SOUTHWESTERN NEWS

Contact: Susan A. Steeves
(214) 648-3404
or E-mail: ssteev@mednet.swmed.edu

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UT SOUTHWESTERN SCIENTISTS FIND CELL DEATH-SIGNALING PATHWAY INVOLVED IN CANCER

DALLAS – November 14, 1997 – The missing link in the chain of molecules that tells cells to die has been found, which may enable scientists to create more effective drugs for cancer, Parkinson's disease and stroke. The discovery by researchers at UT Southwestern Medical Center at Dallas is reported in the Nov. 14 issue of *Cell*.

The investigators used human breast-cancer cells and human cervical-cancer cells to identify and purify a protein they dubbed Apaf-3. The findings indicate Apaf-3 signals apoptosis, programmed cell death. From the Greek word for shedding leaves, apoptosis is the natural way the body eliminates unnecessary or damaged cells and makes room for new ones in the development, growth and maintenance of tissue in animals and plants. The process is necessary for life because some cells are constantly replenished; for instance, cells lining the human intestine live less than a week. Cardiac neurons and skeletal cells can't be replenished and must last a lifetime.

But if a mistake occurs in the signals sent to a cell – because of a mutation in a gene, for instance – normal cell death may not occur. Depending on how the message is scrambled, too many cells may live, or too many cells may die. If apoptosis doesn't occur, cancer or autoimmune diseases may develop. Neurological disorders, paralysis and/or death of the organism itself result when too many cells commit suicide.

"What we define in this paper is how cell death is executed through a cascade of events," said Dr. Xiaodong Wang, UT Southwestern assistant professor of biochemistry and Howard Hughes Medical Institute investigator. He and his research team published two other papers this year showing how various genes and other proteins fit into the pathway to apoptosis.

Scientists previously determined that they still needed to identify one protein in the

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sequence of events leading to apoptosis, Wang said. In the latest study, Wang found that two molecules, cytochrome c and dATP/ATP, bind to activate Apaf-3. This occurrence initiates the cascade of events leading to cell death. Cytochrome c is a regulatory protein released from the cell's principal energy source, the mitochondria. Adenosine triphosphate, ATP, carries energy from the mitochondria to all parts of a cell.

"We now know how cells commit suicide," Wang said. "We determined the pathway that is part of this fundamental biological process. This information can be used to find drugs to activate the pathway, especially in cancer cells. Most chemotherapy drugs work through the pathways, but they are not directed at the exact molecules triggering cell death."

This new knowledge gives scientists better targets for efforts to switch the cascade on and off. A better understanding of apoptosis also could lead to ways to prevent cell death as a result of strokes, myocardial infarction and many neurodegenerative diseases.

Others involved in the study from UT Southwestern were biochemistry research fellows Drs. Imawati Budihardjo and Peng Li; Deepak Nijhawan, a Medical Scientist Training Program fellow; and microbiology and immunology researchers from Thomas Jefferson University Drs. Srinivasa M. Srinivasula, Manzoor Ahmad and Emad S. Alnermri.

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