Vitamin D Holds Promise in Battling a Deadly Breast Cancer

In research published in the Jan. 21 issue of *The Journal of Cell Biology*, a team led by Susana Gonzalo, PhD, assistant professor of biochemistry and molecular biology at Saint Louis University, has discovered a molecular pathway that contributes to triple-negative breast cancer, an often deadly and treatment resistant form of cancer that tends to strike younger women. In addition, Gonzalo and her team identified vitamin D and some protease inhibitors as possible new therapies and discovered a set of three biomarkers that can help to identify patients who could benefit from the treatment.

In the recent breakthrough, which was funded in part by a $500,000 Department of Defense grant, Gonzalo’s lab identified one pathway that is activated in breast cancers with the poorest prognosis, such as those classified as triple-negative. These cancers often strike younger women and are harder to treat than any other type of breast cancer. Women who are born with BRCA1 gene mutations are at increased risk for developing breast and ovarian cancers within their lifetime, and the tumors that arise are frequently the triple-negative type. Although chemotherapy is the most effective treatment for triple-negative breast cancer, it has profound secondary effects. Understanding the biology of triple-negative breast cancers will help to develop less toxic therapeutic strategies.

Experiments performed in Gonzalo's laboratory, in collaboration with the laboratories of Xavier Matias-Guiu and Adriana Duso (IRBLleida, Spain), showed that activation of this novel pathway not only allows tumor cells to grow unchecked, but also explains the reduced sensitivity of these types of tumors to current therapeutic strategies. Importantly, vitamin D plays a role in turning off this pathway, providing a safe and cost-effective strategy to fight these types of tumors.

For molecular biologists like Gonzalo who look for answers below the cellular level to discover why some people develop cancer, the search often involves tracing a chain of events to try to understand cause and effect of the behavior between several genes and the proteins which they express. In order to understand these complex pathways, researchers often turn levels of proteins on or off by expressing one gene or suppressing another. Part of a researcher’s challenge is determining what the function of each component of a pathway is.

The cell employs a complex mechanism to protect genetic information and ensure that damaged DNA is not passed on to daughter cells. Cells have built in checkpoints and fail safes to ensure the accuracy of their DNA code and are able to slow or stop their own proliferation if the information is compromised. Loss of these checkpoints and the accumulation of damaged DNA often leads to cancer.

BRCA1 is a well-established tumor suppressor gene. Women who carry mutations in this gene have a high risk of developing breast and ovarian cancer. Tumors that arise often lack expression of three receptors: estrogen, progesterone and HER2 (thus, “triple-negative”), and do not respond to hormone therapy.

BRCA1 is important because it is involved in repairing DNA double-strand breaks, a kind of DNA damage that is especially dangerous for the integrity of our genome. BRCA1 also is involved in cell-cycle checkpoints after damage, which are control mechanisms during cell proliferation that make sure the DNA information has been accurately replicated and transferred to the daughter cells. Thus, BRCA1 is considered a safeguard of the genome.

Loss of BRCA1 is bad news for the information contained in a cell’s genetic blueprint. It results in genomic instability characterized by unrepaired DNA breaks and chromosomal aberrations that compromise cell viability. How BRCA1-mutated cells are able to form tumors has been a long-standing question. Investigators recently showed that loss of another DNA repair factor, 53BP1, allows proliferation and survival of BRCA1-deficient cells. In addition, decreased levels of 53BP1 were observed in triple-negative breast cancers, and correlated with resistance to drugs at the forefront of cancer treatment, such as PARP inhibitors.

Gonzalo’s team has found a pathway responsible for the loss of 53BP1 in breast cancers with poor prognosis, specifically BRCA1 mutated and triple-negative. It turns out that loss of BRCA1 increases the expression of a protease, known as cathepsin L (CTSL), which causes the degradation of 53BP1. Cells that have lost both BRCA1 and 53BP1 have the ability to repair DNA, maintain the integrity of the genome, and proliferate. Thus, the protease helps cells with faulty BRCA1 to survive.

If lowering the levels of 53BP1 allows BRCA1 deficient cells to thrive and do their worst, increasing the levels of the protein offers a promising strategy for treatment of breast tumors.

So, how to do this? In previous research, Gonzalo’s team showed that vitamin D inhibits CTSL-mediated degradation of 53BP1 in non-tumor cells, as efficiently as specific CTSL inhibitors. This time, they found that treatment of BRCA1-deficient tumor cells with vitamin D restores high levels of 53BP1, which results in increased genomic instability and reduced proliferation. Importantly, their evidence suggests that vitamin D treatment might restore the sensitivity to PARP inhibitors in patients who become resistant. Thus, a combination of vitamin D and PARP inhibitors could represent a novel therapeutic strategy for breast cancers with poor prognosis.

So, with this chain of events, Gonzalo and colleagues demonstrated a pathway by which triple-negative breast cancers proliferate: BRCA1-deficient cells activate CTSL which minimizes levels of 53BP1 to overcome genomic instability and growth arrest.

In a final exceptionally useful discovery, Gonzalo and collaborators found that high levels of nuclear CTSL and low levels of 53BP1 and nuclear vitamin D receptor (VDR) are a clear marker that identifies certain triple-negative breast cancer patients,

biomarkers that offer the potential to customize future breast cancer therapies. In particular, this triple-biomarker signature will allow the identification of patients in whom the pathway is on and who might benefit the most from vitamin D treatment.

Source: Saint Louis University [1]

Links:
[1] http://www.slu.edu/x71202.xml