

Researchers discover how some breast cancers alter their sensitivity to estrogen

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Using human breast cancer cells and the protein that causes fireflies to glow, a Johns Hopkins team has shed light on why some breast cancer cells become resistant to the anticancer effects of the drug tamoxifen. The key is a discovery of two genetic "dimmer switches" that apparently control how a breast cancer gene responds to the female hormone estrogen.

In a report published online July 7 by <u>Human Molecular Genetics</u>, the scientists show how a gene known as RET in <u>breast cancer cells</u> responds to estrogen by dialing up the manufacture of a signaling protein that instructs cells to divide and causes tumors to become aggressive through the escape from estrogen dependence.

Scientists have long known that breast cancers are either estrogenreceptor positive or estrogen-receptor negative. The positive subset, generally associated with better outcomes for patients, is sensitive to the drug tamoxifen, which blunts aggressive tumor growth through estrogen receptor inhibition, according to Zachary E. Stine, the research team's lead author and a <u>postdoctoral fellow</u> working in the McKusick-Nathans Institute of Genetic Medicine, Johns Hopkins University School of Medicine.

Used for decades to prevent and treat <u>breast tumors</u> that kill about 40,000 women a year, tamoxifen works on some types of breast cancers by interfering with the activity of estrogen. However, resistance to the drug frequently develops over time, and previous experiments by other



laboratories have shown that RET plays some role in either altering resistance or maintaining it.

Thus, the Hopkins scientists focused on RET, searching for pieces of DNA in the vicinity of that gene that had the potential, when combined with estrogen, to act as switches controlling the amount of protein product RET manufactures.

After identifying 10 sites in the RET locus that bind with estrogen receptor alpha, the investigators cloned the <u>DNA sequences</u> in those areas, then attached to each a piece of genetic material responsible for producing luciferase, an enzyme that causes the luminescent glow of a firefly. This lab product was then put inside human breast cancer cells in a dish and exposed to estrogen. Two of the 10 sequences lit up much more brightly than the others, revealing increased activity by the RET gene in response to estrogen.

"Those two sequences clearly are genetic hubs for the dialing up and dialing down of RET activity in response to estrogen," says Andrew McCallion, Ph.D., an associate professor in the McKusick-Nathans Institute of <u>Genetic Medicine</u>, and corresponding author on the study.

In a second experiment, the team used the cloned sequence and luciferase concoction, inserted it into a <u>breast cancer gene</u>, and this time added retinoic acid instead of estrogen. Retinoic acid is well known to slow cancer cell growth. The scientists showed that one of the two sequences previously shown to be estrogen responsive also responded to retinoic acid and increased RET activity.

The investigators also found that when they put estrogen and retinoic acid together in breast <u>cancer cells</u> in culture, the increased activity of RET was much greater compared to either estrogen or retinoic acid alone.



Because it appears that increased RET activity is linked to more aggressive and tamoxifen-resistant types of breast cancers, the discovery is potentially important for making decisions about tamoxifen use, McCallion says. Understanding the genetics of these proteins also has the potential to guide the search for new therapeutic targets in <u>breast cancer</u>. With the new information, he says, steps might be taken to "resensitize" tumors that become tamoxifin- insensitive by manipulating the regulators of RET and, therefore, its protein products.

Provided by Johns Hopkins Medical Institutions

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