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Popular breast cancer drugs don't work the way we thought they did

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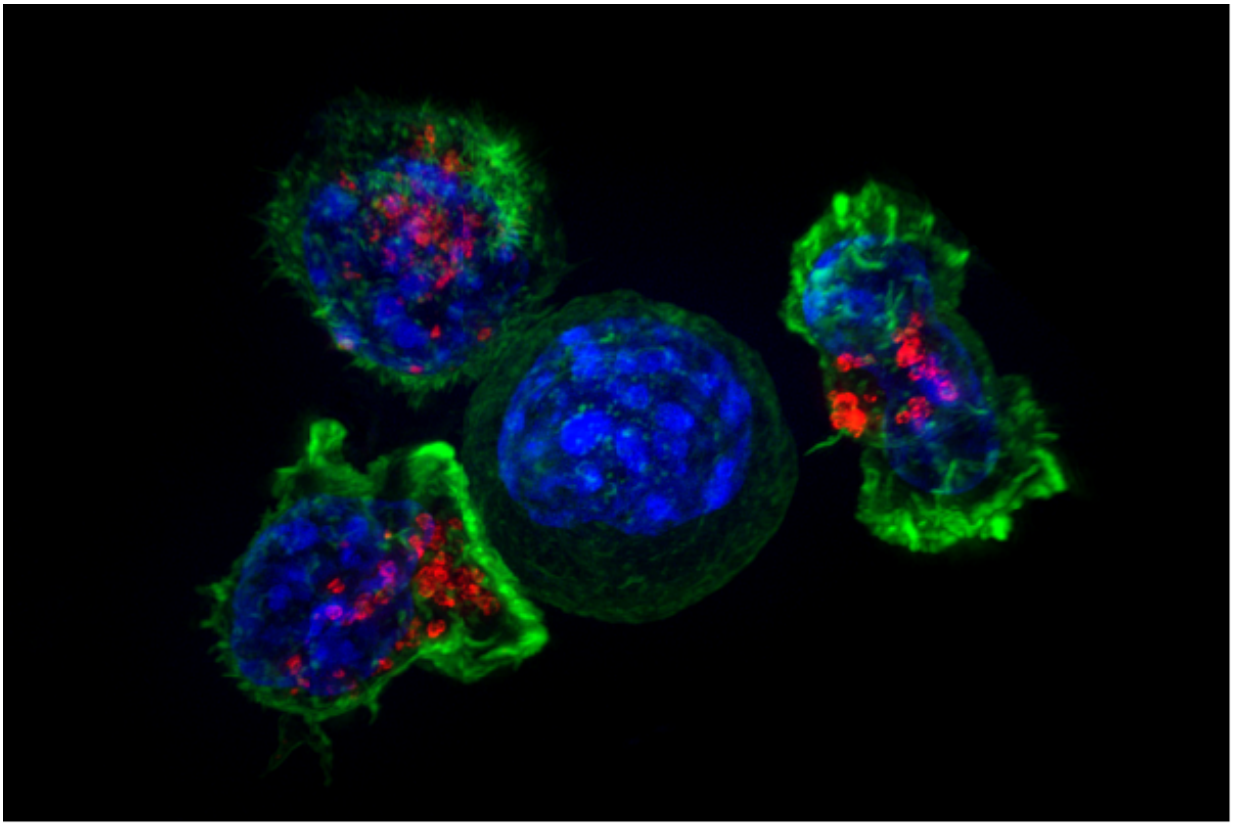

Killer T cells surround a cancer cell. Credit: NIH

Some of the most commonly used drugs for treating hereditary breast and ovarian cancers may not work the way we thought they did, according to new University of Colorado Boulder research.

The paper, published February 2 in the journal *Nature Communications*, sheds new light on how they do work and could open the door to new next-generation medications that work better, the authors said.

"Despite the success of these drugs which sell in the billions of dollars per year and treat many thousands of patients, there are many unknowns about their potency and efficacy that if better understood could lead to improvements," said senior author Karolin Luger, a professor in the Department of Biochemistry. "Our paper provides a fuller picture."

The research centers around a class of drugs known as PARP-inhibitors, broadly prescribed to target cancers fueled by a mutation in the BRCA, or BReast CAncer, gene.

When functioning properly, the BRCA gene plays a key role in repairing damaged DNA inside cells. When the gene is mutated or missing, cancer risk rises.

About one in 10 of the quarter-million women diagnosed with breast cancer annually have a BRCA mutation. And BRCA-fueled cancers tend to come earlier, be more aggressive, and resist treatment.

Enter PARP inhibitors.

First unveiled clinically in 2014, the drugs target a ubiquitous family of proteins called PARPs (poly-ADP-ribose), which were discovered in the 1960s and are also instrumental in fixing broken DNA.

"PARPs are the first responders," explains first author Johannes Rudolph, a senior researcher in the Department of Biochemistry who worked with graduate student Genevieve Roberts on the study. "DNA damage happens, PARP goes in and finds it, and then it sends out a signal to other proteins to come in and help with repairs."

Because both PARP and BRCA also serve to repair DNA damage inside cancer cells, disabling the PARP first-responder in someone who doesn't have a functioning BRCA repair crew delivers what Rudolph describes as a lethal "double whammy" to cancer cells.

With this in mind, pharmaceutical companies have raced to develop more PARP inhibitors, with at least four in use today and others being explored to treat different forms of cancer.

But as it turns out, PARP is not acting alone.

Scientists recently discovered that another protein called HPF1 (histone PARylation Factor 1) is attached to the PARP protein at precisely the location where all the action happens, working closely with it in its role as first responder.

Existing drugs were developed long before HPF1 was even known to exist.

So Rudolph and Luger began to wonder: Does this newly-discovered co-protein influence how well those cancer drugs work? And if so, could drugs designed specifically to target it also work better?

Their findings suggest yes.

"It appears that existing drugs were designed to inhibit only two-thirds of the proteins at play here, because we didn't know this other third existed," says Rudolph.

For the new paper, Rudolph developed a new method to study just how tightly existing drugs bind to PARP inside cells—a measure of potency and efficacy—both in the presence and absence of HPF1.In some cases,

the drugs worked just as well whether it was there or not. But in others, it made a big difference.

For instance, the drug Olaparib bound more tightly and significantly longer to PARP when HPF1 was present than when it was not.

Put simply, this drug may, by sheer coincidence, impact the combination of the two proteins, making it work better. Meanwhile, for other drugs, there is likely room for improvement.

"This suggests that future PARP inhibitors should be aimed at taking advantage of this interaction in order to become more potent," Rudolph said.

Luger notes that such room for improvement is likely there for many drugs currently on the market, as drug candidates are often tested in isolation in test tubes to see if they work, but once inside the cell they interact with a complex network of proteins and enzymes that are not entirely understood.

"Drug development tends to move quickly, moving from in-vitro models to animal models to clinical trials without fully understanding the mechanism of action," she says. "That's a fine approach because it gets you there fast, but if you really want to improve upon these drugs you need to understand why and how they really work. That's what we tried to do with this paper."

More information: Johannes Rudolph et al, Histone Parylation factor 1 contributes to the inhibition of PARP1 by cancer drugs, *Nature Communications* (2021). DOI: 10.1038/s41467-021-20998-8

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