UT SOUTHWESTERN MEDICAL CENTER NEWS

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Synthetic compound promotes death of lung-cancer cells, tumors

DALLAS – Nov. 12, 2007 – Human lung-cancer tumors grown in mice have been shown to regress or disappear when treated with a synthetic compound that mimics the action of a naturally occurring "death-promoting" protein found in cells, researchers at UT Southwestern Medical Center report.

The findings, appearing in today's issue of *Cancer Cell*, suggest that the compound might one day be used in targeted therapies for lung and possibly other cancers, the researchers said.

"We found that certain kinds of lung-cancer cells were sensitive to this compound, which sends a signal to cancer cells to self-destruct," said Dr. Xiaodong Wang, professor of biochemistry and senior author of the study.

In 2000, Dr. Wang announced the discovery of a cellular protein called Smac, which plays a key role in the normal self-destruction apparatus present in every cell. This process, called apoptosis, is activated when a cell needs to be terminated, such as when a cell is defective or becomes unnecessary during normal growth and development. In cancer cells, the self-destruct mechanism is faulty.

In 2004, Dr. Wang and his colleagues developed a compound that mimics the action of Smac. They found that in cell cultures, the compound killed cancer cells but left healthy cells unaffected. In those studies, however, the Smac mimic only killed cancer cells when it was introduced along with another molecule often involved in the cell-death machinery, called tumor necrosis factor-a, or TNFa.

In the current study, Dr. Wang's research group tested 50 human non-small-cell lung-cancer cell lines in culture and found that 22 percent of them were sensitive to the Smac mimic alone, without having to add TNFa. The researchers also found that the Smac mimic alone was effective against some types of breast cancer and melanoma cells in culture.

"The apparent ability of a Smac mimetic, as a single agent, to induce cell death in nearly one-quarter of lung-cancer cell lines tested was quite remarkable," said Dr. Wang, who is a Howard Hughes Medical Institute investigator at UT Southwestern.

The researchers then introduced those sensitive cancer-cell lines into mice, where they grew into tumors. When the lung-tumor-bearing mice were injected with the Smac mimic, the tumors reduced significantly in size, and in some cases, the tumors disappeared completely.

Also tried was a similar experiment treating breast-cancer tumors in mice with the Smac mimic

(MORE)

alone. That treatment, however, showed little effect.

The researchers then investigated what made those particular lung-cancer cell lines so sensitive to the Smac mimic alone.

"We found that these sensitive cell lines produce their own TNFa," Dr. Wang said.

In addition to aiding in cell death, TNFa also is known, paradoxically, to sometimes play a role in aiding cancer-cell survival and growth. In combination with the Smac mimic, however, the role of this molecule is clear: cell death.

"The Smac mimetic is able to exploit certain cancer cells that secrete TNFa and usurp this pro-survival signal to promote cell death," Dr. Wang said.

"Not only is single-agent Smac mimetic treatment highly effective at inducing cell death in these cell lines, but it also offers the possibility of highly specific and relatively nontoxic future therapeutic treatments by exploiting certain cancer cells' own production of TNFa."

Additional research and tests will be needed before the Smac mimic is tested in humans, Dr. Wang said, adding that detecting the presence of TNFa in a patient could serve as a marker to indicate that the cancer might be sensitive to treatment with the Smac mimic alone.

"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 affects cancer cells selectively, it could combat this problem."

Other UT Southwestern researchers involved in the study were: lead author Sean Petersen, graduate student in biochemistry; Dr. Lai Wang, postdoctoral research fellow in biochemistry; Asligul Yalcin-Chin, graduate student in biochemistry; Dr. Patrick Harran, professor of biochemistry; Dr. Michael Peyton, research scientist in the Nancy B. and Jake L. Hamon Center for Therapeutic Oncology Research; and Dr. John Minna, director of the Hamon Center and of the W.A. "Tex" and Deborah Moncrief Jr. Center for Cancer Genetics.

Lin Li of Joyant Pharmaceuticals also participated. Drs. Wang and Harran are cofounders of Joyant Pharmaceuticals, a Dallas-based company and UT Southwestern spin-off that is developing medical applications of Smac-mimetic compounds.

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