A Novel Mechanism to Induce BRCAness in Cancer Cells
Changmeng Cai

Cancer cells with germline deleterious mutations of BRCA1 or BRCA2 are deficient in homologous recombination repair and therefore sensitive to PARP inhibitor treatment. However, wild-type BRCA1/2-expressing cells with defects in other DNA damage repair pathway components may also exhibit “BRCAness,” which in combination with PARP inhibition can similarly induce synthetic lethality. In this issue of Cancer Research, Luo and colleagues report a novel mechanism by which BRCA1 protein degradation in response to DNA double-strand breaks is regulated by deubiquitinase Pin1. Inactivation of Pin1 can establish BRCAness in cancer cells and thus sensitize cells to PARP inhibitor treatment.

See related articles by Luo et al., p. 3033

Center for Personalized Cancer Therapy, University of Massachusetts Boston, Boston, Massachusetts.

Corresponding Author: Changmeng Cai, University of Massachusetts Boston, 100 Morrissey Blvd, ISC/4/4720, Boston, MA 02215. Phone: 617-287-3537; Fax: 617-287-6650; E-mail: changmeng.cai@umb.edu

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olaparib. Moreover, the authors also assessed a recently reported Pin1 inhibitor, all trans retinoic acid (ATRA; ref. 8), in combination with olaparib in BRCA1-proficient TNBC patient-derived xenograft (PDX) models (DDR pathway mutations were not found in these PDXs). The results were very consistent with the effect of Pin1 depletion in the cell line–derived xenograft model and clearly showed that ATRA greatly increased the efficacy of olaparib in these PDXs. Because ATRA is an FDA-approved treatment to treat acute promyelocytic leukemia, this preclinical study may be quickly translated into clinical trials combining PARP and ATRA inhibitors in patients with non-BRCA–mutant breast cancer. However, ATRA being a potent agonist of the retinoic acid receptor may have broader molecular and cellular effects other than inhibiting Pin1. Another covalent Pin1-specific inhibitor, KPT-6566, was shown to inhibit tumor growth and metastasis in preclinical breast cancer models, however, it has not been tested clinically. Nonetheless, more potent and specific Pin1 inhibitors with better therapeutic potential are clearly needed for the future development of combination therapies with PARP inhibitors.

Interestingly, another recent study also reported that Pin1 may regulate BRCA1 through enhancing BRCA1–BARD1 activity for stalled fork repair (9). BRCA1 functioned to protect the replication fork independent of BRCA1–PALB2 interaction and this function required the region of BARD1 containing the RAD51-binding site but did not require the E3 ligase activity of the BRCA1–BARD1 complex. Moreover, BRCA1 Ser114 was phosphorylated by CDK1 or CDK2 to promote fork protection and the phosphorylated-S114/P115 became a substrate of Pin1. Pin1-mediated isomerization at this site facilitated the binding of RAD51 to the stalled replication fork, promoting genomic stability. Importantly, cells expressing the cancer-associated BRCA1 mutations close to the S114 site were generally insensitive to cisplatin or olaparib, further supporting that this specific regulation of BRCA1 is not related to its function in the HRR pathway. Overall, this work revealed a distinct mechanism by which Pin1 promotes stalled fork repair through isomerization of the BRCA1 S114/P115 site independent of its activity on the repair of DSBs, which is mediated by the S1191/P1192 site.

In conclusion, the study by Luo and colleagues provides some novel molecular insights on how BRCA1 expression and activity during DNA DSB repair is regulated by Pin1-mediated isomerization at the phosphorylated S1191/P1192 site. This unique mechanism provides a rationale to induce BRCAness in non-BRCA mutation–associated breast cancer by inactivating Pin1, which sensitizes the cells to PARP inhibitor treatment. In addition to breast and ovarian cancers, HRR gene mutations or alterations are also frequently detected in prostate cancer and this frequency is further increased in metastatic castration-resistant prostate cancer (mCRPC; over 20% are primarily BRCA1/2 and ATM mutations; ref. 10). PARP inhibitor treatments are currently being tested in clinical trials of mCRPC with HRR pathway defects (olaparib, phase III, NCT02987543; rucaparib, phase III, NCT02975934; and niraparib, phase II, NCT02854436). Because Pin1 is overexpressed in prostate cancer, it is plausible that this combination strategy of PARP inhibitors with Pin1 inactivation can also be applied to prostate cancer treatment.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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