

Study reveals how normal cells fuel tumor growth

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A new study published in the journal *Nature Cell Biology* has discovered how normal cells in tumors can fuel tumor growth.

Led by researchers at the Ohio State University Comprehensive [Cancer Center](#) – Arthur G. James Cancer Hospital and Richard J. Solove Research Institute (OSUCCC – James), the study examines what happens when normal cells called fibroblasts in mouse mammary tumors lose an important tumor-suppressor gene called Pten (pronounced "P ten").

The findings suggest new strategies for controlling tumor growth by developing drugs that disrupt the communication between tumor cells and the normal cells within the tumor. They also provide insight into the mechanisms that control the co-evolution of cancer cells and surrounding [normal cells](#) in tumors, and they demonstrate how the Pten gene normally suppresses cancer development, the researchers say.

"Our study is the first to define a specific pathway in tumor fibroblasts that reprograms gene activity and the behavior of multiple cell types in the tumor microenvironment, including tumor cells themselves," says co-principal investigator Dr. Michael Ostrowski, professor and chair of molecular and cellular biochemistry.

"Along with increasing basic knowledge about how tumors grow and spread, these findings have direct translational implications for the treatment of breast-cancer patients," says Ostrowski, who is a member of

the OSUCCC – James Molecular Biology and Cancer Genetics program.

The researchers found that Pten regulates a molecule called microRNA-320 (miR-320), and that the loss of Pten leads to a dramatic drop in levels of that molecule in a tumor fibroblast. With little miR-320 around, levels of a protein called ETS2 (pronounced Ets-two) rise in the fibroblast.

Finally, the abundance of ETS2 activates a number of genes that cause the fibroblast to secrete more than 50 factors that stimulate the proliferation and invasiveness of nearby cancer cells. It also causes the reprogramming of other fibroblasts in the tumor and throughout the mammary gland.

"The cancer field has long focused solely on targeting tumor cells for therapy," says co-principal investigator Gustavo Leone, associate professor of molecular virology, immunology and medical genetics. "Our work suggests that modulation of a few key molecules such as miR-320 in noncancer cells in the tumor microenvironment might be sufficient to impede the most malignant properties of tumor cells."

Ostrowski, Leone and their colleagues began this study by examining human invasive breast tumors from 126 patients for microRNA changes after PTEN loss.

Key technical findings include the following:

- Using mouse models, they found that miR-320 levels and ETS2 levels were inversely correlated in human breast-tumor tissue, suggesting that Pten and miR-320 work together to block ETS2 function and suppress [tumor growth](#).
- miR-320 in mammary fibroblasts influences the behavior of

multiple cell types, making it a critical molecule for suppressing epithelial tumors.

- miR-320 functions as a regulatory switch in normal fibroblasts that operates to inhibit the secretion of more than 50 tumor-promoting factors (i.e., a tumor-promoting secretome). In doing so, it blocks the expression of genes in other cell types in the tumor microenvironment and suppresses tumor-cell growth and invasiveness.
- Overall, loss of Pten in tumor fibroblasts results in downregulation of miR-320 and release of the secretome factors. This causes the genetic reprogramming of neighboring endothelial and epithelial cells of the mammary gland, inciting profound changes in these [cells](#) that are typical of malignant tumors.

"Remarkably, the molecular signature of the miR-320 secretome could distinguish normal breast tissue from [tumor](#) tissue, and it predicted the outcome in breast-cancer patients," says Leone, who is also a member of the OSUCCC – James Molecular Biology and Cancer Genetics program. "This underscores the potential clinical importance of the Pten-miR-320 regulatory pathway on human breast cancer."

Provided by Ohio State University Medical Center

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