Researchers identify a process responsible for therapeutic resistance in breast cancer

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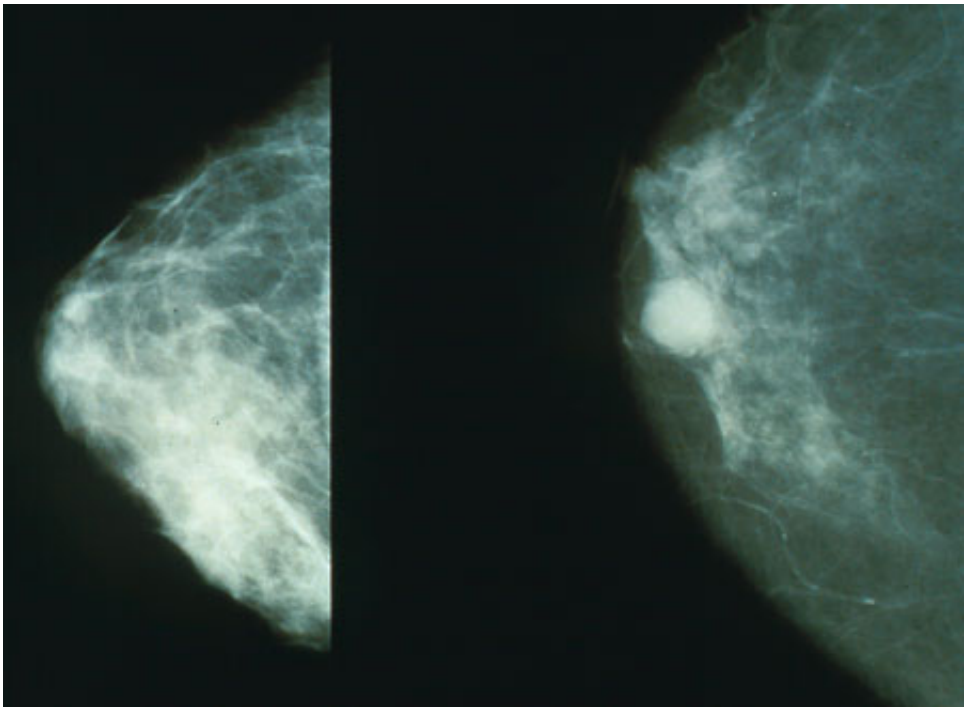

Mammograms showing a normal breast (left) and a breast with cancer (right). Credit: Public Domain

Researchers at the Lady Davis Institute have identified a key protein that is required for resistance to chemotherapy in the most aggressive form of breast cancer. This holds the promise of opening the door to new therapies for overcoming drug resistance.

Using tumor biopsies from patients with chemotherapeutic resistant

triple negative breast cancer (TNBC), researchers at the Lady Davis Institute of the Jewish General Hospital (JGH) have identified changes to the form of the cancer cells that appear to be associated with their capacity to resist usual drug treatment. This discovery is featured on the cover of the December issue of *Molecular Cancer Research*, where it is highlighted for its importance.

"When patients with TNBC respond to treatment, their prognosis is very good," explains Dr. Mark Basik, a surgical oncologist and Medical Director of the Inter-disciplinary Breast Cancer Team at the Segal Cancer Centre at the JGH, who led the research. "However, resistance to treatment is quite common. Chemotherapy resistant TNBC constitutes the most aggressive form of breast cancer, and the prognosis for those patients is not that good. Therefore, it is critical that we determine the processes that promote resistance and target it directly to overcome its influence on the tumor."

The researchers observed that the onset of resistance to the two most common drugs deployed against TNBC is associated with changes in the shape of the cancer cells and the manner in which they process fat. The cells are able to store fat droplets that they can exploit as a source of energy to fight off the effects of chemotherapy. These cells were also seen to develop a dependence on the protein perilipin4, which is highly expressed in resistant tumors. The protein is used by the cancer cell to stabilize the fat droplet, which would otherwise leak free fat into the cell, which is toxic to it and would kill the cell. Dr. Isabelle Sirois, a postdoctoral fellow in Dr. Basik's lab and the first author on the paper, and her colleagues determined that targeting this protein caused nearly all of the resistant cells to stop growing, and most to die.

"This is very promising," said Dr. Basik, who is also the Herbert Black Professor of Surgical Oncology at McGill University, "because if we can eliminate the resistant cells, we will be able to successfully treat far more

TNBC patients."

A key element in treating cancer is finding the active protein that makes possible the disease's unchecked growth. With that, the vulnerability of the cell is revealed, opening the door to new therapies and better patient outcomes.

More information: Isabelle Sirois et al, A Unique Morphological Phenotype in Chemoresistant Triple-Negative Breast Cancer Reveals Metabolic Reprogramming and PLIN4 Expression as a Molecular Vulnerability, *Molecular Cancer Research* (2019). DOI: 10.1158/1541-7786.MCR-19-0264

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