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Most Common Lung Cancers May Begin in Newly Discovered Cells

The most common form of lung cancer may begin in a group of newly isolated lung stem cells, according to researchers from the Howard Hughes Medical Institute.

Working in a mouse model, the researchers isolated a novel type of lung cell that can divide into fresh copies of itself and into the two more specialized kinds of cells deep in the lung. Their experiments show that at the earliest stage of tumor development, the stem cell appears to be the first lung cells that respond to a cancer-causing mutation. The newly identified cell type fulfills all but one of the strictest criteria that scientists look for in defining adult stem cells.

The study is published in the June 17, 2005, issue of the journal *Cell*.

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"The work of Bender Kim and colleagues represents not only a leap forward in our understanding of lung tumorigenesis, it also heralds the arrival of a valuable mouse model for identifying those cells that should be the targets of therapeutic intervention," wrote Anton Berns of The Netherlands Cancer Center in Amsterdam in an accompanying commentary in *Cell*.

The identification of the cells could lead to earlier diagnosis of lung cancer in people. Lung cancer is the leading cause of cancer-related death in the United States, in part because it is usually detected at an advanced stage. Patients in whom the disease has spread to other organs have a five-year survival rate of only two percent. In contrast, lung cancer detected at an early stage boasts a 50 percent survival rate over a five-year period.

“There are many similarities between stem cells and cancer,” said first author Carla Bender Kim, a postdoctoral fellow in the lab of senior author Tyler Jacks, a Howard Hughes Medical Institute investigator at Massachusetts Institute of Technology. “Cancer cells can continue to divide many times. Likewise, stem cells can divide over the lifespan of the organism. Also, tumors are very heterogeneous, composed of many different cells, and stem cells can give rise to different types of cells.”

The researchers do not know if the stem cells play a role in more established tumors, but other scientists have found evidence that some human cancers contain a small but virulent group of cells known as “cancer stem cells” that regenerate the tumor, a capacity that most cells in a tumor lack.

“They may be the cells that we have to eliminate in cancer in order to obtain durable cures for the disease,” said Jacks. “Along the way, we need to know how these cancer stem cells become different from normal stem cells.”

Bender Kim started with a mouse model of non-small cell adenocarcinoma recently developed by another postdoc and graduate student in Jacks's lab to study the progression of lung cancer and the effects of conventional and experimental therapies.

The mouse carries a silent genetic mutation of an oncogene known as *K-ras*, which is found in about one-third of all tested non-small cell lung cancers in people. A specially designed virus can activate the mutation in only a few cells. The mouse is known as a conditional mutant strain. In this case, the mouse inhales a small amount of virus that activates the *K-ras* oncogene in some of the lung cells.

Four years ago, Jacks's lab reported that some of the resulting cancer cells carry the molecular markers of both of the two kinds of cells found in non-small lung cell cancers. In mice, the tumors start deep in the lung, past the trachea and the branches to the lobes. Ciliated cells that catch debris give way to the bronchiolar cells called Clara cells. The airways end with the alveolar cells, which are the grape-cluster-like sacks lined with microscopic vessels, where oxygen and carbon dioxide are exchanged.

At the junction of the bronchioles and alveoli, other groups have found evidence of cells that are resistant to damage and are involved in repair and maintenance of tissue. They have proposed that these junctions might be a stem cell niche.

Bender Kim and her co-authors first isolated the stem cells, which they named bronchioalveolar stem cells (BASCs), from the earliest stage of the mouse tumors. Then, she purified them from the lungs of healthy mice. On the surface of BASCs, Bender Kim found another protein marker that is also present on the surface of better-studied hematopoietic stem cells. She made certain that BASCs were not stem cells of the blood or blood vessels.

The BASCs passed the rigorous tests for stem cells. In response to two types of lung damage that killed the more specialized cells, BASCs proliferated and appeared to give rise to the Clara or alveolar cells lining the airways. In tissue cultures of normal mouse cells, only the BASCs could grow more of themselves or differentiate into Clara or alveolar cells. In tissue cultures of the mutant mouse lung cells, the activated oncogene only triggered growth of the BASCs, not of the more specialized alveolar cells.

"The stem cells may retain mutations from the same damage that kills the more specialized cells," Bender Kim speculates. "If the DNA is not repaired properly, and if the mutation happens to affect a tumor suppressor gene or oncogene, it could start the process of forming a tumor. There are certainly suggestions that various tumors might arise in locations where there has been a previous injury."

The researchers acknowledge that the ultimate stem cell test remains. "One thing we have not done is taken BASCs and put them back into the mouse and show in vivo that they perform as stem cells," Bender Kim said. "We don't have an assay for that yet."

With hematopoietic stem cells, for example, scientists can inject the stem cells into the bone marrow of an irradiated mouse and replace the entire blood system, the basis of bone marrow transplantation. Solid tissue is trickier. Bender Kim and her colleagues do not yet know the optimal microenvironment for stem cells of the lung, including the roles of the neighboring cells that support the stem cells and specialized lung cells. Still, she says their studies are as rigorous as the generally accepted reports of stem cells found in the skin, brain, testes and gut.

The lab has already teamed up with another research group to develop microscopic fluorescent probes to image the unique molecular surface of BASCs and track the progress of the naturally arising tumor, Jacks said. The similar genetic activity profile of mouse tumors with *K-ras* mutations to the profile of human lung cancer samples make the researchers optimistic about the relevance of targeting BASCs for early tumor detection and chemoprevention in the earliest stage of disease in people.

Discovery of the lung stem cells could lead to new therapies for other lung diseases, such as emphysema and cystic fibrosis. "We tend to emphasize cancer, because we are in a lab that studies cancer," Bender Kim said. "Identifying stem cells is the biggest part of the story. This population could be very useful for more than cancer."

In their paper, the researchers envision more medical possibilities, such as using the adult stem cells to restore defective tissue in incurable fatal chronic lung diseases, such as alveolar cells that are destroyed in emphysema. Or scientists could extract the BASCs, alter their genes, and replace them in a kind of cellular gene therapy for genetic diseases such as cystic fibrosis.

“This work has identified a new population of cells that links the normal biology of the lung to lung cancer development,” said Bender Kim. “We need to continue to improve our understanding of how normal cells in the body develop, differentiate, and respond to damage in order to understand the origins of diseases and to develop better ways to treat them.”