Commentary

Turning the concept of synthetic lethality on its head

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One of the most significant discoveries in cancer treatment over the past 15 years has been the advent of poly(ADP-ribose) polymerase (PARP) inhibitors, and their exploitation of the concept of synthetic lethality in the treatment of *BRCA1/2* mutant cancers (1,2). In synthetic lethality, the loss of each gene or protein by itself does not affect cell viability, but the loss of both results in cell death. The goal of this approach is to optimise targeted tumor cell death, while sparing normal tissue (the "magic bullet" first proposed by Paul Ehlrich in the late 19th century). PARP inhibitors in *BRCA1/2* mutant tumors have been the classical example of this, where the loss of homologous recombination-mediated DNA repair through *BRCA1/2* mutation renders cells sensitive to inhibition or loss of PARP1.

However, clinical trials of PARP inhibitors have not resulted in the anticipated dramatic clinical outcomes. Response rates of 41% in *BRCA1/2* mutant ovarian cancer were reported in a phase II study, with 7 of 17 patients experiencing a partial response (3). A further stratified phase II study reported a significant improvement in progression-free survival for patients with a germline *BRCA1/2* mutation (11.2 *vs.* 4.3 months) but this did not translate to an overall survival advantage (4). In addition, there were significant toxicities associated with PARP inhibition, including myelosuppression, nausea, fatigue and a 2.2% risk of developing myelodysplastic syndrome/acute myeloid leukemia (MDS/AML) (4,5).

PARP inhibitor resistance

While the availability of PARP inhibitors for patients with ovarian cancer represents a significant improvement in treatment options, the cause of the observed lack of efficacy of PARP inhibitors in the majority of patients remains in question. Various mechanisms of resistance have been proposed, including reversion mutations where *BRCA1/2* function is restored by a secondary mutation (which has been reported to occur in up to 28% of ovarian cancers) (6). However, the clinical relevance of this mechanism is not known, with a number of PARP inhibitor resistant patients found to maintain resistance to PARP inhibition in the presence of *BRCA1/2* loss (7). The upregulation of P-glycoprotein drug efflux pumps has also been reported to result in PARP inhibitor resistance (8), although again the clinical relevance of this finding is not known, with disappointing results from clinical studies attempting to reverse this mechanism using targeted inhibition of drug efflux pumps in chemotherapy treatments (9). Loss of *53BP1* has also been shown to result in PARP inhibitor resistance, and has been clinically recognized in *BRCA1/2* mutation-associated breast cancer (10).

Shifting the paradigm: synthetic viability

Recently, Sharan and colleagues have challenged the dogma of the synthetic lethality of PARP inhibition in *Brca2* mutations and identified a potential novel mechanism for resistance to treatment (11). By exploring the effect of PARP inhibition (using the PARP inhibitor olaparib) and Parp1 knockdown using a conditional *Brca2* knockout mouse embryonic stem cell model, they found that loss or inhibition of *Parp1* prior to loss of *Brca2* function resulted in viable cells lacking functional homologous recombination.

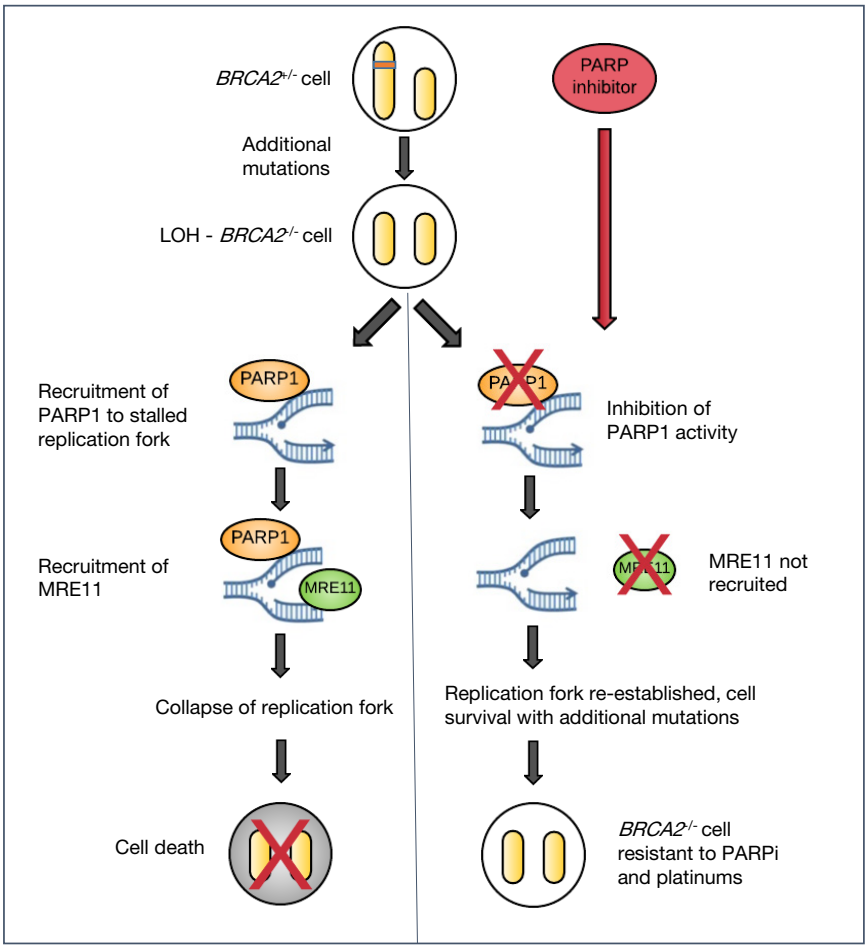

Figure 1 Synthetic viability following PARP inhibition in *BRCA2*$^{-/-}$ cells. In a *BRCA2*$^{+/-}$ cell, a subsequent mutational event leads to BRCA2 loss of heterozygosity (LOH). In the absence of PARP inhibition (A), PARP1 recruits MRE11 to stalled replication fork. The absence of BRCA2 leads to collapse of the replication fork, resulting in cell death. However, in previous PARP inhibition (B) PARP1 and therefore MRE11 are not recruited to a stalled replication fork. The replication fork is re-established and, by means of further mutational events, cell survival is promoted and results in a highly genomically unstable *BRCA2*$^{-/-}$ cell resistant to PARP inhibition and DNA damaging agents such as platinums

Typically, loss of *Brca2* would be expected to result in DNA replication fork collapse and cell death. Intriguingly, no synthetic lethality was observed.

These PARPi-resistant and subsequently *Brca2*-mutant cells (4–8% of those treated) were genomically unstable, with increased sister chromatid exchange and non-homologous end joining. Interestingly, a companion study demonstrated that PARPi resistant tumors were also cross-resistant to topotecan and cisplatin (12). The authors found that loss of *Parp1* function restored replication fork stability in the absence of BRCA2 by preventing the recruitment of the nuclease MRE11, an enzyme that is required in the process of DNA replication fork degradation. Continued PARP inhibition was not required for *Brca2*$^{-/-}$ cell survival, suggesting additional mutational events can promote survival once the cell has survived the initial loss of *Brca2* (*Figure 1*).

Clinical implications

PARP inhibitors are now approved for use in the treatment of *BRCA1/2*-mutant advanced ovarian cancer, in platinum-sensitive disease in the 4th-line setting in the US (in the 3rd-line setting in Europe). However, an adjuvant trial of

PARP inhibitors in early stage *BRCA1/2*-mutant breast cancer (exploring PARP inhibitor maintenance therapy after adjuvant chemotherapy—OlympiA NCT02032823) is now open. The observed pro-survival effect following PARP inhibition may have important clinical implications for patients receiving PARP inhibitors, particularly as increasing use of PARP inhibitors is being advocated in the adjuvant and prophylactic settings (13). In *BRCA2* mutation carriers, exposure to PARP inhibitors, although having a synthetic lethal effect on *BRCA2* mutant cancers, may paradoxically accelerate malignancy in "normal" *BRCA2* heterozygous cells by promoting survival following spontaneous loss of heterozygosity. Even more worryingly, these cancer cells would be predicted to be resistant to conventional DNA damaging chemotherapeutic agents such as platinums as well as PARP inhibition. Indeed, this may be an important mechanism in considering the increased rate of development of MDS/AML in patients with a *BRCA1/2* mutation who receive PARP inhibitor treatment.

Sharan *et al.*'s study also raises a number of unanswered questions. Is the pro-survival effect of PARP inhibition unique to loss of *BRCA2* heterozygosity, or this is a more general phenomenon that also applies to loss of *BRCA1* and other genes related to homologous recombination-mediated DNA repair? Is the observed survival of murine *Brca2*$^{-/-}$ embryonic stem cells with PARP inhibition applicable to loss of heterozygosity in a human epithelial cancer? The authors demonstrated increased epithelial tumor development on a PARP deficient background in *Brca2*$^{-/-}$ mice, does prolonged exposure to PARP inhibition result in accelerated tumorigenesis in *Brca2* heterozygous mice?

Clearly there is an urgent need to better understand the consequences of exposing healthy patients who carry mutations in homologous recombination genes to prolonged PARP inhibition before these agents can be safely used in the prophylactic or adjuvant setting.

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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