Combining cell replication blocker with common cancer drug kills resistant tumor cells

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(Medical Xpress)—Researchers from the University of Pittsburgh Cancer Institute (UPCI), a partner with UPMC CancerCenter, have found that an agent that inhibits mitochondrial division can overcome tumor cell resistance to a commonly used cancer drug, and that the combination of the two induces rapid and synergistic cell death. Separately, neither had an effect. These findings will be presented Monday at the annual meeting of the American Association for Cancer Research Annual Meeting 2014.

"In our earlier work, we found that blocking production of a protein called Drp1 stopped mitochondria, known as the powerhouses of the cell, from undergoing fission, which is necessary for the cellular division process called mitosis," said Bennett Van Houten, Ph.D., the Richard M. Cyert Professor of Molecular Oncology, Pitt School of Medicine, and leader of UPCI's Molecular and Cell Biology Program. "The loss of this critical mitochondrial protein caused the cells to arrest in mitosis and to develop chromosomal errors, and eventually led the tumor cell into the cell death pathway known as apoptosis."

The researchers blocked Drp1 in breast cancer cell lines with an agent called mitochondrial division inhibitor-1 (mdivi-1) and found that when mdivi-1 and the cancer drug cisplatin were given together, they caused DNA damage, DNA replication stress, and greater than expected apoptosis rates. The synergistic drug combination acted through two

independent biochemical pathways that caused the mitochondrial membrane to swell, increasing its permeability and allowing the leak of chemical signals that trigger apoptosis.

"Cisplatin is one of the most widely used cancer drugs today, but some tumors are inherently resistant to it, and many others become resistant, leading to treatment failure," Dr. Van Houten said. "In our studies, this combination overcame cisplatin resistance and caused cancer cell death, which is very encouraging."

The team is testing the regimen's effectiveness in a mouse model of ovarian cancer, a disease that often recurs and no longer responds to cisplatin treatment.

Provided by University of Pittsburgh Medical Center