Protein and microRNA block cellular transition vital to metastasis

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Like a bounty hunter returning escapees to custody, a cancer-fighting gene converts organ cells that change into highly mobile stem cells back to their original, stationary state, researchers report online at *Nature Cell Biology*.

This newly discovered activity of the p53 gene offers a potential avenue of attack on breast cancer stem cells thought to play a central role in progression and spread of the disease, according to scientists at The University of Texas MD Anderson Cancer Center.

Long known for monitoring DNA damage and forcing defective cells to kill themselves, p53 also activates bits of RNA that block two proteins, the researchers found. This prevents conversion of epithelial-differentiated cells, which line or cover an organ, into cells that resemble mesenchymal stem cells when stimulated by the TGF-β growth factor.

Mesenchymal cells are mobile adult stem cells that can reproduce themselves and differentiate into a variety of cell types

"Blocking this conversion from epithelial cell to a mesenchymal cell type is important because that change plays an essential role in cancer metastasis," said senior author Mien-Chie Hung, Ph.D., professor and chair of MD Anderson's Department of Molecular and Cellular Oncology.

Cancer treatment potential

"We found that p53 activates the micro RNA miR-200c, which forces cells that have taken on stem cell traits to revert to epithelial form," Hung said. "Activating this pathway has therapeutic potential to target tumor-initiating cells that have stem cell characteristics."

Research has shown that about 80 percent of all solid tumors begin in the epithelial cells. However, 90 percent of cancer deaths are caused by metastasis, the progression and spread of the disease to other organs.

The epithelial-to-mesenchymal transition (EMT) and its opposite process play important roles in embryonic development. Research has connected EMT activation to cancer progression and metastasis. Recent studies tie EMT to gain of stem cell traits in normal and transformed cells.

Cell status depends on p53, miR-200c levels

A series of experiments established that the p53 protein activates the miR-200c gene to produce the microRNA and that expression of the protein and miR-200c moved up and down together.

- Knockout experiments in normal breast epithelial cells consistently showed that p53 expression stifled the EMT transition.
- Cells with reduced p53 changed into mesenchymal-like cells.
- When miR-200c was overexpressed in cells with low levels of p53, the cells took on epithelial characteristics, indicating that p53 uses the microRNA to block or reverse the transition to

mesenchymal-type cells.

- Mutated p53 failed to produce miR-200c, increasing stem cells in the cell culture.

- Tissue array analysis of gene expression in 106 human breast tumor samples showed that low p53 expression correlated with higher expression of two genes associated with EMT. Increased p53 raised levels of miR-200c and the expression of a gene associated with epithelial status.

Mutations of p53 occur in more than half of cancers and loss of p53 activity correlates with poor prognosis in several cancer types. Restoring functions lost by p53 mutation by re-expressing miR-200c might be a good therapeutic strategy for treatment of p53-deficient tumors, Hung said.

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