The investigators hypothesized that because not all lung tumors have spread before diagnosis and removal, metastasis may depend on some added feature beyond the mutations that initiate these tumors.

> Our findings suggest that using treatments that target the WNT pathway may help prevent lung cancer from repeatedly seeding itself throughout the vital organs of patients at risk for metastasis.
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> Joan Massagué, PhD, Chair of MSKCC Cancer Biology and Genetics Program and a Howard Hughes Medical Institute investigator

Researchers used bioinformatics to interrogate large collections of lung tumor samples. They found that the WNT cell-signaling pathway was the only one out of the six pathways tested that was hyperactive in lung tumors that went on to metastasize and was normal in those that did not spread. They also observed that WNT hyperactivity was associated with aggressive biological tumor characteristics and poor clinical outcome, suggesting that cancer metastasis is linked to poor survival.

“Mutations that activate the WNT pathway are a common cause of colon cancer, but lung tumors are initiated by mutations in other genes so we were surprised that a hyperactive WNT pathway would be responsible for metastasis in lung cancer,” said the study’s senior author Joan Massagué, PhD, Chair of the Cancer Biology and Genetics Program at MSKCC and a Howard Hughes Medical Institute investigator.

This finding was confirmed with additional experiments in mice that showed that lung cancer cells with tumor-initiating mutations in the genes *KRAS* and *EGFR* also depended on a hyperactive WNT pathway for metastasis. The researchers went on to find two genes - *HOXB9* and *LEF1* - that are activated by WNT and enhance the ability of lung cancer cells to swiftly invade and reinitiate tumor growth. These are functions that cancer cells need in order to conquer other organs and that are being enabled by the WNT pathway in the primary tumor.

“Our findings suggest that using treatments that target the WNT pathway may help prevent lung cancer from repeatedly seeding itself throughout the vital organs of patients at risk for metastasis,” said Dr. Massagué.

The following investigators at MSKCC contributed to this research: Don X. Nguyen, Anne C. Chiang, Xiang H. F. Zhang, Juliet Y. Kim, Mark G. Kris, Marc Ladanyi, and the late William L. Gerald.

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