Scientists find key to gene that promotes cancer metastasis

April 12 2010

The molecular machinery that switches on a gene known to cause breast cancer to spread and invade other organs has been identified by an international team led by scientists at The University of Texas M. D. Anderson Cancer Center. The paper was published Sunday in *Nature Cell Biology*'s advanced online publication.

The discovery provides a target-rich environment for development of drugs to thwart expression of the RhoA gene, according to Hui-Kuan Lin, Ph.D., the paper's senior author and an assistant professor in M. D. Anderson's Department of Molecular and Cellular Oncology. RhoA overexpression has been implicated in cancer metastasis.

"There are four components to this complex, which starts RhoA expression by transcribing the gene, and we found that all of them are important to metastasis," Lin said. "Knock down any one of the four, and you can stop breast cancer metastasis by preventing RhoA expression."

Researchers built their case with a series of laboratory experiments on cell lines, followed by confirmation in a mouse model of breast cancer metastasis and then analysis of 64 prostate cancer tumors that showed overexpression of RhoA or three of its transcription complex components were strongly correlated with metastatic disease.

Transcription is the first step on a gene's path to expressing its protein. Transcription factors bind to the promoter region of the gene, causing a

copy of RNA to be made from the DNA of the gene. The RNA is then translated into the corresponding protein.

The team first established the Myc protein as a transcription factor that binds to RhoA's promoter region. Knocking down Myc in cancer cell lines decreased RhoA expression, cell migration and invasion, while Myc overexpression increased all three.

Next, they found that the Skp2 overexpression also results in more RhoA, and that both Skp2 and Myc were required for the metastasis-producing RhoA to be overexpressed.

This cancer-promoting pathway is the second way Skp2 fuels cancer growth, Lin said. Skp2 has been shown to work through a separate E3 ligase pathway to destroy tumor-suppressing proteins, causing heightened cellular proliferation and the transition from normal cell to tumor.

"Skp2's E3 ligase activity is required for tumorigenesis, but not involved at all in metastasis," Lin said. Lin and colleagues also previously found that Skp2 blocks cellular senescence - a halt in cell division - in cancer cells.

The research team then found that Skp2 recruits two other proteins, p300 and Miz1, to join Myc and form the complex that transcribes RhoA.

Experiments in a mouse model of breast cancer metastasis to the lung showed that deficiency of either Myc, Skp2 or Miz1 restricted metastasis, while overexpression of each of the three proteins increased cell migration and invasion. Skp2 knockdown, for example, resulted in no metastatic nodules in the lung, compared with an average of 40 nodules when Skp2 was expressed.

Directly knocking down RhoA expression produced the same effect as blocking the Myc-Skp2-Miz1 complex. Knocking down expression of p300 resulted in decreased expression of RhoA.

In the analysis of prostate cancer tumors, expression of RhoA, Myc, Skp2 and Miz1 were significantly correlated with metastasis. Expression of the RhoA and the Myc-Skp2-Miz1 complex also were highly correlated.

Lin and colleagues note that Miz1 is thought to be a tumor-suppressor that contends with the oncogene Myc to regulate genes. In this case, the tumor-suppressor cooperates with the oncogene to launch RhoA and promote metastasis.

"Right now, there are no small-molecule agents to inhibit any of these targets," Lin said. "One future direction of research will be to find ways to target the entire transcription complex or its individual components."

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