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Small, Smac-like molecule encourages death of cancer cells

DALLAS – Sept. 2, 2004 – Researchers at UT Southwestern Medical Center at Dallas have developed a small molecule that mimics the action of a key "death-promoting" protein in cells, a finding that could lead to more effective cancer therapies with fewer side effects.

In the Sept. 3 issue of the journal *Science,* the researchers report on this new compound and how it behaves like the cellular protein Smac, a molecule that lifts barriers to cell death. Dr. Xiaodong Wang, professor of biochemistry and one of the authors of the *Science* paper, discovered Smac in 2000.

"Every cell in our body has a self-destruction apparatus that becomes activated when a cell needs to be terminated," Dr. Wang said. "The Smac protein is one component of this normal cell-suicide process, called apoptosis."

Apoptosis, for example, is required for the removal of webbing between the toes and fingers of a developing fetus, as well as for the elimination of surplus neurons during the development of the human brain.

In healthy cells, Smac is sequestered within cell compartments called mitochondria, where the protein resides until mitochondria receive signals to release it. Smac then interacts with other molecules called inhibitor-of-apoptosis proteins (IAPs), which, if not countered by Smac, will keep the cell alive and growing.

In cancer cells, IAPs tend to be overexpressed, and the signals that tell mitochondria to release Smac are often defective. That's why the UT Southwestern-developed Smac mimic, which can enter the cytoplasm of cells unhindered, is an important step in developing new cancer therapies, said Dr. Patrick Harran, associate professor of biochemistry and an author of the study.

The compound, which so far has only been tested on cells in culture, does not appear to harm normal cells, just cancer cells, said Dr. Wang, who is a Howard Hughes Medical Institute investigator and holds the George L. MacGregor Distinguished Chair in Biomedical Science at UT Southwestern. He said other research groups as well as pharmaceutical companies have been trying to develop a small- molecule Smac mimic.

(MORE)

The challenge for cancer therapies now is that they also tend to kill normally growing cells as well as cancer cells, which results in undesirable side effects," he said. "Because this compound appears to impact cancer cells selectively, it could combat this problem."

The Smac mimic was actually discovered by accident. Based on information about how Smac binds to IAPs, the researchers designed molecules they thought would mimic this interaction. They prepared and screened hundreds of candidates. Smac is a large molecule and is also a dimer, which means that is it made up of two identical halves. Dr. Harran, an organic chemist, said their original candidate molecules were monomers, able to imitate just one half of the two-headed protein.

"While working with a particular monomer, we performed a chemical reaction that caused it to dimerize," Dr. Harran said. "Even though we didn't realize this had happened at first, the dimer's activity as a Smac mimic was off the charts relative to everything else in our collection."

The monomer also showed activity, but it was not nearly as effective at facilitating cell death as the dimer. One of the advantages of the Smac mimic, Dr. Wang said, is that if cancer treatments were to be developed from it, dosages would likely be small.

"There is reason to believe that this could be one of the first examples of a catalytic drug," Dr. Harran said. "You may not need one Smac-mimic molecule for each IAP in a cell. You likely need fewer of our Smac mimics than IAPs to neutralize IAP effects, because once the cell death program gets started, it generates more Smac-like activity as it proceeds."

Dr. Wang said, "If this turns out to be true, it's remarkable, because then you would only need a tiny amount to have a dramatic impact."

The next step in the research is to test the compound in animals. "If it does well, hopefully it will someday find its way to people," he said. "That's the ultimate goal."

Other UT Southwestern authors on the paper are Dr. Jef K. DeBrabander, associate professor, postdoctoral researchers Dr. Ranny Thomas and Dr. Hidetaka Suzuki, and Lin Li, research associate, all in the Department of Biochemistry.

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