# Cells re-energize to come back from the brink of death

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The discovery of how some abnormal cells can avoid a biochemical program of self-destruction by increasing their energy level and repairing the damage, is giving investigators at St. Jude Children's Research Hospital insights into a key strategy cancer cells use to survive and thrive.

The finding offers an explanation of how abnormal cells that have cheated death once by disabling the main suicide pathway called apoptosis can also foil a backup self-destruct program, which allows them to survive and become cancerous.

The St. Jude study also suggests that a drug that disrupts a cancer cell's ability to block this backup program would allow that program to kill the cell. Such a specifically targeted drug might be more effective and less toxic than standard chemotherapy. A report on this work is in the June 1 issue of "Cell."

Apoptosis is triggered by a variety of factors, including gene mutations that can make the cell become cancerous. During apoptosis, the membrane covering the cell's mitochondria develop holes and leak a molecule called cytochrome c, which triggers the activity of enzymes called caspases. In turn, caspases trigger a series of events that kills the cell. Mitochondria are tiny structures that act as power plants to supply the cell with energy, but also hold the keys to the cells' life and death.

The process by which the membranes develop holes—mitochondrial

outer membrane permeability (MOMP)—is often the “point of no return” for self-destruction, said Douglas Green, Ph.D., chair of the St. Jude Immunology department and the study’s senior author. MOMP triggers apoptosis, but if apoptosis fails because there is no caspase available, the backup program called caspase-independent cell death (CICD) takes over the process.

Previous research has shown that cells that become cancerous lack caspase and other proteins needed to support apoptosis after MOMP releases cytochrome c. But this victory over death is short-lived if CICD is activated. However, some cancerous cells not only dodge death from apoptosis by eliminating caspase activation, but they also foil CIDC. “Our study sought to understand how a cancer cell without caspase activation bypasses CICD as well,” Green said.

The St. Jude team discovered that a cell that lacks caspase activation and cannot undergo apoptosis increases the levels of an enzyme called GAPDH in order to counteract CICD. GAPDH appears to prevent CICD by supporting the functioning of the mitochondria and triggering the activity of certain genes that prevent or repair cell damage. The findings also suggest that the increase in GAPDH provides energy to increase autophagy—the process by which a cell “chews up” debris and broken components, such as damaged mitochondria. After disposing of damaged mitochondria the cell can replace these vital components.

“We found that in the absence of caspase activation, cells that avoided CICD took about a week or so to begin multiplying again,” Green said. “This might represent the time it takes for the cell to restore enough mitochondria to allow the cell to function normally.”

The discovery that GAPDH appears to save cells from CICD suggests that blocking this enzyme would kill abnormal cells that lack caspase activation and cannot undergo apoptosis. That strategy would be the

basis of novel anti-cancer drugs.

The St. Jude study was conducted in culture dishes in which normal cells were exposed to cancer drugs or other agents that triggered apoptosis. The researchers then blocked apoptosis in order to study CICD. “The GAPDH response appears to represent a basic, reproducible event. But in order to verify that hypothesis, we’ll need to study it in the body, especially as we try to develop ways to force cancer cells without caspase to undergo CICD,” Green said. “Our goal is to find better ways to treat these diseases.”

Source: St. Jude Children's Research Hospital