PAR caps the poles: a specific role for PARP2-inhibition to target the 'clustering' of extra spindle poles in cancer cells

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PARP-inhibitors are an attractive cancer treatment option given their oral administration, excellent tolerability, and often surprising activity. Initially identified as exerting synthetic lethality on cancers with germline (g) loss-of-function BRCA1/2 mutations,[1] there is a continuous effort to explore their efficacy beyond their current indication, i.e., breast cancers associated with gBRCA1/2 mutations,[2] platinum-sensitive ovarian cancer,[3] prostate cancer with a range of mutations[4] and gBRCA1/2-associated pancreatic cancer.[5] Yet, in the pivotal studies leading to these indications, a pathogenic BRCA1/2 mutation has proven an imperfect predictive biomarker for response to PARP-inhibition, prompting the search for alternative markers for 'BRCAness' such as homologous recombination deficiency (HRD) scores and signatures developed from next-generation or whole genome sequencing, with incremental improvement in the ability to predict PARP-inhibitor responses.

PARylation catalyzed by PARPs regulates DNA damage repair, replication, chromatin remodeling, translation, metabolism, cell death, and immunity.[6] In cancer cells with HRD, PARylation is important for the recruitment of DNA damage repair proteins, and its inhibition can be lethal. Normal cells are heavily PARylated during S-phase, and excessive PARylation on Okazaki fragments, achieved by inhibition of the opposing enzyme, poly(ADP-ribose) glycohydrolase (PARG), during DNA replication can also cause cell death.[7] These findings suggest that fine-tuning of PARylation is vital for cell survival. In the recent issue of *eBioMedicine*, Yue et al. find that the negatively charged PAR caps mitotic spindle poles, and protects cancer cells from multipolar, asymmetric mitoses.[8]

The work by Yue et al. starts by considering factors other than HRD as potentially sensitizing to PARP inhibition. It focuses on a well-known biological function of BRCA1, its ability to prevent centrosome amplification and the formation of extra spindle poles, a phenomenon that has not been linked to the PARP inhibitor response until now. Centrosome amplification has been suspected to cause aneuploidy since the 1880s (Boveri et al., translated by J. Harris[9]), with modest aneuploidy causing cancer, while gross aneuploidy causes senescence and cell death. However, most cells can cluster extra centrosomes to form pseudo-bipolar spindles thus avoiding the catastrophic consequences of a multi-polar cell division, and intact BRCA1 is intimately involved in this salvage 'centrosome clustering'.

Utilizing CRISPR-based knock-in, Yue et al. established stable cancer cells with mutations in the middle of the BRCA1 molecule (R1085I and E1222Q) that are not typically linked to HRD. They found that these mutant BRCA1 molecules lost their ability to bind to the spindle poles, which turned out to be heavily decorated with poly (ADP) ribose (PAR), i.e. PARylated, specifically by PARP2, and PARylation of extra spindle poles prevented mitotic catastrophe by promoting the 'clustering' of these extra spindle poles (a well-known protective mechanism reviewed in[10]). PARP-inhibition with inhibitors that cover both PARP1/2, but not with a PARP1-selective inhibitor, prevented the clustering of extra spindle poles in these BRCA1 mutant cancer cells, leading to senescence, a phenomenon that was rescued by wildtype BRCA1. An analysis of centrosomal proteins and their charge properties identified candidate proteins, i.e., SFI1 and ZNF721, that have a high affinity for PAR and thus promote centrosome clustering. Importantly, when the authors examined tumors with 'BRCA1 middle section' mutations as patient-derived xenografts, they found that they responded equally well as tumors with 'classical', HRD-causing BRCA1 mutations to PARP-inhibition, but through a different mechanism: Tumors with 'middle section' BRCA1 mutations had large numbers of cells with extra spindle poles they couldn't cluster and thus died after senescence.

Currently, patients are frequently accrued to clinical trials with PARP-inhibitors based on a 'pathogenic' mutation in BRCA1/2, typically proven to cause HRD and cataloged in ClinVar as predisposing to the development of cancer. This new study suggests that the spectrum of cancer-associated BRCA1/2 mutations that respond to PARP-inhibition, i.e., 'PARP-inhibitor-sensitizing' mutations, is potentially much broader than the spectrum of 'pathogenic' mutations. 'PARP-inhibitor sensitizing' BRCA1 mutations, including those that are associated with extra spindle poles, may include some that typically would be characterized as variants of uncertain significance (VUS). Identifying patients with 'PARP-inhibitor sensitizing' mutations, likely through

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computational approaches, and validating their responsiveness in clinical trials will, therefore, be a challenge for clinical trials going forward.

Centrosome abnormalities are a common feature in many types of cancer, and strategies to target the 'clustering' of the extra spindle poles have been proposed.[10] The new research by Yue et al. suggests that PARP2-inhibition could be a promising approach to achieve this, as it may inhibit the PARylation of the spindle pole, removing its distinctive negative charge and anchor point for specific proteins. The findings raise the possibility that there are tumors with extra spindle pole formation caused by mechanisms other than a BRCA1 mutation that might potentially be responsive to combined PARP1/2-inhibition. How to reliably identify these will be a subject for research going forward. This potential application of PARP2-inhibition in cancer treatment underscores the importance of the findings by Yue et al.

Contributors

LW and GMW jointly drafted and edited the manuscript. Both authors read and approve the final manuscript.

Declaration of interests

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