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Previously unseen switch regulates breast cancer response to estrogen

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A tiny modification called methylation on estrogen receptors prolongs the life of these growth-driving molecules in breast cancer cells, according to research by scientists at Emory University's Winship Cancer Institute. The results are published in the May 9, 2008 issue of the journal *Molecular Cell*.

Most breast cancers contain estrogen receptors, which enable them to grow in the presence of the hormone estrogen. Their presence can determine whether tumors will respond to the estrogen-blocking drug tamoxifen.

The finding will help researchers sort out how mutations change the estrogen receptor's function and allow some breast cancers to resist tamoxifen, says Paula Vertino, PhD, associate professor of radiation oncology at Emory University School of Medicine.

"The problem is that a significant fraction of estrogen receptor positive tumors don't respond to tamoxifen," Vertino says. "Development of new drugs that interfere with the methylation of the estrogen receptor may be an alternative way to treat those tumors."

Until recently, scientists thought methylation enzymes acted only on DNA molecules or on histones, proteins that bundle DNA into spool-like packages. Methylation enzymes add tags called methyl groups to other molecules, influencing their ability to turn genes on or off.

Vertino and her colleagues found that one of the modification enzymes, called SET7, methylates a flexible part of the estrogen receptor. When they created breast cancer cells with reduced levels of SET7, the estrogen receptor molecules lasted only half as long and were less effective in turning on genes.

Vertino's team showed that a mutation in the estrogen receptor found in more aggressive breast tumors interferes with methylation in cells. Also, the methylation appears in exactly the same spot where another protein called BRCA1 adds a different kind of regulatory marking, and may block BRCA1's restrictive effects on the estrogen receptor.

Women who inherit a mutation in the gene that encodes BRCA1 have up to an 80 percent lifetime risk of developing breast cancer, several times the risk of those who don't have it, according to the National Cancer Institute. BRCA1 mutations are estimated to account for about a third of all inherited breast cancers and roughly 2-3 percent of all breast cancers.

Scientists are beginning to look for drugs that could modulate methylation enzymes. Vertino says that methylation probably affects several other proteins similar to the estrogen receptor.

"I expect this will be just the tip of the iceberg," she says. "Methylation may be just as common as other protein modifications, and even more complicated."

Source: Emory University