

NOVEMBER 14, 1997

Hughes Researchers Discover Key Component of Cell Death Pathway

The puzzle of how cells commit suicide has finally been solved, yielding a solution that may translate into effective drugs to treat cancer and other diseases.

"This research may provide new targets for therapy that blocks or initiates cell death," said Xiaodong Wang, a Howard Hughes Medical Institute investigator at the University of Texas Southwestern Medical Center at Dallas. Wang led a research team that discovered the protein that initiates the final stage of cell death, known as apoptosis. The finding, reported in the November 14 issue of the journal *Cell*, is the third molecule that Wang has identified this year as vital in the cascade of events that leads to apoptosis.

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This model is likely to be relevant to all organisms, said Wang. "This appears to be one of the global mechanisms of apoptosis," he said.

Paradoxically, cell death is important in the early development of many organisms because it helps to generate the proper number of cell types in the right places. If apoptosis doesn't occur, cancer or autoimmune diseases can arise. Conversely, neurological disorders and paralysis due to disease or trauma can cause too many cells to die. So drugs that accelerate or prevent apoptosis could be helpful in treating a wide range of diseases.

At the cellular level, apoptosis occurs quickly and leaves no traces: A cell's nucleus condenses and fragments, the cell shrivels, and then is quickly engulfed and digested by macrophages or other neighboring cells. Once inside the macrophage, the dying cell is quickly disassembled and its components recycled.

The cell's intrinsic death program was first discovered and described in nematode worms by Hughes investigator H. Robert Horvitz at MIT and a number of other researchers. The worm generates about 1,000 somatic cells

in the course of development, but 131 of those cells are programmed to die. Researchers have subsequently shown that the cell death program and the molecular henchmen that deliver the death sentence are highly conserved in organisms as diverse as worms and humans.

Three genes, *ced-3*, *ced-4*, and *ced-9* encode proteins that execute the apoptotic program in nematode worms (ced stands for "cell death abnormal.") *Ced-9* prevents cell death, while *ced-3* and *ced-4* promote death. Wang and others have been searching for the human homologues of the worm genes. The Bcl-2 family of proteins contains the mammalian relatives of *ced-9*; and *ced-4* is homologous to the recently identified human protein, Apaf-1. The mammalian *ced-3* homologue is caspase-3.

Wang's two-year search for other members of the cell death pathway has paid off handsomely. In February, his team discovered that Bcl-2, a protein in the outer membrane of mitochondria, the cell's principal energy source, prevents the release of cytochrome c, a carrier in the cell's energy chain (February 20, 1997, *Science*). This outflow of cytochrome c from the mitochondria signals the beginning of cell death. The discovery connected Bcl-2 previously shown to be involved in cell survival by Hughes investigator Stanley Korsmeyer at Washington University to cytochrome c, a chemical trigger of cell death. And in August, Wang's group published a paper in *Cell* linking cytochrome c to Apaf-1. (August 8, 1997, *Cell*).

In the latest paper, Wang's team uses human breast cancer and cervical cancer cells to purify Apaf-3. They found that Apaf-3 binds to Apaf-1 in the presence of cytochrome c and dATP or ATP, which carries energy from the mitochondria to all parts of the cell. This complex of molecules then turns on the protease caspase-3, the final trigger that initiates cell death.

According to Wang, such detailed knowledge of the apoptotic pathway gives scientists better targets for their efforts to switch the cascade on to destroy cancer cells or off to prevent cell death due to strokes, heart attacks or neurological diseases.

"We now begin to understand how cell death is initiated, which is really the middle of the pathway," said Wang. "Now we plan to look at the beginning and end of the process to determine what triggers these events and understand how the cell breaks up."