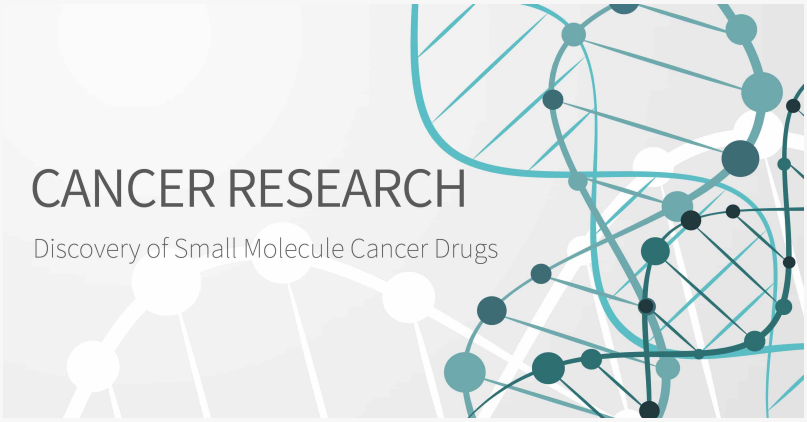
A Fuller Picture on How Commonly-Used Breast Cancer Drugs Work

A class of drugs known as PARP-inhibitors used to treat hereditary breast and ovarian cancers, may not work the way we thought they did. VulcanChem



VulcanChem - Cancer Research

PASADENA, CALIFORNIA, UNITED STATES, February 8, 2021 /EINPresswire.com/ -- A paper, recently published in the journal Nature Communications, sheds new light on how commonly-used drugs for treating hereditary breast and ovarian cancers work and could open the door to new next-generation medications that work better. The research centers around a class of drugs known as PARP-inhibitors, broadly prescribed to target cancers fueled by a mutation in the BRCA gene.

BRCA proteins are important for the repair of double-strand DNA breaks by the error-free homologous recombinational repair, or HRR, pathway. When the gene for one of these proteins is mutated, the change can lead to errors in DNA repair that can eventually cause breast cancer. When subjected to enough damage at one time, the altered gene can cause the death of the cells. PARP is a protein important for repairing single-strand breaks. If the single-strand breaks persist unrepaired until DNA is replicated (which must precede cell division), then the replication itself can cause double-strand breaks to form. Drugs that inhibit PARP1 cause multiple double-strand breaks to form in this way, and in tumors with BRCA mutations, these double-strand breaks cannot be efficiently repaired, leading to the death of the 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. However, according to the new study, PARP is not acting alone. As the paper describes, another protein called HPF1 is attached to the PARP protein at precisely the location where all the action happens, working closely with it in its role as the first responder. But the existing drugs were developed long before HPF1 was even known to exist. So the researchers started to wonder, does this newly-discovered co-protein influence how well those cancer drugs work?

To answer this question, 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.

The take-away from the study is that for some drugs, it might be sheer coincidence that they impact the combination of the two proteins, making it work better. Meanwhile, for other drugs, there is likely room for improvement. 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.

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