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New Drug Combo Targets Multiple Cancers

Sugar molecule primes cancer cells for early death from second compound

Researchers at the University of California, San Diego School of Medicine and Kyushu University Medical School say a novel combination of a specific sugar molecule with a pair of cell-killing drugs prompts a wide variety of cancer cell types to kill themselves, a process called apoptosis or programmed cell death.

The findings are reported online in the journal *Cancer Research*.

“The goal of targeted therapy is to stop the growth of cancerous cells while doing little or no harm to healthy tissue,” said Guy Perkins, PhD, associate project scientist at the Center for Research in Biological Systems at UC San Diego. “Cancer researchers are always looking for new therapies to target a variety of cancers and kill tumor cells in various stages of development.”

Unfortunately, added co-author Ryuji Yamaguchi, PhD, senior researcher at Kyushu University Medical School in Fukuoka, Japan, “even the best new drugs seem to be limited to specific cancer types and too often tumor cells develop resistance to these drugs, leading to eventual treatment failure.”

The new two-part therapy described by Perkins and Yamaguchi focuses on depriving cancer cells of their fundamental need for sugar to fuel growth and multiplication. The first component is a modified glucose or sugar molecule called 2-deoxyglucose (2-DG). Although readily taken in by sugar-hungry cancer cells, it cannot be broken down to produce energy. Instead, it hampers cancer cell growth and primes the cells for early death by opening access to an internal protein that can trigger apoptosis.

Cells primed with 2-DG are then exposed to a pair of drugs, ABT-263/737, which signal the internal protein to initiate cell death. Researchers say only cancer cells sensitized for death by 2-DG and exposed to ABT-263/737 are broadly impacted. Healthy brain cells, which are also

highly glycolytic like cancer cells, are protected because ABT-263/737 cannot cross the body's blood-brain barrier.

After first determining that *in vitro* cancer cells incubated with 2-DG and exposed to low concentrations of ABT-263/737 died, the researchers conducted animal studies. They found that when 2-DG was injected into animals, it predominantly accumulated in cancer cells that were subsequently killed by an injection of ABT-263/737. The two-step approach successfully induced apoptosis in leukemia, hepatocarcinoma, lung, breast and cervical cancers. Yamaguchi said it caused cell death at many stages of cancer development, including a difficult-to-treat, chemo-resistant, highly metastasized form of prostate cancer.

"Since the combination of 2-DG and ABT-263/737 induces rapid apoptosis through the intrinsic pathway, meaning through mitochondria, it leaves little room for interference by a cancer cell's highly active mutagenic programs," Perkins said.

The combined treatment, however, does not work on all cancers. "There are certain cancers that are resistant or in which this would cause lymphopenia and thrombopenia," said Yamaguchi. Lymphopenia and thrombopenia are a loss of white blood cells or platelets, respectively. The scientists are developing "workarounds" to counteract these adverse effects, possibly by using stored hematopoietic stem cells for transplant after treatment.

"We are now trying to initiate a clinical trial for the combination," said Yamaguchi. "Since both 2-DG and ABT-263 (Navitoclax) are already in Phase II clinical trials (for other treatments), we know something about the safety of these agents. Once we take precautionary measures, the 2-DG-ABT combination therapy may prove an effective alternative to some existing cancer therapies. We may have found a simple, partial solution to a very complex disease."

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