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Why some cancers may respond poorly to key drugs discovered

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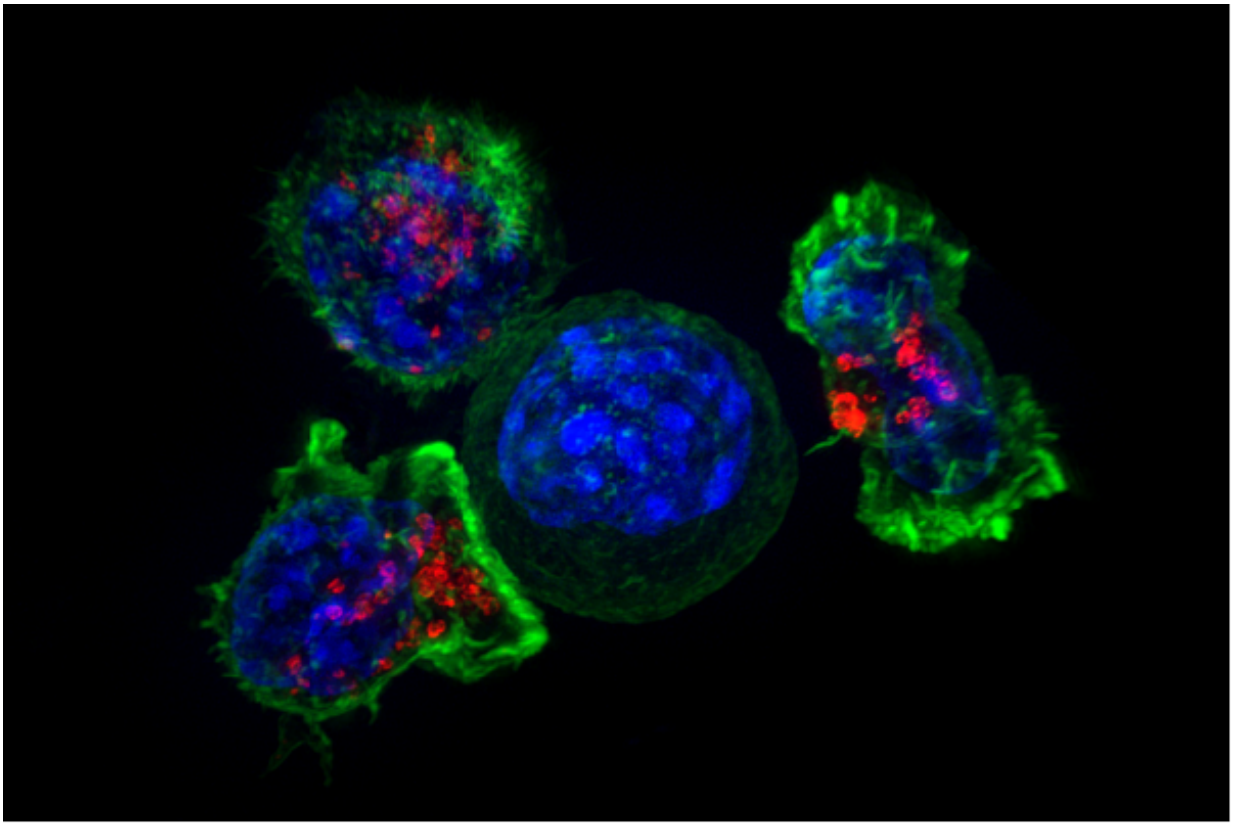

Killer T cells surround a cancer cell. Credit: NIH

Patients with BRCA1/2 mutations are at higher risk for breast, ovarian and prostate cancers that can be aggressive when they develop—and, in many cases, resistant to lifesaving drugs. Now scientists at The

University of Texas at Austin and Ajou University in South Korea have identified a driver of the drug resistance that can make a life or death difference for patients with these cancers.

"A major issue with cancer treatments is the development of resistance," said Kyle Miller, a UT Austin associate professor of molecular biosciences. "When treatments stop working for patients, it's incredibly demoralizing and it's been a huge drive in research to understand these resistance mechanisms."

In a paper published today in the journal *Molecular Cell*, the researchers describe a protein that may help doctors predict which patients will become resistant to a class of drugs frequently used to treat BRCA 1/2-deficient tumors. The finding could help create more effective treatment plans for their patients.

The scientists identified that a protein called PCAF promotes DNA damage in BRCA 1/2-mutated cancer cells. Patients with low levels of this protein are likely to have poor outcomes and develop resistance to a type of drug that is used to treat BRCA-deficient tumors, called a PARP inhibitor.

"PARP inhibitors are an important breakthrough in treating these aggressive cancers," Miller said. "What we found is that when levels of PCAF are low, it actually protects the cancer cells from this drug. By testing biopsy samples, doctors may be able to tell using PCAF as a molecular marker for PARP inhibitor responses what treatment may work best for a patient."

Fortunately, there is already another class of drugs on the market, called HDAC inhibitors, that can boost the effectiveness of the PCAF protein. HDAC inhibitors and PARP inhibitors have the potential to be prescribed as a combination therapy.

"Previous studies have shown that these two drugs work well together," Miller said. "We believe we've found the reason why."

It is possible to test for PCAF levels in biopsy or tissue samples, Miller said, and in the future, the test could be included on a standard panel for cancer testing.

But unlocking the workings of PCAF doesn't just offer clues to combatting cancer. Because this protein is responsible for modifying chromatin, the stuff that organizes 6 feet of DNA in each of our cells so that it fits into its nuclear volume, PCAF also may offer important clues about cell replication.

"The focus in my lab is on understanding chromatin and its impact on replicating DNA, protecting DNA and controlling access to DNA," Miller said. "Our goal is to understand how every molecule is interacting inside our cells, as this gives clues to what is going wrong in human diseases."

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