Profiling of cancer genes may lead to better and earlier detection

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A research team at UT Southwestern Medical Center has for the first time identified several genes whose expression is lost in four of the most common solid human cancers – lung, breast, prostate and colon cancer.

The findings, which researchers say could form the basis for a new early detection screen for certain cancers, are published today in the online journal *Public Library of Science Medicine*.

The expression of genes that inhibit cancer development, so-called tumor suppressor genes, is often lost in tumor cells. This can occur through a mutation in the gene's DNA sequence or through deletion of the gene. Loss of tumor suppression function also can occur in a process called methylation, where a chemical called a methyl group is attached to a DNA region near the gene and prevents it from being activated, essentially "silencing" the gene.

"These results show the power of studying tumors on a genome-wide basis, looking at many genes at the same time," said Dr. John Minna, the study's senior author and director of the W.A. "Tex" and Deborah Moncrief Jr. Center for Cancer Genetics and the Nancy B. and Jake L. Hamon Center for Therapeutic Oncology Research at UT Southwestern.

In an effort to identify new tumor-suppressor genes that might be important to lung and breast cancer development, the UT Southwestern team examined which genes are active in those kinds of tumors and compared them to gene expression profiles from normal lung epithelial

cells. The researchers then examined the gene expression profiles of these various cell types before and after treatment with a drug that inhibits methylation.

The researchers identified approximately 130 genes that may be methylated and thus silenced in lung, breast, prostate and colon cancers. They analyzed 45 of these new genes in both normal and cancerous tissues from the same patients and found that many of the genes were methylated specifically in the tumor samples.

"We ended up with a large number of genes that are involved in the development of lung cancer that, despite years of work in the field, I had never connected to lung cancer before," said Dr. Minna.

Patient samples from UT Southwestern's new Harold C. Simmons Comprehensive Cancer Center tissue repository and previous results from study author Dr. David Euhus allowed the research team to quickly extend its findings to breast, prostate and colon cancer. A Hamon Center postdoctoral researcher and lead study author Dr. David Shames was instrumental in identifying the genes, Dr. Minna said.

"What would have normally taken us several years, David Shames was able to determine in less than a month," Dr. Minna said. "The new genes Dr. Shames discovered are now forming the basis for a new early detection screen that could be mounted against the most common human cancers."

The genes the researchers found to be methylated specifically in the tumor samples might control the conversion of normal cells into cancer cells, Dr. Minna said, but this possibility needs to be tested on a case-by-case basis.

Although it is known that gene expression patterns in tumors vary greatly

from tissue to tissue, the researchers hope that the similarities of the methylation patterns found in this study might lead to a better approach to detect cancer early and help identify new promising therapeutic targets to treat some of the most prevalent cancers.

"The findings from our study suggest that it may be possible to develop a methylation profiling platform that could be used to screen patients for common solid tumors, while at the same time identify what type of tumor the patient may have," Dr. Shames said.

The study also illustrates that some of the basic processes that underlie the development of breast and lung cancer are identical, even though the chemicals that initiate those processes – estrogen and tobacco carcinogens, for example – may be different, said Dr. Euhus, associate professor of surgical oncology.

"I was also struck that some of these processes could be detected in benign breast cells from high-risk women, more so than in lower-risk women," said Dr. Euhus, co-director of the Mary L. Brown Breast Cancer Genetics and Risk Assessment Program. "Methylation is potentially a reversible change and there may be some interventions that would effectively reduce the risk of several types of cancer simultaneously."

Source: UT Southwestern Medical Center