MedicalXpress

Scientists find new genes linked to lung cancer

October 22 2008

Working as part of a multi-institutional collaboration, scientists at Washington University School of Medicine in St. Louis have assembled the most complete catalog to date of the genetic changes underlying the most common form of lung cancer. The research, published Oct. 23 in *Nature*, helps lay the foundation for more personalized diagnosis and treatment of a disease that is the leading cause of U.S. cancer deaths.

The research team identified 26 genes that are frequently mutated in a type of cancer called lung adenocarcinoma, a finding that more than doubles the number of genes already known to be linked to the deadly disease. What's more, by casting a wide net in their search for genetic alterations, the scientists are now beginning to see intriguing relationships. They found that some of the same genes associated with lung tumors are also defective in other cancers, that smokers and non-smokers with lung cancer have distinct genetic defects and that several molecular pathways underlie most of the mutations.

"This genomic approach has given us a completely different view of lung cancer," says Richard K. Wilson, Ph.D., director of Washington University's Genome Sequencing Center and one of the study's lead authors. "This broad view will allow scientists to more accurately categorize tumors, which should speed efforts to develop more targeted therapies to fight the disease."

More than 1 million people worldwide die of lung cancer each year, including more than 160,000 in the United States. About 40 percent of

them are adenocarcinoma, a type of non-small cell lung cancer and one that is exceedingly difficult to treat. Only about 15 percent of patients are still alive five years after diagnosis.

"By harnessing the power of genomic research, this pioneering work has painted the clearest and most complete portrait yet of lung cancer's molecular complexities," says Alan E. Guttmacher, M.D., acting director of the National Human Genome Research Institute, the agency that funded the research.

The Nature study was conducted as part of the Tumor Sequencing Project, a collaborative effort to assemble a genome-wide catalog of the genetic mutations in lung adenocarcinoma. Like most cancers, lung adenocarcinoma arises from changes that accumulate in people's DNA over the course of their lives. However, little is known about the precise nature of these genetic alterations, how they occur and how they disrupt biological pathways to cause cancer's unfettered cell growth.

Working with lung cancer samples donated by 188 patients from across the United States, the group sequenced 623 suspect genes and compared them to the same genes in healthy tissues from the same patients. Initially, they found more than 1,000 mutations across the samples. Looking more closely, the researchers identified 26 genes mutated in a significant number of samples. Most of the genes had not previously been associated with lung cancer but are found in other tumors.

The new genes fingered in lung adenocarcinoma include:

-- Neurofibromastosis 1: Mutations in this gene cause a rare inherited neurological disorder that increases the risk of tumors that form on nerve tissues, including the brain, spinal cord and individual nerves;
-- Ataxia telangiectasia mutated (ATM): Mutations of this gene have been found in a rare inherited neurological disorder and in various types

of leukemia and lymphoma;
-- Retinoblastoma 1: Mutations in this gene have linked to a rare childhood cancer that begins in the retina;
-- Adenomatosis polyposis coli (APC): Mutations of this gene are common in colon cancer.

The team also examined the effects of the genetic mutations on biological pathways and determined which of the pathways is most crucial to lung adenocarcinoma. This line of discovery is essential to efforts to develop new and better treatments for cancer.

For example, the researchers discovered that more than 70 percent of the 188 tumors had at least one mutation affecting the mitogen-activated protein kinase (MAPK) pathway, indicating it plays a pivotal role in lung cancer. Based on those findings, the researchers suggested new treatment strategies for some subtypes of lung adenocarcinoma might include compounds that affect this pathway. One such group of compounds, the MEK inhibitors, has produced promising results in mouse models of lung cancer.

"Looking at the pathways helps simplify the picture," Wilson explains. "Generally, we found that each mutation only occurs in a small percentage of the tumor samples, but when we looked at all the mutations that intersect a particular signaling pathway, we were surprised to find a lot of overlap in only a handful of pathways. This gives us a much better idea of what goes wrong in cells when they become cancerous."

Additionally, the finding that more than 30 percent of tumors had mutations affecting the rapamycin (mTOR) pathway raises the possibility that the drug rapamycin might be tested in lung adenocarcinoma. The drug, which inhibits mTOR, is approved for use in organ transplants and renal cancer.

The researchers also analyzed the patterns of genetic changes in both smokers and non-smokers with lung cancer. About 90 percent of lung cancer is linked to smoking, but 10 percent of patients diagnosed with the disease have never smoked. They found that the number of mutations detected in tumor samples from smokers was significantly higher than in tumors from never-smokers. Smokers' tumors contained as many as 49 mutations, while none of the never-smokers' tumors had more than five.

More work is needed to determine the clinical significance of these differences. However, doctors do know that in some other types of cancer, high mutation levels may cause a tumor to spread rapidly or be resistant to treatment.

The study also confirmed previous observations that indicated lung cancer in never-smokers may be triggered by different genetic mutations than those in smokers. For example, mutations in the epidermal growth factor (EGFR) gene were prevalent in tumors from non-smokers, while mutations in the KRAS and Src tyrosine kinase 11 genes were common in tumors from smokers.

"Our findings underscore the value of systematic, large-scale genome studies for exploring cancer. We now must move forward to apply this approach to even larger groups of samples and a wider range of cancers," Wilson says.

Source: Washington University