Molecular signature for outcomes of triple negative breast cancer

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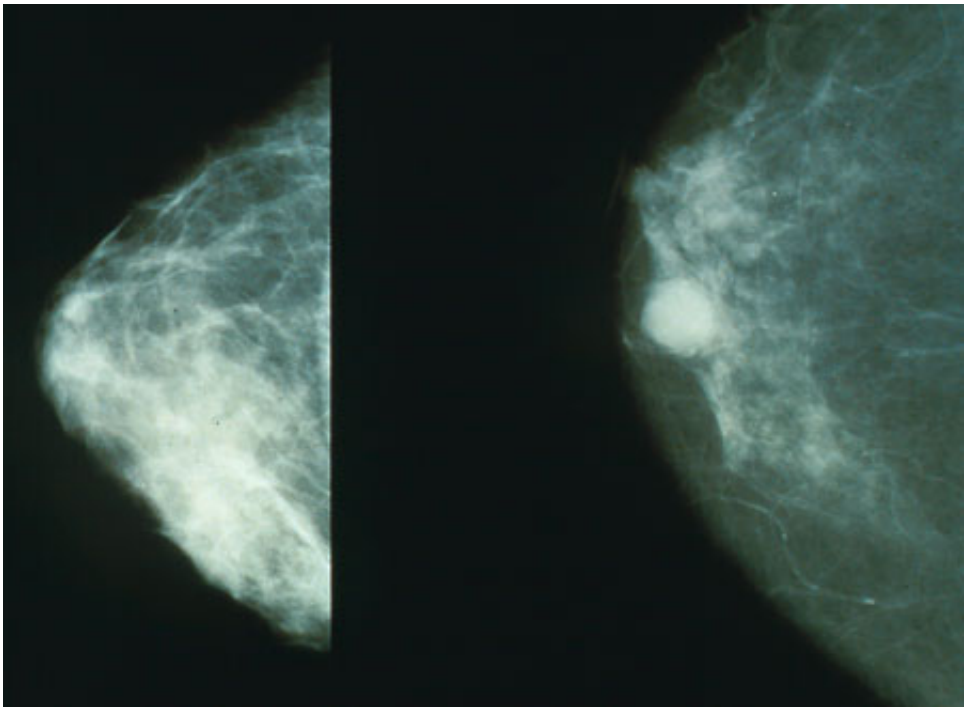

Mammograms showing a normal breast (left) and a breast with cancer (right). Credit: Public Domain

Compared to other types of breast cancer, triple negative breast cancers are often more aggressive and have fewer treatment options. In a new study published in the journal *Proceedings of the National Academy of Sciences* (*PNAS*), researchers at Huntsman Cancer Institute and the University of Utah have identified a molecular mechanism that triple negative breast cancer cells use to survive and grow.

According to senior author Don Ayer, Ph.D., an investigator at Huntsman Cancer Institute and a professor in the Department of Oncological Sciences at the University of Utah, many cancer cells, including triple negative cells, are addicted to the sugar glucose and the amino acid glutamine. "Normal cells do use glucose and glutamine," he said, "but cancer cells use them at a very elevated rate and they actually become addicted to these nutrients and they are required for their growth."

The researchers found that two proteins, one called Myc, the other called thirodoxin-interacting protein, or TXNIP, normally work in opposition to each other in cells in culture. Myc helps cancer cells take up and use glucose so they can grow and survive, while TXNIP blocks glucose uptake, limiting the growth-inducing functions of Myc. By contrast, in triple negative breast cancer cells, the researchers discovered that Myc reduces the expression of TXNIP. This increases glucose uptake, which supports the growth-inducing functions of Myc.

The data suggests that high levels of Myc and low levels of TXNIP promote triple negative breast cancer cell growth and survival. Corroborating this finding, high levels of Myc combined with low levels of TXNIP correlate with poor patient outcome when examined in large clinical datasets. Further, the relationship between Myc and TXNIP is not observed in other types of breast cancer, suggesting that it is a feature of only aggressive triple negative breast cancers and not other less aggressive breast cancer types.

It may be possible to exploit this vulnerability in triple negative breast cancer, said Ayer. "From a therapeutic standpoint you could imagine that the cells that are addicted to these nutrients could be starved and killed more easily than normal cells."

While this current study primarily focused on the role of Myc and

TXNIP in triple negative cancer nutrient uptake and utilization, Ayer said the proteins also appear to play a role in metastasis, the process by which cancer cells spread to other parts of the body.

"What we discovered was that if tumors are taken from relatively young women, under age 53 with stage 1 or stage 2 breast cancer, and they have a high Myc, low TXNIP gene signature, these patients are more likely to have secondary metastasis later in life. We think this signature may be an early marker for metastatic disease."

Ayer said that if this result is validated in clinical trials, then looking for the high Myc, low TXNIP signature will identify women at high risk for recurrence who could then be treated more aggressively and watched more closely.

More information: Metabolic reprogramming in triple-negative breast cancer through Myc suppression of TXNIP, *PNAS*, www.pnas.org/cgi/doi/10.1073/pnas.1501555112

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