

Editorial

PARP inhibitors and the treatment of breast cancer: beyond *BRCA1/2*?

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Published: 26 November 2009

This article is online at <http://breast-cancer-research.com/content/11/6/111>

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Breast Cancer Research 2009, **11**:111 (doi:10.1186/bcr2451)

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Abstract

Poly(ADP-ribose) polymerase (PARP) inhibitors have been explored as therapeutic agents for the treatment of hereditary breast and ovarian cancers harboring mutations in *BRCA1* or *BRCA2*. In a new study, Inbar-Rozensal and colleagues show that phenanthridine-derived PARP inhibitors promote cell cycle arrest and cell death in breast cancer cells lacking *BRCA1* and *BRCA2* mutations and prevent the growth of tumors from xenografts of these cells in immunocompromised mice. These results suggest a potential broader utility of PARP-1 inhibitors in the treatment of breast cancer, although further mechanistic studies are needed.

Recent studies have suggested that chemical inhibitors of poly(ADP-ribose) polymerases (PARPs) might be effective as therapeutic agents for the treatment of hereditary breast and ovarian cancers harboring mutations in *BRCA1* or *BRCA2*. In a recent article from the Cohen-Armon group published in *Breast Cancer Research*, Inbar-Rozensal and colleagues [1] provide evidence that certain PARP inhibitors might also inhibit the growth and promote the death of non-hereditary breast cancer cells lacking mutations in *BRCA1* or *BRCA2*. These intriguing results might lead the way to new approaches for treating a broad spectrum of breast cancer subtypes.

PARPs comprise a family of enzymes that catalyze the polymerization of poly(ADP-ribose) chains on target proteins, thereby modifying the activity of those proteins [2]. Nuclear PARPs, such as PARP-1 and PARP-2, play key roles in genome maintenance, cell death, inflammatory responses, and the control of gene expression programs [2,3]. PARP enzymatic activity increases in response to various cellular stresses [2,3]. Given the central role of PARPs in vital cellular processes as well as disease states, chemical inhibitors of PARP have been explored as therapeutic agents for a wide variety of diseases, including cancer [4,5].

Increasing evidence has linked PARP-1 to breast cancer. For example, PARP-1-deficient mice exhibit increased spontaneous mammary carcinoma formation, the latency of which is increased by mutations in *p53* [6]. In addition, PARP activity in human peripheral blood lymphocytes has been linked with breast cancer [7] and low levels of PARP-1 gene expression are associated with increased genetic instability in breast cancer [8]. Furthermore, certain polymorphisms in PARP-1 may contribute to the development of breast cancer and influence the effectiveness of hormone therapies [9]. Interestingly, PARP inhibition (a) sensitizes *p53*-deficient breast cancer cells to doxorubicin-induced apoptosis [10] and (b) selectively kills breast cancer cells with hereditary inactivating mutations in *BRCA1* and *BRCA2*, which encode proteins critical for DNA repair by homologous recombination [5]. Finally, the PARP inhibitor, olaparib, has anti-tumor activity in breast and ovarian cancers containing *BRCA1* and *BRCA2* mutations at safely administrable doses with minimal side effects [11].

Building upon these exciting studies, Inbar-Rozensal and colleagues [1] show that phenanthridine-derived PARP inhibitors (for example, PJ-34) promote cell cycle arrest at G₂/M and cell death in breast cancer cell lines lacking *BRCA1* and *BRCA2* mutations (that is, MCF-7 and MDA-MB-231). These effects were evident even after a short (6-hour) treatment, and no recovery was observed after drug removal. In contrast, although a transient cell cycle arrest was also observed in normal breast epithelial cells (that is, MCF-10A) and mouse embryo fibroblasts, recovery was apparent within hours, even with continued drug exposure. Furthermore, in immunocompromised nude mice, PJ-34 prevented the growth of tumors from subcutaneous xenografts of MCF-7 or MDA-MB-231 cells. From these studies, the authors

ER = estrogen receptor; ERK = extracellular signal-regulated kinase; PARP = poly(ADP-ribose) polymerase; PR = progesterone receptor.

conclude that phenanthridine-derived PARP inhibitors cause cell cycle arrest and subsequent cell death in non-hereditary breast cancer cells. Additional studies are needed, however, to fully explore the activity of other structural classes of PARP inhibitors. If these results translate into similar effects in clinical studies, this would truly be a remarkable finding with great therapeutic potential.

As with any promising initial study, many questions remain, especially regarding the mechanism of action. Based on the previous results with the *BRCA1/2*-deficient cells, the assumption is that the ultimate target of the PARP inhibition is a DNA repair pathway. Although MCF-7 and MDA-MB-231 cells are apparently wild-type for *BRCA1* and *BRCA2*, they may harbor mutations in genes encoding other DNA repair and checkpoint proteins (for example, Rad51 and Chk1/2) that could render them sensitive to PARP inhibitors. Importantly, nuclear PARPs, such as PARP-1 and PARP-2, also play key roles in gene regulation [2,3], so transcriptional effects cannot be ruled out as the cause of PARP inhibitor sensitivity. Experiments with depletion of specific PARPs will help to determine the relevant targets.

Inbar-Rozensal and colleagues suggest a possible mechanism underlying G₂/M arrest by the PARP inhibitors through signal transduction pathways involving cell cycle proteins (for example, p21, cyclins, and cdc2) and extracellular signal-regulated kinase (ERK)-dependent kinase cascades. This is a reasonable hypothesis given the involvement of these pathways in cell cycle progression and proliferation in a variety of cancers, but additional experimental support is needed. The Cohen-Armon group [12] previously demonstrated that a signaling pathway involving ERK2 can support sustained DNA-independent activation of PARP-1, which is tied to signal-dependent chromatin modulation and gene regulation.

Interestingly, PARP-1 expression levels are increased in triple-negative breast cancer (that is, those that do not express estrogen receptor [ER], progesterone receptor [PR], and the human epidermal growth factor receptor HER2 [13]). Although MCF-7 cells and MDA-MB-231 cells differ in their expression of ER and PR (that is, MCF-7 cells express both ER and PR whereas MDA-MB-231 cells do not), neither cell line expresses HER2 [14]. HER2 is a cell membrane receptor tyrosine kinase involved in signaling pathways leading to cell proliferation, including those mediated by ERKs [15]. Functional connections between HER2, ERKs, and PARP-1 might play a role in determining the sensitivity of breast cancer subtypes to PARP inhibitors. Comparing the effects of phenanthridine-derived PARP inhibitors in MCF-7 and MDA-MB-231 cells with forced expression of HER2 would be informative in this regard.

In summary, the intriguing results of Inbar-Rozensal and colleagues point to a broader utility of PARP inhibitors in

the treatment of breast cancer beyond hereditary *BRCA1*- and *BRCA2*-deficient types. Further mechanistic studies are needed, however, to understand the full spectrum of breast cancer types for which chemical inhibition of PARPs might be therapeutically beneficial. In addition, clinical studies will be required to assess the efficacy *in situ*. Nonetheless, this study deserves attention and should stimulate much-needed further research in this area.

Competing interests

The authors declare that they have no competing interests.

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