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Contribution of tumor microenvironment to cancer phenotype after DNA damage

The tumor microenvironment consists of a diverse and variable array of cell types that includes fibroblasts, endothelial cells, and immune cells. It has been shown to influence cancer cell growth and progression through a variety of mechanisms. However, less is known about effects on the tumor microenvironment (TME) following DNA damage that occurs in systemic cancer therapy. The authors of this study evaluated quiescent, or nondividing, human prostate fibroblasts and their influence on adjacent cancer cells after exposure to the chemotherapy agent mitoxantrone or ionizing radiation. The focus on quiescent cell status is important because many TME cells reside in a quiescent state. Yet many prior studies have instead analyzed the effects on TME using rapidly dividing cells in cell culture systems. To establish their model, the authors first confirmed quiescent conditions in the fibroblasts, using gene expression signatures to verify cell cycle status. They then induced DNA damage using either ionizing radiation or mitoxantrone in quiescent cells and evaluated the effects on gene expression and the DNA-damage response "secretory" program that reflects the secretion of proteases, growth factors, and cytokines used under noncancerous conditions to promote senescence, or regulated cell death, of damaged cells. Subsequent proliferation of these cells resulted in an increase in the secretory response that, in the setting of cancer, could influence cancer cell behavior. To test this, conditioned media were collected from these DNA-damaged fibroblasts and applied to prostate cancer cells. In response to this conditioned media, prostate cancer cells showed increased invasive behavior, cell proliferation, and resistance to mitoxantrone. To determine the clinical relevance of this finding, the authors used prostate tissue from men with prostate cancer enrolled in a clinical trial of the DNA-damaging agent mitoxantrone and the microtubule poison docetaxel. Dissection and analysis of the benign TME cells around the cancer showed an increase in gene transcripts that encode components of the secretory program. The results of this study suggest that associated TME cells may be able to influence the behavior of adjacent cancer cells and should be considered when designing treatments for patients with cancer.

Gomez-Sarosi L, Sun Y, Coleman I, et al. DNA damage induces a secretory program in the quiescent TME that fosters adverse cancer phenotypes. *Mol Cancer Res.* March 29, 2017. doi:10.1158/1541-7786.MCR-16-0387.

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BRCA1 and metabolism: Partners in the development of ovarian cancer?

Cancer cells can change how metabolic processes are used in order to promote cancer cell evolution and growth. One of the best known of these metabolic alterations is the Warburg effect, which was described in the 1920s by Otto Warburg. The Warburg effect describes how cancer cells switch their energy production from oxygen-based mitochondrial respiration to glycolysis, a process by which energy is derived from glucose. The use of glycolysis to fuel cancer cell growth has been reported in a large number of cancer types, including ovarian cancer, although the mechanism underlying this adaptation is not well understood. The authors sought to link the *BRCA1* mutation spectrum in ovarian cancer cells to changes in energy metabolism, including glycolysis. *BRCA1* mutations are an important contributor to the development of ovarian cancer, and women with a germline *BRCA1* mutation have up

to a 46 percent risk of developing ovarian cancer by age 70, while the general population has a lifetime risk of only 1.4 percent. Under normal conditions, *BRCA1* can assist in DNA damage repair. However, in cells in which *BRCA1* is mutated, DNA damage is repaired through an alternative and somewhat faulty mechanism that leads to chromosomal instability and contributes to cancer development. The authors conducted a study in which they tested the mechanism by which *BRCA1* mutations could affect metabolic processes relevant to cancer development and then examined possible methods to reverse this mechanism using rationale drug treatment. Both ovarian surface epithelial cells and fallopian tube cells were used in the study because both cells of origin have been implicated in the development of ovarian cancer. In both cell types, *BRCA1* mutation and knockdown showed an increase in glycolytic activity and an increase in expression of hexokinase 2 (HK2), an enzyme within the glycolytic pathway. In examining the mechanism by which BRCA1 loss affected HK2 expression, the authors discovered that both MYC and STAT3, proteins identified as key factors in cancer development, were responsible for HK2 increases in the absence of *BRCA1*. The authors next tested a series of drugs, including aspirin and luteolin, that have been reported to protect against ovarian cancer development to determine their effects on regulating HK2 expression. Both drugs could partially reverse the changes caused by BRCA1 loss and, therefore, may be candidates for future study in patients with *BRCA1* mutation. This indication is supported by other studies, including the Iowa Women's Health Study, in which aspirin appeared to reduce the incidence of ovarian cancer. In addition to its role in regulating glycolysis, *BRCA1* alteration also appeared to reduce fatty acid oxidation, increase NADPH production, and upregulate oxidative phosphorylation. The results of this study suggest that *BRCA1* mutations go beyond DNA damage repair and may contribute to cancer-contributing alterations in metabolic pathways within ovarian and fallopian tube cells.

Chiyoda T, Hart PC, Eckert MA, et al. Loss of BRCA1 in the cells of origin of ovarian cancer induces glycolysis: a window of opportunity for ovarian cancer chemoprevention. *Cancer Prev Res.* 2017;10(4):255–266.

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