Vitamin A derivative provides clues to better breast cancer drugs

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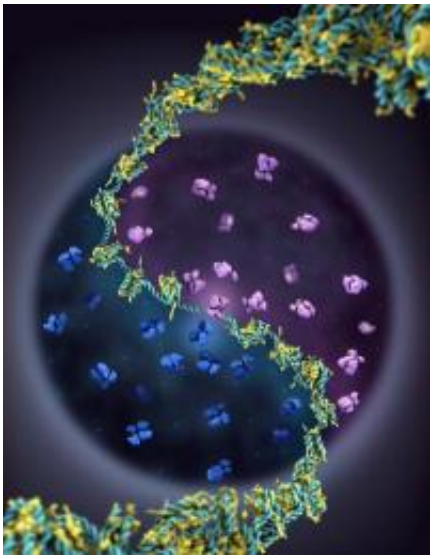

This is an artistic depiction of the proposed competitive binding of Retinoic Acid Receptors (blue) and Estrogen Receptor alpha (purple) to a genomic target site to achieve the antagonistic transcriptional effects indicated by the yin and yang symbol. Credit: Artwork by Janet Iwasa for the University of Chicago.

Retinoic acid, a derivative of vitamin A, could lead researchers to a new set of drug targets for treating breast cancer, researchers from the University of Chicago report in the June 25, 2009, issue of the journal *Cell*.

The most common forms of breast cancer are fueled by the female hormone estrogen. By comparing the effects of estrogen and retinoic

acid on the entire genome, the researchers found that they have a "yin-yang" effect. They alter the expression of many of the same genes, with estrogen tipping the scales towards cell proliferation and retinoic acid restoring the balance by inhibiting cellular growth.

This balanced control of gene expression regulates fundamental cellular processes, say the authors. When it is dysregulated, it can lead to cancer.

"Understanding all the components of this process could be used against breast cancer care in three ways," said study leader, Kevin White, PhD, professor of human genetics and director of the Institute for Genomics and System Biology at the University of Chicago. "It suggests new ways to think about preventing the disease in those at high risk. It offers molecular tools that could provide a more precise diagnosis and predict outcomes. It could also be used to enhance current therapies, making existing drugs, such as tamoxifen, that selectively block estrogen's effects even more powerful, or even to develop new anti-cancer drugs."

White's team studies the effects of nuclear receptors, a class of proteins found within cells that control the response to various hormones. When a hormone enters a cell and connects with its receptor, that receptor alters the pattern of expression of specific genes--often hundreds or more.

For this study, White and colleagues Sujun Hua and Ralf Kittler focused on the retinoic acid receptors. Retinoic acid, known for its anticancer effects and already in use to treat a rare form of leukemia, has also been associated with anti-proliferative changes in breast cancer cells.

So the team combined two laboratory techniques--a process known as "ChIP-chip analysis" that blends chromatin immunoprecipitation (ChIP), to see where the retinoic acid receptors bound to the genome, with micro-array gene-chip analysis, to measure expression levels of specific genes.

The combination enabled them to map out all the genetic effects of retinoic acid and its receptors in a cell line derived from patients with breast cancers that were fueled by estrogen.

They found that 39 percent of the genomic regions bound by estrogen receptor alpha overlapped with those bound by retinoic acid. They also found that the binding of estrogen and retinoic acids receptors to target sites were often mutually exclusive. This means the two hormones compete to activate or repress many of the same genes.

The two signaling pathways were mainly antagonistic. Estrogen increased expression of 139 genes that retinoic repressed. Retinoic acid activated 185 genes that retinoic acid repressed. For about 140 genes, estrogen and retinoic acid had the same effect.

"Collectively, note the authors, "these findings indicate an extensive crosstalk" between the effects of estrogen and retinoic acid. Despite their opposing effects, certain versions of the estrogen and retinoic acid receptors actually activate each other. This provides "an additional level of control," say the authors, "for achieving a balanced regulation of gene expression."

This competition between the two signals also provides a new tool to predict outcomes. The researchers compared the effects of retinoic acid on tissues from 295 breast cancer patients against the results from their initial study using a typical breast cancer cell line. They found that the more responsive a tumor was to retinoic acid, the better the odds of long-term relapse-free survival.

Some of the genes that respond to retinoic acid were expressed even in difficult-to-treat tumors, such as those that do not have estrogen receptors or the molecule targeted by the drug Herceptin, the so-called double- or triple-negative breast cancers. "Some of these genes may

provide new drug targets," White said.

Although retinoic acid is approved for treatment of leukemia, it can be quite toxic and patients can develop resistance to the drug. This study suggests a long series of downstream targets that are activated by the RA receptor.

"The goal would be to develop drugs that could activate these cancer-inhibiting targets," said White. "Retinoic acid itself is probably not the solution because of its side effects and metabolic byproducts," He cautioned, "but our results provide a molecular justification for finding ways to overcome its limitations in the clinic."

"This work reveals important insights on the interplay between vitamin A and estrogen action," said Myles Brown, MD, professor of medicine at Harvard Medical School and the Dana Farber Cancer Institute. "These insights will hopefully lead to new approaches for the prevention and treatment of the most common form of breast cancer."

Source: University of Chicago Medical Center