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Mechanisms of acquired resistance of BRCA1/2-driven tumors to platinum compounds and PARP inhibitors

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Abstract

Molecular pathogenesis of tumors arising in *BRCA1/2* germ-line mutation carriers usually includes somatic inactivation of the remaining allele of the involved gene. Consequently, *BRCA1/2*-driven cancers are sensitive to platinum-based therapy and poly (ADP-ribose) polymerase inhibitors (PARPi). Long-term exposure to these drugs may result in the emergence of secondary *BRCA1/2* mutations, which restore the open-reading frame of the affected allele. This platinum/PARPi cross-resistance mechanism applies both for *BRCA1* and *BRCA2* genes and has been repeatedly validated in various laboratory models and multiple clinical studies. There are some other routes associated with the partial rescue of *BRCA1/2* function or the development of *BRCA1/2*-independent pathways for genomic maintenance; however, their actual clinical relevance remains to be established. In addition, studies on the short-term neoadjuvant therapy for ovarian cancer revealed that even chemonaive *BRCA1*-driven tumors contain a small proportion of *BRCA1*-proficient cells. These pre-existing cells with retained *BRCA1* heterozygosity rapidly repopulate the tumor mass during platinum exposure, but become outcompeted by *BRCA1*-deficient cells during therapy holidays. Understanding of the platinum/PARPi resistance pathways has led to the development of novel therapeutic approaches, which aim to improve the management of *BRCA1/2*-related cancers and are currently undergoing preclinical and clinical evaluation.

Key Words: *BRCA1/2* mutations; Platinum-based therapy; Poly (ADP-ribose) polymerase inhibitors; Drug resistance; Secondary mutations; Intratumoral heterogeneity; Neoadjuvant therapy

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Core Tip: BRCA1/2-associated tumors are highly sensitive to platinum compounds and poly (ADP-ribose) polymerase inhibitors; however, they eventually acquire resistance to this type of therapy. Restoration of *BRCA1/2* function *via* the second mutation is the most known mechanism of tumor adaptation to the therapeutic pressure. Some studies demonstrate that even chemo-naïve BRCA1-driven tumors contain a small fraction of BRCA1-proficient cells suggesting that the loss of the remaining allele of this gene is not the first event in tumor pathogenesis. These pre-existing platinum-resistant cells rapidly repopulate tumor mass during neoadjuvant therapy for ovarian cancer and explain inevitability of the disease relapses after seemingly successful surgical debulking.

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INTRODUCTION

Germ-line mutations in *BRCA1* and *BRCA2* genes are the most well-known cause of hereditary cancer predisposition. *BRCA1/2* pathogenic variants contribute to approximately 5%-10% and 15%-30% breast and ovarian cancer morbidity, respectively[1-6]. In addition, both mentioned genes are involved in the pathogenesis of a subset of stomach cancers, and the inheritance of *BRCA2* inactive alleles is associated with an increased risk of prostate and pancreatic malignancies[7,8]. *BRCA1/2*-driven tumors tend to have particular clinical characteristics, being associated with younger age at onset and highly malignant phenotype[9,10]. Breast carcinomas (BCs) occurring in *BRCA1* mutation carriers usually lack the expression of estrogen and progesterone receptors, and *BRCA1/2*-associated ovarian cancers (OCs) are characterized by serous high-grade histological appearance[10,11].

Breast and ovarian tumors arising in patients with *BRCA1/2*-associated hereditary cancer syndrome usually develop *via* somatic inactivation of the remaining allele of the involved gene. *BRCA1* and *BRCA2* play a key role in the maintenance of genomic integrity. Consequently, cancers lacking functional *BRCA1* or *BRCA2* proteins are deficient in DNA repair by homologous recombination (HR). Platinum compounds and poly (ADP-ribose) polymerase inhibitors (PARPi) induce massive DNA damage, which requires an HR-mediated repair. *BRCA1/2*-null cells are deficient for HR and consequently die upon the action of platinum salts or PARPi. This drug sensitivity is tumor-selective, as the normal cells of the patient retain one functional copy of *BRCA1/2* gene and therefore remain capable of coping with the DNA damage[12-14].

As mentioned above, *BRCA1/2*-related hereditary tumors constitute a significant portion of OCs. In addition, many high-grade serous OCs have other causes of HR deficiency, *e.g.*, somatic biallelic inactivation of *BRCA1/2* genes or the presence of germ-line mutations in other members of DNA repair pathways[1,15]. This explains the high efficacy of platinum-based chemotherapeutic regimens in OC, which were developed empirically before the discovery of *BRCA1/2* genes and constitute a standard-of-care for OC management. As expected, platinum therapy demonstrates increased efficacy in hereditary *vs* sporadic ovarian tumors[2,16]. In contrast to OC, *BRCA1/2* deficiency is characteristic only for a minority of breast tumors; therefore, platinum compounds are not incorporated in the conventional treatment schemes for non-selected BC patients. Several trials demonstrated that platinum salts might outperform other chemotherapeutic agents when applied to *BRCA1/2*-driven BCs[17-19]. PARPi have been developed specifically for targeting tumors characterized by *BRCA1/2* and/or HR deficiency. There are several PARPi approved for clinical use with slightly varying medical indications[20,21].

Although *BRCA1/2*-driven tumors have a clear-cut vulnerability, the use of platinum salts or PARPi does not usually result in a cure from metastatic disease. Platinum- and PARPi-exposed cancers eventually manage to escape from the action of *BRCA1/2*-specific therapy. Multiple preclinical and clinical studies have identified

various BRCA1/2-restoring mechanisms or bypass pathways, which resume resistance to DNA damage in initially HR-deficient tumor cells. Recent investigations also provided evidence for an alternative scenario, where the emergence of the platinum-resistant tumor clone is attributed to a selection of pre-existing BRCA1-proficient cells; these therapy-resistant cells persist in small amounts in chemo-naïve tumors but are enriched in the residual lesion. This paper provides a brief overview of the mechanisms of acquired platinum and PARP-resistance in BRCA1/2-driven tumors.

RESTORATION OF *BRCA1/2* FUNCTION BY SECONDARY SOMATIC MUTATIONS

The vast majority of *BRCA1/2* inherited pathogenic alleles are represented by small alterations in the nucleotide sequence, which cause a frameshift and emergence of premature stop-codons. The open reading frame (ORF) can be rescued by a nearby second mutation if it restores an original 3-letter genetic code, or by small deletion, which excises the pathogenic allele and reconstitutes the ORF, or by the true back mutation (Figure 1)[22-24]. A secondary ORF-restoring *BRCA2* mutation was first described in an acute myeloid leukemia cell line obtained from a patient with Fanconi anemia[25]. The discovery of PARPi and the recognition of BRCA1/2-specific action of platinum compounds stimulated intense investigations of the mechanisms of tumor resistance to these drugs. A series of studies revealed that the emergence of secondary *BRCA1/2* mutations is the most reproducible hallmark of the acquisition of a drug-resistant phenotype. Indeed, the reversion mutations have been repeatedly observed in the experiments with cell lines, patient-derived xenografts (PDX) and clinical samples[26,27].

For the time being, the development of secondary ORF-restoring mutations in *BRCA1/2* genes is the only clinically proven mechanism of the tumor adaptation to the therapy, which is relevant both to platinum compounds and PARPi, characteristic both for *BRCA1* and *BRCA2* genes, and has been convincingly validated in patient samples. The true incidence of secondary *BRCA1/2* mutations is difficult to presently define due to various selection biases and technical limitations of available molecular genetic assays: They appear to be found in approximately a quarter of PARPi/platinum-resistant tumors, although some studies provide even higher estimates. Importantly, many reports describe the emergence of multiple distinct *BRCA1/2* ORF-restoring mutations in independent drug-resistant clones obtained from the same patient, thus providing evidence for the functional convergence of tumor adaptation pathways[26, 27].

Some data suggest that the genetic reversion is somewhat more characteristic for *BRCA2*- than for *BRCA1*-driven tumors. Distinct pathogenic variants of *BRCA1* and *BRCA2* may differ in their ability to be rescued by the second mutation: It is hypothesized that the genetic reversion is more acceptable for non-conservative regions of the above genes, which are more or less dispensable for their function. Indeed, in all cases, except genuine back mutations, the involved region of *BRCA1* and *BRCA2* genes undergoes subtle alterations (*i.e.* the deletion of a few coding nucleotides or the change of the sequence for a few amino acids); therefore, highly conserved parts of these genes may not tolerate this mechanism of genetic adaptation[14,26,27].

In addition to secondary mutations affecting the coding sequence of *BRCA1/2* genes, there are functionally similar events resulting in the production of hypomorphic but still functional protein. For example, loss of exon 11 is compatible with the participation of *BRCA1* in HR; consequently, alternative splicing resulting in the *BRCA1* exon 11 skipping may contribute to the acquired drug resistance[28]. The mutation located in the N-terminal portion of the *BRCA1* gene can be bypassed by the production of a hypomorphic protein, whose translation starts after the frameshift[29]. Another mechanism of the partial rescue of *BRCA1* function involves gene rearrangements, which terminate *BRCA1* translation before the mutation-containing BCRT domain, consequently preventing the proteasomal degradation of *BRCA1*. These truncated versions of *BRCA1* are capable of maintaining HR and mediate PARPi resistance[30]. Upregulation of HSP90 may stabilize some *BRCA1*-mutant proteins and thus support their function[31]. Amplification of mutated *BRCA2* was shown to compensate for partial loss of *BRCA2* function and rendered PARPi resistance in cell line experiments [32].

Some *BRCA1/2* germ-line pathogenic alleles are represented by so-called large gene rearrangements (LGRs), which may involve deletions of multiple exons. By definition, these tumors cannot be repaired by the second ORF-restoring mutation. One would

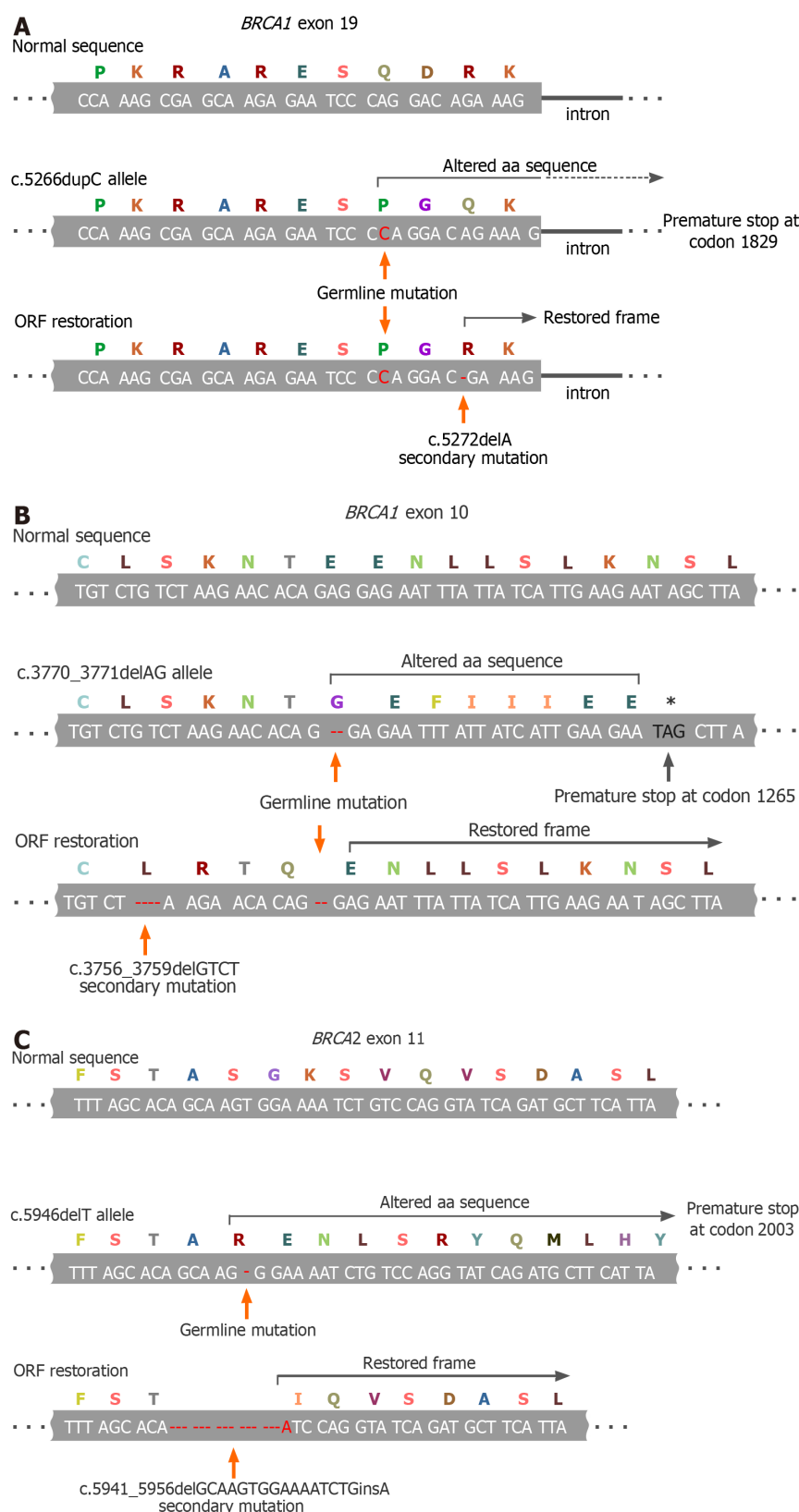


Figure 1 Examples of *BRCA1/2* open-reading frame restoration in *BRCA1/2*-mutated tumors during systemic therapy. A: Secondary 1-bp deletion occurring downstream to the germline mutation (*BRCA1* c.5266dupC; described in[22]); B: Secondary 4-bp deletion located upstream to the germline mutation (*BRCA1* c.3770_3771delAG; an example from[23]); C: Secondary in-frame deletion/insertion excising the mutation-containing gene fragment (*BRC42* c.5946delT; an example from[24]). ORF: Open-reading frame.

expect that these tumors are likely to demonstrate a more pronounced and prolonged response to *BRCA1/2*-specific therapy. *BRCA1/2* LGRs are not specifically considered in the studies on tumor drug sensitivity. However, there are case reports supporting

exceptional responsiveness of *BRCA1/2* LGR-associated tumors to PARPi[33].

BYPASS MECHANISMS

There are two key mechanisms of the repair of DNA double-strand breaks (DSB). Accurate correction of DNA sequence can be achieved exclusively by HR. In the absence of functional HR, error-prone non-homologous end-joining (NHEJ) becomes a prevailing mechanism of DSB repair. The choice between HR and NHEJ is mediated by the balance between their regulators, *BRCA1* and *53BP1*. When *BRCA1* is inactivated by mutation, NHEJ-driven DNA repair prevails. This results in the accumulation of multiple DNA lesions and eventual cell death. *BRCA1*-deficient cells may adapt to the platinum or PARPi pressure by down-regulation of *53BP1*. As a result of consequent NHEJ suppression, tumor cells re-activate HR and eventually become resistant to the drug exposure[31,34,35]. Down-regulation of *53BP1* has been observed in some clinical samples that failed platinum-based or PARPi therapy[31,36,37]. *In vitro* studies revealed several other proteins whose loss also contributes to the switch from NHEJ to HR or to other bypass pathways. Noticeably, the involvement of *53BP1* exemplifies the differences between *BRCA1*- and *BRCA2*-mutated tumors, as the loss of *53BP1* or related proteins is relevant only for the treatment escape of *BRCA1*-deficient cancers[34]. Preclinical studies also identified HR-independent platinum/PARPi resistance mechanisms, which involve stabilization of replication forks[38].

BRCA1/2-NON-RELATED MECHANISMS OF ACQUIRED RESISTANCE TO PLATINUM COMPOUNDS AND PARPi

The above-described mechanisms of acquired therapy resistance are more or less specific for the *BRCA1/2*-associated action of platinum salts and PARPi. There are also general mechanisms for the adaptation of tumor cells to the therapy, which are indirectly related to the targeted biological pathway and may involve activation of the drug efflux, down-deregulation of apoptosis, preservation of tumor cancer stem cells (CSCs) and epithelial-mesenchymal transition (EMT)[39]. Up-regulation of *ABCB1* (MDR1) transporter has been implicated in multidrug resistance. Therapy-resistant ovarian and breast carcinomas are characterized by gene fusions, which result in increased expression of the *ABCB1* gene[40]. The translational implications of these observations are not immediately clear: Drug transporters are involved in multiple physiological processes and are characterized by significant redundancy, so their targeting may be associated with significant adverse events and insufficient clinical efficacy[41]. There are reports demonstrating the selection of CSCs upon PARPi exposure[42]. The role of EMT in the development of PARPi resistance has been shown in preclinical studies involving *BRCA2*-deficient cells[43].

SELECTION OF PRE-EXISTING BRCA1-PROFICIENT CELLS DURING PLATINUM-BASED THERAPY

A significant portion of OC patients present with the inoperable disease; therefore, they undergo neoadjuvant (first-line) therapy aimed to reduce the tumor burden and permit surgical excision of the remaining cancer lumps. *BRCA1*-driven cancers are particularly sensitive to systemic platinum-based treatment; hence, this category of OC is usually amenable to complete surgical debulking. Despite that presumably efficient platinum-based therapy is administered again after the surgery, it apparently cannot eliminate the residual cancer cells, given that almost all OC treated by this scheme eventually relapse[44].

Comparison of tumor specimens obtained before the start of the treatment and after a few weeks of neoadjuvant therapy revealed surprising findings (Figure 2). While chemonaive *BRCA1*-associated OCs are characterized by somatic loss of heterozygosity (LOH) of the remaining allele, the residual tumors obtained after a few weeks of neoadjuvant therapy often show the retention of the wild-type *BRCA1* copy. This “restoration of heterozygosity” occurs due to the selection of preexisting *BRCA1*-proficient cells, which persist in small amounts in chemonaive tumors; these isolated tumor cells with retained *BRCA1* function can be visualized by various imaging

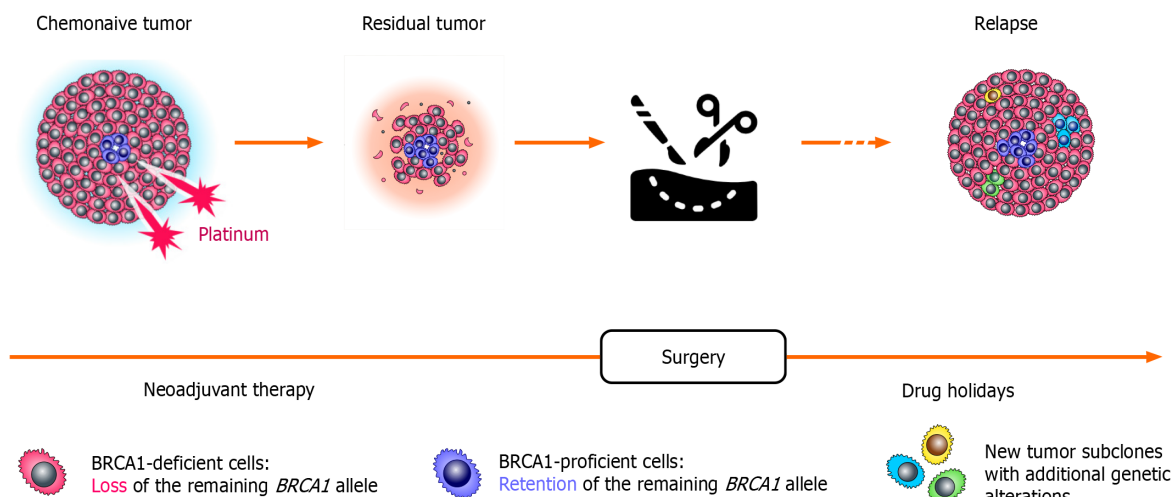


Figure 2 Selection of pre-existing BRCA1-proficient cells during platinum-based therapy. Loss of the remaining *BRCA1* allele is observed in the majority of cells forming the tumor; however, even chemo-naïve BRCA1-driven ovarian cancers contain a small fraction of transformed cells with retained *BRCA1* heterozygosity. These cells are platinum-resistant and rapidly repopulate tumor mass during neoadjuvant therapy for ovarian cancer. During platinum-free interval, which occurs after the completion of the adjuvant therapy, these BRCA1-proficient cells become outcompeted by cells carrying *BRCA1* LOH. Therefore, ovarian cancer relapses resemble primary tumors with regard to the *BRCA1* status, as they demonstrate again the *BRCA1* deficiency and the sensitivity to platinum compounds.

techniques. Importantly, both primary cancers and residual tumor masses were shown to retain the same mutation in the *TP53* gene. Loss of *BRCA1* in normal cells triggers apoptosis, while cells with inactive *TP53* may survive *BRCA1* deficiency. It appears that *TP53* mutation must be acquired in the very initial stages of the tumor evolution, while *BRCA1* LOH, being a key event in the pathogenesis of BRCA-driven cancers, can emerge and be tolerated only after *TP53* inactivation. The persistence of isolated BRCA1-proficient cells within a gross tumor mass is common for BRCA1-driven cancers, as the “restoration” of *BRCA1* heterozygosity is observed approximately in two-thirds of BRCA1-associated OCs[45].

Intriguingly, the relapse OC tissues obtained from the same patients after therapy holidays show *BRCA1* LOH again, thus providing a mechanistic explanation for the platinum sensitivity of recurrent BRCA1-associated cancers (Figure 2). Exome sequencing revealed that only *TP53* mutation is stably maintained throughout the natural history of BRCA1-driven cancers, while the profiles of somatic point mutations and chromosome number alterations show some variations between chemo-naïve, post-neoadjuvant and recurrent tumor specimens. Overall, it appears that BRCA1-driven tumors present an ecosystem: While the gross majority of tumor mass is BRCA1-deficient, there are apparently some biological reasons to maintain the persistence of small amounts of BRCA1-proficient cells. In the absence of external hazards, BRCA1-deficient cells clearly outcompete cells with retained *BRCA1* function. However, these cells are sensitive to platinum exposure and perhaps to some other kinds of unfavorable environment, so the maintenance of the reservoir of invulnerable (BRCA1-proficient) cells is important for warranting tumor plasticity. Upon drug pressure, BRCA1-proficient cells take advantage and increase their relative fraction in residual tumor mass; however, they again lose the competition after the cessation of the systemic treatment[46]. The above observations fit very well with the concept of tumor “stem cells” as a cause of acquired drug resistance.

The platinum-induced selection of pre-existing BRCA-proficient cells has been demonstrated only for the *BRCA1* gene, while similarly designed studies have not been performed yet for BRCA2-associated tumors. It is not self-explanatory that the same phenomenon is applicable to BRCA2-driven cancers. Indeed, although both *BRCA1* and *BRCA2* proteins are involved in the response to DNA damage, they have essential dissimilarities in their structure and function[14]. Consequently, they demonstrate differences regarding the spectrum of associated tumors, with prostate and pancreatic cancer been strongly linked to *BRCA2* but not to *BRCA1* heterozygosity[7]. Breast carcinomas arising in *BRCA1* germ-line mutation carriers are usually triple-negative with regard to the receptor status (ER, PgR and HER2), while *BRCA2*

pathogenic alleles are generally associated with the development of tumors expressing steroid hormone receptors[10,11]. *BRCA1* but not *BRCA2* is essential for taxane-mediated cell death, so the resistance to taxanes is characteristic for *BRCA1*- but not for *BRCA2*-deficient cells[12]. The emergence of ORF-restoring secondary mutations in heavily pretreated tumors appears to be somewhat more common for *BRCA2* than for *BRCA1* gene[26,27]. *BRCA1* deficiency is lethal for normal cells; therefore, the development of cancers in *BRCA1* germ-line mutation carriers always involves mutation-driven inactivation of the *TP53* gene, which results in down-regulation of apoptosis and provides the ground for the survival of *BRCA1*-null cells. In contrast, *BRCA2* inactivation is compatible with cell viability, so *BRCA2*-associated tumors often have wild-type *TP53* status[47]. While the persistence of *BRCA1*-proficient cells in chemo-naïve *BRCA1*-driven tumors is essential for the adaptation of OC to platinum-based therapy, it is unclear how this intratumoral heterogeneity supports the maintenance of tumor mass in “natural” conditions. This intratumoral heterogeneity may not necessarily be characteristic for the cancers arising in *BRCA2* germ-line mutation carriers. Further studies are needed to reveal whether the persistence of isolated HR-proficient “stem” cells is relevant for *BRCA2*-driven tumors or sporadic OCs with BRCAness phenotype.

CONTROVERSIAL AND UNRESOLVED ISSUES

Platinum compounds and PARPi converge in their mechanisms with regard to targeting HR-deficient cells; however, there are also some differences in their action. For example, platinum salts appear to target tumors with deficient nucleotide excision repair[34]. Consequently, while secondary *BRCA1/2* mutations or other HR-restoring events are likely to result in cross-resistance between platinum and PARPi, other modes of tumor adaptation to the therapy may be more drug-specific. Platinum is commonly used for the treatment of ovarian cancer, and the clinical trials demonstrated that the use of PARPi results in significantly better outcomes in platinum-sensitive *vs* platinum-resistant disease[48,49]. Similarly, the advantage of talazoparib was more pronounced in *BRCA1/2*-driven breast cancer patients who did not receive prior cisplatin or carboplatin[50]. However, some presumably platinum-resistant ovarian tumors still demonstrate some sensitivity to PARPi[48,49]. On the other hand, PARPi therapy may result, for example, in the emergence of mutations in the *PARP1* gene, which alter *PARP1* trapping to DNA but are unlikely to affect tumor sensitivity to drugs other than PARPi[51]. It needs to be stressed that in the clinical setting, the platinum sensitivity of ovarian cancer is usually defined not by the actual tumor response to carboplatin or cisplatin but by the time interval exceeding 6 mo since the last platinum exposure. It is not impossible that some tumors may actually restore HR deficiency within a shorter period of time, so their response to PARPi could be explained by conventional PARPi-associated biological mechanisms. While the use of PARPi after chemotherapy has been evaluated in many clinical trials[49], we are unaware of a systematic analysis of chemotherapy response in PARPi-resistant tumors.

BRCA1 and *BRCA2* germ-line mutations are usually viewed as equivalent in all clinical trials involving DNA damaging treatments. Although this approach is generally well justified, some differences between these two genes need to be acknowledged. Preclinical experiments have demonstrated mechanisms for therapy escape that are relevant for *BRCA1*- but not for *BRCA2*-driven tumors[34]. The spectrum of associated cancers is somewhat different for these two genes; for example, the analysis of PARPi-resistant prostate malignancies is almost entirely limited to *BRCA2* mutation carriers, as *BRCA1* plays a negligible role in the predisposition to this disease[26].

The regimens of administration of platinum salts and PARPi significantly differ. Cisplatin or carboplatin are usually administered in several cycles, so there are peak drug concentrations and significant intervals between chemotherapy infusions. In contrast to this intermittent drug administration of platinum drugs, PARPi are used at a continuous dose for a prolonged period of time. It is very likely that the mode of drug administration may influence the pathways of tumor adaptation to therapeutic intervention. Furthermore, published clinical experiments included very heterogeneous groups of patients with regard to the duration of prior treatment. It appears that the majority of secondary *BRCA1/2* mutations were detected mainly in heavily pretreated patients, while the initial cycles of chemotherapy rarely resulted in the genetic reversion of the *BRCA1/2* sequence[26,27,46,52].

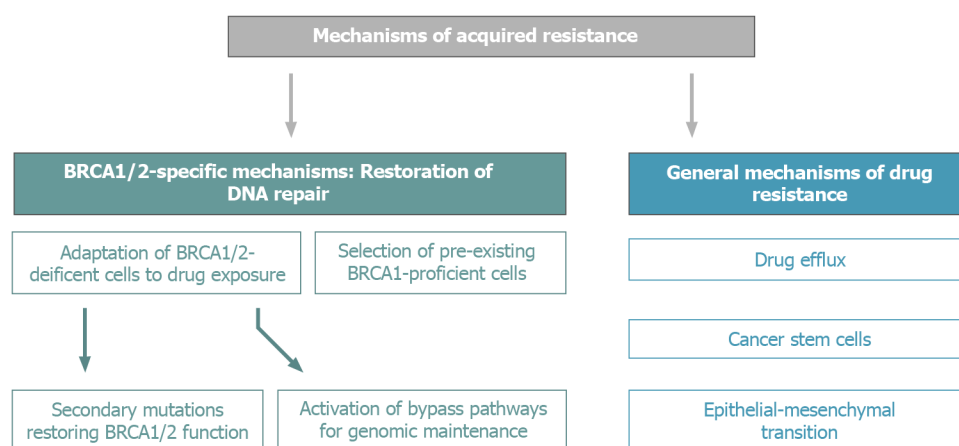


Figure 3 Mechanisms of acquired resistance of BRCA1/2-driven tumors to platinum compounds and PARP inhibitors.

Cell and animal experiments cannot fully recapitulate the complexity of intratumoral heterogeneity, tumor microenvironment, interplay with the immune system, drug dosing, *etc.*, characteristic for a clinical setting. The investigation of biological material obtained from cancer patients is challenging, particularly when it comes to the analysis of acquired therapy resistance. Tumor re-biopsy, by definition, requires sound clinical and ethical justification; therefore, some studies relied on circulating tumor DNA (ctDNA). Liquid biopsy is capable, in theory, to uncover the entire spectrum of subclonal secondary mutations, although it may underestimate the frequency of back mutations and does not account for the proportion of BRCA1/2-restored cells within a tumor mass. Current technologies for gene sequencing, which are utilized for the detection of secondary mutations, may miss some large deletions of genetic material[26]. It is highly desirable to continue the collection of platinum- and PARPi-resistant tumor samples from cancer patients, to subject these specimens to comprehensive molecular profiling, and to monitor the response of these tumors to subsequent treatment modalities. This effort may identify gene-response correlation and help to guide the clinical management of BRCA1/2-related cancers after the failure of the standard therapy.

CONCLUSION

BRCA1/2-driven tumors have a number of in-built mechanisms of adaptation to conventional schemes of platinum-based therapy and PARPi (Figure 3). Nowadays, an increasing number of OC patients are subjected to long-term PARPi maintenance therapy, which certainly affects the biological and clinical properties of recurrent tumors. It is somewhat surprising that the available medical research literature does not put an emphasis on the potential treatment options for tumors arising on the background of continuous PARPi exposure, despite that multiple lines of preclinical and clinical data suggest the involvement of cross-resistance mechanisms[34].

Genome profiling of drug-resistant tumors obtained from BRCA1/2 mutation carriers has not identified recurrent actionable molecular lesions[46]. However, despite the restoration of HR proficiency or the emergence of bypass pathways, these tumors continue to contain the genomic scar of BRCAness, *i.e.* the existence of multiple genomic rearrangements. These genetic lesions may underlie an increased antigenicity of BRCA1/2-driven tumors. Interestingly, second mutations, which are the cause of drug resistance, are often associated with the emergence of additional antigenic epitopes[26]. The feasibility of the use of immune therapy against platinum/PARPi-resistant OCs has not been evaluated systematically, although case series support the promise of this option[53].

The best approach would be to implement treatment that would prevent the appearance of drug-resistant clones. There is a number of ongoing trials evaluating the efficacy of combinations of PARPi with other drugs[34,54]. Several studies demonstrated the potentially curative impact of high-dose chemotherapy for BRCA1/2 mutation carriers; however, the use of this treatment is associated with excessive adverse effects [55]. Neoadjuvant combination of cisplatin and mitomycin C resulted in complete pathological responses, *i.e.* in the elimination of all detectable cancer cells, in some

BRCA1/2-driven OCs[44].

There are several recent breakthroughs in the management of BRCA1/2-driven tumors, which resulted in significant improvement of disease outcomes. Continued understanding of the mechanisms of platinum/PARPi resistance inspired the development of a multitude of novel therapeutic approaches, which are likely to contribute to further advances in cancer treatment. BRCA1/2-associated carcinomas have well-defined vulnerabilities and are characterized by pronounced drug sensitivity. They are similar in this respect to germ-cell tumors and some hematological malignancies, which are generally curable by already available therapeutic tools. There are reasonable chances that cure rates for BRCA1/2-associated malignancies will significantly increase in the near future.

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