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Biologists pinpoint a genetic change that helps tumors move to other parts of the body

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MIT cancer biologists have identified a genetic change that makes lung tumors more likely to spread to other parts of the body. The findings, to be published in the April 6 online issue of *Nature*, offers new insight into how lung cancers metastasize and could help identify drug targets to combat metastatic tumors, which account for 90 percent of cancer deaths.

The researchers, led by Tyler Jacks, director of the David H. Koch Institute for Integrative Cancer Research at MIT, found the alteration while studying a mouse model of lung cancer. They then compared their mouse data to genetic profiles of human lung tumors and found that reduced activity of the same gene, NKX2-1, is associated with higher death rates for lung-cancer patients.

This study represents an important step in understanding how changes that disable this gene would make tumors more aggressive, says Monte Winslow, a senior postdoctoral associate in Jacks' lab and lead author of a paper.

Understanding the role of NKX2-1 may help scientists pursue drugs that could counteract its loss. Right now, "the sad reality is that if you could tell a patient whether their cancer has turned down this gene, you would know they will have a worse outcome, but it wouldn't change the treatment," Winslow says.

Winslow and his colleagues at the Koch Institute studied mice that are

genetically programmed to develop lung tumors. The mice's lung cells can be induced to express an activated form of the cancer-causing gene Kras, and the tumor suppressor gene p53 is deleted. While all of those mice develop lung tumors, only a subset of those tumors metastasizes, suggesting that additional changes are required for the cancer to spread.

The researchers analyzed the genomes of metastatic and non-metastatic tumors in hopes of finding some genetic differences that would account for the discrepancy. The absence of NKX2-1 activity in metastatic tumors was the most striking difference, Winslow says.

The NKX2-1 gene codes for a transcription factor — a protein that controls expression of other genes. Its normal function is to control development of the lung, as well as the thyroid and some parts of the brain. When cancerous cells turn down the expression of the gene, they appear to revert to an immature state and gain the ability to detach from the lungs and spread through the body, seeding new tumors.

Once the researchers identified NKX2-1 as a gene important to metastasis, they started to look into the effects of the genes that it regulates. They zeroed in on a gene called HMGA2, which had been previously implicated in other types of cancer. It appears that NKX2-1 represses HMGA2 in adult tissues. When NKX2-1 is shut off in cancer cells, HMGA2 turns back on and helps the tumor to become more aggressive.

They also found that human tumors with NKX2-1 missing and HMGA turned on tended to be metastatic, though not all metastatic tumors fit that profile.

It would be difficult to target NKX2-1 with a drug because it's much harder to develop drugs that turn a gene back on than shut it off, Winslow noted. A more promising possibility is targeting HMGA2 or

other genes that NKX2-1 represses.

Jacks' lab is now looking at other types of cancer, to see if NKX2-1 or HMGA2 have the same role in other metastatic cancers. "It's great to find something that's important in lung cancer metastasis, but it would be even better if it controlled metastasis in even a subset of other cancer types," Winslow says.

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