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REVIEW ARTICLE

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Crosstalk of DNA double-strand break repair pathways in poly(ADP-ribose) polymerase inhibitor treatment of breast cancer susceptibility gene 1/2-mutated cancer

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Germline mutations in breast cancer susceptibility gene 1 or 2 (BRCA1 or BRCA2) significantly increase cancer risk in hereditary breast and ovarian cancer syndrome (HBOC). Both genes function in the homologous recombination (HR) pathway of the DNA double-strand break (DSB) repair process. Therefore, the DNA-repair defect characteristic of cancer cells brings about a therapeutic advantage for poly(ADP-ribose) polymerase (PARP) inhibitor-induced synthetic lethality. PARP inhibitor-based therapeutics initially cause cancer lethality but acquired resistance mechanisms have been found and need to be elucidated. In particular, it is essential to understand in detail the mechanism of DNA damage and repair to PARP inhibitor treatment. Further investigations have shown the roles of BRCA1/2 and its associations to other molecules in the DSB repair system. Notably, the repair pathway chosen in BRCA1-deficient cells could be entirely different from that in BRCA2-deficient cells after PARP inhibitor treatment. The present review describes synthetic lethality and acquired resistance mechanisms to PARP inhibitor through the DSB repair pathway and subsequent repair process. In addition, recent knowledge of resistance mechanisms is discussed. Our model should contribute to the development of novel therapeutic strategies.

KEYWORDS
DNA replication, HBOC syndrome, homologous recombination, non-homologous DNA end-joining, PARP inhibitor

1 | INTRODUCTION

Hereditary breast and ovarian cancer syndrome is caused by germline mutations in BRCA1 or BRCA2 genes.[1,2] Approximately 10% of all breast cancer cases are inherited, and half of them are HBOC.[3] These patients have elevated risks of developing ovarian, breast and other cancers.

Breast cancer susceptibility gene 1 and 2 proteins function in a DNA repair pathway for DSB by a process called HR.[4,5] It uses homologous DNA sequences of sister chromatids to ensure genomic stability. In cancer cells, however, DNA repair function is often modulated. Many anticancer agents induce cell death by damaging DNA and accumulating mutations. Therefore, cell death is rarely stimulated in cancer cells with enhanced functions of DNA repair (chemotherapy resistance).

Advances in BRCA1 and BRCA2 research have led to the development of novel therapeutic regimens based on synthetic lethality

Abbreviations: 53BP1, p53-binding protein 1; APE, AP-endonuclease; BER, base excision repair; BRCA1/2, breast cancer susceptibility gene 1/2; CtIP, C-terminal-binding protein interacting protein; DSB, double-strand break; HBOC, hereditary breast and ovarian cancer syndrome; HR, homologous recombination; MRE11, meiotic recombination 11; NHEJ, non-homologous end joining; PARP, poly(ADP-ribose) polymerase; PARylation, poly ADP-ribosylation; RIF1, Rap1-interacting factor 1; seDSB, single-ended DSB; SSB, single-strand break.

such as PARP inhibitors. Synthetic lethality is frequently induced in cells with reduced repair function (chemotherapy sensitivity). Consequently, HBOC patients are highly sensitive to DNA-damaging agents such as PARP inhibitor, platinum-based agents, and topoisomerase inhibitors.[6] In synthetic lethality theory, cells survive even if one of two specific genes involved in cell survival is inhibited. However, cell death is induced when two genes are simultaneously repressed. Poly(ADP-ribose) polymerase inhibitor treatment is a novel therapy for HBOC patients that targets BRCA1/2 mutations as well as PARP.[7,8] This polymerase plays a role in DNA single-strand break (SSB) repair. The inhibitor suppresses PARP's SSB repair function during the S-phase of the cell cycle resulting in unrepaired DNA and DSB formation. Notably, this cell cycle-specific DSB requires HR for correct repair. Therefore, although HR-proficient cells can repair DNA lesions, HBOC patients have BRCA1 and BRCA2 mutations whose cancer cells cannot repair DSB as a result of dysregulation of the HR repair pathway and are sensitive to PARP inhibitors. Indeed, recent studies show that complicated molecular mechanisms affect DSB repair.

Normal cells mainly repair DSB by two mechanisms during the cell cycle: HR and NHEJ.[9] Optimum pathway selection is necessary for DSB repair under specific conditions. Although NHEJ repairs DSB throughout the cell cycle, HR only functions in the S/G2 phase following DNA replication.[10-13] Many reports have investigated the mechanism of "DSB repair pathway choice" in the S/G2 phase where NHEJ overlaps with HR. Understanding of this pathway choice may best explain how PARP inhibitor-induced DSB in S-phase is repaired in several situations.

In the present review, we summarize our current knowledge on the synthetic lethality between BRCA1/2 dysfunction and PARP inhibitors focusing on the molecular mechanisms that regulate the two major DSB repair pathways, molecular defects, and pathway choice. We also discuss the synthetic lethal effect and acquired resistance to PARP inhibitors.

2 | PARP INHIBITOR-INDUCED DNA DAMAGE

Poly(ADP-ribose) polymerase-1 (PARP1) is a member of the PARP family that plays a vital role in the repair process of SSB in base excision repair (BER).[14,15] Cells receive constitutive attacks by endogenous and exogenous factors that lead to DNA damage. Base lesions are mainly repaired by BER. At first, damaged sites cleaved by glycosylase and APE create a single-strand DNA nick. Then, PARP-1 recognizes it as a SSB and synthesizes PAR polymers covalently at the site as PARylation.[16,17] As a result, PARP1 interacts with proteins such as DNA polymerase β (pol β), DNA ligase III, and X-ray repair cross-complementing protein 1 (XRCC1), which are recruited at the SSB site in the BER process. However, in the presence of a PARP inhibitor, PARylation is inhibited by PARP-1 activity trapping.[18] The unrepaired damaged DNA encounters the replication fork during replication in S-phase. The collision causes the fork to stall and makes a DSB.[19] In general, DSB induced by DNA-damaging agents has two DNA ends; however, DSB generated through replication fork stalling has only one DNA end, called seDSB (Figure 1). Double-strand break could be a severe threat to genomic stability and must be corrected. Moreover, unlike two-ended DSB, seDSB needs to be repaired by a more limited pathway to avoid genomic instability and cell lethality.

3 | DSB REPAIR PATHWAY CHOICE

Two principal pathways repair DSB: HR or NHEJ. Homologous recombination error-free repair uses sister chromosomes as a homologous template. NHEJ error-prone repair directly ligates damaged DNA ends. DSB repair is regulated in a cell cycle-dependent method where HR functions in S/G2 and NHEJ in all phases in a competitive way. When DSBs are generated, abundant Ku heterodimers (Ku70 and Ku80 subunits) bind to DSB ends with high affinity.[20] Then,

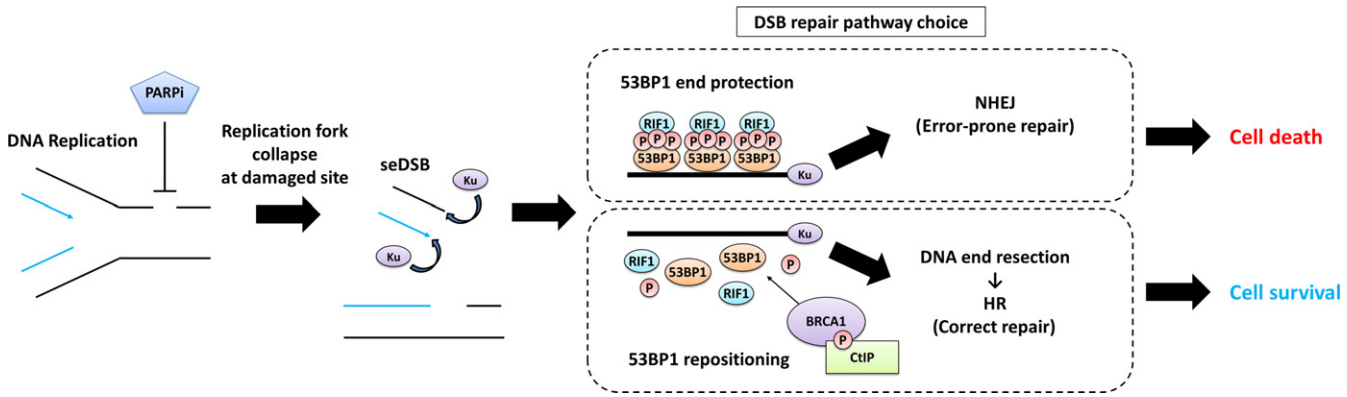

FIGURE 1 Poly(ADP-ribose) polymerase (PARP) inhibitor-induced cell fate through double-strand break (DSB) repair pathway choice. Single-ended DSB (seDSB) is generated after PARP inhibitor-induced DNA replication fork collapse during S phase. The DSB end protected by the p53-binding protein 1/Rap1-interacting factor 1 (53BP1-RIF1) complex is repaired by error-prone non-homologous end joining (NHEJ) pathway causing cell death. In contrast, the DSB end released by breast cancer susceptibility gene 1/C-terminal-binding protein interacting protein (BRCA1-CtIP) interaction is resected, leading to the homologous recombination (HR) pathway, resulting in cell survival

either the NHEJ process, recruitment of DNA-dependent protein kinase catalytic subunit (DNA-PKcs), X-ray cross-complementation group 4 (XRCC4), and DNA ligase IV (Lig4),[21] starts, or DNA ends are resected (DNA end resection) as an initiating step for HR. Molecular mechanisms regulate each DSB repair pathway (Figure 1).

53BP1, RIF1, CtIP, and BRCA1 play key roles in pathway choice. 53BP1 rapidly participates in repair by surrounding DSB sites after its generation and protects damaged ends from excessive end resection.[22,23] Then, ataxia telangiectasia mutated kinase (ATM)-dependent phosphorylation of 53BP1 recruits the 53BP1-binding factor RIF1[24] and blocks CtIP-dependent DNA end resection.[25] These steps lead to the NHEJ pathway. By contrast, BRCA1 modulates DSB repair pathway with its antagonistic relationship to 53BP1 and RIF1. Several studies reported that cyclin-dependent kinase (CDK)-dependent CtIP interaction with BRCA1 is important for promoting end resection and suppression of 53BP1-RIF1 signaling.[26-28] It was also shown that BRCA1-induced dephosphorylation of 53BP1 causes RIF1 release from the damaged site and repositioning of 53BP1.[29] In contrast, the mechanism of DNA end resection suppression by 53BP1-RIF1 activity is consistent with a report that loss of BRCA1 decelerates CtIP-dependent DNA end resection.[30] Therefore, dysfunction of this process would allow MRE11-induced endonuclease activity to be an initiation step[31] such that CtIP-BRCA1 signaling directs the repair pathway from NHEJ to HR.[32,33] Also, the number of replication protein A (RPA) foci resections is reduced in the absence of BRCA1 but is still moderate compared to when CtIP is depleted.[29] These findings indicate that CtIP-dependent end resection is available even when BRCA1 is not present.[34] Loss of BRCA1 directs repair to the NHEJ pathway but may not induce a strong inhibition of end resection. In summary, CtIP-BRCA1 and 53BP1-RIF1 regulate each pathway during S/G2 phases (Figure 2A) but the detailed mechanisms need to be further investigated.

4 | PARP INHIBITOR-INDUCED SYNTHETIC LETHALITY

Breast cancer susceptibility gene 1/2-mutated cancer cells respond well to Poly(ADP-ribose) polymerase (PARP) inhibitors through synthetic lethality.[7,8] Poly(ADP-ribose) polymerase inhibitor-induced cell cycle-dependent seDSB could be repaired by HR through the same pathway selection mechanism in the S/G2 phase. Although cells require NHEJ for two-ended DSB repair to survive,[35] it causes chromosomal aberration, genomic instability in PARP inhibitor-treated cells, and cell death because seDSB has no other DNA end that can be correctly ligated.[36] Therefore, stalled replication fork-induced

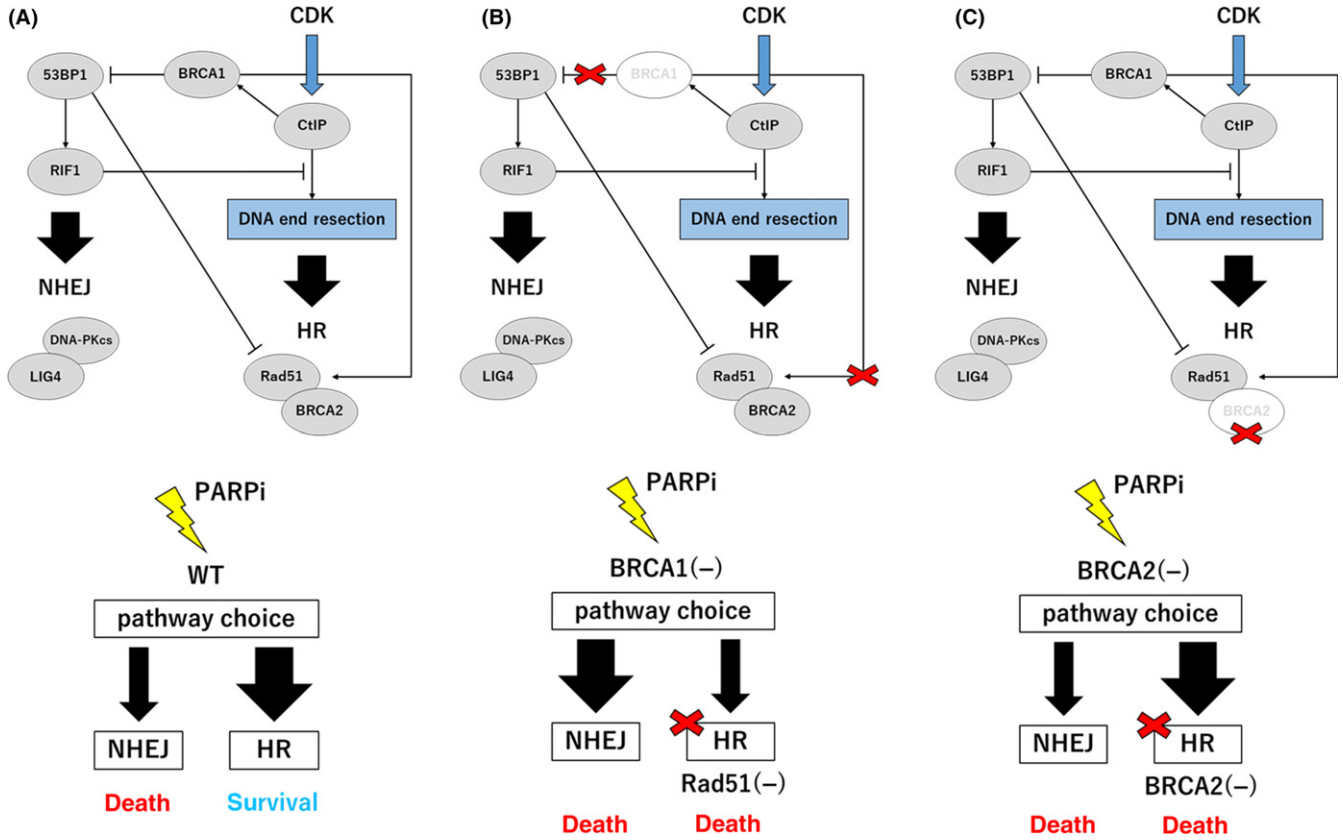

FIGURE 2 Mechanisms of synthetic lethality to poly(ADP-ribose) polymerase (PARP) inhibitor in breast cancer susceptibility gene 1/2 (BRCA1/2)-deficient cells through double-strand break (DSB) repair and ensuing pathways during S/G2 phase. PARP inhibitor-induced cell fate analyzed in (A) wild-type (WT), (B) BRCA1-deficient, and (C) BRCA2-deficient cells. 53BP1, p53-binding protein 1; CDK, cyclin-dependent kinase; CtIP, C-terminal-binding protein interacting protein; DNA-PKcs, DNA-dependent protein kinase catalytic subunit; HR, homologous recombination; Lig4, DNA ligase IV; NHEJ, non-homologous end joining; RIF1, Rap1-interacting factor 1

seDSB needs to be repaired by HR (Figures 1, 2A). Both BRCA1 and BRCA2 are known to play critical roles in the HR pathway. Their roles in synthetic lethality will be discussed in the context of other molecules. In addition, the mechanism of synthetic lethality in BRCA1/2-mutated cells based on the DSB repair pathway models will be explained.

Breast cancer susceptibility gene 1, a key player in DSB repair, directs HR with CtIP by promoting DNA end resection by suppression of the 53BP1-RIF1 pathway.[29,32] The presence of BRCA1 leads to dysfunctional NHEJ and functional HR in DSB repair. It could also help maintain genomic stability by preventing error-prone repair of accidentally generated seDSB.[37] Conversely, loss of BRCA1-induced 53BP1-RIF1 signaling restoration directs the repair pathway to NHEJ and causes RIF1-dependent partial suppression of end resection. BRCA1 also recruits Rad51 onto the resected DNA strand by replacing RPA and colocalizing with Rad51 and BRCA2 to activate HR[38,39] such that it cannot function in BRCA1-deficient cells. Therefore, impaired BRCA1 facilitates NHEJ and suppresses HR leading to genome instability. The dysfunctional HR-induced persistently unrepaired DSB leads to senescence or apoptosis in cells[40,41] and promotion of NHEJ results in chromosome aberrations and cell death. Thus, acceleration of NHEJ and suppression of HR could be a promising target for PARP-inhibitor cancer treatment (Figure 2B).

Different situations arise in BRCA2- and BRCA1-mutated cells because BRCA2 does not affect DSB repair selection but functions downstream of the HR pathway. Functional BRCA1 suppresses the 53BP1-RIF1 signaling in the S/G2 cell cycle phase so that the HR pathway is chosen for PARP inhibitor-induced seDSB repair in both normal and BRCA2-mutated cells. Then, seDSB undergoes HR after end resection. However, DSB repair will be stalled and BRCA2 loss of function results in cell death (Figure 2C). Also, NHEJ inhibition reduces error-prone repair, chromosome aberrations, and rescued PARP inhibitor-induced cell lethality.[42,43] This model shows that cells harboring the BRCA1 mutation contain more gene variability and response to PARP inhibitor than those with the BRCA2 mutation because of NHEJ pathway predominance. Hence, BRCA1 and BRCA2 have different mechanisms of cellular lethality. Furthermore, Fanconi anemia-related tumor suppressors, including BRCA1 and BRCA2, protect nascent DNA from MRE11-dependent nucleolytic degradation in the replication fork and maintain genome stability.[44] Consequently, impairment of replication fork protection as a result of BRCA1 or BRCA2 dysfunction is considered to be an important mechanism for synthetic lethality by PARP inhibition.[45]

Some investigations indicated that other molecules besides BRCA1/2 could be potential targets of synthetic lethality. Loss of CtIP sensitized tumors both in vitro and in vivo to PARP inhibitor.[46,47] This response may be a result of CtIP-dependent end resection suppression that promotes the NHEJ pathway. Interestingly, dysfunction of Rad51 and other molecules involved in the HR pathway also triggered a sensitive response, blocking HR as BRCA2 defective.[48,49] Taken together, end resection and HR-related factors (CtIP, BRCA1, MRE11, Rad51, BRCA2 etc.) are potential PARP inhibitor targets for cancer treatment.

5 | PARP INHIBITOR RESISTANCE MECHANISMS

Poly(ADP-ribose) polymerase inhibitor-induced seDSB requires HR to be correctly repaired, and NHEJ is toxic to cells with seDSB. Consequently, resistance to PARP inhibitor might be acquired when the pathway choice shifts from NHEJ to HR. Here we present examples of resistance mechanisms that include restoration of HR function and avoidance of the NHEJ pathway.

5.1 | Secondary mutations in BRCA1/2

Cancer recurrence frequently occurs in HBOC patients despite the targeted treatment of tumors with BRCA1/2 mutations with several DNA damaging agents. Sakai et al[50,51] (2008 and 2009) first elucidated the in vitro mechanism by which the secondary mutations that restored BRCA2 function recovered DNA repair capacity, and became resistant to DNA-damaging agents such as cisplatin and PARP inhibitor. Functional restoration in BRCA2 caused by additional mutations canceled the original mutation-induced frameshift by reverting to an unimpaired C-terminal DNA-binding domain, nuclear localization signal, and Rad51-binding domain.[51,52] This type of resistance mechanism was also found in BRCA1-mutated cancer cells.[53] Furthermore, clinical data showed that secondary mutations restored not only BRCA1/2 but also Rad51 in recurrent and metastatic tumors from several cancers.[54-57] These findings indicate that replication stress-induced DNA damage would mainly depend on the HR pathway. Functional recovery of BRCA1/2-mediated HR would induce a therapeutic window collapse in the clinical strategy that uses DNA repair capacity differences between normal and cancer cells. Consequently, functional restoration may be a major resistance mechanism in PARP inhibitor-based therapy.

5.2 | Loss of 53BP1 in BRCA1-mutated cells

In BRCA1-mutated cells, PARP inhibitor effectively induces cell death by promoting NHEJ by activation of the 53BP1-RIF1 pathway and reducing HR efficiency through incomplete end resection and Rad51 recruitment. Several groups discovered that the loss of 53BP1 function caused PARP inhibitor resistance in BRCA1-defective cells.[25,58] Dysfunctional 53BP1 by frameshift mutation was also identified in PARP inhibitor-resistant BRCA1-mutated tumors in mice.[59] Considering the preference for the DSB repair pathway, loss of 53BP1 inactivates RIF1-dependent regulation of end resection in the absence of BRCA1, resulting in the promotion of HR. Moreover, loss of 53BP1 causes ring finger protein 8 (RNF8)-induced Rad51 recruitment even in the absence of BRCA1.[60] This combined HR pathway restoration of end resection and Rad51 recruitment functions as a cell survival backup mechanism in BRCA1-mutated cells treated with PARP inhibitor (Figure 3A). Markedly, 53BP1 rescues proliferation defects in BRCA1 but not in BRCA2-deficient mouse embryonic fibroblasts (MEF).[58] Both BRCA1 and BRCA2 defects in cells tend to induce spontaneous replication stress because of lower

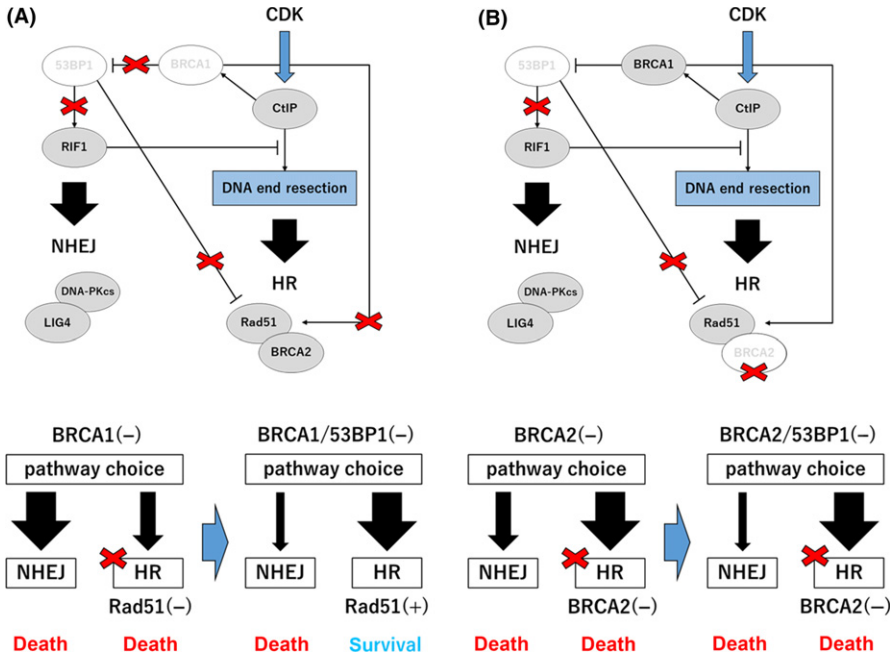

FIGURE 3 Loss of p53-binding protein 1 (53BP1)-induced resistance mechanism to poly(ADP-ribose) polymerase (PARP) inhibitor in breast cancer susceptibility gene 1 (BRCA1)- and breast cancer susceptibility gene 2 (BRCA2)-deficient cells through double-strand break (DSB) repair and ensuing pathways during the S/G2 cell cycle phase were compared. Pathway differences in PARP inhibitor sensitivity with additional loss of 53BP1 were analyzed in (A) BRCA1-deficient and (B) BRCA2-deficient cells. CDK, cyclin-dependent kinase; CtIP, C-terminal-binding protein interacting protein; DNA-PKcs, DNA-dependent protein kinase catalytic subunit; HR, homologous recombination; Lig4, DNA ligase IV; NHEJ, non-homologous end joining; RIF1, Rap1-interacting factor 1

HR activity. However, BRCA2 is an indispensable factor in the HR process after end resection. Therefore, the repair pathway shift through 53BP1 loss may not affect cell survival in BRCA2-deficient cells (Figure 3B).

5.3 | Additional resistance mechanisms to PARP inhibitor therapy

To date, in addition to secondary mutation and loss of 53BP1 function, different mechanisms underlying PARP inhibitor resistance have been described and resistance mechanisms can be divided into three groups (Table 1). The first group, "restoration of homologous recombination" includes demethylation of the BRCA1 promoter,[61] the aforementioned secondary mutation of BRCA1/2,[50-57] and loss of HR suppression factors such as 53BP1.[58-60,62-64] The second contains acquisition of replication fork protection.[65-69] The third has the P-glycoprotein (also known as multidrug resistance protein 1 [MDR 1] or ATP-binding cassette sub-family B member 1 [ABCB 1]). Indeed, increased PARP inhibitor efflux by overexpression of this transmembrane transporter has recently been reported.[70,71]

6 | CONCLUSIONS/FUTURE DIRECTIONS

Studies on PARP inhibitor-based clinical investigations are subject to heated discussions not only for HBOC but also for other types of cancer with DNA repair defects. The practical knowledge gained from clinical data preceded detailed elucidation of the PARP inhibitor-induced DNA damage mechanism and subsequent complicated repair process. Here, we have discussed synthetic lethality and potential resistance mechanisms to PARP inhibitor mainly in connection with DSB repair pathways. In particular, BRCA1, together with several other molecules, has several roles as a mediator of the HR pathway to sustain genome stability. Also, the factor-like loss of 53BP1 recovers the HR pathway even in the absence of BRCA1. Therefore, the clinical strategies to overcome the acquired resistance

TABLE 1 PARP inhibitor resistance mechanisms in BRCA1/2-associated cancers

Resistant type	HR defect	PARP inhibitor resistance mechanism	References
Restoration of homologous recombination	*BRCA1/2* mutation	*BRCA1/2* second mutation	50-57
	Hypermethylation of BRCA1 promoter	Demethylation of *BRCA1* promoter	61
	BRCA1 mutation	Dysfunction of HR suppression factors 53BP1, REV7, JMJD1C, RIF1	25,58-60, 62-64
Protection of replication forks	*BRCA2* mutation	Restoration of fork protection: Inhibition of molecules related with degradation of stalled replication forks	65-69
Increased efflux of PARP inhibitor	*BRCA1/2* mutation	Increased expression of P-glycoprotein (MDR1)	70,71

53BP1, p53-binding protein 1; BRCA1/2, breast cancer susceptibility gene 1/2; HR, homologous recombination; PARP, poly(ADP-ribose) polymerase; RIF1, Rap1-interacting factor 1.

to PARP inhibitor treatment for BRCA1- and BRCA2-mutated tumors should be different. In addition, other DSB repair pathways (microhomology-mediated end joining [MMEJ] and single-strand annealing [SSA]) could be sensitized to PARP inhibitor, but this hypothesis requires further investigation. The present review will contribute to the future development of both fundamental and clinical studies.

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CONFLICT OF INTEREST

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