

Protein central to cancer stem cell formation provides new potential target

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Researchers have identified a pivotal protein in a cellular transformation that makes a cancer cell more resistant to treatment and more capable of growing and spreading, making it an inviting new target for drug development.

Additionally, the international team led by scientists at The University of Texas MD Anderson Cancer Center found the cancer drug sunitinib potentially has a new role in treating triple-negative, claudin-low [breast cancer](#), a particularly resistant version of a type of cancer that is already difficult to treat.

"We found that FOXC2 lies at the crossroads of the cellular properties of cancer [stem cells](#) and cells that have undergone epithelial to mesenchymal transition (EMT), a process of cellular change associated with generating cancer stem cells," said senior author Sendurai Mani, Ph.D., assistant professor in MD Anderson's Department of Translational [Molecular Pathology](#) and co-director of the Metastasis Research Center.

Cancer stem cells are fewer in number than other tumor cells, yet research has tied them to cancer progression and resistance to treatment. Abnormal activation of the epithelial to mesenchymal transition can create cancer stem cells, Mani noted.

Sunitinib stifles growth of cancer stem cells

"There are multiple [molecular pathways](#) that activate EMT," Mani said. "We found many of these pathways also activate FOXC2 expression to launch this transition, making FOXC2 a potentially efficient check point to block EMT from occurring," Mani said.

Research uncovering this connection, published in the journal *Cancer Research*, focused on cell line and mouse model experiments. The next important step will be to assess the expression and activity of FOXC2 in human tumor samples, Mani said.

In the meantime, sunitinib, known commercially as [Sutent](#) and approved by the U.S. Food and Drug Administration for three other cancers, provides interesting, more immediate, potential.

"FOXC2 is a transcription factor, a protein that binds to DNA in the promoter region of genes to activate them. For a variety of reasons, [transcription factors](#) are hard to target with drugs," Mani said.

The team found that FOXC2 also regulates the platelet derived growth factor receptor (PDGFR-Beta). In cancer [cell lines](#), they found that the PDGFR-Beta inhibitor sunitinib inhibited growth of cells with EMT or cancer stem cell properties that have active FOXC2.

Mice with triple-negative breast cancer treated with sunitinib had smaller primary tumors, longer survival, and fewer incidences of metastasis. There also was a steep drop in the cells' ability to form mammospheres, a hallmark of cancer stem cells.

EMT: an embryonic development process reactivated by cancer

Mani is an expert on EMT and cancer stem cells and was the first author

on the original EMT study in Cell when he was with Robert Weinberg, Ph.D., at the Whitehead Institute/Massachusetts Institute of Technology.

Epithelial to mesenchymal transition is important to embryonic development, turning stationary epithelial cells into mobile mesenchymal cells to move them within the embryo. For example, a cell might be converted and then gather with other cells forming, for example, the kidney. Once there, it transitions back to an epithelial cell again and stays put.

Research has shown that carcinomas, tumors that form in the epithelium (lining) of organs are able to reactivate EMT. About 85 percent of all solid tumors are carcinomas.

The researchers focused on a recently discovered subtype of triple-negative breast cancer, so called because these cells lack receptors for three common treatments for breast cancer and thus are hard to treat. The claudin-low/basal B subtype is deficient in claudin, a membrane protein that binds epithelial cells together, and is particularly aggressive.

Building on an earlier paper that showed FOXC2 is expressed more heavily in cells after EMT is induced by a variety of factors, Mani and colleagues followed up first by using short hairpin RNA to suppress FOXC2 in breast [cancer cells](#).

Blocking FOXC2 had no effect on cell growth, but it altered both the physical appearance of the cells, increased their ability to cluster like epithelial cells, reduced protein biomarkers of mesenchymal cells and increased levels of E-cadherin, an important epithelial cell marker.

Additional experiments showed that FOXC2 did not regulate three proteins known to separately launch EMT. They also found that breast cancer cells primed to undergo EMT became less invasive when FOXC2

was knocked down.

Impact on cancer stem cells

Knocking down FOXC2 in mammary epithelial cell lines with stem cell properties caused:

- A reversal of expression of two cell surface cancer stem cell markers, CD44 and CD24.
 - A reduction in their ability to form mammospheres.
 - Heightened sensitivity to the chemotherapy drug paclitaxel.
- Chemo resistance is a hallmark of cancer stem cells.

They also found FOXC2 elevated in cancer cells with stem cell properties.

Examining cell lines in malignant human mammary epithelial cells showed:

- Forced expression of FOXC2 alone is sufficient to induce EMT resulting in cancer stem cells.
- Overexpression of the FOXC2 protein led to more efficient tumor formation.
- Aggressive growth and metastasis in mice, with FOXC2-enhanced cells spreading to the lungs, liver, hind leg bone and to the brain, while unenhanced cancer cells did not spread at all.

FOXC2 boosts claudin-low breast cancer cells

FOXC2 was found overexpressed in metastatic tumors compared to primary tumors in two claudin-low human breast cancer xenografts. A

second experiment showed all six claudin-low cell lines overexpressed FOXC2 compared to none of the other 7 cell lines. FOXC2 is required both for mesenchymal and invasive capacity of three claudin-low breast cancer cell lines. Blocking FOXC2 increased the cells' epithelial properties and decreased mesenchymal characteristics.

Mani and colleagues had earlier found increased expression of PDGFR-B in cells forced to undergo EMT. "We thought PDGFR-B might be a druggable target in these FOXC2-expressing [cells](#)," Mani said. They found suppressing FOXC2 reduced the ability of three cancer cell lines to migrate towards PDGF-B.

Mani said the team believes that targeting FOXC2 pathway using either PDGFR-beta inhibitors or other yet-to-be-known small-molecule inhibitors will be an effective therapeutic strategy for inhibiting EMT and consequently reducing EMT/[cancer](#) stem cell-associated metastasis, relapse and therapy resistance.

MD Anderson has filed a patent application connected to this study.

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

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