Lung cancer suppresses miR-200 to invade and spread

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Primary lung cancer shifts to metastatic disease by suppressing a family of small molecules that normally locks the tumor in a noninvasive state, researchers at The University of Texas M. D. Anderson Cancer Center report in the Sept. 15 edition of *Genes and Development*.

"Existing treatments have little success against cancer that has spread to other organs, so finding a way to prevent metastasis could have a huge impact on survival," said senior author Jonathan Kurie, M.D., professor in M. D. Anderson's Department of Thoracic/Head and Neck Medical Oncology.

"To do that, we need to understand the cues that initiate metastasis. In this paper we show that microRNA-200 is one of those central cues," Kurie said. MicroRNAs are single-stranded bits of RNA that regulate messenger RNA expressed by genes to order the creation of a specific protein.

All primary tumors in a strain of mice prone to metastatic lung cancer became invasive and spread when miR-200 was suppressed. Protecting miR-200 from blockade completely prevented metastasis in another group of the mice, the researchers found.

Tumors shift between noninvasive and invasive state

The team found that miR-200 needs to be shut down for the primary tumor to change from stationary epithelial cells to mobile mesenchymal cells. This epithelial-to-mesenchymal transition (EMT) is recognized as a crucial step in metastasis, which causes 90 percent of all cancer deaths.

An estimated 80 percent of all solid tumors originate in the epithelial cells, which line an organ or its cavities and are generally immobile. Mesenchymal cells are mobile and can differentiate into many different cell types.

When the team profiled a panel of 40 human lung cancer cell lines that had been characterized on the basis of EMT features (epithelial versus mesenchmyal) and site of origin (primary lung tumor versus metastasis), miR-200 expression was highest in those cells with epithelial features and was the best of more than 700 microRNAs tested as an indicator of metastatic or primary origin.

"Highly metastatic lung cancer cells had completely shutdown miR-200 expression, that's what triggered EMT in those cells," Kurie said. "When we went back and forced overexpression of miR-200, the cells remained locked in the epithelial state and could no longer metastasize."

The team also found that the cancer cells could shift from epithelial to mesenchymal and back depending on the cell's context. The same cells that remain epithelial in Matrigel become "blatantly mesenchymal" when moved to the mouse model and assume an intermediate state when growing in plastic dishes.

Matrigel is a gelatinous mixture that is designed to simulate the complex environment that cells occupy called the extracellular matrix.

"If you take the tumors out of the mice and back to the matrigel, they revert to epithelial cells," Kurie said. "These cells are highly plastic and responsive to the extracellular environment.

"The idea that these highly plastic cells are the source of metastasis indicates that metastatic capacity is a regulatable tumor cell function. That's new," Kurie said. "Identifying the signals that govern plasticity could lead to a novel way of targeting and preventing metastasis."

Kurie and colleagues continue to work on identifying upstream regulators of miR-200 that

might provide targets for therapy.

The researchers started with a strain of mice that develops metastatic lung cancer based on mutations in the Kras oncogene and the tumor-suppressing p53 gene. Cell lines isolated from these mice were introduced in wild type mice and the resultant tumors characterized for metastatic potential.

All tumor cell lines were profiled for gene expression. "The thing that popped out strongly was an EMT signal present in the metastatic cells but not in the non-metastatic cells," Kurie said.

The team then profiled the tumors for microRNA expression. Out of thousands of miRNAs, only the miR-200 family of five miRNAs, along with three others, emerged as differentially expressed. The other three are being studied.

Source: University of Texas M. D. Anderson Cancer Center (news : web)