Research reveals what drives lung cancer's spread

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(PhysOrg.com) -- A new study by researchers at Memorial Sloan-Kettering Cancer Center (MSKCC) reveals the genetic underpinnings of what causes lung cancer to quickly metastasize, or spread, to the brain and the bone - the two most prominent sites of lung cancer relapse. The study will be published online in the journal *Cell* on July 2.

Researchers discovered that the same cellular pathway that has been shown to be involved with the spread of colorectal cancer is also responsible for providing lung cancer with an enhanced ability to infiltrate and colonize other organs without delay and with little need to adapt to its new environment. This is a dramatic departure from other cancers, like breast cancer, in which recurrences tend to emerge following years of remission, suggesting that such cancer cells initially lack - and need time to acquire - the characteristics and ability to spread to other organs.

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.

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.

Source: Memorial Sloan-Kettering Cancer Center