Vitamin A derivative can inhibit early forms of breast cancer

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A nutrient found in carrots and sweet potatoes may prove key to fighting breast cancer at early stages, according to a new study by researchers at Fox Chase Cancer Center. Sandra Fernandez, PhD, an assistant research professor at Fox Chase, will present the findings at the AACR 102nd Annual Meeting 2011 on Tuesday, April 5.

Retinoic acid, a derivative of vitamin A, could be a promising cancer therapy because it affects cell growth, proliferation, and survival. Although it is being tested in a number of clinical trials, so far its success at combating cancer has been inconsistent. However, Fernandez and her colleagues have now pinpointed critical aspects of retinoic acid's mode of action-a potentially important step toward developing successful treatments for patients.

Retinoic acid binds to retinoic acid receptor beta (RAR-?), and it may be through this action that it can suppress tumors. A decrease in RAR- ? levels in tumors is associated with cancer progression, and an increase is linked to positive responses to certain clinical interventions. It is thought that the activated receptor limits cell growth by regulating gene expression, but its underlying mechanisms are not completely understood.

To identify the specific conditions under which retinoic acid inhibits and even reverses the growth of abnormal masses in the breast, however, Fernandez developed a culture system consisting of four cell lines representing different phases of cancer: normal-like human breast cells; transformed cells (which give rise to solid masses upon exposure to carcinogens); invasive cells (which are capable of breaking through breast tissue barriers and spreading to other parts of the body); and tumor cells (which form when invasive cells are injected into the mammary fat pad of mice and show all of the characteristics of fully malignant breast cancer cells).

"We found that the RAR-? gene was active in the two earliest stages of cancer, but silenced in the final two stages," says Fernandez. "These changes in gene activation were caused by a type of chemical modification called methylation, which involves the addition of a methyl group to DNA."

In three-dimensional cultures containing a collagen matrix, normal-like cells formed tubules resembling a normal mammary gland, while the transformed cells also gave rise to solid masses. The cells that produced solid masses in collagen produced tubules when they received retinoic acid for 15 days. By contrast, invasive and tumor cells did not generate tubules in response to treatment with retinoic acid, even in combination with a drug that activates RAR-? by inhibiting DNA methylation.

The results suggest that retinoic acid can stop tumor progression early on, but not at later timepoints because the genetic changes related to cancer have become too severe. "There appears to be no way to revert the tumors with retinoic acid when they become too advanced," Fernandez says.

The study also shows that the methylation status of RAR-? can act as a biomarker for the early detection of breast cancer. In addition, drugs that reactivate this receptor by decreasing DNA methylation may help breast cancer patients. These medications are already being used to manage a certain type of leukemia, offering hope that it will also be approved to treat other diseases.

Provided by Fox Chase Cancer Center