UT SOUTHWESTERN MEDICAL CENTER NEWS

Media Contact: Connie Piloto
214-648-3404
connie.piloto@utsouthwestern.edu

Substance in tree bark could lead to new lung-cancer treatment

DALLAS – June 27, 2007 – Researchers at UT Southwestern Medical Center have determined how a substance derived from the bark of the South American lapacho tree kills certain kinds of cancer cells, findings that also suggest a novel treatment for the most common type of lung cancer.

The compound, called beta-lapachone, has shown promising anti-cancer properties and is currently being used in a clinical trial to examine its effectiveness against pancreatic cancer in humans. Until now, however, researchers didn't know the mechanism of how the compound killed cancer cells.

Dr. David Boothman, a professor in the Harold C. Simmons Comprehensive Cancer Center and senior author of a study appearing online this week in the *Proceedings of the National Academy of Sciences*, has been researching the compound and how it causes death in cancerous cells for 15 years.

In the new study, Dr. Boothman and his colleagues in the Simmons Cancer Center found that beta-lapachone interacts with an enzyme called NQO1, which is present at high levels in non-small cell lung cancer and other solid tumors. In tumors, the compound is metabolized by NQO1 and produces cell death without damaging noncancerous tissues that do not express this enzyme.

"Basically, we have worked out the mechanism of action of beta-lapachone and devised a way of using that drug for individualized therapy," said Dr. Boothman, who is also a professor of pharmacology and radiation oncology.

In healthy cells, NQO1 is either not present or is expressed at low levels. In contrast, certain cancer cells – like non-small cell lung cancer – overexpress the enzyme. Dr. Boothman and his colleagues have determined that when beta-lapachone interacts with NQO1, the cell kills itself. Non-small cell lung cancer is the most common type of lung cancer.

Beta-lapachone also disrupts the cancer cell's ability to repair its DNA, ultimately leading to the cell's demise. Applying radiation to tumor cells causes DNA damage, which results in a further boost in the amount of NQO1 in the cells.

"When you irradiate a tumor, the levels of NQO1 go up," Dr. Boothman said. "When you then treat these cells with beta-lapachone, you get synergy between the enzyme and this agent and you get a whopping kill."

In the current study, Dr. Boothman tested dosing methods on human tumor cells using a synthesized version of beta-lapachone and found that a high dose of the compound given for only two to four hours caused all the NQO1-containing cancer cells to die.

Understanding how beta-lapachone works to selectively kill chemotherapy-resistant tumor cells

(MORE)

creates a new paradigm for the care of patients with non-small cell lung cancer, the researchers said.

They are hoping that by using a drug like beta-lapachone, they can selectively target cancer tumors and kill them more efficiently. The current therapy for non-small cell lung cancer calls for the use of platinum-based drugs in combination with radiation.

"Future therapies based on beta-lapachone and NQO1 interaction have the potential to play a major role in treating devastating drug-resistant cancers such as non-small cell lung cancer," said Dr. Erik Bey, lead author of the study and a postdoctoral researcher in the Simmons Cancer Center. "This is the first step in developing chemotherapeutic agents that exploit the proteins needed for a number of cellular processes, such as DNA repair and programmed cell death."

About 85 percent of patients with non-small cell lung cancer have cancer cells containing elevated levels of the NQO1 enzyme, which is produced by a certain gene. Patients who have a different version of the gene would likely not benefit from treatment targeting NQO1, Dr. Boothman said.

Dr. Boothman cautioned that clinical trials of beta-lapachone in lung cancer patients will be needed to determine its effectiveness as a treatment. He and his team have created a simple blood test that would screen patients for the NQO1 enzyme.

Along with Dr. Jinming Gao's laboratory in the Simmons Cancer Center and a joint collaboration with the bioengineering program at UT Dallas, researchers in the new "Cell Stress and Cancer Nanomedicine" initiative within the Simmons Cancer Center have developed novel nanoparticle drug delivery methods for the tumor-targeted delivery of this compound. These delivery methods have the promise of further improving this drug for non-small cell lung cancer.

Other Simmons Cancer Center researchers involved in the study were Drs. Ying Dong, postdoctoral researcher; Chin-Rang Yang, assistant professor; and Dr. Gao, associate professor. UT Southwestern's Dr. John Minna, director of the Nancy B. and Jake L. Hamon Center for Therapeutic Oncology Research and the W.A. "Tex" and Deborah Moncrief Jr. Center for Cancer Genetics, and Dr. Luc Girard, assistant professor of pharmacology, also participated along with researchers from Case Western Reserve University and UT M.D. Anderson Cancer Center.

The research was supported by the National Institutes of Health.

###