Newly discovered vulnerability in breast tumor cells points to new cancer treatment path

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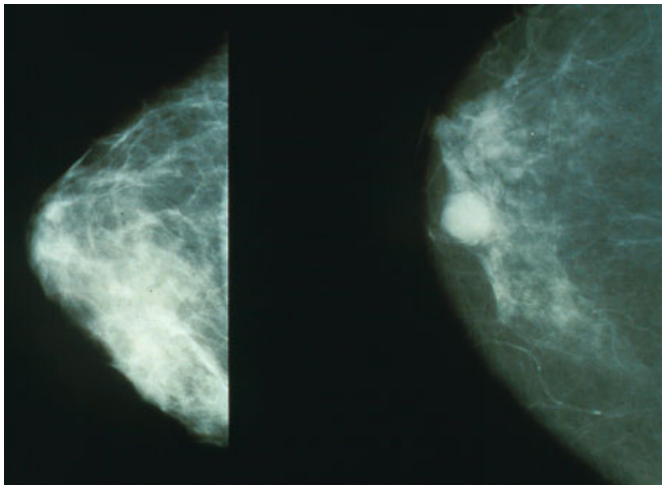

Mammograms showing a normal breast (left) and a breast with cancer (right). Credit: Public Domain

Cancer cells often devise ways to survive even in the presence of toxic chemotherapy. Now, a research team led by investigators at Beth Israel Deaconess Medical Center (BIDMC) has found a way to attack a process that tumor cells use to escape the effects of standard cancer drugs. The discovery is published online today in the journal *Nature Cell Biology*.

Cancer drugs are no longer limited to toxic chemicals that can cause significant side effects. Many are specially designed targeted therapies that seek out and destroy cancer cells while sparing normal cells in the body. Currently, patients often receive a combination of these two approaches to ensure the best chance of treatment success.

Many targeted therapies in development act on the PI3K/AKT pathway, one of the most frequently aberrantly activated signaling pathways in human cancer cells. The pathway is involved in both tumor development and progression. In their new research, BIDMC's Alex Toker, PhD, Harvard Medical School (HMS) student Evan Lien and colleagues found that in breast cancer cells, abnormal signaling through the PI3K/AKT pathway drives the production of glutathione, a major cellular antioxidant.

This adaptation can allow cancer cells to survive even in the face of toxic chemotherapy. Therefore, the investigators decided to test the effectiveness of standard chemotherapy in combination with a drug that blocks glutathione production. This combination caused significant regression of breast cancer with PI3K/AKT pathway mutations, both in laboratory dishes and in mice.

"Our work has uncovered a vulnerability in human breast cancer that is used by tumor cells to escape the lethal effects of conventional chemotherapy and that leads to resistance to such therapies," explained Toker, Chief of the Division of Signal Transduction in the Departments of Medicine and Pathology and the Cancer Center at BIDMC. "By targeting this vulnerability with specific drug combinations, the hope is that efficient therapeutic responses will be observed and with reduced toxicity."

Pier Paolo Pandolfi, MD, PhD, Director of the Cancer Center at BIDMC and George C. Reisman Professor of Medicine at HMS, added, "These findings are important as they further highlight how targeting the specific metabolic requirements of cancer cells can prove effective in their selective eradication."

Toker, who is also Professor of Pathology at Harvard Medical School, noted that several

questions remain, including whether a specific inhibitor of glutathione production can be developed that is safe to use in human patients. Further research is also needed to determine if enhanced glutathione production is also observed in tumors that harbor mutations other than those in the PI3K/AKT pathway. Moreover, because glutathione is only one of several antioxidants within cells, the researchers wonder whether there are other antioxidant pathways in tumor cells that are hijacked by the PI3K/AKT pathway to drive cancer.

More information: Glutathione biosynthesis is a metabolic vulnerability in PI(3)K/Akt-driven breast cancer, *Nature Cell Biology*, DOI: 10.1038/ncb3341

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