SOUTHWESTERN NEWS

Media Contact: Worth Wren Jr.
214-648-3404
worth.wren@utsouthwestern.edu

ANOTHER PROTEIN IDENTIFIED AS PLAYER IN NORMAL CELL DEATH MOVES SCIENTISTS CLOSER TO NEW CANCER TREATMENTS

DALLAS – July 5, 2001 – A biochemist at UT Southwestern Medical Center at Dallas has been tracking proteins that direct the life and death of animal cells, and now his team has identified another key player in the natural programming that seals the cell's doom.

Dr. Xiaodong Wang, associate professor of biochemistry at UT Southwestern, and Lily Li, a student in the Medical Scientist Training Program, have found that the endonuclease G protein, an enzyme dubbed EndoG, plays a crucial role in the death of a cell by destroying DNA.

This study, published in the July 5 issue of *Nature*, revealed that EndoG splits DNA apart during the final stages of cell death.

Another study published in the journal and led by University of Colorado researchers who collaborated with Li and Wang confirmed their biochemical findings on EndoG.

This work, Wang said, has added another piece to the puzzle of decoding nature's programming for cell destruction – and understanding what hinders or facilitates it.

The continuing research could lead to treatments – including biochemical manipulation of abnormal cells in neurological diseases such as Alzheimer's and Parkinson's – or drugs designed to trigger death of the abnormal cells that otherwise would become cancerous, said Wang, an assistant investigator in the Howard Hughes Medical Institute at UT Southwestern.

He and colleagues have previously identified genes that play crucial roles in the initial process of natural cell death, or apoptosis. They found that nature's signal to start cell decline and death is carried by another enzyme/protein, labeled Apaf-1.

The detective work that led to uncovering EndoG's role in destroying DNA stems from Wang's earlier research showing that the Bcl-2 family of proteins can regulate cell death through interaction with the cell's primary energy source – the mitochondria. The pro-death members of this protein family can release cytochrome c, a mitochondrial enzyme involved in both energy production and the startup of cell death by working in partnership with Apaf-1.

"Dr. Wang determined that cytochrome c is a dual-edged sword, playing roles in both the death and the life of the cell," said Li, Wang's lead research associate on the latest study and a M.D./Ph.D. student.

(MORE)

Wang's earlier studies showed that cytochrome c and Apaf-1 normally work in concert to chew up other proteins in the cell, again as part of the death process.

"We theorized that there may be something other than the cytochrome c and Apaf-1 pathways, also initiated from the mitochondria, that could be involved in the destruction of DNA," Li said.

From there, the researchers identified EndoG, also a mitochondrial protein, as another player in the cell-death process. In healthy cells, an outflow of energy from the mitochondria signals the start of cell death.

For the latest study, Li and Wang purified EndoG from a mouse liver. Cells were induced to die in laboratory dishes, and fluorescent microscopy was used to investigate EndoG's role in mouse embryonic fibroblast, cells that look like fibers. Cell processes in mice are similar to those in humans, Li said.

In the sister study, Boulder, Colo.-based researchers examined worms that have a defined cell-death pattern and looked at mutants affecting this pattern. Their study identified EndoG as one of the mutants. They also found that EndoG's function has remained largely the same – despite or as a result of evolution – in the worm cells and in human cells, Wang said.

Thus, EndoG's role confirms that cell death follows "an ancient pathway" in animal cells, and the study's findings confirm that the worm research results are valid for explaining similar processes in human cells, Li and Wang said.

The genetic study was also the first research to confirm the role of mitochondria in the death of cells in worms, indicating the existence of a similar pathway in human cells, the researchers said.

More biochemical and genetic research is needed to further investigate the role of EndoG in cell death, Wang said.

Dr. Xu Luo, a UT Southwestern fellow in biochemistry, also assisted with the research.

The studies were supported by the Leukemia Society of America, the National Institutes of Health, the Robert Welch Foundation and others.

###