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Silencing the speech gene FOXP2 causes breast cancer cells to metastasize

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It is an intricate network of activity that enables breast cancer cells to move from the primary breast tumor and set up new growths in other parts of the body, a process known as metastasis.

Now a research team led by investigators at Beth Israel Deaconess Medical Center (BIDMC) has identified an unexpected link between a transcription factor known to regulate speech and language development and metastatic colonization of breast cancer.

Currently described online in *Cell Stem Cell*, the new findings demonstrate that, when silenced, the FOXP2 transcription factor, otherwise known as the speech gene, endows breast cancer cells with a number of malignant traits and properties that enable them to survive – and thrive.

"We have identified a previously undescribed function for the transcription factor FOXP2 in breast cancer," explains senior author Antoine Karnoub, PhD, an investigator in the Department of Pathology at BIDMC and Assistant Professor of Pathology at Harvard Medical School. "We have found that depressed FOXP2 [a member of the forkhead family of transcriptional regulators] and elevated levels of its upstream inhibitor microRNA 199a are prominent features of clinically advanced breast cancers that associate with poor patient survival."

Karnoub's lab investigates the roles that mesenchymal stem cells (MSCs) play in the development and metastasis of breast cancer. MSCs are adult

progenitor cells that function as the body's early responders, poised to take action to help repair damaged tissues, jumping from their niches in the bone, for example, into the blood, migrating to areas of inflammation, and orchestrating the body's reactions during wound healing. Previous work by Karnoub revealed that MSCs respond to breast tumors akin to the way they react to a wound or infection and that these cells participate in the formation of the breast tumor stroma, the supporting network of cells and their secretions that exist in the microenvironment of cancer cells.

"We think that by direct actions on the cancer cells and by manipulating other cells in the microenvironment, MSCs end up providing cancer cells with better abilities to survive and a safe haven in which to thrive," says Karnoub. Despite expanding knowledge of the role of MSCs to breast malignancy, the underlying molecular responses of breast cancer cells to MSC influences has not been fully delineated. In this new paper, the investigators set out to specifically identify the role that microRNAs were playing in the process.

miRNAs are short noncoding RNAs that play critical functions in cancer pathogenesis,. "An expanding body of evidence has documented miRNA deregulation in multiple aspects of tumor development, including invasion and metastasis," says Karnoub. The induction by MSCs of one such miRNA, miR199a, facilitated the acquisition of malignant properties by the cancer cells, including cancer stem cell and metastatic traits. (Cancer stem cells are thought to be the most virulent cells that lie within the core of most tumors, and are believed to be responsible for the resurgence of tumors following chemotherapy treatment.)

"After we found that miRNA-199a instigated in the cancer cells by MSCs was indeed promoting these cancer stem cells phenotypes and was facilitating cancer metastasis, we probed the mechanistic details of miR-199a's actions, " explains Karnoub. "miRNAs function

predominantly by suppressing target mRNA expression, and we analyzed an overwhelming majority of the published targets that have been associated with these miRNAs, but none was repressed in our systems. We then made a screen and serendipitously fished out a gene called FOXP2." At that time, he adds, basically nothing was known about this protein in relation to breast cancer.

FOXP2 has primarily been implicated in regulating speech and language development and several reports have described functions for this protein in developmental neurogenesis. Additional reports have also linked FOXP2 to tissue development, such as the lung.

"We were curious and wanted to find out the business of FOXP2 in breast cancer," he adds. "Surprisingly, we found that its suppression in the tumor cells was sufficient to expand cancer stem cell traits and caused the cancer cells to metastasize much more vigorously."

These findings agreed with similar results in which the authors determined that miR-199a upregulation and FOXP2 repression are prominent features of aggressive clinical breast cancers and represent independent prognostic parameters for overall patient survival.

"We are one step closer to understanding how cells in the tumor microenvironment, such as MSCs, promote the malignancy of neighboring cancer cells," says Karnoub. "We're now more closely investigating FOXP2's potential role as a metastasis suppressor that needs to be downregulated for metastasis to take place."

Provided by Beth Israel Deaconess Medical Center

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