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BRCA2 inhibition enhances cisplatin-mediated alterations in tumor cell proliferation, metabolism, and metastasis

Tumor cells have unstable genomes relative to non-tumor cells. Decreased DNA integrity resulting from tumor cell instability is important in generating favorable therapeutic indices. However, intact DNA repair mediates resistance to therapy. Targeting DNA repair to promote the action of anticancer agents is therefore an attractive therapeutic strategy. BRCA2 is involved in homologous recombination repair. BRCA2 defects increase cancer risk but, paradoxically, cancer patients with BRCA2 mutations have better survival rates. We queried TCGA data and found that BRCA2 alterations led to increased survival in patients with ovarian and endometrial cancer. We developed a BRCA2-targeting second-generation antisense oligonucleotide (ASO), which sensitized human lung, ovarian, and breast cancer cells to cisplatin by as much as 60%. BRCA2 ASO treatment overcame acquired cisplatin resistance in head and neck cancer cells, but induced minimal cisplatin sensitivity in nontumor cells. BRCA2 ASO plus cisplatin reduced respiration as an early event preceding cell death, concurrent with increased glucose uptake without a difference in glycolysis. BRCA2 ASO and cisplatin decreased metastatic frequency *in vivo* by 77%. These results implicate BRCA2 as a regulator of metastatic frequency and cellular metabolic response following cisplatin treatment. BRCA2 ASO, in combination with cisplatin, is a potential therapeutic anticancer agent.

Biography

James Koropatnick is Director of the Cancer Research Laboratory Program of the Lawson Health Research Institute and University of Western Ontario. His research program is focused on development of novel antisense drugs to enhance effectiveness of anticancer chemotherapy, development of new platinum-based anticancer compounds, development of novel anticancer compounds based on *in silico* targeting prediction, and development of novel antibody-drug conjugates for treatment of breast and colorectal cancer. He is also the Chief Scientific Officer and cofounder (with Dr. Mark Vincent) of Sarissa, Inc. (a biotech discovery company) and sits on the Scientific Advisory Boards of Critical Outcomes Therapeutics, Inc., AvidBiologics, Inc., ID Laboratories, Inc., and MedVax Pharma, Inc.

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