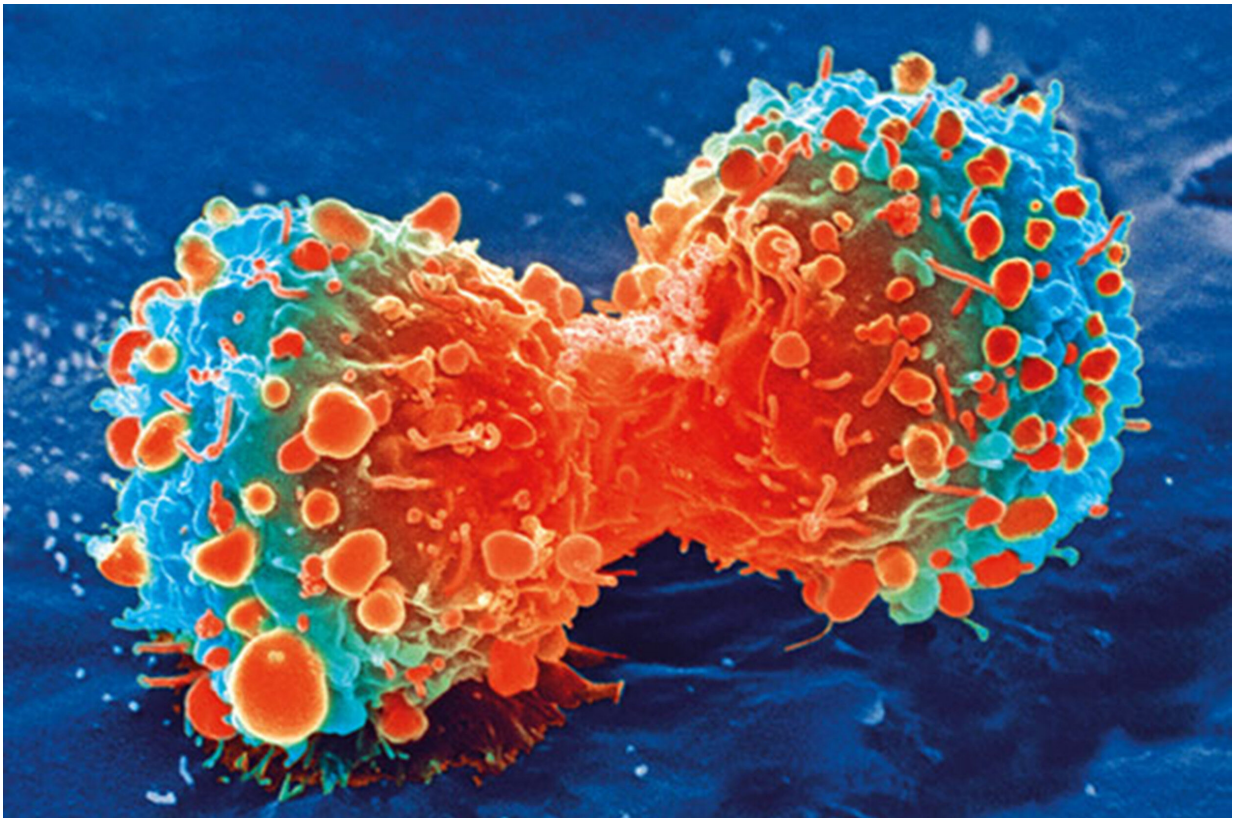
MedicalXpress

Powerful new ovarian cancer treatments may benefit more patients

July 29 2021



Cancer cell during cell division. Credit: National Institutes of Health

WEHI researchers have made a discovery that could help more Australian women with ovarian cancer gain access to game-changing cancer treatments called PARP inhibitors.

The research team found tumors from some ovarian cancer patients had changes that silenced a gene involved in DNA repair and showed that this made tumors sensitive to PARP inhibitors.

The discovery identifies a new group of patients who are likely to benefit from the therapy and who should be included in trials of PARP inhibitors. It also indicates these women should be closely monitored for changes that affect gene silencing, which could render their cancers resistant to therapy.

The research, published in the journal *Cancer Research*, was led by WEHI researchers Dr. Ksenija Nesic, Dr. Matthew Wakefield and Professor Clare Scott, QIMR Berghofer researcher Dr. Olga Kondrashova and Associate Professor Alexander Dobrovic from the University of Melbourne Department of Surgery, together with Australian and U.S. collaborators.

'Silencing' key to drug response

A PARP inhibitor is a type of targeted cancer therapy that is effective in cancers that have acquired faults in the way they repair DNA repair, making them particularly sensitive to DNA-damaging drugs. BRCA1 and BRCA2 are well-known DNA repair genes that, when faulty, make cancer cells susceptible to PARP inhibitors.

In this study, the research team studied samples donated by women with high-grade serous cancer, an aggressive type of ovarian cancer.

Dr. Nesic said the cancer cells that were susceptible to PARP inhibitors shared a unique characteristic. "We observed that ovarian cancers with 'epigenetic marks' which silenced the RAD51C gene were susceptible to PARP inhibitor therapy," Dr. Nesic said.

Epigenetic marks are "notations" on DNA that can, among other things, instruct the genes to be switched on (expressed) or switched off (silenced). RAD51C is also associated with DNA repair in cells.

Dr. Nesic said the team used sophisticated preclinical models called PDX (patient-derived xenografts) to study the complex pattern of epigenetic marks associated with PARP inhibitor sensitivity.

"We showed that RAD51C silencing has to be absolute for the PARP inhibitors to work. If the cancer has any residual DNA repair capabilities, or if these epigenetic marks are lost during treatment, it became resistant to the therapy," Dr. Nesic said.

"This builds on previous work from the Scott laboratory that PARP inhibitors become ineffective if the BRCA1 gene is not completely silenced—the first time that incomplete gene silencing had been linked to PARP inhibitor resistance."

A game-changer for ovarian cancer

Professor Scott is joint head of clinical translation at WEHI and a medical oncologist at the Royal Melbourne and Royal Women's Hospitals and Peter MacCallum Cancer Centre. She said PARP inhibitors have had a profound impact in treating BRCA1/2 mutated ovarian cancers.

"Ovarian cancer is often diagnosed at an advanced stage and many women relapse after treatment," Professor Scott said. "PARP inhibitors are currently approved in Australia for treating women with BRCA1/2 mutated cancers, with unprecedented success. In these women, first cancer recurrence is delayed by 3.5 years and, in advanced disease, progression free survival is extended. This is significant for women with ovarian cancer, considering we have seen little improvement in survival

rates in the past 30 years.

Research guides personalized medicine

Dr. Nesic said the studies highlighted how medical research provided much needed guidance about personalized treatment options, and improved patient outcomes.

"This research has identified more women who would benefit from PARP inhibitor therapy and showed us that the best therapy for a patient can change over time," Dr. Nesic said.

"In the future, we propose that women undergoing treatment for ovarian cancer should have their tumors monitored over time. If their cancers lose their gene silencing, then women should be offered alternative therapies, as PARP inhibitors will no longer be effective."

Validation of research findings in patient tumor samples with RAD51C silencing relied on international collaborations with the Mayo Clinic, U.S., and the University of Washington, US. A cohort of 13 patients was assembled from these collaborations, the Australian Ovarian Cancer Study (AOCS), and the WEHI-Stafford Fox Rare Cancer Program. Complex silencing patterns were observed in approximately 50 percent of cases.

More information: Ksenija Nesic et al, Acquired RAD51C promoter methylation loss causes PARP inhibitor resistance in high grade serous ovarian carcinoma, *Cancer Research* (2021). DOI: 10.1158/0008-5472.CAN-21-0774

Provided by Walter and Eliza Hall Institute of Medical Research