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## Smac-ing Lung Cancer to Death

Howard Hughes Medical Institute researchers have developed a small molecule that can turn the survival signal for a variety of cancer cells into a death signal. The molecule mimics the activity of Smac, a protein that triggers the suicide of some types of cancer cells.

The researchers say their findings suggest that Smac-mimetic compounds could be useful as targeted cancer treatments for lung and other cancers. Such therapy may be less toxic to healthy cells than current compounds used in cancer chemotherapy.

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— **Xiaodong Wang**

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The researchers, led by Howard Hughes Medical Institute investigator Xiaodong Wang, published their findings in the November, 2007, issue of the journal *Cancer Cell*. Wang is at the University of Texas Southwestern Medical Center

Cells that are defective or that become unnecessary during growth and development are induced to commit suicide through a finely balanced process known as apoptosis, or programmed cell death. A protein called Smac, which is a shortened version of second mitochondria-derived activator of apoptosis, is a part of the cell's programmed cell death machinery. When that machinery is switched on, Smac is released from the mitochondria and triggers the pathway that kills damaged or abnormal cells. Cancer cells, however, can survive Smac's death signal by switching off the apoptotic machinery.

To see if they could get around this problem, Wang and other researchers have developed small-molecule mimetics of Smac that can enter the cell and trigger apoptosis. These mimetic molecules do their damage without the need for the Smac signal from the mitochondria. In earlier studies, Wang and his colleagues found that a Smac mimetic that they developed in the lab could kill cancer cells in culture. But they found that the cancer cells are only killed when the mimetic molecule is introduced in conjunction with another component of the apoptotic machinery known as TNF $\alpha$ .

In the new studies published in *Cancer Cell*, Wang and his colleagues found that a significant percentage of human non-small-cell lung cancer cell lines were sensitive to treatment by the Smac mimetic alone. When the researchers introduced those sensitive cells into mice and allowed them to produce tumors, they found that the Smac mimetic caused the tumors to regress and, in some cases, even disappear.

These findings made us wonder what it was about these cell lines that made them sensitive to the Smac mimetic alone, said Wang. Cancer cells are hard to kill, but these cell lines seemed to have already become sensitized to apoptosis.

The researchers' studies revealed that the sensitive cell lines produced their own TNF $\alpha$ , so they were already primed for apoptosis. The paradox, said Wang, is that TNF $\alpha$  signaling is also part of a complex pathway that gives cancer cells a survival signal, offering them a growth advantage. The researchers also found that some breast cancer and melanoma cell lines were sensitive to the Smac mimetic alone.

Thus, in these cancer cell lines, the TNF $\alpha$  survival advantage turns out to be a fatal flaw, because the same pathway can be switched to apoptosis by Smac mimetics, said Wang. So, for some cancers, we might be able to use Smac mimetics as a single treatment agent. And we can use the presence of TNF $\alpha$  as a marker to tell us which tumors will respond to the Smac mimetic alone.

People have been suspecting for a long time that some cancer cells may somehow turn on their apoptotic pathway already, said Wang. And now we know what pathway they turn on and why. We can take advantage of this phenomenon for potential cancer therapy by switching a signal into a deadly one with Smac mimetics.