



# Synthetic lethality vs. synthetic viability due to *PARP1* and *BRCA2* loss

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The commentary entitled “Turning the concept of synthetic lethality in its head” by Parkes and Kennedy not only clearly highlighted our recent work on the genetic interaction between *BRCA2* and *PARP1* but also raised some valid questions (1,2). We would like to clarify that while our findings suggest that loss of *PARP1* and *BRCA2* can result in synthetic viability, it does not challenge the dogma of synthetic lethality by *PARP* inhibition in *BRCA2*-deficient cells. We found that although *Brca2*<sup>ko/ko</sup> mouse embryonic stem (ES) cells fail to survive, we could rescue their lethality by treating *Brca2* heterozygous (*Brca2*<sup>ko/ko</sup>) cells with olaparib prior to Cre-mediated deletion of the conditional allele. Interestingly, these “rescued” *Brca2*<sup>ko/ko</sup> cells were found to be sensitive to olaparib, consistent with the concept of synthetic lethality. We obtained similar results in mouse hematopoietic stem cells (HSC), when mice carrying *Brca2* conditional alleles were treated with olaparib and then the conditional alleles were deleted in the HSC. Like in the case of ES cells, we obtained viable *Brca2*<sup>ko/ko</sup> HSC, but they were still sensitive to olaparib. Our observations led us to conclude that the order of loss of *PARP1* and *BRCA2* is important. The two opposite outcomes i.e., synthetic viability and synthetic lethality are dependent on the order in which *BRCA2* and *PARP1* are lost. In *BRCA2*-deficient cells, *PARP* inhibition results in synthetic lethality. In contrast, in *Parp1* deficient or *PARP* inhibited cells, when *Brca2* is deleted, it results in cell viability. When *PARP* is inhibited or its levels are reduced, the cells are able to protect the replication fork from MRE11-mediated degradation, which contributes

to cell viability when *BRCA2* is deleted. Whether *PARP* inhibitor pretreatment can result in synthetic viability of other *BRCA2* deficient cells, especially mammary epithelial cells remain to be explored. However, we did observe a significant increase in epithelial tumors in *Parp1* heterozygous mice when *Brca2* was deleted using Cre under the control of *K14* promoter.

The effect of *PARP* inhibition on the viability of *Brca1*<sup>ko/ko</sup> ES cells is not known. However, it was shown by Chaudhuri *et al.* that *Parp1* deficiency protects stalled replication forks in *Brca1*<sup>ko/ko</sup> B-cells (3). Among other questions that currently remain unanswered, the mechanism of survival of cells by a short pretreatment of *PAPR* or MRE11 inhibitors is quite interesting. It is puzzling how these cells continue to survive even after *PARP1* or MRE11 activity is restored. Although we do not fully understand, we proposed that MRE11 or *PARP* inhibition results in transient protection of the replication fork, which allows the survival of *Brca2*<sup>ko/ko</sup> ES cells. However, because of the presence of chromosomal aberrations and increased sister chromatid exchange, these cells may acquire secondary mutations that enable them to overcome the growth arrest even after the fork protection is lost. These secondary mutations are essential for their subsequent survival.

Our findings do not challenge the importance of olaparib in treating *BRCA2*-deficient tumors. Our study has revealed that *PARP* inhibitors are not as innocuous in homologous recombination proficient cells as suggested by previous studies. Our conclusions are supported by a recent showing a significant increase in sister chromatid exchange

in *BRCA2* proficient cells by PARP inhibitors (4). Because PARP inhibition in *Brca2* heterozygous cells can contribute to cell viability, our findings raise concerns about the long term effect of PARP inhibitors as well as its use for cancer prevention in *BRCA2* mutation carriers.

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### Footnote

*Conflicts of Interest:* The authors have no conflicts of interest

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to declare.

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