Scientists reveal alternative route for cell death

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Researchers at St. Jude Children's Research Hospital have uncovered a new pathway for mitochondrial cell death that involves the protein BCL-2 ovarian killer otherwise known as BOK. The discovery, which is described online in the journal *Cell*, may lead to new ways to trigger cell death in some types of cancer cells.

"The newly discovered mechanism for mitochondrial cell death is by the effector protein BOK which is normally targeted for destruction at the endoplasmic reticulum," said Doug Green, Ph.D., chair of the St. Jude Department of Immunology and corresponding author of the study. "This pathway of molecular events appears to be intrinsically tied to the levels of stress experienced by the cell and ensures the rapid, programmed destruction of both the cell and its contents."

Cell death is a mechanism used by multicellular organisms to help them survive by removing infected, damaged or unwanted cells. Mitochondria are known as the energy-generating organelles of the cell. However, they may also activate cell death under certain conditions and assist in the removal of damaged cells from the body.

The mitochondrial pathway of cell death (apoptosis) starts by permeabilization of the mitochondrial outer membrane which becomes peppered with small holes. The leakage of proteins like cytochrome c and other molecules from the space between the inner and outer membranes of the mitochondria into the cytosol activates caspase proteases and sets in motion a series of reactions that lead to the rapid

demise of the cell.

"BOK is an effector of mitochondrial apoptosis that appears to work in a different way to known proteins that initiate mitchondrial cell death," said Fabien Llambi, Research Laboratory Specialist at St. Jude and the first author of the paper. "The stability of BOK appears to be directly related to the amount of cellular stress experienced within the endoplasmic reticulum."

The researchers revealed that BOK is controlled at the level of protein stability by components of the Endoplasmic Reticulum Associated Degradation or ERAD pathway. ERAD is a quality control mechanism that helps to detect and eliminate damaged and often unfolded proteins.

The scientists were also able to show that BOK works independently of BAK and BAX, two other members of the BCL-2 family of proteins that regulate and contribute to mitochondrial cell death.

"The fate of the cell during stress appears to be intricately wired to the signaling pathways, such as the BOK pathway we have discovered, that trigger mitochondrial cell death," added Green. "Our work also suggests that cancer cells expressing high levels of BOK may be particularly sensitive to inhibitors that target the proteasome or the ERAD pathway."

The development of specific inhibitors that target the ERAD pathway could provide useful alternatives to some of the known proteasome inhibitors that stop the growth of cancer cells. Some proteasome inhibitors affect multiple targets in ways that do not meet the desired level of specificity. An ERAD inhibitor might overcome this drawback. Further work is needed to identify suitable protein targets that would be amenable to this type of interference.

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