enhance HR. This further induces PARPi resistance and rescues the cells from cytotoxicity induced by Olaparib (Clements et al., 2020). However, in favor of the present theory, increased activation of TRIP13ATPase was found in a big cohort study of PARPi-resistant BRCA1 mutant cancers. As mentioned earlier, TRIP13ATPase inhibits NHEJ function indirectly by downregulating the REV7 gene. Increased susceptibility to Olaparib has also been found in cell models lacking TRIP13. Moreover, TRIP13ATPase is also engaged in initiating susceptibility to PARPi by regulating NHEJ function (Singh et al., 2021).

MicroRNAs (miRNAs) are highly protected sites of non-sense coding RNAs that are thought to play a major role in regulating gene function. A recent screening study showed that overexpression of micro RNAs such as miR577, miR644, miR126, miR-622, miR613, and miR492 is linked to resistance to PARPi (Choi et al., 2016). miR-622 overexpression reduced the sensitivity of BRCA mutant ovarian and breast cancerous cell lines to treatment with Veliparib and Olaparib. This desensitization was mediated because miR-622 downregulates the expression of Ku 70/80, which is hypothesized to block the NHEJ function and promote HR function (Raimundo et al., 2021). Thus, previous results favor the proposed theory that the downregulation of NHEJ by increased HR activity may play an important role in acquiring resistance to PARPi (Fig. 4a).

6.2 Enhanced drug efflux

Enhanced drug efflux refers to the increased rate of clearing cells of certain compounds, such as PARPi. PARPi resistance might also be linked to enhanced activation of genes involved in the efflux of drugs from the cell. This is thought to be initiated explicitly by ATP-binding cassette (ABC) 1 or 2 genes of the B subfamily, as results have shown that ABCB1a/b expression is enhanced in breast cancer cells resistant to Olaparib (He et al., 2021). In addition, the expression of ABC1a/b was found to be correlated with resistance to Rucaparib and Olaparib in ovarian cancerous cells (Giudice et al., 2022). This type of resistance can be reversed after therapy with either of two commonly used ABCB1a/b inhibitors, Elacridar or Verapamil (Kubalanza and Konecny, 2020). Furthermore, ABCB1a/b overexpression was noted not only in cancerous cells resistant only to PARPi but also in cells resistant to PARPi analogs such as AZD2461, an Olaparib analog PARPi (Noordermeer and Van Attikum, 2019) (Fig. 4b).

6.3 Maintenance of blocked replication fork

Maintenance of blocked replication forks further suppresses their collapse and leads to the generation of DSBs in DNA. Preclinical data suggest that this stability may help patients acquire resistance to PARPi, as shown by a deficiency of PTIP, an MLL3/4 family protein, which leads to avoidance of PARP inhibitor-induced arrest of the replication forks in BRCA-lacking cells. Once the replication site is determined, PTIP recruits MRE-11 at the site of disruption and speeds up the disruption of the blocked replication fork. This allows the resumption of the stopped replication fork and improves the excision at that site. Thus, PTIP deficiency stops MRE11 recruitment into stalled replication forks and minimizes DNA strand degradation during development. This reduces DSBs associated with destroying the replication fork of cells lacking BRCA1/2 and confers resistance to PARPi (Berti et al., 2020). Furthermore, EZH2 is a histone methyl-transferase protein and the active component of PRC-2, thought to participate in the effectiveness of PARPi (Wang et al., 2022). PARP1 activates EZH2 and PARylates, which separate it from PRC2 and then degrade it. As the replication fork stops, the EZH2 binds with the replication fork and enhances the methylation of histone H3. This methylation step further helps

to mobilize the MUS81 nuclease into the replication fork to accelerate breakdown of the fork. However, deficiency or inactivation of MUS81 or EZH2 has been found to be involved in acquiring resistance by PARPi, contributing to the stabilization of replication forks (Fig. 4c) (Haynes et al., 2018).

6.4 Decrease in expression of PARG protein

PARP1 protein undergoes auto-PARylation. This promotes full expression and the PARylation of various types of chromatin linked to other proteins. Moreover, PARylation is found to be well differentiated as reverse post-translational modifications by poly (ADP-ribose) glycohydrolase (PARG), which has been recognized as a major PARP disrupting enzyme (Fig. 4d). Since PARPi are expected to stop PARylation, further deficiency and non-functional activity of PARG promote the accumulation of PARP, maintain proper PARP activity, prevent PARP removal, and increase resistance to PARPi (Matanes et al., 2021). However, further research is needed to check if alterations in the PARG level are associated with acquiring resistance against PARPi in human cancer.

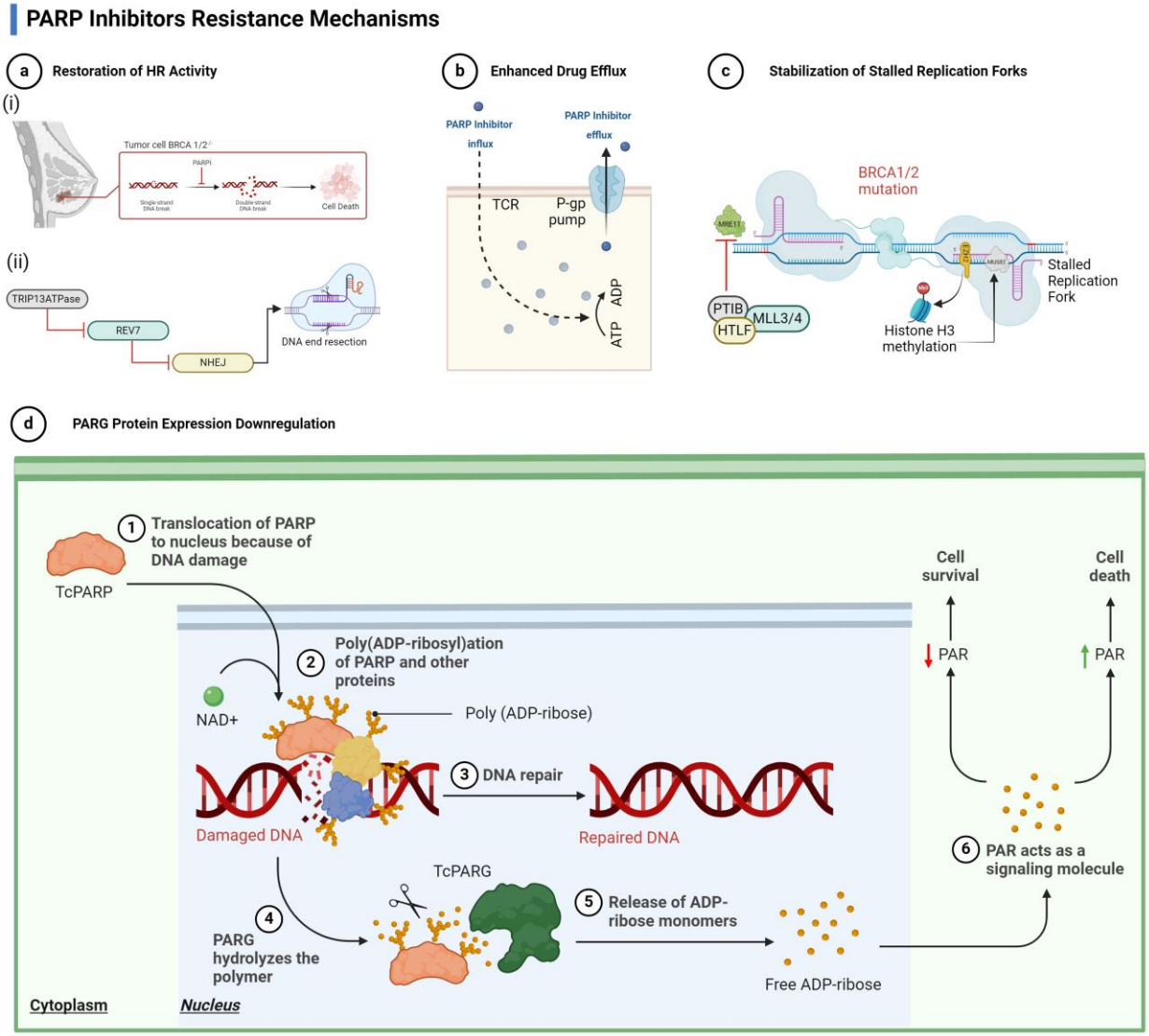

Fig. 4 Mechanisms of PARPi resistance. Cancer cells (a) restore homologous recombination activity by (i) secondary mutation or through (ii) co-destruction of genes regulating NHEJ (b) enhance the drug efflux through activation of ATP-binding cassette 1 or 2 genes of B subfamily (c) stabilization of stalled replication forks by stopping the recruitment of DNA nucleases (d) downregulation of poly (ADP-ribosyl) glycohydrolase (PARG) protein expression. Created in BioRender.com

7 PARPi resistance modulation in combination with other therapies

Due to the need for high doses and the acquisition of PARPi resistance, combined therapies have shown promising outcomes in *in-vitro*, *in-vivo*, and clinical studies with regard to minimizing dose requirements and increasing the efficacy of PARPi and the survival of patients.

7.1 PARPi in combination with chemotherapeutic agents

PARPi combined with cytotoxic chemotherapeutic agents, is one of the most widely used combination therapies. Previous research has shown that PARPi with platinum leads to increased levels of myelosuppression, which is proposed to be due to the enhanced trapping capability of PARPi (Yusoh et al., 2020). Thus, it is hypothesized that Veliparib may exhibit low-level myelotoxicity compared to other PARPi due to its low PARP trap activity. Further, recent Phase III clinical trials have shown that Veliparib, when given in combination with other chemotherapeutic agents, significantly improves progression-free survival (PFS) as the first treatment option and regular therapy for high-grade stage III/IV ovarian carcinomas (Swisher et al., 2022). In addition, a phase III BROCADE clinical study showed that 34% of patients with HER2-/BRCA mutated breast carcinoma therapy with Carboplatin, Paclitaxel, and Veliparib experienced no further spread for 24 months compared with patients who were treated with Paclitaxel or Carboplatin alone (Han et al., 2018). Another phase III clinical study showed that Veliparib in combination with Paclitaxel or Carboplatin in HER2 negative, metastatic, mutated, and germline breast cancer resulted in an increased PFS rate without significant toxic effects (Ray-Coquard et al., 2019).

Alkylating agents also act as a chemotherapeutic agent in combination with PARPi. For example, Temozolomide induces an SSB of N7-methylated guanine and N3-methylated adenine through the addition of a methyl group to guanine at N7 and O6 positions and to adenine at the N3 position (Zhang et al., 2012). PARP1 is required for induced SSB repair and thus induces PARP1 recruitment, which is then blocked by the presence of PARPi. Given the increased uptake of PARPi in the presence of Temozolomide, it is hypothesized that the synergistic effect detected between the two therapeutic agents depends on inhibition of the PARP catalytic function and the capability for uptake of PARPi (Higuchi et al., 2020). This is evidenced by a clinical study showing that Talazoparib and Olaparib act synergistically with Temozolomide but not with Veliparib or PARP1/2 gene inactivation (Hirota, et al., 2022). The contribution of increased PARPi uptake to increased myelosuppression was shown by a phase II clinical trial in which patients with metastatic melanoma were treated with combination therapy with Rucaparib and Temozolomide (Chan et al., 2021).

7.2 PARPi in combination with radiotherapy

Several studies have shown that PARPi can sensitize tumor cells regardless of their BRCA type (Jonuscheit et al., 2021). PARPi significantly inhibit the remodeling mechanism of SSBs initiated by radiation, which further leads to disruption of the replication fork and ultimate S-phase DSBs (Dias et al., 2021). A number of *in-vitro*, *in-vivo*, and clinical studies have been carried out to determine the effectiveness of PARPi along with radiotherapy to sensitize tumor cells and act in a synergistic way. For example, a phase-I clinical trial by Lakomy et al. (2020) evaluated the combined effect of Talazoparib and radiotherapy in patients suffering from ovarian cancer and noted promising effects.

7.3 PARPi in combination with immunotherapy

Immunotherapy is a new class of anticancer therapy that has shown promising results in both monotherapy and combination therapy. Initially, in non-specific immune responses, there are pattern recognition receptors (PAMPs) that detect the pathogen and damage-associated molecular patterns (DAMPs) (Amarante-Mendes et al., 2018). Cytosolic DNA resulting from damage to the nuclear membrane or from DNA degrading proteins due to loss of functional mutations binds to cyclic guanosine monophosphate (GMP)-adenosine monophosphate (AMP) synthase (cGAS) and induces DAMP in cGAS changes (Li and Chen, 2018). This conformational change converts guanosine triphosphate (GTP) and ATP into GMP-AMP cyclic second messenger. GMP-AMP

functions as an important endogenous receptor for the IFN gene stimulator, activating various transcription factors and stimulating the non-specific immune mechanism (Van Den Bulk et al., 2018). Further, the interlinkage between DNA disruption and the immune mechanism suggests that PARPi treatment may significantly affect anti-tumor immune feedback. Several clinical studies have investigated the impacts of PARPi in combination with immunotherapeutic agents such as PD-1 inhibitors (Heeke et al., 2020). The outcomes of a phase I trial of 49 patients with solid tumors treated with a PARPi in combination with Tislelizumab showed that 20% of the patients showed the required response. Moreover, in 32% of the patients, the disease was stabilized without increasing the tumor size (Friedlander et al., 2018).

Replication gaps, defined as sections of unreplicated DNA remnants from DNA replication processes, can potentially instigate genome instability, particularly within HRD cells. The presence of these gaps, particularly in cases of faulty HR repair, amplifies the burden of DNA damage. PARPi accentuate this susceptibility by impeding the repair of these gaps, consequently increasing cell death rates in HRD tumors. This suggests that replication gaps are not merely incidental outcomes of HRD but may indeed have a pivotal role in dictating the responsiveness of these cells to PARPi, thereby providing a more intricate understanding of their mode of operation (Cong, et al., 2021).

Combining PARPi with immune checkpoint inhibitors (ICI) has been proposed as the best approach to overcome PARPi resistance, considering the relationship between DNA damage in tumors and the activated immune system. The reasoning for this combination hinges on two main ideas. Firstly, the high tumor mutational burden (TMB) in HRD tumors is due to the defective DNA repair system. This causes an increase in tumor-specific neoantigen burdens and triggers the antitumor immune response (Mouw et al., 2017; Yarchoan et al., 2017). Secondly, PARPi inhibit antitumor immunity by increasing PD-L1 expression. Furthermore, they encourage the buildup of cytosolic DNA fragments, which in turn stimulates the DNA-sensing cGAS-STING pathway and triggers a type 1 interferon (IFN)-mediated antitumor immune response that involves the recruitment of T cells (Shen et al., 2019).

Clinical trials, such as the phase I/II TOPACIO study with Niraparib and Pembrolizumab (a PD-1 inhibitor) in metastatic TNBCs and platinum-resistant ovarian malignancies, have shown that PARPi and ICI work together synergistically (Konstantinopoulos et al., 2019; Vinayak et al., 2019). Specifically, in patients with BRCA wild-type and non-HRD ovarian cancer, the clinical effectiveness of the combination of Pembrolizumab (200 mg) and Niraparib (200 mg) was higher than that of monotherapy, with an overall response rate (ORR) of 18% and a disease control rate (DCR) of 65% (Konstantinopoulos, et al., 2019). The efficacy of the proposed Niraparib and Pembrolizumab combination in treating ovarian cancer was independent of BRCA and HRD status. In a study of breast cancer patients with metastatic TNBCs and BRCA-mutated tumors, the combination showed a therapeutic synergistic effect (ORR of 47% v. 11% and PFS of 8.3 months v. 2.1 months, respectively) (Vinayak, et al., 2019). There has been recent, comprehensive research using BRCA wt patients. Triplet therapy with 300 mg of Olaparib, 1.5 g of Durvalumab, and 10 mg/kg of Bevacizumab indicated an improved tumor response rate (ORR of 77.4%) compared to doublet therapy and monotherapy with PARP or VEFG inhibitors (Drew et al., 2020).

Additionally, in both first-line and pretreated patient populations, a number of larger randomized phase III studies combining PARPi and ICI are underway. A new study, ENGOT-OV43/KEYLYNK-001 (NCT03740165), is investigating the efficacy of Olaparib in advanced epithelial ovarian cancer patients who do not have the BRCA1/2 mutation and have previously received chemotherapy in addition to Pembrolizumab (a PD-1 inhibitor) (Fujiwara et al., 2019). During the 2023 ASCO Annual Meeting, the findings of the phase III DUO-O study (NCT03737643) were presented. For patients with recently diagnosed advanced ovarian cancer who did not have BRCA mutations, this trial aimed to determine the safety and effectiveness of a maintenance therapy regimen consisting of three drugs: Bevacizumab, Olaparib, and Durvalumab. The trial included 1,130 patients (Harter et al., 2023). In patients with HRD-positive malignancies, they found that triplet maintenance treatment improved PFS more than Bevacizumab monotherapy, which was both statistically and clinically significant (median PFS of triplet arm, 37.3 months; median PFS of Bevacizumab alone arm, 23 months).

Median PFS in the triplet group was 24.2 months in the intent-to-treat (ITT) group, compared to 19.3 months in the Bevacizumab alone group (19.3 months). The complete results of the analysis, which will include OS and other secondary endpoints, are still lacking. Many other clinical trials are now active and examining the target population's safety, toxicity, and optimal dosage of combination PARPi and ICI treatments (NCT02849496) (Lorusso et al., 2020).

7.4 PARPi in combination with DNA methyltransferase (DNMT) inhibitors

DNA methyltransferase (DNMT) is a group of conserved enzymatic proteins involved in the shifting of methyl groups through S-adenosylmethionine (SAM) molecules. DNMT plays an important function in the activation of transcription, gene silencing, and gene regulation through post-transcriptional modifications (Lyko, 2018). Increased DNMT activity is involved in many components of carcinogenesis, including silencing of tumor suppressor genes and increasing the methylation of genes linked with cancer promotion (Lu et al., 2020). Increased DNMT function is linked to tumor development. DNMT inhibitors (DNMTi) are excellent anti-cancerous agents that work by inhibiting the methylation of DNA residues. Presently, Azacitidine and Decitabine are two DNMT inhibitors that are approved by the Food and Drug Administration (FDA) and European Medicines Agency (EMA) for the cure of amyloid leukemia (AML) and myelodysplastic syndrome (Short et al., 2022). However, more than 50% of patients treated with DNMT inhibitors did not respond to the treatment (Giri and Aittokallio, 2019). This suggests the need for a much more targeted and effective perspective on DNMT inhibitors as a treatment. Baer et al. (2022) evaluated the anti-therapeutic potential of PARPi in combination with DNMTi decitabine against AML in patients in the USA and noted enhanced anti-tumor activity via increased DNA demethylation, suppressed HR activity, enhanced PARP chromatin trapping, and enhanced γH2AX foci accumulation.

8 Therapeutic role of PARPi alone and in combination with other therapies against various types of cancers

PARPi are potent anti-cancerous agents in clinical trials for the treatment of various cancers such as pancreatic, prostate, ovarian, and breast cancers. Currently, numerous *in vitro*, *in vivo*, and clinical trials have been completed and are going on, which represent the importance of PARPi as therapeutic agents against various cancers.

8.1 Ovarian cancer

Among the various gynecological cancers, ovarian cancer is the leading cause of death among cancer patients in Western nations. The BRCA1/2 mutation has been recognized in about 10-15% of patients suffering from ovarian carcinomas (Litton et al., 2020). Researchers have found that PARPi showed clinical benefits as a first-line treatment for ovarian carcinoma. In a recent PRIMA phase III clinical trial study conducted by González-Martín et al. (2019), 733 patients diagnosed with ovarian carcinoma received Niraparib PARPi or placebo treatment, after platinum chemotherapeutic treatment. The results of the study found that the middle PFS was considerably higher in the Niraparib treatment group compared to the control group. In particular, this rise in PFS was noted to be greater in cancers lacking HR. However, a rise in PFS has not yet been noted in HR-competent cancers. Another study was designed to evaluate Veliparib as a first-line treatment for ovarian carcinoma. More than 1000 women recently diagnosed with ovarian tumors received Veliparib or a placebo in addition to first-line chemotherapy along with maintenance treatment with Veliparib or control treatment. Veliparib was found to increase survival by almost 7 months compared to the control (24 v. 17 months) (Boussios et al., 2020). Several recent *in-vitro*, *in-vivo*, and clinical studies, completed or underway, are listed in Table S1.

8.2 Breast cancer

Breast cancer (BC) has been documented as impacting 2.3 million women in the year 2020, establishing itself as the most prevalent form of cancer detected on a global scale (Sung et al., 2021; Bhutta et al., 2024). About 5-10% of patients suffering from breast carcinoma have associated hereditary genome changes. Like ovarian tumors, it is most commonly caused by BRCA1/2 mutations. Individuals who have the BRCA1/2 mutation have a 69% and 62% danger of progressing into breast cancer 1 and 2, respectively. However, the danger of developing breast tumors in people without BRCA mutations is only 12% (Armstrong et al., 2019). Phase III clinical studies have shown that maintenance treatment with Olaparib increases the PFS in individuals with HER-2 negative metastatic breast carcinoma with BRCA mutations compared with standard chemotherapeutic treatment (Robson et al., 2017). Based on the results, the FDA approved Olaparib in 2018 as a therapy for metastatic breast carcinoma with negative HER2 BRCA mutation (Le and Gelmon, 2018). Talazoparib was endorsed by the FDA and EMA in 2018 as a treatment therapy for progressed HER2-negative breast cancer patients with the BRAC1/2 germline mutation. In addition, *in-vitro*, *in-vivo*, and clinical studies have shown that using PARPi as therapeutic agents significantly improves the standard of life of treated patients compared to some standard therapies (Table S2). Taken together, these results highlight the importance of PARPi alone and in combination with other agents found to be effective for treating breast carcinoma.

8.3 Prostate cancer

Prostate cancer accounts for 7.1% of all diagnosed cancers in men and 13.3% of deaths related to cancer (Gandaglia et al., 2021). Radical prostatectomy is still the gold standard of care, but treatment options are improving. Although radical prostatectomy is a minimally invasive surgery, several patients experience long term side effects that considerably reduce their quality of life. The use of PARPi as a therapeutic treatment for prostate carcinoma began in 2015 after mutations in BRCA1, BRCA2, or ATM were found in 19.6% of prostate cancers (Sachdev et al., 2019). Many clinical investigations are currently underway to check the efficiency of PARPi as a monotherapy and combined therapy as a better treatment option for prostate carcinoma (Table S3). The clinical phase II TOPARP study by Mateo et al. (2020) on patients suffering from castration-resistant prostate cancer (CRPC) with DNA damage repair (DDR) found that 54.3% showed a good response after two years of follow-up with 400 mg of Olaparib. In short, these studies indicate that PARPi can be used alone or in combination with other agents for the treatment of prostate cancer.

8.4 Pancreatic carcinoma

Among the GIT cancers, pancreatic cancer is known to be a highly malignant, easily proliferating, and a bad prognostic type of cancer (Boumehira et al., 2022). The location of the pancreas in the body results in no early signs of cancer, and most patients are diagnosed at an advanced stage of cancer. According to the American Society of Cancer, pancreatic cancer will be the second leading etiology of cancer-related mortalities in the USA by 2030 (Rahib et al., 2021). The BRCA1/2 mutation was found in 4-7% of pancreatic carcinoma patients. In addition, such mutations are linked with reduced survival rates in patients suffering from pancreatic carcinoma (Golan et al., 2019). Golan, et al. (2019) conducted a POLO study that found that individuals with BRCA1/2 mutant cancer responded well to chemotherapy, and 22.1% of patients managed with Olaparib had no further cancer progression after two years. However, in comparison, only 9.6% of patients treated with the control had no further spread of the tumor. The clinical study conducted by Golan, et al. (2019) showed the efficiency of PARPi among patients suffering from pancreatic carcinoma and ultimately led to the approval of Olaparib as a treatment option in patients suffering from germline BRCA1/2-mutated metastatic pancreatic carcinoma. After the emergence of PARPi resistance, combination therapy was found to be more effective in treating pancreatic cancer. Short summaries of *in-vitro*, *in-vivo*, and clinical studies highlighting the importance of PARPi in combination with other therapies are listed in Table S4.

8.5 Lung cancer

Lung cancer, the second most frequently diagnosed cancer and the primary cause of cancer-related mortality in 2020, accounting for about 2.2 million new cases and 1.8 million deaths (Sung, et al., 2021). The classification of lung cancer based on histology encompasses two main types, Small Cell Lung Cancer (SCLC) and Non-Small Cell Lung Cancer (NSCLC), with NSCLC further categorized into adenocarcinoma, squamous cell carcinoma, and large cell carcinoma (Kim et al., 2023; Maharjan et al., 2023). Moreover, DDR-related mutations are obvious in most lung carcinoma patients, including PTEN, FANCA, ATM, and MRE11 (Heeke, et al., 2018). In particular, 5.0% of lung cancer patients have been recognized with the BRCA1/2 mutation (Lee et al., 2020). Taken together, this information supports the use of PARPi as therapy for lung cancer patients. A Phase II STOMP study has shown that Olaparib as a maintenance single therapy for SCLC did not considerably increase PFS compared with placebo. In a phase I and II clinical study investigating the combined efficacy of Olaparib+Temozolomide as therapy for relapsed SCLC, about 41.7% of the patients experienced fully pathological feedback (Farago et al., 2019). PARPi are known to cause sensitization in multiple types of cancers in combination with radiotherapy. Furthermore, xenograft mice-model and *in-vitro* studies on cell lines have shown the first indication that Talazoparib sensitizes a large part of the xenograft model to radiotherapy (Laird et al., 2018). Similar effects were noted after treatment with Veliparib (Kozono et al., 2021). Fluzoparib was recognized as a unique PARPi at the start of the clinical trial (Wang et al., 2019). Fluzoparib has also exhibited valuable outcomes in phase I and II clinical trials in patients suffering from lung carcinoma as a radio-sensitizer and as a combined therapy with the PD-L1 inhibitor SHR-1316 (Luo et al., 2020). Other studies are listed in Table S5.

8.6 Acute myeloid leukemia

Acute myeloid leukemia (AML) is considered to be a common cause of adult leukemia, accounting for about 80% of cases (Short et al., 2018). However, AML is not well associated with BRCA1/2 types of mutations. A number of preclinical trials have identified genetic mutations that justify the use of PARPi as therapeutic agents for AML (Faraoni et al., 2019). First, a microsatellite instability-positive cell model of AML has been shown to exhibit silencing and mutations in the HR genes CtIP and MRE11 (Terry et al., 2013). In addition, increased sensitivity to Veliparib and Olaparib has been tested in patients with myeloproliferative cancers, regardless of their BRCA1/2 mutation status. However, higher sensitivity to PARPi was detected in samples with defects in DNA repair (Faraoni, et al., 2019). Multiple AML-induced adhesion proteins have been found to increase the susceptibility of cell models to PARPi. For example, in an MLL-AF9 positive mouse model, Olaparib has been found to have a remarkable additive effect on the antitumor activity of two chemotherapeutic agents, doxorubicin and cytarabine (Stavropoulou et al., 2018). A number of clinical trials are presently in progress to investigate the use of PARPi in patients with AML (Table S6). However, most are still under recruitment.

9 Conclusion and future perspectives

Since the discovery of PARPi about a half-century ago, the PARP family of proteins has been thought to play several roles in cellular mechanisms, including DNA repair, transcription, and apoptosis. Particularly, an understanding of the underlying molecular biology and role of PARP1 in the repair pathway of DNA led to the discovery of PARPi, which work as target-oriented treatments for various types of cancers. Numerous preclinical and clinical trials have highlighted the potential of PARPi therapy to treat multiple cancer subtypes, showing superiority over conventional chemotherapy in certain cases. Additionally, combining PARPi with other antitumor agents has shown significant antitumor effects and tumor regression. Nevertheless, despite the encouraging outcomes, the clinical use of PARPi remains limited due to their toxic nature and the incomplete understanding of the fundamental pathways of the PARP pathway. This deficiency in understanding hinders the

discovery of potential targets and pathways that could lead to treatment resistance. Recent studies have started to examine alternative targets, such as DNA ligases, to alleviate the toxicity linked with PARPi. Further investigations into the mechanisms of PARPi and the validation of additional biomarkers for PARPi treatment evaluation are essential to maximize the therapeutic benefits of PARPi therapy for patients.

Data availability statement

This article is a review and does not involve the generation of new primary data. The information presented in this review is based on previously published research articles, books, reports, and other relevant sources. As such, the original datasets used in the individual studies cited are not directly available from the authors of this review. However, the references provided in this article can be used to locate and access the original data, if needed. We encourage readers to consult the original sources for further details on data availability and methodology. In cases where publicly available datasets or repositories were utilized in the cited studies, the corresponding references have been included in this review. Readers are advised to follow the data availability statements provided in the original studies to access and utilize these datasets. It is important to note that the authors of this review have not conducted any new experiments or analyses using the original datasets. The purpose of this review is to summarize and interpret the existing research in a given field. Therefore, data availability for this review article itself is not applicable.

Acknowledgments

This work was supported by the Agricultural Science and Technology Innovation Program of the Chinese Academy of Agricultural Sciences (25-LZIHPS-03). This work was supported by the Basic Research Lab Program (2022R1A4A1025557) through the National Research Foundation (NRF) of Korea, funded by the Ministry of Science and ICT. In addition, this study was also supported by the "Regional Innovation Strategy (RIS)" through the National Research Foundation of Korea (NRF) funded by the Ministry of Education (MOE; 2021RIS-001) in 2024.

Author contributions

Muhammad SHOAIB and Zeeshan Ahmad BHUTTA conceived and designed the study. Ahsan JAVED, Muhammad Nabeel AMJAD, and Wenzhu LI collected the data. Muhammad SHOAIB and Zeeshan Ahmad BHUTTA wrote the manuscript. Muhammad SHOAIB, Zeeshan Ahmad BHUTTA, Ahsan JAVED, Muhammad Nabeel AMJAD, Wenzhu LI, Kyung-Chul CHOI, and Wanxia PU revised the manuscript. All authors read and approved the final manuscript and, therefore, had full access to all the data in the study and take responsibility for the integrity and security of the data.

Compliance with ethics guidelines

Muhammad SHOAIB, Zeeshan Ahmad BHUTTA, Ahsan JAVED, Muhammad Nabeel AMJAD, Wenzhu LI, Kyung-Chul CHOI, and Wanxia PU declare that they have no conflict of interest. This article does not contain any studies with human or animal subjects performed by any of the authors.

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Supplementary information:
Tables S1-S6