The Mechanism of IB-DNQ-induced Cell Death in NQO1 Positive BRCA2-mutant Breast Cancer Cells

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Abstract

BRCA1 and BRCA2 are tumor suppressor genes that are involved in the processes of DNA repair and gene transcription. When mutated, BRCA1/2 can lead to the development of breast cancer and are the cause of 5-10% of all breast cancer cases. Unfortunately, current treatments for BRCA1/2 mutant cancers are not always successful and cause off-target effects in normal tissues. Previous work has shown that the expression of NAD(P)H:quione oxidoreductase-1 (NQO1) is higher in breast cancer tissues and cell lines than normal tissues. In the presence of certain quinones, such as lapachol, deacyloxyquinones (IB-DNQ), NQO1 performs a two-electron oxidation reaction resulting in futile redox cycling and reactive oxygen species (ROS) generation. We hypothesize that treatment of NQO1+ BRCA2-mutant breast cancer cells with IB-DNQ will cause DNA damage and activation of the repair enzyme poly(ADP-ribose) polymerase-1 (PARP-1). Co-treatment of IB-DNQ with PARP-1 inhibitors, ABT-888 or Olaparib (OLA), will then show greater toxicity in BRCA2-mutant cells due to their inability to repair DNA damage. To test this hypothesis, the BRCA2-mutant breast cancer cell line HCC1142 was treated with various doses of IB-DNQ with or without the NQO1 inhibitor dicoumarol or co-treated with PARP inhibitors and assessed for viability. To determine whether the NQO1-mediated metabolism of IB-DNQ caused DNA damage, western blot analysis was performed and cell lysates probed with antibodies to phosphorylated H2AX and p53. Results from these experiments suggest that IB-DNQ-induced toxicity in BRCA2-mutant cells is NQO1-dependent and causes DNA damage. Future studies will continue to examine the mechanism of IB-DNQ-induced cell death in BRCA2-mutant breast cancers.

Methods

BRCA2-mutant Cells Show Increased Toxicity when Co-Treated with PARP Inhibitor

IB-DNQ-mediated PARP-1 Activation is Prevented with PARP Inhibitors

Working Hypothesis

Future Directions

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