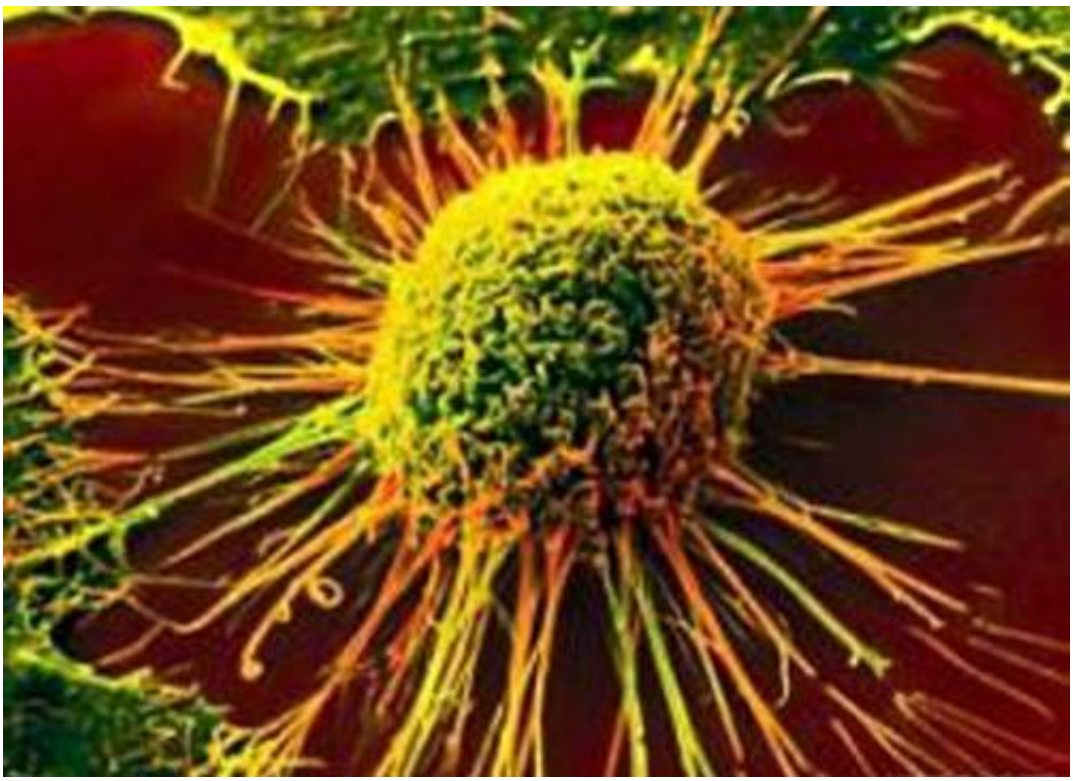
MedicalXpress

New drug resistance mechanism has implications for breast, ovarian cancer treatment

March 5 2015, by Mark L. Shelton



Research to understand why hereditary cancers develop resistance to a powerful cancer drug has identified an important new pathway key to chemoresistance in BRCA2-mutant cancers. The research, published in the current issue of *Genes & Development*, is the work of Sharon Cantor,

PhD, associate professor of molecular, cell & cancer biology, and colleagues. They used an innovative genome-wide RNA screen to determine why so many instances of ovarian cancers develop resistance to the cancer drug cisplatin.

"Germline BRCA1 or BRCA2 mutations are the most common cause—more than 90 percent—of hereditary breast and ovarian cancers," said Dr. Cantor. "BRCA1 and BRCA2 proteins promote DNA repair as part of their tumor suppression function, so BRCA1/2-mutant cancers are initially sensitive to therapies that target DNA, such as cisplatin, or that inhibit DNA repair pathways, such as PARP inhibitors. The potential of these therapies is limited, however, by the development of chemoresistance. To date, the only known mechanism of chemoresistance in BRCA1/2-mutant cancers is restored DNA repair that occurs either by genetic reversion or in BRCA1-mutant cells by 53BP1 loss."

What Cantor's group found is that chemoresistance is also achieved independently of restored DNA repair in BRCA2-mutant cells through loss of a nucleosome-remodeling factor, CHD4. CHD4 depletion reduces the toxicity of cisplatin by enabling BRCA2 mutant cells to switch on a pathway known as "DNA damage tolerance." Interestingly, this switch is unique to BRCA2 mutant cells. Normally, CHD4 loss akin to BRCA2 loss sensitizes to chemotherapy, but CHD4 loss in BRCA2 mutant cells enhances resistance to cisplatin as well as PARP inhibitors.

"Sharon Cantor has a long-standing interest in the BRCA1/2 breast and ovarian cancer susceptibility genes," said Michael R. Green, MD, PhD, Howard Hughes Medical Institute Investigator, the Lambi and Sarah Adams Chair in Genetic Research, and chair and professor of molecular, cell & cancer biology. "Ovarian cancers lacking BRCA1/2 are susceptible to treatment with cisplatin. Unfortunately, resistance often develops by mechanisms that remain to be determined. Sharon's elegant

work has revealed a new and important cisplatin resistance mechanism that has both prognostic and therapeutic implications."

The paper also provides clarity as to how chemotherapy resistance can occur in such a large number of cancers; Cantor and colleagues found a statistically significant correlation between low levels of CHD4 and shorter progression-free and overall survival in BRCA2 mutant ovarian cancers.

More information: "Resistance to therapy in BRCA2 mutant cells due to loss of the nucleosome remodeling factor CHD4" *Genes Dev*. March 1, 2015 29: 489-494; DOI: 10.1101/gad.256214.114

Provided by University of Massachusetts Medical School