Triple Negative Breast Cancer (TNBC): Lipid Autophagy

Quantum biology modeling has address CPT1 and CPT2 that are referenced in the following article.

The document affixed to this article is provided for discussion purposes with qualified bioinformatics professionals to pursue mutation of autophagy as one of the near certain causes of TNBC. .

https://medicalxpress.com/news/2019-05-starve-triple-negative-breast-cancer.html

MAY 13, 2019

How to starve triple negative breast cancer

by American Society for Biochemistry and Molecular Biology

A team of Brazilian researchers has developed a strategy that slows the growth of triple negative breast cancer cells by cutting them off from two major food sources.

Triple-negative breast cancer, or TNBC, makes up approximately 15% to 20% of all breast cancers and is most common in African American women. These tumors lack estrogen and progesterone receptors and HER2 protein which are present in other breast cancers and permit certain targeted therapies. And because every TNBC tumor has a different genetic makeup, finding new markers that could guide treatment has been a difficult task.

"There is intense interest in finding new medications that can treat this kind of breast cancer," said Sandra Martha Gomes Dias, a cancer researcher at the Brazilian Biosciences National Laboratory in Campinas, Brazil. "TNBC is considered to be more aggressive and have a poorer prognosis than other types of breast cancer, mainly because there are fewer targeted medicines that treat TNBC."

In a new study in the *Journal of Biological Chemistry*, Dias and colleagues demonstrate that in addition to glutamine, a well-known cancer food source, TNBC cells can use fatty acids to grow and survive. When inhibitors that block both glutamine and fatty acid metabolism were used in concert, TNBC growth and migration slowed, Dias said.

To maintain their ability to grow at a breakneck pace, cancer cells consume nutrients at an increased rate. Glutamine, which is the most abundant amino acid in plasma is one of them. Some types of cancer become heavily reliant on this versatile molecule as it offers energy, carbon, nitrogen, and antioxidant properties, all of which support tumor growth and survival, Dias said.

The drug Telaglenastat, also known as CB-839, prevents the processing of glutamine and is currently in clinical trials to treat TNBC and other tumor types. CB-839 works by deactivating the enzyme glutaminase, preventing cancer cells from breaking down and reaping the benefits of glutamine. However, recent research has shown that some TNBC cells can resist the drug treatment.

To see if alterations in gene expression could explain how these cells survive, the authors of the study exposed TNBC cells to CB-839, defined those that were resistant and those that were sensitive to the drug, and sequenced their RNA, Dias said.

In the resistant cells, molecular pathways related to the processing of lipids were highly altered, Dias said. In particular, levels of the enzymes CPT1 and CPT2, which are critical for fatty acid metabolism, were increased.

"CPT1 and 2 act as gateways for the entrance of fatty acids into mitochondria, where they will be used as fuel for energy production," Dias said. "Our hypothesis was that closing this gateway by inhibiting CPT1 in combination with glutaminase inhibition would decrease growth and migration of CB-839-resistant TNBC cells."

The double inhibition proved significant as it slowed proliferation and migration in resistant TNBC cells more than individual inhibition of either CPT1 or glutaminase. These results provide new genetic markers that could better guide drug choice in patients with TNBC, Dias said.

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Epigenetic modeling of CPT1A has identified it as one of three members of carnitine palmitoyltransferase (CPT1A - C: aka CPT1 - 3) that comprise the enzyme for autophagy conversions of lipids.

The amino acid constituents of this enzyme (DNAJB5) are histidine - arginine - lysine.

https://medicalxpress.com/news/2018-08-therapeutic-strategy-blood-vessel-disorders.html

Novel therapeutic strategy for blood vessel related disorders, such as cancer and retinopathy

August 31, 2018, VIB (the Flanders Institute for Biotechnology)

A multi-disciplinary team of scientists, led by prof. Peter Carmeliet (VIB-KU Leuven Center for Cancer Biology) has made several breakthrough discoveries concerning the metabolism of the individual building blocks of blood vessels—the so-called endothelial cells. They identified three key proteins that determine how blood vessels grow and behave, and that may become new therapeutic targets in blood vessel related disorders,

such as life-threatening cancers and blinding eye diseases. The findings have been published in *Nature* and *Cell Metabolism*.

All organs in the human body rely on blood vessels for a continuous supply of nutrients and oxygen. This makes the vasculature—the entire network of blood vessels—one of the largest and most important organs in the body. In healthy individuals, the vasculature is stable and diligently performs its tasks. However, in several serious diseases like cancer or diabetes, the blood vessels derail and start growing excessively or lose their normal function altogether. Given the increasing prevalence of cancer and diabetes, novel therapies for blood vessel-related disorders are urgently needed. Additionally, such novel therapies should be based on entirely different molecular mechanisms than currently available strategies (mostly anti-VEGF), which show limited success due to resistance mechanisms and overall low efficacy.

To pinpoint what determines normal and abnormal blood vessel behavior, research has focused for decades on endothelial cells (ECs), the individual building blocks of blood vessels. ECs have long been considered as passive building blocks, but Carmeliet and colleagues were the first to reveal a pivotal role for EC metabolism in blood vessel formation and function. This challenging and pioneering research has now identified three new possible therapeutic targets in blood vessel related disorders.

In a new study, researchers Joanna Kalucka, Laura Bierhansl, Nadine Vasconcelos Conchinha and Rindert Missiaen found that ECs need to burn fatty acids in order to stay healthy and withstand stress insults. They discovered that a protein called 'CPT1A'

plays an essential role in this phenomenon and published these insights in the latest edition of *Cell Metabolism*.

Another publication in the same issue of *Cell Metabolism*, describes the work of Drs. Ulrike Brüning and Francisco Morales-Rodriguez, who showed that inhibition of an enzyme involved in the synthesis of fatty acids, called FASN, prevents excessive blood vessel growth in eye disease.

Finally, Drs. Guy Eelen and Charlotte Dubois unraveled a totally unexpected role for the enzyme glutamine synthetase in sustaining motility of the ECs through a mechanism requiring a fatty acid called palmitate. Their research results are published in *Nature*. This makes CPT1A, FASN and glutamine synthetase possible new therapeutic targets to fight blood vessel related disorders. This highly novel therapeutic approach starting from the metabolism of the endothelial cells is truly promising, and might outperform currently available anti-VEGF therapies in terms of efficacy in the near future.

Explore further: **New target for the fight against cancer as a result of excessive blood vessel formation**

More information: Guy Eelen et al. Role of glutamine synthetase in angiogenesis beyond glutamine synthesis, *Nature* (2018). **DOI: 10.1038/s41586-018-0466-7**
Joanna Kalucka et al. Quiescent Endothelial Cells Upregulate Fatty Acid β-Oxidation for Vasculoprotection via Redox Homeostasis, *Cell Metabolism* (2018). **DOI: 10.1016/j.cmet.2018.07.016**

Journal reference: Nature Cell Metabolism