Molecular Mechanisms of Resistance to PARP Inhibitors

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PARP1 enzyme plays an important role in DNA damage recognition and signalling. PARP inhibitors are approved in breast, ovarian, pancreatic, and prostate cancers harbouring a pathogenic variant in *BRCA1* or *BRCA2*, where PARP1 inhibition results mainly in synthetic lethality in cells with impaired homologous recombination. However, the increasingly wide use of PARP inhibitors in clinical practice has highlighted the problem of resistance to therapy. Several different mechanisms of resistance have been proposed, although only the acquisition of secondary mutations in *BRCA1/2* has been clinically proved.

PARP inhibitors BRCA1 BRCA2 homologous recombination non-homologous end joining fork stabilization

1. Introduction

Poly-(ADP-ribose) polymerase (PARP) enzyme PARP1 plays an important role in DNA damage recognition and signalling, as it binds single-stranded DNA breaks (SSBs) and then organizes their repair by synthesising PAR chains on target proteins (the so-called PARylation) [1]. In detail PARP1, once bound to SSBs via N-terminal zinc-finger DNA-binding domain, catalyses the polymerization of ADP-ribose moieties from NAD+ on target proteins, mainly PARP1 itself and histones. This process leads to chromatin relaxation and recruitment of other DNA repair enzymes such as XRCC1 [2][3][4][5]. The scaffolding protein XRCC1 stimulates the DNA kinase and DNA phosphatase activities of polynucleotide kinase at SSBs, accelerating the base excision repair reaction [6]. It is also reported that PARP1 promotes recruiting of MRE11, ATM and BRCA1, which are involved in double-stranded DNA break (DSB) repair by homologous recombination (HR) [7][8][9]. While PARP1 DNA binding is independent of its catalytic activity, dissociation of PARP1 from DNA requires PARylation presumably through a steric mechanism due to highly negatively charged PAR chains [10].

PARP inhibitors (PARPi) act mainly in a double way. The first proposed mechanism is the inhibition of the catalytic activity of PARP1, which results in synthetic lethality in cells with impaired HR [11][12][13]. In fact, inhibition of PARP1 promotes SSBs, which, if unrepaired, consequently lead to DSBs by collapse of the stalled replication fork during DNA replication [14]. In eukaryotic cells, DSBs are mainly resolved by the error-free mechanism of HR, which uses the intact sister chromatid as a template. HR deficiency induces activation of the more error-prone template-independent non-homologous end-joining (NHEJ) pathway, therefore, together with PARPi causing genomic instability followed by cell death [15][16]. Subsequent studies have revealed that most PARPi cause cytotoxicity by

trapping PARP1 at sites of DNA damage [17][18][19]. According to the hypothesis proposed by Murai et al. [18], PARPi binding to the catalytic domain of PARP1 allosterically modifies interactions between DNA and the N-terminal DNA-binding domain of the protein, to the point that PARP1 becomes trapped on DNA. More recently, a third mechanism of PARPi sensitivity has been identified [20][21]. In cells with HR deficiency, aside from the NHEJ pathway, DSBs can be repaired by the microhomology-mediated end joining (MMEJ or Alt-EJ) pathway. Similarly to NHEJ, MMEJ is intrinsically error-prone, as the use of regions of microhomology inside DNA leads to deletions of nucleotides from the strand being repaired and to chromosomal translocations. In this pathway, the efficient recruitment of the DNA polymerase POLQ to the DSB requires PARP1. A PARPi will, therefore, block the MMEJ pathway and cause HR-deficient cell death.

PARP inhibitors are actually approved in breast, ovarian, pancreatic and prostate cancers harbouring a pathogenic or likely pathogenic variant in *BRCA1* or *BRCA2* (*BRCA1/2*) [22][23][24]. *BRCA1/2* mutation prevalence varied widely from 1.8% in sporadic breast cancer to 36.9% in estrogen receptor/progesterone receptor low HER2 negative breast cancer [25]. Germline mutations in *BRCA1/2* have been identified in 13–15% of women diagnosed with ovarian cancer, and somatic mutations are found in an additional 7% [26][27][28]. Germline *BRCA1/2* mutations can be found in up to 8% of patients with sporadic pancreatic cancer [29]. In a sample of 692 patients with metastatic prostate cancer, unselected for family history or age at diagnosis, 5.3% carried a *BRCA2* mutation, and 0.9% carried a *BRCA1* mutation [30]. The increasingly wide use of PARPi in clinical practice is highlighting the problem of resistance to therapy. Considering the complex interaction between PARP1, HR and other DNA damage repair pathways in the setting of *BRCA1/2* mutated cancers, several different mechanisms of resistance have been proposed, although some of them have been only described preclinically. The aim of this entry is to outline the key molecular findings that could explain the mechanisms of primary or secondary resistance to PARPi (summarised in **Table 1**).

Table 1. Proposed mechanisms of PARPi resistance.

Resistance Mechanism	Evidence	References
Primary resistance		
PI3K/AKT pathway activation	Cell lines	Yi et al. [31]
Wild-type PTEN	Cell lines	Dedes et al. [32]
Loss of NHEJ	Cell lines	Balmus et al. [33], Patel et al. [34], Mc Cormick et al. [35]
ALC1 overexpression	Cell lines	Juhász et al. [36]
Secondary resistance		
Upregulation of ABC transporters	Mouse models, cell lines	Jaspers et al. [37], Vaidyanathan et al. [38]

Resistance Mechanism	Evidence	References
Decreased PARP1 trapping	Mouse models, cell lines	Pettitt et al. [39], Gogola et al. [40]
Restoration of HR		
-*BRCA1/2* reversion mutations	Tumour DNA and ctDNA from cancer patients	Tobalina et al. [41]
-Hypomorphic *BRCA1* allele	Cell lines, mouse models, PDXs	Drost et al. [42], Wang et al. [43], Cruz et al. [44], Wang et al. [45], Castroviejo-Bermejo et al. [46]
-Loss of *BRCA1* promoter methylation	Cell lines, PDXs	Ter Brugge et al. [47], Veeck et al. [48], Wang et al. [49]
-Loss of end resection regulation (53BP1, RIF1, REV7, Sheldin complex or DYNLL1 depletion)	Cell lines	Belotserkovskaya et al. [50], Xu et al. [51], Noordermeer et al. [52], Gupta et al. [53], He et al. [54]
-RAD51 overexpression	Ovarian cancer samples, cell lines	Kondrashova et al. [55], Liu et al. [56], Marzio et al. [57]
Stabilization of stalled fork (FANCD2 overexpression, RADX depletion, SMARCAL1 inactivation,)	Cell lines	Michl et al. [58], Chaudhuri et al. [59], Taglialatela et al. [60], Dungrawala et al. [61]

NHEJ: non-homologous end-joining. PDXs: patient-derived xenografts.

2. Primary Resistance

2.1. PTEN Deficiency and PI3K/AKT Pathway Activation

Phosphatase and tensin homolog (PTEN) is a dual protein/lipid phosphatase that acts as a tumour suppressor gene inhibiting the PI3K/AKT pathway. In detail, PTEN converts phosphatidylinositol 3,4,5-triphosphate (PIP3) into phosphatidylinositol 4,5-bisphosphate (PIP2), antagonising PI3K action and preventing AKT activation and consequent cell growth and cell proliferation [62][63]. *PTEN* is often inactivated in different cancers [64]. Although AKT activation promotes BRCA1 expression through phosphorylation [65], it has been shown that BRCA1 can downregulate AKT activation in different ways: by acting on upstream kinases of AKT [31][66], by ubiquitin-mediated proteasomal degradation or by activating a protein serine/threonine phosphatase, PP2A, in breast cancer cells (**Figure 1**) [67]. Therefore, negative mutations and/or reduced expression of *BRCA1* may activate the PI3K/AKT pathway [67]. Significantly, PTEN loss is highly associated with *BRCA1*-defective breast cancers, probably due to genomic instability resulting from deficient DSB repair [68], and the resulting PI3K/AKT activation stimulates the growth of those cancers [69].

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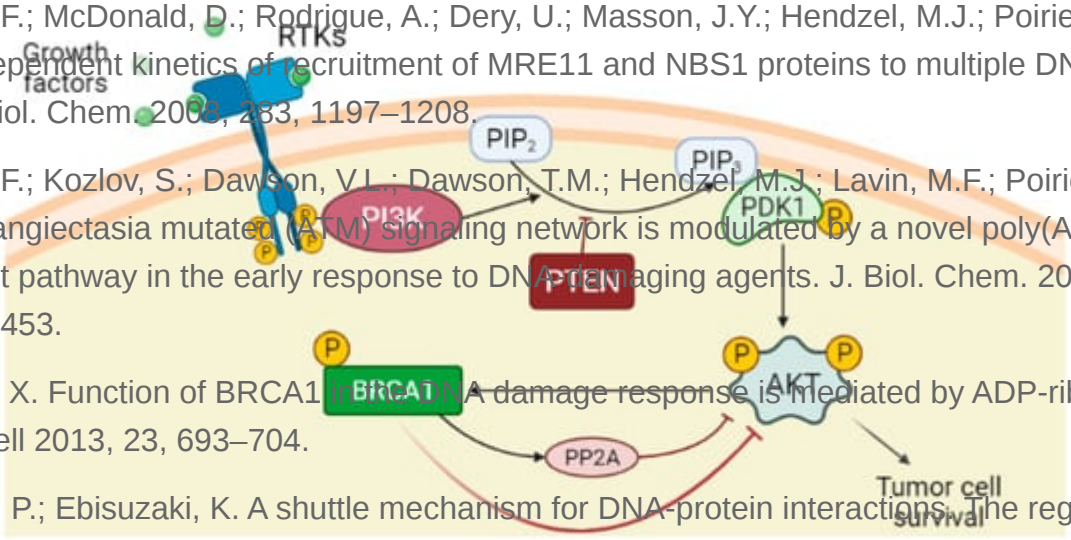

Figure 1. PI3K/AKT pathway is an intracellular signal transduction pathway that promotes cell growth and proliferation in response to extracellular signals. The binding of the ligands such as growth factors to the receptor tyrosine kinases (RTKs) induces dimerization of RTK monomers, which consequently leads to activation of the intracellular tyrosine kinase domain and auto-phosphorylation by each monomer. The phosphatidylinositol 3-kinase (PI3K), once activated through direct stimulation of the regulatory subunit bound to the activated receptor, converts phosphatidylinositol 4,5-bisphosphate (PIP2) into phosphatidylinositol 3,4,5-triphosphate (PIP3). PIP3 binds the 3-phosphoinositide-dependent protein kinase-1 (PDK1) at the plasma membrane. PDK1 in turn phosphorylates and activates AKT protein. Once activated, AKT via phosphorylation regulates activation or suppression of several proteins involved in cell growth and proliferation. Phosphatase and tensin homolog (PTEN) is the main downregulation protein that can convert PIP3 into PIP2. Although AKT activation promotes BRCA1 expression through phosphorylation, BRCA1 can downregulate AKT activation by different mechanisms, among which are the activation of protein phosphatase 2A (PP2A), which dephosphorylates AKT.

Apart from its role in regulating the PI3K/AKT pathway, PTEN loss of function causes genetic instability, as *PTEN*-*null* cells lack competent HR DNA repair. In detail, PTEN has been suggested to contribute to RAD51 expression [70][71][72]. Dedes et al. [32] demonstrated that endometrioid endometrial cancer cell lines lacking PTEN function are unable to elicit competent HR DNA repair and are relatively sensitive to PARPi, and, as a consequence, *PTEN*-silencing significantly increases the sensitivity to PARPi reducing RAD51 foci formation. Re-expression of *PTEN* in PTEN-mutant endometrioid endometrial cancer cells leads to relative resistance to PARPi [32].

Together, these observations corroborate the hypothesis that PTEN loss, which is highly associated with *BRCA1*-defective breast cancer, contributes to PARPi sensitivity. On the other hand, wild-type *PTEN* tumours could demonstrate relative resistance to PARPi. Considering that the PI3K/AKT pathway is constitutively active in *BRCA1*-defective human cancer cells [73], the combination of PTEN-related PI3K/AKT pathway inhibitors such as perifosine with DNA topoisomerase I (TOP1) or PARPi results in enhanced cancer cell killing in these tumours [74][75], suggesting a new possibly targetable pathway in case of PARPi resistance. A phase I trial of the PARPi

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Olaparib with the AKT inhibitor capivasertib, including patients with advanced solid tumours carrying a germline *BRCA1/2* mutation or somatic DNA damage response and PI3K/AKT pathway alterations, demonstrated the safety, tolerability and pharmacokinetic–pharmacodynamic activity of this combination [76].

2.2. ATM Roles and Loss of NHEJ Pathway

The choice between NHEJ and HR to repair DSBs is determined by several mechanisms, including activation of HR by cyclin-dependent kinase (CDK) activity (while NHEJ operates throughout interphase, HR is restricted to the S and G2 phase of the cell cycle, when a homologous sister chromatid is available as template) [16], or direct competition between HR and NHEJ stimulating factors at DSB sites [77]. During G2/S, HR is activated by binding of the MRE11–RAD50–NBS1 (MRN) complex to DSB ends. The MRN complex initiates DNA end resection, leading to the formation of single-strand DNA (ssDNA) at the extremity of the DSB. The ssDNA is protected from degradation by the loading of replication protein A (RPA) [78]. CtIP phosphorylated by CDK binds MRN complex to facilitate end resection [79]. The MRN complex recruits and activates the protein kinase ATM [80], while the sensor protein RPA finally drives ATR activation [81]. ATM and ATR phosphorylate several proteins involved in the HR [82]. The tumour suppressor complex BRCA1-BARD1 phosphorylated by ATM facilitates DNA end resection and interacts with PALB2, which in turn promotes the recruitment of BRCA2 [54]. PALB2 and BRCA2 remove RPA and facilitate the assembly of the RAD51 recombinase nucleoprotein filament. RAD51 nucleoprotein filament mediates the invasion of ssDNA into the intact sister chromatid, searching for a homologous template for DNA synthesis and repair [83][84][85]. During G1/2, 5′-3′ end resection is suppressed, and HR is inhibited due to the lack of sister chromatid [86]. ATM phosphorylates 53BP1 in multiple residues [87]. Once phosphorylated, 53BP1 binds and recruits RIF1 and PTIP that, together with the downstream effectors REV7 and Shieldin, inhibit 5′-3′ end resection and promote NHEJ [88]. Classical NHEJ starts when Ku70/80 heterodimer binds DSBs and recruits the DNA-dependent protein kinase catalytic subunit (DNA-PKcs) to form the DNA–PK complex. The latter engages XRCC4 and DNA ligase IV (LIG4) to align and ligates DNA ends regardless of sequence homology [89]. BRCA1 antagonizes 53BP1 by limiting its interaction with the chromatin in the S phase and stopping the translocation of RIF1 to DSBs in the G2/S phase, promoting HR [90][91]. Additionally, the different recruitment kinetics of the MRN and Ku complexes, which activate HR and NHEJ repair, respectively [92], as well as MRN/CtIP-dependent removal of Ku complex from DSBs [93], influence the choice between the two pathways (**Figure 2**).

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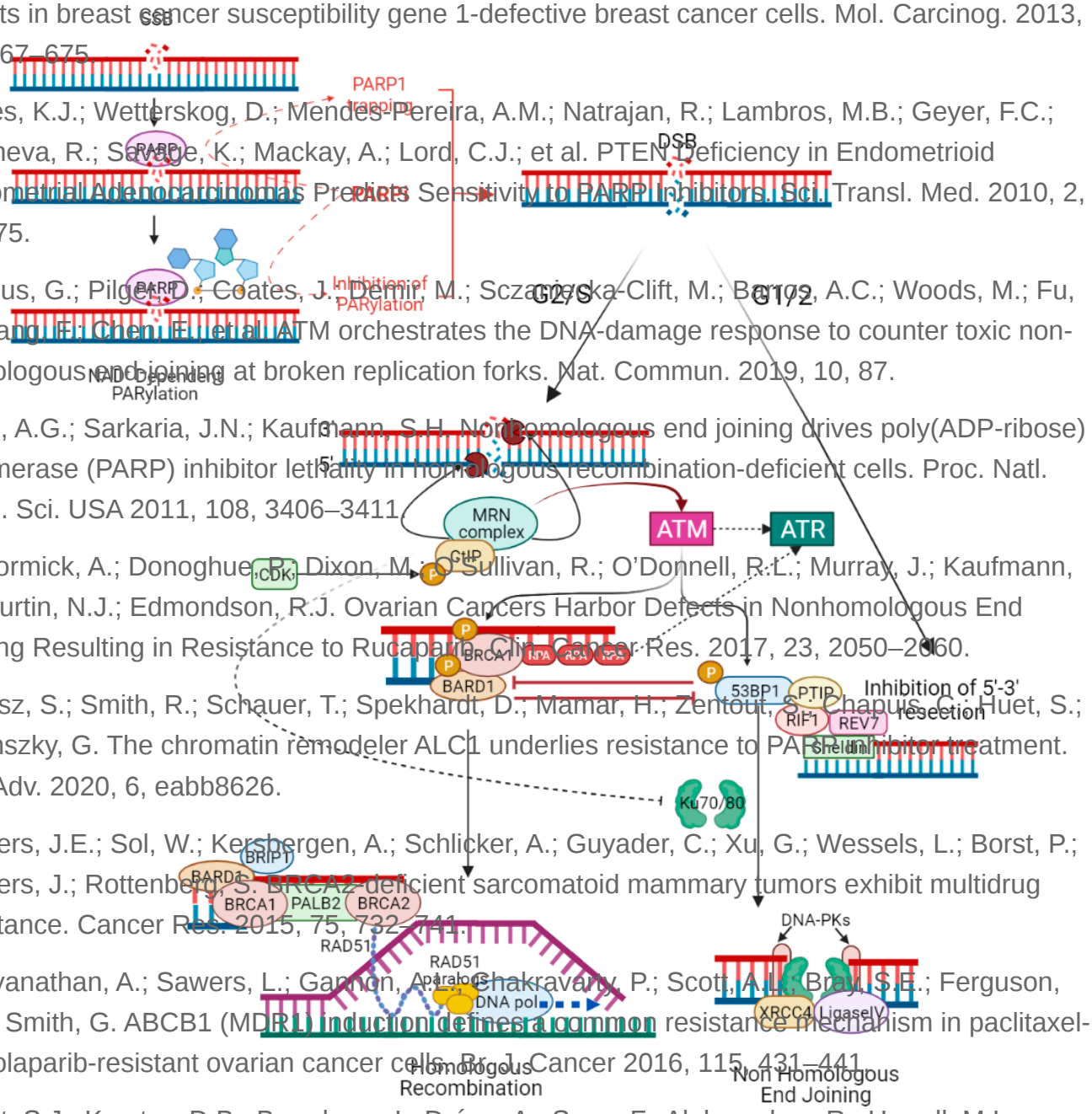

Figure 2. PARP inhibitors and the interactions between homologous recombination and non-homologous end joining. PARPi act mainly in a double way: inhibiting the catalytic activity of PARP1 (the so-called PARylation) and trapping PARP1 at sites of single-stranded DNA breaks (SSBs). In both cases, unrepaired SSBs lead to double-stranded DNA breaks (DSBs), which can be resolved mainly by HR or NHEJ. The choice between NHEJ and HR to repair DSBs is determined by several mechanisms, including activation of HR by cyclin dependent kinase (CDK) activity. HR is restricted to G2/S phase when a homologous sister chromatid is available as template), or direct competition between HR and NHEJ stimulating factors at DSB sites. During G2/S, HR is activated by the binding of the MRN complex to DSB ends; MRN complex initiates DNA 5′-3′ end resection, leading to the formation of single-strand DNA (ssDNA) at the extremity of the DSB. CDK phosphorylated CtIP binds MRN complex to facilitate end resection. The ssDNA is protected from degradation by the loading of replication protein A (RPA). The MRN complex recruits and activates the protein kinase ATM, while RPA finally drives ATR activation.

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3. Secondary Resistance

Secondary or acquired resistance can be defined as the onset of the lack of response to treatment despite being successfully used before. Under therapeutic selective pressure, resistance to cytotoxic or target agents can emerge due to the expansion of pre-existing subclonal populations or from the evolution of drug-tolerant cells [97]. Several mechanisms of acquired resistance to PARPi have been suggested, although only reversion mutations in *BRCA1/2* have been proved in the clinical setting.

3.1. Upregulation of ABC Transporters

Increased expression of the membrane-bound ATP-dependent efflux pump P-glicoprotein, encoded by *ABCB1* (MDR1), is one of the most well-characterised mechanisms of multidrug resistance [98], in particular for doxorubicin, paclitaxel and related drugs [99][100][101]. A chromosomal amplification event that has been reported to increase *ABCB1* copy number and consequent P-glycoprotein levels in paclitaxel-resistant cancer cells [102].

Using a mouse model of *BRCA2*-deficient sarcomatoid breast cancer, Jaspers et al. [37] found that multidrug resistance was strongly associated with high expression of the ABCB1, known to be efflux transporter of Olaparib [103], docetaxel [104], and doxorubicin [105]. In novel A2780-derived ovarian cancer cell lines, paclitaxel-resistant cells were cross-resistant to the PARPi Olaparib and Rucaparib but not to Veliparib. This resistance correlated with increased ABCB1 expression and was reversible following treatment with ABCB1 inhibitors [38]. These findings, although cell-line based, could help in PARPi choice in paclitaxel-resistant patients, especially in second-line or maintenance therapy.

3.2. Decreased PARP1 Trapping

Through a genome-wide and high-density CRISPR-Cas9 mutagenesis screen to identify mouse embryonic stem cell mutants resistant to the PARPi Talazoparib, Pettitt and colleagues [39] identified point mutations in the N-terminal zinc-finger domain of PARP1 that, abolishing DNA binding, cause PARPi resistance and alter PARP1 trapping. In support of this finding, they also observed a PARP1 mutation that abolished trapping in a patient with de novo resistance to Olaparib. In this experimental model, also mutations in amino-acid residues involved in hydrogen-bonding interactions that bridge the DNA-binding domain and the catalytic domain can cause PARPi resistance, likely by impairing PARP1 trapping; this reinforces the observations that inter-domain interactions are critical for PARP1 binding and activation [2][3][4].

PAR glycohydrolase (PARG) is the main enzyme responsible for degrading PAR chains, counteracting PARylation catalyzed by PARP1 [106]. By combining genetic screens with multi-omics analysis of matched PARPi-sensitive and resistant *BRCA2*-mutated mouse mammary tumours, Gogola et al. [40] identified loss of PARG as a major resistance mechanism. In a cohort of 94 PARPi-resistant tumours, they observed decreased expression of *Parg* in 17 tumours and acquired copy-number loss of the *Parg* locus in 22 tumours. Moreover, they demonstrated that PARG depletion does not increase PARP1 trapping per se but prevents excessive PARP1 binding to chromatin, thus reducing PARPi-dependent accumulation of toxic PARP1–DNA complexes. As a confirmation of this, PARG depletion also resulted in resistance to Talazoparib, a highly potent PARP1–DNA trapping agent. Finally, they found PARG-negative cell clones in a subset of human serous ovarian and triple-negative breast cancers (TNBCs), suggesting that this mechanism can contribute to PARPi resistance in vivo.

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