Promising approach against treatment-resistant cancer

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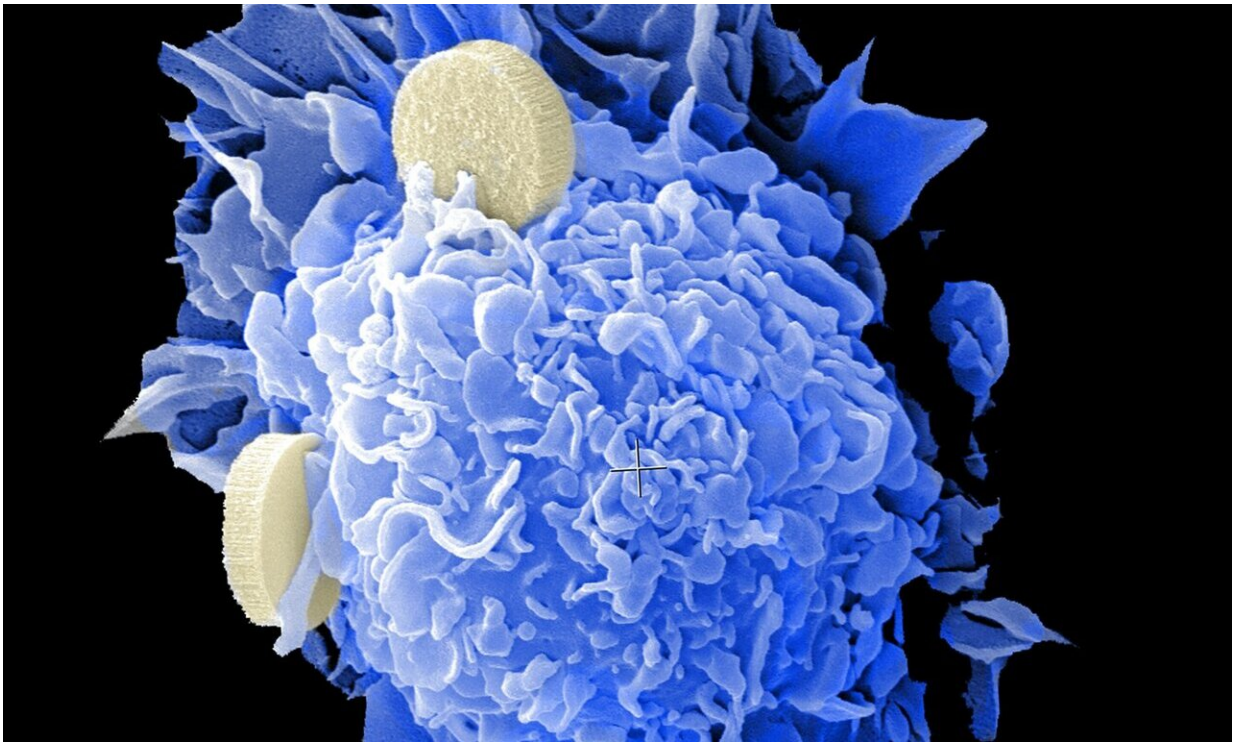

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As described in the March 7 issue of *Nature Communications*, investigators used a two-drug combination to achieve chemotherapy's goal: to make cancer cells self-destruct via the biological process known as apoptosis, often referred to as programmed cell death. The treatment worked against human cancer cell lines that resisted apoptosis despite

exposure to different types of chemotherapy, and also against apoptosis-resistant human tumors implanted in mice (i.e., xenograft mouse models).

"Targeted therapies that home in on specific genetic vulnerabilities of cancers have vastly improved treatment in recent years, but not everyone has benefited," said Evripidis Gavathiotis, Ph.D., professor of biochemistry and of medicine at Einstein, co-leader of the Cancer Therapeutics Program at the NCI-designated Albert Einstein Cancer Center, and corresponding author on the paper. "We need new, broadly active therapies that can attack a range of cancers while causing fewer side effects than current treatments, and we hope our new therapeutic strategy will prove to be a viable option."

Eliminating Unwanted Cells

The body relies on apoptosis for getting rid of unwanted cells—excess cells pruned during embryological development, for example, and damaged cells that need to be removed so they don't survive to develop into cancer cells. Both chemotherapy and radiation rely on damaging cancer cells severely enough that they'll undergo apoptosis—which, unfortunately, does not always happen.

Every cell in the body contains the seeds of its own destruction: some two dozen apoptotic proteins that engage in a life-or-death balancing act. Some proteins stimulate apoptosis (pro-apoptotic proteins), while others block the process (anti-apoptotic proteins). DNA damage, for example, tips the balance in favor of cell death—causing the cell to express and activate pro-apoptotic proteins that ultimately kill the cell by poking holes in its mitochondria. The new drug combination discovered by Dr. Gavathiotis and colleagues kills apoptosis-resistant cancer cells by boosting the active form of one pro-apoptotic protein in particular: BAX, dubbed the "executioner protein."

Enhancing the "Executioner Protein"

In 2012, Dr. Gavathiotis discovered the first small, man-made molecule capable of directly activating BAX. In their new study, he and his team evaluated whether BTSA1.2—their third-generation BAX activator—would prove effective against a diverse group of 46 human blood and solid tumor cell lines, including non-small cell lung cancer, breast, colorectal, pancreatic, melanoma, leukemia, and lymphoma cell lines. Most of those cell lines had resisted all pro-apoptotic drugs developed so far.

BTSA1.2 did not perform impressively against several solid-tumor cell lines. The problem: Even as BTSA1.2 was increasing levels of active pro-apoptotic BAX in solid-tumor cells, an anti-apoptotic protein called BCL-XL was neutralizing BAX. The researchers then devised a novel strategy for killing apoptosis-resistant cancer cells: Combine BAX-boosting BTSA1.2 with Navitoclax, an investigational pro-apoptotic cancer drug that inhibits BCL-XL.

The combination of BTSA1.2 and Navitoclax proved to be a game-changer. When Dr. Gavathiotis and colleagues, led by co-first author Andrea Lopez, Ph.D., tested the drug duo against the 46 cell lines, it packed a one-two punch, with BTSA1.2 boosting active BAX to toxic levels in cancer cells, and Navitoclax acting as BAX's bodyguard by preventing BCL-XL from neutralizing BAX.

Limiting Side Effects

The two orally administered drugs were then tested against apoptosis-resistant tumor xenografts—in this case, mice implanted with tumor cells from a colorectal-cancer cell line that had resisted BTSA1.2 and Navitoclax as individual drugs but had succumbed to their combined use. The in vivo experiment produced similar results: After xenografts were

established, the mice were treated with BTSA1.2, Navitoclax, or the two drugs combined. Individually, each drug had limited effectiveness in reducing tumor growth, while combining them significantly suppressed tumor growth, indicating that the two drugs act synergistically to defeat apoptosis-resistant tumors.

"Equally important, mice receiving the two-drug combination tolerated it remarkably well," noted Dr. Gavathiotis. "Moreover, analysis of the treated mice showed that healthy cells were not affected by the two-drug combination—likely making it safer than standard chemotherapies, which are toxic to all dividing cells, both cancerous and normal."

More information: Andrea Lopez et al, Co-targeting of BAX and BCL-XL proteins broadly overcomes resistance to apoptosis in cancer, *Nature Communications* (2022). DOI: 10.1038/s41467-022-28741-7

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