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Diverse mechanisms of PARP inhibitor resistance in ovarian cancer

Matthew John Wakefield[1,2,*] matthew.wakefield@wehi.edu.au, Ksenija Nesic[1,3], Olga Kondrashova[4], Clare L. Scott[1,2,*] scottc@wehi.edu.au
[1]Walter and Eliza Hall Institute of Medical Research, Parkville, Victoria, 3052, Australia.

[2]Department of Obstetrics and Gynaecology, University of Melbourne, Royal Women's Hospital, Parkville, Victoria, 3052, Australia.

[3]Department of Medical Biology, University of Melbourne, Parkville, Victoria, 3010, Australia.

[4]QIMR Berghofer Medical Research Institute, Herston, Queensland, 4006, Australia.

Corresponding authors.

ORCIDs:
MJW 0000-0001-6624-4698
KN 0000-0001-9972-9819
OK 0000-0003-0022-5149
CLS 0000-0002-3689-5956

Introduction

Inhibitors of poly-ADP ribose polymerase (PARP) are promising therapy for treating high grade serous ovarian cancers (HGSOC) driven by defects in the homologous recombination (HR) DNA repair pathway. While *BRCA1/2* mutations are the most common HR defect in ovarian cancer, present in 17-25% of cases, methylation of *BRCA1* is present in 7-17% of cases (Bernards, 2017; Cancer Genome Atlas Research, 2011) making it the second most common class of HR aberration ahead of other HR pathway gene mutations (*RAD51C, RAD51D* and *PALB2:* 6 - 10%) and methylation of the *RAD51C* promoter (1.5%-3%) (Bernards, 2017; Cunningham, 2014). In HGSOC these HR defects occur in the context of near ubiquitous TP53 mutations, with nearly two thirds being hotspot hypermorphic mutations rather than complete loss [1].

Treatment with PARP inhibitors provides significant benefit to patients with *BRCA1/2* mutations (Coleman, 2017; Ledermann, 2012; Ledermann, 2014; Matulonis, 2016; Mirza, 2016), *RAD51C* or *D* mutations [2,3] and epigenetic silencing of *BRCA1* [4]. PARPi are now

approved in both the treatment and maintenance settings in relapsed OC by the European Medicines Agency and the US Food and Drug Administration and have gained widespread adoption.

Although strong initial responses to therapy are observed, this response is rarely durable in the long term. Rates of progression vary between a third of patients within 36 months on 1st line maintenance olaparib treatment for *BRCA1/2* mutant OC [5] to 50% of patients within 12.8 months on rucaparib treatment in HGSOC [3]. As strong initial responses are observed in the majority of patients and durable responses seen in a minority, the molecular basis for this resistance, its timing, and possible treatment strategies to avoid its development are of keen clinical interest.

PARP inhibitors act via synthetic lethality, generating catastrophic DNA damage and cell death when HR DNA repair is absent, whilst generating only low toxicity in normal adult cells where HR DNA repair is present. Although several mechanisms of action have been proposed since the initial discovery of synthetic lethality in *BRCA1* mutants [6], there is now a strong consensus that the major effect of PARPi occurs via 'trapping' of the PARP protein at sites of DNA damage during replication [7,8], causing stalling and collapse of replication forks. Normal activity of PARP1 limits the rate of replication fork progression and inhibits premature restart of reversed replication forks [9–12]. When PARP inhibition occurs in the presence of HR defects, a larger fraction of single strand breaks are processed into double strand breaks, leading to unrepaired damage that persists into mitosis [13,14]. This mechanism is supported by the observations that loss of PARP1 in the absence of HR does not cause synthetic lethality, and the localization of PARP1 to stalled replication forks [6,13]. While in normal cells, PARylation of PARP1 modulates its binding leading to its dissociation; some PARylation of PARP1 is required for lethality, most likely via signalling to downstream repair proteins [13].

Mechanisms of Resistance

Due to the pressing clinical need to address the development of resistance to PARPi therapy, a substantial number of studies have addressed the molecular basis of this resistance, utilizing *in vitro* and *in vivo* models as well as characterisation of resistant clinical cases. These studies have identified five main classes of resistance – drug efflux, deletion of the target protein or binding site mutation, changes in PAR metabolism, restoration of homologous recombination, and rewiring of stalled replication fork protection.

Drug Efflux

Efflux by multidrug resistance pumps is a common pathway by which chemotherapeutic resistance emerges across many classes of drugs, and PARPi are no exception to this mechanism. Resistance to olaparib by efflux was the primary mechanism to evolve in model systems, via overexpression of ABCB1 (also known as MDR1 or p-glycoprotein), and the mechanism was functionally validated by reversal with the efflux inhibitor tariquidar [15]. Analysis of PARPi resistance in clinical breast and ovarian cancer cases has shown that fusions are a frequent mechanism for driving the overexpression of ABCB1, with multiple highly expressed fusion promoters involved. Fusions frequently involved genes located near *ABCB1*. Rearrangements were predominantly intrachromosomal with *SLC25A40*, a highly expressed gene in the same orientation upstream of *ABCB1*, being most frequently observed fusion partner [16].

Although directly assaying drug efflux in a clinical setting is difficult, in one expression based study over half of the assayed samples showed some elevation of *ABCB1,* with more than 10% having over 200 fold increase in expression[16]. The frequency of fusions also strongly correlates with past therapy using ABCB1 substrates - including topotecan and paclitaxel [16]. It is likely that a significant proportion of resistance observed in the clinic is directly attributable to efflux, and that even low levels of efflux can reduce effective intracellular concentrations of drug and combine with other resistance mechanisms to produce clinically significant PARPi resistance.

Loss of PARP1 function

Mutation or loss of the target site is a mechanism of resistance frequently observed across multiple targeted therapeutic classes. In other targeted therapies the aim of inhibition is to completely remove the function of the enzyme, which is usually a cancer driver gene. This results in a strong selection for mutations that inhibit drug binding while maintaining the function of the target protein. Due to both the synthetic lethal nature of PARPi therapy and mechanism of action by PARP trapping, a more complex spectrum of PARP1 mutation is seen in PARPi resistance.

As *PARP1* is not a cancer driver gene, there is no oncogene addiction selective constraint that prevents complete loss of PARP1 function; however, complete loss may be synthetic lethal with *BRCA1* and *BRCA2* null mutations in some backgrounds [6,17,18]. In mouse B cell models dual knockout of *PARP1* and *BRCA1* protects replication forks and decreases chromosomal abnormalities compared to *BRCA1* null, and in *BRCA2* null mESC restores viability [19,20], predicting that PARP1 deletion causes resistance by abolishing interaction of autoPARylated PARP1 and MRE11 [19].

The essential domains of PARP1 that are required for PARPi therapy response have been determined through high density CRISPR screening in a triple negative breast cancer cell line, that harbours a hypomorphic mutation producing BRCA1 protein that lacks exon 11 but retains some function (see Restoration of HR below). DNA binding of PARP1 is required for PARPi action, with mutations abolishing evolutionarily conserved residues in first two zinc fingers resulting in loss of chromatin binding, and PARPi resistance [21]. In addition to the DNA binding domain, mutations in the WGR, regulatory and a very limited number of sites on the solvent-exposed helix of the catalytic domains were shown to cause resistance [21]. The mutations in the WGR domain are clustered at sites where the proteins folding creates interactions with the zinc finger domain on one face, and the hinge domain interaction with the catalytic domain on the other side of the WGR domain. These mutations strongly suggest that epistatic signalling, via conformational changes due to binding in the catalytic domain, are important in modulating PARP chromatin binding and synthetic lethality [21]. Functional loss of PARP1 has also been validated for a de novo resistance mutation identified in an olaparib treated ovarian cancer patient, demonstrating the clinical relevance of this mechanism [21].

PAR metabolism

Metabolism of PARP's substrate ADP ribose has been implicated in resistance via cleavage of PAR chains. Degradation of the polymerised PAR is mediated by PARG, and as such acts in parallel to PARP inhibition also reducing PARylation of PARP1 targets. In PARPi treated cells, some limited PARP enzymatic activity remains, and PARG degradation of PAR is required to reduce PAR signalling to a level that results in unrestrained replication fork progression [13]. Loss of PARG can lead to accumulation of polymerised PAR, rescuing downstream PAR signalling and reducing PARP1 binding at sites of damage, while maintaining PARPi induced trapping of PARP1 that does bind chromatin [13]. Alternatively PARG may interfere with DNA independent interactions between PARP1 and MRE11 [19]. Loss of PARG has also been observed at significant rates in clinical samples and increased frequency with treatment [13,22].

Restoration of homologous recombination

Resistance due to the restoration of HR is the most common form of PARPi resistance observed in the clinic. This can occur due to secondary mutations that remove or compensate for the original genetic lesion [23–26]. The repertoire of potential reversionary events is dependent on the exact nature of the original mutation. In addition to any DNA damaging

effects of chemotherapy the loss of HR is inherently mutagenic, and both mechanisms can drive secondary mutations. Reliance of HR mutant cells on error-prone double stranded break repair mechanisms will result in rapid and continuing evolution of the tumour. As the major mutational process under PARPi therapy will be insertions and deletions, mutations that cause a frameshift are the most likely to be reverted by this mechanism. The probability of reversion will be influenced by the tolerance for sequence changes in the local region and the distance between out of frame stop codons and the primary mutation – providing opportunity for prediction of reversion based on the patient mutation. Although distant mutations, such as at splice sites, can also cause reversions, the restriction of likely secondary mutation resistance events to a small region around the primary mutation makes liquid biopsy a powerful approach for monitoring development of this type of resistance [27–29].. The repertoire of potential reversionary events is dependent on the exact nature of the original mutation. In addition to any DNA damaging effects of chemotherapy the loss of HR is inherently mutagenic, and both mechanisms can drive secondary mutations. Reliance of HR mutant cells on error prone double stranded break repair mechanisms will result in rapid and continuing evolution of the tumour. As the major mutational process under PARPi therapy will be insertions and deletions, mutations that cause a frameshift are the most likely to be reverted by this mechanism. The probability of reversion will be influenced by the tolerance for sequence changes in the local region and the distance between out of frame stop codons and the primary mutation – providing opportunity for prediction of reversion based on the patient mutation. Although distant mutations, such as at splice sites, can also cause reversions, the restriction of likely secondary mutation resistance events to a small region around the primary mutation makes liquid biopsy a powerful approach for monitoring development of this type of resistance [27–30].

Currently the majority of published data on the rate of secondary mutations comes from platinum treated cohorts where high rates of reversions are observed and rates increase with treatment intensity. In one of the landmark breast cancer papers this was an increase from 3% in primary carcinomas to 28% in recurrent disease, and 66% in recurrent disease and a prior history of breast carcinoma [31]. Reversions have been observed in both *BRCA1* and *BRCA2* [28] as well as other HR pathway genes such as *RAD51C* and *RAD51D* [2].

Reversion mutations are frequently late events, resulting in a highly subclonal distribution in the patient. This can occur both at the level of large metastatic masses that have different

responses to therapy, as well as fine grained differences in resistance allele frequency within the tumour [2,32].

While epigenetically silenced allele reversion is functionally equivalent to reversion of a mutation allele to the wildtype protein, the tumour evolution dynamics of methylated and silenced alleles appears to favour more rapid reversion under therapy than is observed for mutated alleles [4]. Although there is a predominance of reversion events long term responders that maintain stable epigenetic silencing are observed, and it will be important to identify if this difference relates to inherently different classes of epigenetic silencing, or if it is entirely due to differences in the treatment regimens. Stability of epigenetic silencing may be impacted by common treatments, including platinum therapy. Intrastrand cross links between guanidine residues (GpG and GpNpG) represent more than 99% of cisplatin lesions and are enriched at CpG islands [33]. Repair of cisplatin adducts is primarily via the Nucleotide Excision Repair (NER) [34] and by DNA excision and chromatin decompaction has potential to disrupt both DNA and chromatin based epigenetic silencing. Care will also need to be exercised when utilising combinations that include epigenetic inhibitors (reviewed [35]) to ensure highly targetable HR defects are not prematurely erased due to poor patient stratification or therapy sequencing.

When mutations lie within dispensable exons, the expression of alternative isoforms that are present in normal cells at a low level, or the mutation of splice sites can allow expression of proteins that retain at least some of the biological function of the gene. The best studied case of these hypofunctional alleles related to PARP inhibitor resistance is the BRCA1 delta 11q isoform. This isoform is generated from a cryptic splice site within the large exon 11 of BRCA1, resulting in a transcript that produces a functional protein that is missing the distal end of exon 11. In cases where a mutation occurs in the distal portion of exon 11 this transcript can provide sufficient function to result in resistance to both cisplatin and PARP inhibitor resistance [36].

In *BRCA1* mutants HR can also be restored by loss of 53BP1 pathway end resection antagonists [37,38]. In the absence of BRCA1 resection of break ends does not occur, resulting in a failure to recruit RAD51 and initiate homologous recombination. The resection at these breaks is limited by members of the 53BP1 pathway and include RIF1, REV7, Shieldin and the CST complex [39–42]. Loss of function in this pathway results in resection,

RAD51 recruitment and partial restoration of HR function – resulting in PARP inhibitor and cisplatin resistance.

Changes in replication fork biology

With our developing understanding of replication fork protection failure being the core mode of action for PARP inhibitor synthetic lethality, replication fork biology has become a key area of research for understanding PARP inhibitor resistance.

One of the key roles of BRCA1 and BRCA2 in replication is the protection of nascent DNA at stalled replication forks. In normal cells stalled forks are protected from MRE11 mediated degradation by RAD51 that is loaded onto the exposed ssDNA by BRCA1 and BRCA2 [20,43,44]. In the absence of BRCA1 or BRCA2, the trapping of PARP1 combined with a reduced level of autoPARylation leads to extensive nucleolytic degradation through the action of MRE11 that depends on the formation of a reversed replication fork "chicken foot" structure[45].

Stalled replication fork protection can be restored by loss of proteins involved in the remodelling of the replication forks (SMARCAL1, HLTF, or ZRANB3) [46–48], loss of proteins in the MRE11 chromatin modifier complex (MLL3–4, PTIP or MRE11)[20], enhanced action of RAD51 through loss of its negative regulator RADX [49,50], and in *BRCA2* mutants, loss of CHD4 or EZH2 [51,52]. In addition to gene loss, upregulation of the FANCD2 gene has also been shown to protect replication forks and lead to resistance [53,54].

Although RAD51 paralogs prevent degradation of stalled forks and promote the restart of halted replication to avoid replication fork collapse [55] and *RAD51C/RAD51D* mutations cause sensitivity to PARPi therapy [2], the precise role of RAD51 paralogs and the potential for mutations to restore replication fork protection remains unknown.

The complex interplay between multiple overlapping pathways in fork protection appears to provide a large diversity of potential re-wirings. These fork protection mutations bypass otherwise lethal states by directing rescue through alternative pathways or the substantially limiting processes that would otherwise become damaging. To date the most fruitful investigations of these pathways have been conducted with loss of function screens and validation in clinical cases, an approach that may bias against discovering resistance

mechanisms involving gene upregulation. While some of the rules of these rewiring processes, such as the requirement for at least limited *BRCA1* function for some, have been elucidated, significantly more research will be required before we have a comprehensive understanding of the full repertoire and limitations of this resistance mechanism. As such the diversity of this resistance mechanism will present significant challenges in resistance diagnosis, prognosis and the development of post-PARPi resistance therapies.

For a more detailed exploration of replication fork protection see the recent reviews by [56] and [57].

Treating Resistance

The diversity of potential mechanisms of resistance provides significant issues for the treatment of high-grade ovarian carcinomas. The complexity of the resistance landscape complicates both prognosis and monitoring for resistance, in addition to the complexity of selecting appropriate post-resistance therapies. Several combination therapies that are currently being trialled for their enhancement of PARPi response prior to resistance development also have potential to maintain effectiveness post-PARPi resistance, including immunotherapy and checkpoint inhibitors [58–60].

Therapies that target the G2/M checkpoint - including ATR, CHK1 and WEE1 inhibitors – show great promise, as the replication fork instability and requirement for cell cycle delay that they target is rarely completely abolished by the acquisition of PARPi resistance. Mechanistically, ATR inhibition has been shown to also inhibit PALB2-BRCA1-based HR and fork protection by the additional loading of RAD51 [61] and CHK1 inhibitor limits trans-nuclear localization of RAD51 [62] and will increase progression through S/G2. Checkpoint inhibition is also likely to be beneficial not just for replication fork rewiring-based resistance, but also for secondary mutation reversion of homologous recombination. Stalled fork protection is impaired in heterozygous-*BRCA1* and *BRCA2* mutants [63,64], and in combination with replication stress caused by extensive genomic rearrangement, TP53 loss and rapid growth presents a potentially exploitable differential toxicity to checkpoint inhibition. Other vulnerabilities may also be induced by resistance, such as the increased radiosensitivity with restored HR due to 53BP1 pathway mutations [65].

The real resistance landscape in patients has the potential to be more complex than that which has been observed to date in model systems, which are by their nature simplified to focus on an individual mechanism. As *BRCA1* mutations are an early truncal driver event when they

occur in HGSOC, with 'all' tumour cells harbouring the underlying mutation, a substantial degree of selection for advantageous mutations that enhance the tumour phenotype has occurred in the BRCA mutant context. Although a certain level of ongoing mutation is advantageous for diversification of the tumour phenotype, the replication fork stability phenotype will also frequently limit the replication rate of the tumour due to cell cycle checkpointing at G2/M. In light of selection for fast tumour cell growth, this is likely to result in ongoing selection for fork stabilizing mutations throughout the tumour's development, and not just under the direct influence of PARPi therapy selection. The possibility of pre-existing selection for fork stability mutations is supported by the relatively high rate at which some of these mutations have been observed in clinical breast and ovarian cancer. For example 25-50% of cancers showed areas 10-20% in size for loss of PARG expression – significantly higher than would be expected due to chance loss [13]. This is likely to have significant impact on the character of resistance mutations observed in the clinic, as ongoing weak selection in absence of therapy will favour multipoint mutations and stepwise improvement, rather than the single events that are selected for in experimental models with stringent selection for PARPi resistance.

Reduction of the tumour diversity by optimal debulking will continue to be an important tool in therapy and reducing tumour diversity that can lead to resistance [66]. Early scheduling of effective PARPi therapy, most importantly, at an effective PARP-inhibitory dose, rapid retreatment upon progression, with a minimal disease burden [32] and early use of combination therapy, likely including immune-checkpoint inhibitor therapy to boost immune response, will be important tools in fulfilling the promise of PARPi therapy in the face of the cancer's tenacious ability to evolve resistance to evade the therapy it is exposed to.

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