

Promoting Suicide in Cancer Cells

A PROTEIN widely known to cause uncontrolled cell growth can be manipulated to induce cancer cells to commit suicide, providing a

Ras that there is to know,” says Mark R. Phillips, M.D., Professor of Medicine, Cell Biology, and Pharmacology, who led the study. “But here

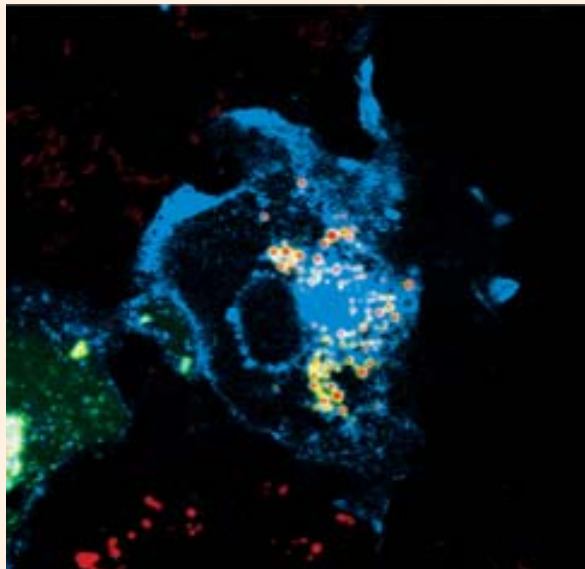
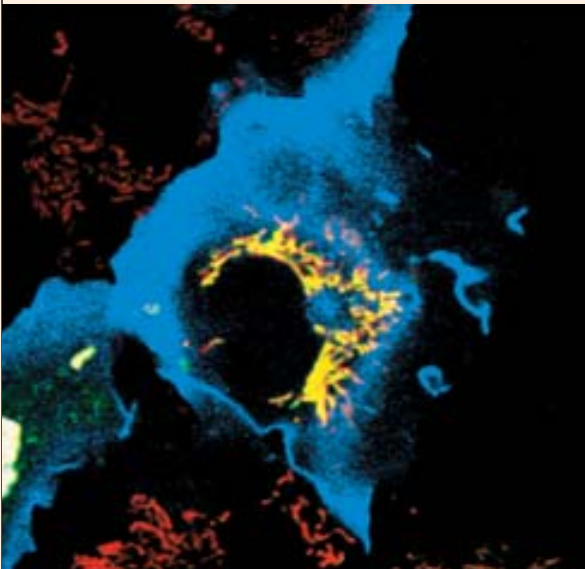
K-Ras acts like a molecular switch. In its normal form, the protein is turned on and off to control pathways that regulate cell growth. The mutant form, however, is locked in the *On* position, which causes cells to grow uncontrollably and, at the same time, turns off programmed cell death, or apoptosis, the normal process that tells a cell when it is time to die. The result is cancer.

Until recently K-Ras was thought to function only at the cell membrane and was

that power the cell and are thought to be involved in apoptosis.

In the current study Dr. Phillips and his colleagues sought to determine (1) the mechanism that causes K-Ras to relocate and (2) the protein’s role in its new home. They discovered that PKC causes a phosphate molecule to be added to K-Ras. This phosphorylation process weakens the electrostatic bonds that help anchor the protein, allowing it to dislodge from the plasma membrane.

Once dislodged, K-Ras travels to the surface of the mitochondria, where the protein appears to play a role in promoting apoptosis, the researchers learned. “That was very surprising because ras is usually thought of as an oncogene,” says Dr. Phillips.



THE PHOTOMICROGRAPH AT LEFT SHOWS THE PROTEIN K-RAS (BLUE) AT THE PERIPHERY OF THE CELL AND MITOCHONDRIA (YELLOW). A NEW NYU STUDY SHOWS THAT K-RAS CAN, IN FACT, MOVE TO THE MITOCHONDRIA, WHICH IS SHOWN IN THE IMAGE AT RIGHT.

novel target for the development of anti-cancer drugs, according to an NYU study.

In the study, featured in a recent issue of the journal *Molecular Cell*, researchers report they have discovered a new mechanism that they believe regulates the action of K-Ras, a cellular protein that plays a key role in many human cancers. “The general feeling was that we had learned everything about K-

is a completely new twist.”

Ras proteins have captured the interest of cancer researchers since the late 1970s, when the first oncogenes—genes that cause the transformation of normal cells into cancerous ones—were discovered. One of those oncogenes was ras. There are three ras genes, and the one that produces K-Ras is the most important in terms of its impact on human cancer.

permanently anchored in place by lipid molecules and electrostatic forces. “We discovered that the position of K-Ras in membranes is not permanent, and its positioning can be regulated by a signaling enzyme called protein kinase C,” says Dr. Phillips.

The inspiration for the study came from a separate experiment, in which cells were exposed to substances that stimulate protein kinase C (PKC). To the researchers’ surprise, K-Ras began to appear on the mitochondria, organelles

“Oncogenes generally promote uncontrolled growth and block cell death. And here we were seeing a situation wherein ras was promoting cell death.”

Intriguingly, the study identifies a potential mode of suppressing tumors, says Dr. Phillips. “Our data suggested that if we could find a way to phosphorylate K-Ras, we might be able to promote programmed cell death in tumors driven by the ras oncogene, such as lung, colon, and pancreatic cancers.” ●

— Gary Goldenberg