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BRCA1: a movement toward cancer prevention

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Abbreviations: BER, base-excision repair; BRCA1, breast cancer susceptibility gene 1; HER2, human epidermal growth factor receptor 2; SERM, selective estrogen receptor modifier.

Breast cancer susceptibility gene 1 (*BRCA1*) was first identified in 1994 and has since been shown to encode a tumor suppressor protein that maintains genetic stability through DNA damage response pathways. Carriers of mutations in *BRCA1* are predisposed to breast and ovarian cancer; however, their cancers lack the targets for existing anticancer drugs. We describe a novel chemoprevention approach that uses DNA repair-activating agents to enhance the repair of oxidative DNA damage and, in turn, prevent tumorigenesis in the presence of mutant BRCA1.

There's a will

Individuals who inherit a deleterious *BRCA1* mutation[1] are in urgent need of a targeted anticancer approach because of their overwhelming 75–80% lifetime risk for developing breast or ovarian cancer. Furthermore, *BRCA1*-mutated cancers present at a relatively early age, tend to be highly aggressive, and have limited treatment options. Their tendency to be 'triple-negative' for estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2 (HER2) and to contain mutant TP53 renders them relatively insensitive to hormonal manipulation, HER-directed therapy, and drugs that rely on TP53-dependent apoptosis. Instead, their DNA repair defects are often exploited using DNA damaging agents, which can be detrimental in the long term for carriers of *BRCA1* mutations who cannot readily repair DNA damage caused by agents that are typically delivered systemically. Inhibitors of poly(ADP-ribose) polymerase hold promise for therapeutics, and one, olaparib, has only recently received FDA approval for use in third-line ovarian cancer. As a result, it makes sense to combat BRCA1-mutated cancers prior to their development.

Where there's a will, there's a way

Because carriers of *BRCA1* mutations are readily identified by family history and genetic testing, this population is primed for a suitable prevention strategy. The current standard of care for carriers includes risk-reducing prophylactic bilateral salpingo-oopherectomy by age 40 and/or prophylactic mastectomy.[2] Prophylactic surgery, while effective, is not a desirable option due to the morbidity and irreversibility of removing normal organs, particularly at a relatively early age. Therefore, chemoprevention represents an alternative anticancer approach for carriers of *BRCA1* mutations.

FDA-approved chemopreventive agents for breast cancer include selective estrogen-receptor modifiers (SERMS); however, no chemopreventive agents currently exist for ovarian cancer. The use of SERMs for cancer prevention in carriers of *BRCA1* mutation is unproven and controversial because of the frequent lack of expression of estrogen and progesterone receptors in BRCA1-mutated tumors. Additionally, tamoxifen is a known carcinogen, and the use of tamoxifen for chemoprevention has not been well received by patients due to fear of the associated risk for endometrial carcinoma. A chemoprevention option that functions independent of hormone status may be ideal.

Where there's a will, there's a better way?

BRCA1 plays a well-established role in DNA double strand-break repair.[3] However, in the last decade or so BRCA1 has been found to have a wider involvement in DNA damage response pathways.[4-7] Interestingly, BRCA1 plays a role in the repair of oxidative DNA damage via the base-excision repair (BER) pathway, and indeed BRCA1-mutated/deficient cells exhibit compromised BER of oxidative DNA damage.[5] This finding is important because oxidative DNA damage, when left unrepaired,

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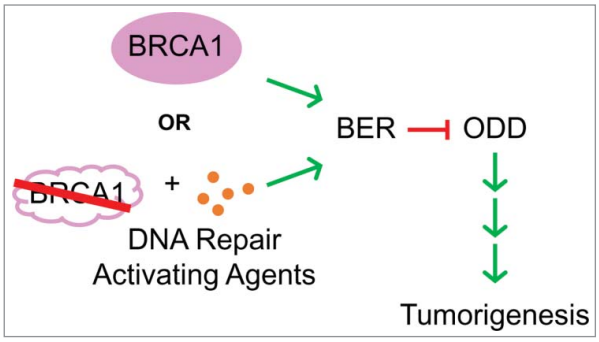

Figure 1. Links between BRCA1 and tumorigenesis. Oxidative DNA damage (ODD), the most common form of DNA damage, is typically repaired by the base-excision DNA repair pathway (BER). If left unrepaired, oxidative DNA damage leads to mutagenesis, genetic instability, and ultimately tumorigenesis. The BRCA1 tumor suppressor protein activates BER, reduces levels of oxidative DNA damage, and thereby prevents tumorigenesis. When BRCA1 is mutated, DNA repair-activating agents may enhance BER of oxidative DNA damage, and in turn prevent tumorigenesis.

is an early trigger of tumorigenesis, which implied to us that enhancing the repair of oxidative DNA damage may be an ideal means for preventing BRCA1-mediated tumorigenesis prior to the accumulation of mutations and genetic instability (**Fig. 1**).[8]

We conducted a high-throughput chemical screen to identify a series of compounds that we have classified as "DNA repair-activating agents". Two DNA repair-activating agents, benserazide and acetohexamide, enhanced BER and also decreased basal and hydrogen peroxide-induced levels of oxidative DNA damage in a dose-response and/or time-dependent manner. Moreover, these effects were specific to cells with mutant BRCA1. Both benserazide and acetohexamide activated BER directly, rather than indirectly by inducing DNA damage, as evidenced by a lack of an increase in levels of DNA damage following treatment with the DNA repair-activating agent. Therefore, DNA repair-activating agents target a functional defect that leads to tumorigenesis associated with mutant BRCA1.

We also provided *in vitro* and *in vivo* data that support a function for DNA repair-activating agents in preventing BRCA1-mediated tumorigenesis. Specifically, benserazide reduced anchorage-independent growth in BRCA1-mutant/deficient breast cancer cells and also delayed tumor formation, decreased the average weight of tumors, and prevented metastasis in a xenograft mouse model that was treated with drug prior to implantation with BRCA1-mutant tumor cells. Importantly, these mice experienced an increase in serum levels of a biomarker for repair of oxidative DNA damage (8oxodG) that correlated with a decrease in mean tumor weight. Together, these proof-of-principle experiments provided evidence that DNA repair-activating agents might be developed as chemopreventive agents for BRCA1-mutated breast cancers.

Benserazide and acetohexamide have been used for other clinical indications, and thus have been through human trials for safety. We found that both drugs exhibited minimal cytotoxicity at concentrations that enhanced BER of oxidative DNA damage, and lacked chemical, toxicological, and environmental health concerns according to the US National Library of Medicine TOXNET database. Therefore, DNA repair-activating agents may readily translate to the clinic as safe chemopreventive agents.

Concluding Remarks

DNA repair-activating agents represent a practical approach for the chemoprevention of BRCA1-mutated cancers. Hait and Levine propose that it is perhaps time to shift the current model of treating cancers toward one that relies more heavily on preventing them.[9] In the case of carriers of *BRCA1* mutation, rather than damaging the DNA with chemotherapeutic agents, we suggest preserving the highly coveted genomic integrity via chemoprevention with DNA-repair activating agents. These agents offer advantages over existing chemoprevention options for BRCA1-mutated cancers as they target a defect specific to BRCA1-associated tumorigenesis and lack reports of carcinogenicity and causal relationships with other malignancies, making them ideal for use by *BRCA1* mutation carriers who are susceptible to carcinogen-induced DNA damage. To our knowledge, this is the first description of a targeted chemoprevention approach for BRCA1-mutated cancers. However, whether DNA repair-activating agents will be effective for chemoprevention remains to be determined as these drugs move through the drug development process.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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References

1. Miki Y, Swensen J, Shattuck-Eidens D, Futreal PA, Harshman K, Tavtigian S, Liu Q, Cochran C, Bennett LM, Ding W et al. A strong candidate for the breast and ovarian cancer susceptibility gene BRCA1. Science 1994; 266:66-71; PMID:7545954; http://dx.doi.org/10.1126/science.7545954

2. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology Version 2.2014. Hereditary Breast and/or Ovarian Cancer Syndrome; [cited 2014 Oct 14].

3. Zhang J,Powell SN. The role of the BRCA1 tumor suppressor in DNA double-strand break repair. Mol Cancer Res 2005; 3:531-9; PMID:16254187; http://dx.doi.org/10.1158/1541-7786.MCR-05-0192
4. Alli E, Sharma VB, Hartman AR, Lin PS, Mcpherson L, Ford JM. Enhanced sensitivity to cisplatin and gemcitabine in Brca1-deficient murine mammary epithelial cells. BMC pharmacology 2011; 11:7; PMID:21771338; http://dx.doi.org/10.1186/1471-2210-11-7
5. Alli E, Sharma VB, Sunderesakumar P, Ford JM. Defective repair of oxidative dna damage in triple-negative breast cancer confers sensitivity to inhibition of poly (ADP-ribose) polymerase. Cancer Res 2009; 69:3589-96; PMID:19351835; http://dx.doi.org/10.1158/0008-5472.CAN-08-4016
6. Hartman AR, Ford JM. BRCA1 induces DNA damage recognition factors and enhances nucleotide excision repair. Nat Genet 2002; 32:180-4; PMID:12195423; http://dx.doi.org/10.1038/ng953
7. Saha T, Rih JK, Roy R, Ballal R, Rosen EM. Transcriptional regulation of the base excision repair pathway by BRCA1. J Biol Chem 2010; 285:19092-105; PMID:20185827; http://dx.doi.org/10.1074/jbc.M110.104430
8. Alli E, Solow-Cordero D, Casey SC, Ford JM. Therapeutic targeting of BRCA1-mutated breast cancers with agents that activate DNA repair. Cancer Res 2014; 74:6205-15; PMID:25217519
9. Hait WN, Levine AJ. Genomic complexity: a call to action. Science translational medicine 2014; 6:255cm210; PMID:25253671; http://dx.doi.org/10.1126/scitranslmed.3009148