

JULY 02, 2009

Study Pinpoints Genetic Drivers of Lung Cancer's Spread

For the first time, researchers have cracked open a genetic playbook that lung cancer uses to seed deadly new tumors in the brain, bone marrow, and other organs. Lung cancer cells, it turns out, hijack a master cellular signal that normally directs the development of embryos and helps maintain stem cell populations. Once it controls this genetic megaphone, a rogue lung cancer cell can settle into a new environment and grow rapidly.

The research identifies a factor that “gives cells the extra impulse to go above and beyond just being tumor cells to becoming metastatic cells,” says study leader Joan Massagué, a Howard Hughes Medical Institute investigator at Memorial Sloan-Kettering Cancer Center in New York. Massagué and his colleagues published their findings online July 2, 2009, in the journal *Cell*.

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Lung cancer is the deadliest cancer in the United States, killing more than 150,000 people each year. The disease is devastating because lung tumors are highly metastatic—sending out wayward cells that invade the brain, bone marrow, and other organs, where they often form new, deadly tumors. Unlike breast cancer and prostate cancer, lung cancer metastasizes quickly; within weeks of the primary tumor’s formation, cells break off and enter the bloodstream. Some of these cells seed new tumors in other organs.

But metastasis is poorly understood, and nobody knew how the colonizing lung cancer cells accomplished their feat.

To find out, Massagué’s team genetically screened cells from 107 lung tumors that surgeons had removed from patients. Most of the tumors were early stage, excised before any metastasis had occurred in the patients. Physicians tracked all of the patients to determine if metastases ever appeared.

Massagué and his colleagues scrutinized the samples for signatures of a specific type of gene activity—activity that could help a cell integrate into a new environment and begin growing. Over the past two decades, various researchers have identified many genes that can help cells do this; most are involved in one of six pathways—flowchart-like sequences of genes that roust a cell to perform a high-level function, such as moving or dividing.

“We decided to ask if any of these pathways might be active in the tumors that went on to metastasize, but were not so active in those tumors that didn’t metastasize, where the patient was saved,” Massagué says.

His screen highlighted genes involved in one such pathway, called the WNT pathway. Certain WNT genes were turned on in tumors that eventually metastasized, but inactive in quiescent tumors.

“We were surprised,” says Massagué. “WNT is an important pathway in stem cell biology, in embryo development, and in the maintenance of adult tissues, such as the mucosa of the gut. And, in fact, colon cancer often begins when the WNT pathway becomes mutated. But no one had seen WNT activity in lung cancer. In fact, other research had ruled out the WNT pathway as an initiator of lung cancer.”

To see if the results accurately reflected tumor behavior, Massagué devised a second series of experiments. His team extracted cells from two different lung tumors, grew the cells, and injected them into mice. They then watched the animals, looking for those that rapidly developed metastases in the brain and bone marrow. The team extracted cells from the metastatic sites and compared them to the cells they had started with. Again, they found that the WNT pathway was overactive in the aggressive cells.

Next, the team artificially suppressed the activity of the WNT pathway in the aggressive cells and injected them back into mice. This reined in the cells, and they formed very few metastases.

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The researchers then drilled down into the WNT pathway, which involves dozens of different genes, to search for the specific genes involved in lung metastasis. They found two, LEF1 and HOXB9, that were hyperactive in the metastatic cells. When they impeded the activity of these two genes, the previously metastatic cells languished, unable to form new tumors. These two genes act as “middle managers,” says Massagué, orchestrating other genes to perform complex cellular behaviors such as cell division, growth, and movement. Exactly how they get activated in lung cancer remains unknown, but this is a question that Don Nguyen, a Memorial Sloan Kettering colleague, is trying to answer.

Massagué hopes drug developers will now search for compounds that block the activity of the WNT pathway and then test whether such drugs will stanch metastases in patients.

In the meantime, he's happy to have opened a biological black box. For too long, he says, cancer researchers shied away from studying the genetics of metastasis, thinking the problem too tough to crack. But in May, Massagué published another paper, in *Nature*, highlighting specific genes that help breast cancer metastasize.

“We no longer need to be afraid, as investigators, that metastasis is too difficult to study,” he says. “This is not true anymore. We've shown it's possible to break the problem open.”