

Editorial

Development of 'synthetic lethal' strategies to target BRCA1-deficient breast cancer

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Published: 23 September 2009

This article is online at <http://breast-cancer-research.com/content/11/5/108>

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Breast Cancer Research 2009, **11**:108 (doi:10.1186/bcr2362)

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Abstract

Recent clinical trials demonstrating the efficacy of poly(ADP-ribose) polymerase (PARP) inhibitors for the treatment of BRCA1-deficient breast cancer have provided support for the 'synthetic lethal' concept of targeted cancer therapeutics. A new study provides further preclinical validation of this concept by demonstrating that BRCA1-deficient mouse mammary tumor cells are selectively sensitive to an inhibitor of the polycomb gene *EZH2*. The development of polycomb gene inhibitors may provide a novel approach to selectively exploit the molecular alterations in BRCA1-deficient breast tumors.

In the previous issue of *Breast Cancer Research*, Puppe and colleagues [1] describe a novel approach to selectively target BRCA1-deficient breast tumors. One of the most exciting recent developments in clinical oncology has been the demonstration of significant clinical efficacy of inhibitors of poly(ADP-ribose) polymerase (PARP) in BRCA1-deficient breast tumors [2]. The development of PARP inhibitors was based on the concept of 'synthetic lethality', which posits that a compound targeting a particular pathway may be selectively 'lethal' to cells harboring a mutation in a complementary pathway. It was demonstrated, consistent with such a concept, that cells lacking BRCA1 repair function were 1,000-fold more sensitive to PARP inhibition than cells with intact DNA repair pathways [3,4]. Puppe and colleagues [1] use a mouse model of BRCA1-deficient breast tumors to identify *EZH2* as another 'drugable' synthetic lethal target. They used expression profiling to identify *EZH2* as a gene that was significantly overexpressed in BRCA1-deficient mouse mammary tumors as well as in breast tumors from women with BRCA1 germline mutations. Importantly, cells derived from BRCA1-deficient mouse mammary tumors were 20-fold more sensitive to the small-molecule *EZH2* inhibitor (DZNep) than were cells derived from mouse mammary tumors with normal BRCA1 expression. The specificity of this

effect was demonstrated by similar 'synthetic lethality' of BRCA1-deficient cells to *EZH2* knockdown by a short interfering RNA. Furthermore, this effect was reversed upon restoration of BRCA1 expression.

EZH2 function

EZH2 is a subunit of the large 'polycomb repressor complex 2', which initiates gene silencing by trimethylating lysine 27 in histone H3 (H3-K27 ME3). PRC1 complex genes, including *Bmi-1*, are then recruited to these marked histone sites, where they mediate repression of gene expression [5]. *EZH2* has been reported to be expressed mainly in human basal carcinomas, where this expression is associated with high proliferation and poor patient outcome [6,7]. *EZH2* has been reported to regulate cell proliferation through interaction with key growth-regulating pathways, including members of the Rb family as well as Ink4A and Ink4B [5,8]. Although PRC2 and PRC1 polycomb genes function in a 'linear fashion' in normal development, it has been suggested that their overexpression may have different functional consequences for breast tumorigenesis [9]. Nevertheless, both *EZH2* and *Bmi-1* have been shown to play important roles in regulating the self-renewal and differentiation of normal stem cells. This occurs through modulation of stem cell self-renewal and inhibition of genes promoting cellular differentiation [8].

BRCA1 and breast development

Recent studies have demonstrated that, in addition to its well-known role in DNA repair, BRCA1 plays an important role in breast development. Liu and colleagues [10] demonstrated that BRCA1 regulates the differentiation of estrogen receptor (ER)-negative breast stem cells into ER-positive luminal progenitors. Recently, Lim and colleagues [11] reported that breast tissue from BRCA1 mutation carriers contains expanded luminal progenitor cells, suggesting a broader role

ER = estrogen receptor; PARP = poly(ADP-ribose) polymerase.

for BRCA1 in the regulation of breast, stem, and progenitor cells. Together, these studies suggest that the loss of BRCA1 function may result in the expansion of the breast stem and progenitor cell populations, providing targets for further carcinogenic events. Although the exact relationship between BRCA1 and *EZH2* is not yet clear, Gonzalez and colleagues [12] recently demonstrated that BRCA1 is required for *EZH2* to mediate proliferation in breast cancer cell lines. Downregulation of *EZH2* decreased the growth of ER-negative breast cancer cells, an effect reversed by BRCA1 knockdown.

Targeting of breast cancer 'stem cells'

Recent studies have suggested that many tumors, including those of the breast, may be initiated and maintained by a cellular population that displays 'stem cell' properties. These properties include self-renewal, which drives tumorigenesis, and differentiation, which generates the non-self-renewing population comprising the tumor bulk. Breast cancer stem cells may mediate metastasis and contribute to treatment resistance [13]. Although *EZH2* and BRCA1 play a role in the biology of normal stem cells, the role of these genes in the regulation of breast cancer stem cells is not well defined. It will be most interesting to determine whether *EZH2* inhibition is able to target 'breast cancer stem cells' in addition to bulk cell populations in BRCA1-deficient tumors. The demonstration by Puppe and colleagues that DZNep reduced tumorsphere formation, a property of stem cells, is consistent with this possibility. However, the systemic toxicity of this compound precluded its use *in vivo*, making an assessment of its effect on 'tumor initiating' capacity difficult. An additional important unanswered question is whether the approach described by Puppe and colleagues will also show utility in the therapy of sporadic basal breast tumors, many of which have decreased BRCA1 activity as a result of gene methylation [14]. *EZH2* inhibition could potentially be combined with PARP inhibition as a 'double synthetic lethal' strategy for the treatment of this category of breast tumors. In any case, this study reinforces the feasibility of developing 'synthetic lethal' strategies aimed at selectively targeting genetically altered cancer cell populations. Hopefully, these strategies will result in the development of therapies that are more effective and less toxic.

Competing interests

MSW has financial holdings in and is a scientific advisor for OncoMed Pharmaceuticals, Inc. (Redwood City, CA, USA).

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