UT SOUTHWESTERN MEDICAL CENTER NEWS

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Gene information predicts survival time, possible new treatment options for lung-cancer patients, UT Southwestern researchers find

DALLAS – Dec. 14, 2010 – Researchers at UT Southwestern Medical Center have discovered sets of genes active in cancer cells and normal tissue that predict survival time and potential new treatments for patients with non-small cell lung cancer.

"Patient responses to cancer treatment vary widely and often depend on subtle biological differences among tumors," said Dr. David Mangelsdorf, chairman of pharmacology at UT Southwestern and co-lead author of the study, published Dec. 14 by *PLoS Medicine*.

"These findings are important because the ability to determine which genes are being expressed in each person's tumor, as well as a patient's likely survival time, can guide physicians to the most effective and appropriate personalized treatments," he said.

Researchers involved in the study at UT Southwestern and UT M.D. Anderson Cancer Center carefully microdissected lung tumors and adjacent healthy lung tissue from 30 patients. To determine which genes were active, they examined each sample for the presence of messenger ribonucleic acid (mRNA) associated with the 48 known genes for molecules called nuclear hormone receptors.

The research team then compared the set of active genes, also called a gene expression profile or gene signature, with the actual clinical outcome of each study patient. They found that the expression of genes for specific nuclear hormone receptors was an excellent predictor of which patients were likely to survive the longest. They validated their test by screening more than 500 additional lung-tumor samples and accurately predicting those patients' outcomes.

In particular, the presence of two nuclear receptors – the short heterodimer partner (SHP) and the progesterone receptor (PR) – in tumor tissue was predictive of a good prognosis. Patients with those so-called biomarkers in their cancer cells lived the longest.

In normal lung tissue, a good prognosis was associated with the presence of nuclear receptors called nerve growth factor induced gene B3 (NGFIB3) and mineralocorticoid receptor (MR).

Dr. Mangelsdorf, a National Academy of Sciences member who is a leading expert on nuclear receptors, said the investigators focused on screening for the activity of these 48 nuclear receptor genes

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because several of them are known to be involved in promoting or inhibiting cancer. In addition, drugs that target certain nuclear receptors already are being used as front-line therapy in humans against breast cancer, prostate cancer and acute leukemia.

"The goal of identifying these genetic signatures in lung cancer is not just to determine how long a cancer patient will live, but also to home in on the most relevant drug or therapy targets that act specifically on these particular gene products," said Dr. Mangelsdorf, who also is an investigator with the Howard Hughes Medical Institute.

The results are a significant step toward personalized medicine, said 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 who has been investigating the biology of lung cancer for more than 30 years.

"Our long-term goal is to be able to sample a patient's lung cancer and perform molecular tests that can predict both how a patient will do and, more importantly, the best treatment for that individual," said Dr. Minna, co-lead author of the study.

"We were amazed to find that the pattern of expression of nuclear receptors in both lung cancers and normal lung tissue were so predictive of a patient's outcome. Because available drugs already target so many of these receptors, our next step is to find out which drugs will kill lung cancer cells expressing these specific receptors."

Other UT Southwestern researchers involved in the study were lead authors Dr. Yangsik Jeong, a former graduate student and postdoctoral researcher now at the Yonsei University in Korea, and Dr. Yang Xie, assistant professor of clinical sciences; Dr. Guanghua Xiao, assistant professor of clinical sciences; and Dr. Luc Girard, assistant professor of pharmacology. Dr. Ignacio Wistuba at M.D. Anderson also contributed.

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