Medical Xpress

Diet high in leucine may fuel breast cancer's drug resistance

April 17 2019

Senthil K. Muthuswamy, PhD, of the Cancer Center at Beth Israel Deaconess Medical Center. Credit: BIDMC

About one in eight women in the United States will develop breast cancer in their lifetime. The vast majority of these cancers rely on the

hormone estrogen to grow. Estrogen-receptor positive (ER+) breast cancer tumors are frequently treated with the drug tamoxifen, which blocks the hormone's effect on the tumor. However, many tumors eventually become resistant to tamoxifen, allowing cancer to recur or metastasize.

Now, a team of researchers at the Cancer Center at Beth Israel Deaconess Medical Center (BIDMC) has discovered an unexpected relationship between levels of the amino acid leucine and the development of tamoxifen resistance in ER+ breast cancer. Led by Senthil K. Muthuswamy, Ph.D., the researchers further identified a key protein that imports leucine into cells and modulates sensitivity to tamoxifen in ER+ cells in the lab setting. The findings, published today in the journal *Nature*, reveal a potential new strategy for overcoming resistance to endocrine drugs in ER+ breast cancer patients.

"Patients with ER+ breast cancer who develop endocrine-resistant and metastatic cancer have very poor life expectancy, usually less than five years survival, because they have limited treatment options available," said Muthuswamy, who is Director of the Cell Biology Program and Deputy Director of Translational Research in the Cancer Research Institute at BIDMC. "Our findings in the lab demonstrate that decreasing leucine levels suppresses proliferation of tumor cells, whereas increasing leucine enhances it. Furthermore, the findings open up the possibility that a low-leucine diet could be beneficial for patients with ER+ breast cancer."

Leucine is one of the 20 amino acids—the building blocks of all proteins in our body—and is among the 9 essential amino acids that must be obtained via food. Beef, chicken, pork and fish are all rich sources of leucine. Because cells can't produce leucine on their own, Muthuswamy and colleagues were able to test how manipulating levels of leucine in cells cultured in a dish would affect the growth of human derived ER+

breast cancer cells. The researchers reported that decreasing leucine levels suppressed ER+ breast cancer cells' division, while a tenfold increase of the amino acid enhanced it.

"Because animal proteins have higher amount of leucine compared to plant proteins, this study begins to identify a diet intervention strategy to help patients with ER+ breast cancers," said Muthuswamy. "Our research does not imply that animal proteins will enhance growth of breast cancer cells—only that lowering leucine levels can be beneficial for patients diagnosed with ER+ breast cancer."

Surprisingly, the scientists also discovered that cells that were induced to become resistant to tamoxifen gained the ability to grow despite low levels of leucine. Further investigation revealed that a protein on the surface of cells, called SLC7A5, required for ferrying leucine into the cell, is present at higher levels in cells resistant to tamoxifen. Increasing the levels of SLC7A5 allows cells to absorb more leucine and was sufficient to make breast cancer cells resistant to tamoxifen and inhibiting SL7A5 using chemical inhibitor was sufficient to shrink ER+ tumors in mice. Muthuswamy believes inhibiting SLC7A5 could be a potential therapeutic approach in the treatment of ER+ breast cancers.

"Before this research, there was no reason to expect that estrogen biology has anything to do with affecting intracellular levels of leucine in cells," said first author, Yasuhiro Saito, Ph.D., a research fellow in the Department of Medicine and Pathology at BIDMC. "We have uncovered a new area of estrogen receptor biology, which will lead to new strategies to help patients with endocrine resistant breast cancer."

Even so, the discovery is in keeping with previous reports that decreasing overall leucine intake can lead to better metabolic health, Muthuswamy added. Decreasing the amount of total protein in the diet is known to improve metabolic health and longevity in rodent studies.

Recent studies in human and mice demonstrated that that a low leucine diet can provide similar benefits. While protein restriction can make it difficult to meet daily nutrient requirements, a diet made-up of low-leucine plant proteins may be a better alternative for patients with ER+ breast cancer.

In follow up, Muthuswamy's team is investigating whether a leucine restricted diet can prevent growth or enhance response to therapy for ER+ breast cancer cells in mice.

"A properly controlled clinical study to assess clinical benefit of actively decreasing leucine intake in diet during treatment for ER+ breast cancer will be of significant value because a positive outcome can provide a simple intervention strategy that can help us better care for patients with endocrine-sensitive and resistant breast cancer," Muthuswamy said.

More information: LLGL2 rescues nutrient stress by promoting leucine uptake in ER+ breast cancer, *Nature* (2019). DOI: 10.1038/s41586-019-1126-2 , www.nature.com/articles/s41586-019-1126-2

Provided by Beth Israel Deaconess Medical Center