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Study puts notch on the jagged edge of lung cancer metastasis

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Researchers discovered a new, key component in the spread of lung cancer as well as a likely way to block it with drugs now in clinical trial. The study was published today (Monday, March 14) in the *Journal of Clinical Investigation*.

A team led by scientists at The University of Texas MD Anderson Cancer Center found a way to identify metastasis-prone lung cancer cells and then uncovered a mechanism that shifts primary tumor cells into a more deadly type of cell with the capacity to move elsewhere in the body.

"We think tumors have to learn how to metastasize because they can't do it initially," said paper senior author Jonathan Kurie, M.D., professor in MD Anderson's Department of Thoracic/Head and Neck Medical Oncology. "Cells change in response to cues from their external environment."

About 90 percent of all cancer deaths are caused by metastasis - the spread to, and invasion of, other organs. Lung cancer is the leading cause of cancer-related death in the United States, accounting for more than 157,000 deaths annually. The median five-year survival rate is 3.5%

Jagged2 silences protective microRNA

The researchers found that when a protein called Jagged2 binds

externally to Notch, a membrane protein that sticks out through the surface of a cell, it suppresses a microRNA that thwarts metastasis inside the cell.

"Jagged2 suppresses miR-200 and drives metastasis as a consequence." Kurie said. "It's been known for some time that Notch is involved in cancer, but no one really knew how."

Two Notch inhibitors are in clinical trial at MD Anderson. "These drugs might suppress the ability of primary tumors to metastasize," Kurie said.

"One question is who is supposed to get these drugs," Kurie said. "Our data suggest that low levels of miR-200 may indicate a tumor's susceptibility to Notch inhibitors."

Jailing tumor cells

While the drugs don't kill a primary tumor, they do "keep the primary lung tumors in jail," holding them in place and blocking their transition to mobile cells, Kurie said.

This transition, from immobile epithelial cells, which line or cover an organ, to a migratory cell with the properties of a mesenchymal cell, is an early event in metastasis. Kurie and colleagues previously showed that miR-200 blocks this epithelial-to-mesenchymal transition. About 80 percent of all cancers begin in the epithelial cells of organs.

Telltale surface protein identifies metastatic cells

The first crucial research step was to identify and study non-small cell lung cancer cells prone to metastasizing.

Yanan Yang, Ph.D., study first author and a postdoctoral fellow in Kurie's lab, studied lung cancer cells in mice, searching for markers of metastasis. He homed in on a surface protein called CD133.

"In primary lung tumors, CD133 cells are under 1 percent of cells," Yang said. "In metastatic lesions, more than 80 percent of the cells have CD133."

Follow up studies determined that CD133-expressing cells were located on the perimeter of tumors, ideally situated for metastasis. More than half of mice injected with CD133-positive lung cancer cells had metastatic cancer, compared to less than 20 percent of those injected with CD133-negative cells.

Intensive study of CD133 metastatic cells revealed that they highly expressed Notch ligands (proteins that bind to specific receptors on other cells). Yang said they separately depleted two Notch ligands - Jagged1 and Jagged2 - from tumor cells. Removing Jagged1 had no effect, but cells with little Jagged2 did not metastasize.

"Because epithelial-to-mesenchymal transition (EMT) is a very early step in metastasis," Yang said, "we thought Jagged2 might regulate EMT." When they knocked down Jagged2 again, they found levels of the EMT-stifling miR-200 increased.

External signals drive change

Additional research found that Jagged2 reduced miR-200 by tipping a delicate balance between the microRNA and a protein called GATA3, which inhibit one another. Stimulating production of more GATA3 reduced levels of miR-200.

"Jagged2 increases the levels of GATA3, which in turn binds to the

promoter of miR-200 and suppresses production of miR-200," Yang said.

"The study is among the first to show that mir-200 is regulated by specific signals emanating from the environment surrounding cancer cells. These signals are keys to understanding metastasis", Yang said.

One surprise, Kurie said, is that GATA proteins had been thought to suppress tumors. "In this case it's exactly the opposite."

The next step is to determine which of the four known Notch receptors suppress miR-200 and promote metastasis. The drugs currently under study are designed to inhibit an enzyme that cleaves and activates all Notch receptors. Drugs that target specific Notch receptors might be more effective inhibitors of metastasis, Kurie said.

Provided by University of Texas M. D. Anderson Cancer Center