Examining how some cancer cells cheat treatment-induced cell death

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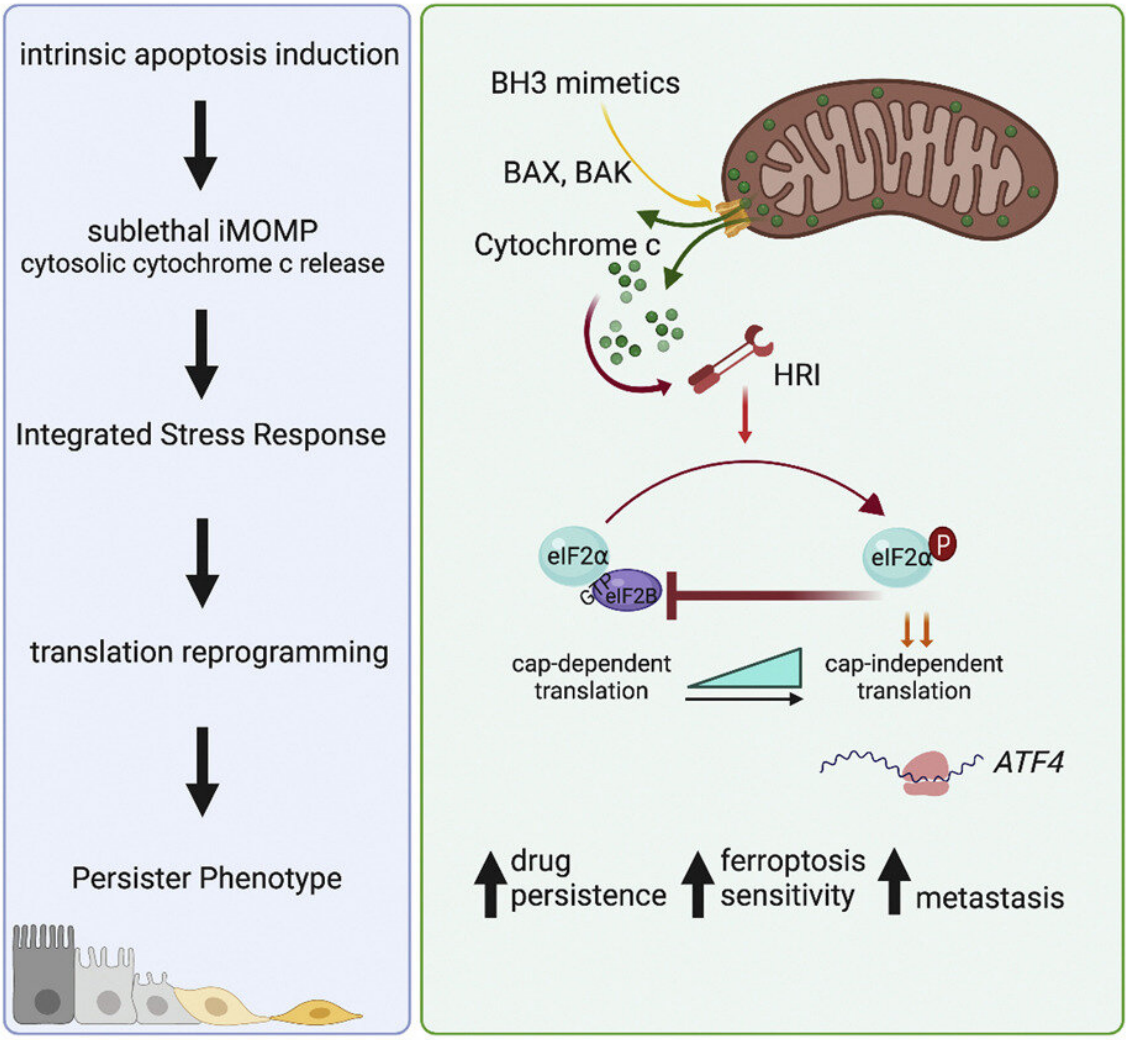

Graphic abstract. Credit: *Cell* (2022). DOI: 10.1016/j.cell.2022.07.025

Scientists at St. Jude Children's Research Hospital have identified how some cancer cells cheat treatment-induced cell death. In doing so, they persist and lead to cancer recurrence. The findings may serve as the basis for drugs that prevent relapses by inhibiting cancer cells from gaining these persistence traits. The research was published today in *Cell*.

After treatment, sometimes the cancer returns, called a recurrence. Researchers knew that a small population of cancer cells sometimes become drug resistant and persist after treatment. These "persister" cells can then reconstitute a more aggressive form of the same cancer. Until now it was unclear how these cells initially change to become persistent.

"When it comes to cancer cells, what doesn't kill them makes them stronger," said corresponding author Doug Green, Ph.D., Department of Immunology chair. "The field has begun to recognize that just because a cell engages apoptosis [a cell death pathway] doesn't mean it will die. Our conceptual leap was that such 'near death experiences' could be responsible for the generation of persister cells. This was unexpected—it was like finding a piece of a treasure map that you never knew was missing—new paths to discovery have opened up."

A near-death experience

Many drugs to treat cancer trigger apoptosis. St. Jude researchers found that a key event that leads to apoptosis, the release of the protein cytochrome c from mitochondria, occurs in persister cells. Historically, researchers believed that once cytochrome c was released into the cell, apoptosis could not be stopped. The evidence that some cells survive the process has grown, but it was unclear how, or why survival would lead to

more aggressive cancer.

The St. Jude group showed in the lab that these persistor cells do start apoptosis and that this near-death experience is key to their survival.

Investigators showed that cytochrome c release kickstarts another process that can override the cell death pathway. In this study, the scientists found that when cytochrome c is released, persister cells activate a pathway called the integrated stress response in addition to apoptosis. The stress response pathway is normally used by cells to detect a problem and fix it. In persister cells, the stress response pathway stops apoptosis and promotes the expression of genes that prolong survival.

"The phenomenon of persistence is caused by the 'near death experience' of engaging the mitochondrial pathway of apoptosis without dying," Green said. "We found that the generation of persister cells requires the process that leads to cytochrome c release, but instead of undergoing apoptosis, the cells survive and become persisters. In effect, these are cells that have undergone 'failed apoptosis.'"

The simultaneous promotion of survival and inhibition of apoptosis also may explain why persister cells become resistant to other treatments in addition to the original drug used to treat the cancer. Though such treatments do have different mechanisms of action, most drugs ultimately induce apoptosis. Because apoptosis is inhibited, these persister cell have a general resistance to cancer therapies.

Potential drug targets

The research can serve as a basis for drugs that may prevent cancer recurrence by interfering with the key protein in the stress response.

In persister cells, the stress response results in an increase of the protein activating transcription factor 4 (ATF4) within the cell. ATF4 is a master regulator of the stress response, resulting in the elimination of proteins that promote cell death and the upregulation of genes that promote survival. The change in gene expression due to ATF4 appears to be critical to persister cells. If ATF4 is knocked out or inhibited, the cancer cells are unable to resist the initial cancer treatment. The same happens when the protein that activates ATF4, Heme-regulated Inhibitor (HRI), is removed or inhibited.

The team discovered that genes that are regulated by ATF4 in their persister cells were similarly regulated in cancer cells from patients that had survived chemotherapy, suggesting that the process occurs during cancer treatment.

A model of persister formation

The authors propose a model of how persisters form. When a cancer is subjected to a pro-apoptotic drug, cytochrome c is released into the cell. This begins the process of apoptosis. Simultaneously, the protein HRI is activated by cytochrome c, as part of the stress response pathway. HRI in turn causes more ATF4 to be expressed. ATF4 then changes the cells state from dying to survival.

The researchers were able to show that their artificially induced persister cells were more aggressive and formed more colonies in mouse models than the original cancer cells, matching the metastatic nature of recurrent tumors.

More information: Halime Kalkavan et al, Sublethal cytochrome c release generates drug-tolerant persister cells, *Cell* (2022). DOI: 10.1016/j.cell.2022.07.025

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