Culprit found in breast cancer resistance to tamoxifen

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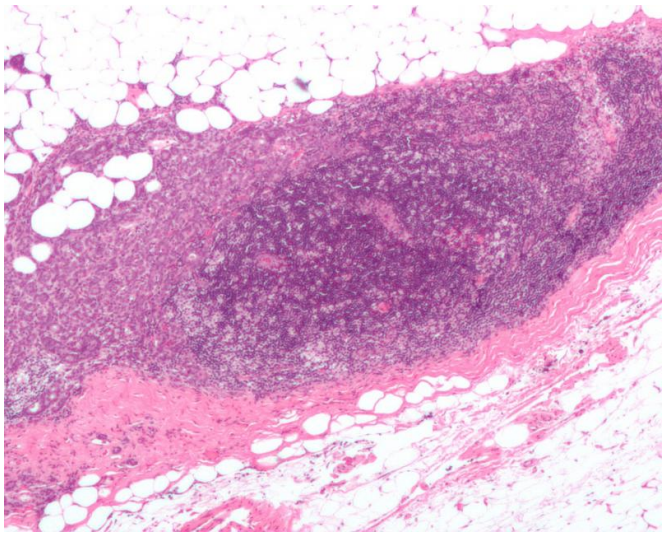

Micrograph showing a lymph node invaded by ductal breast carcinoma, with extension of the tumour beyond the lymph node. Credit: Nephron/Wikipedia

Researchers have discovered that a protein found naturally in cells that provides some protection from viruses is responsible for creating mutations that drive resistance to tamoxifen treatment in breast cancer. Because the protein, known as APOBEC3B, is found in elevated quantities in other kinds of cancer cells, the finding explains differential responses to treatment and opens the door to boosting the effectiveness of tamoxifen and related breast cancer therapies that inhibit the ability of estrogen to stimulate tumor growth.

As they report today in the journal *Science Advances*, University of Minnesota Professor and Howard Hughes Medical Institute Investigator Reuben Harris, Ph.D., Professor of Medicine and Masonic Cancer Center Director Douglas Yee, M.D., and colleagues analyzed primary breast cancers from human patients along with studies of human breast cancer cell lines growing in mice to elucidate the relationship between presence of APOBEC3B and development of tamoxifen resistance. They found that 1) the more APOBEC3B a breast cancer contained, the less benefit patients received from tamoxifen for treatment of their recurrent disease; 2) depletion of APOBEC3B in a cancer cell line results in delayed development of tamoxifen resistance; and 3) increased production of active APOBEC3B by a cancer cell line accelerates development of resistance.

Previous studies had linked higher concentrations of the protein APOBEC3B with increased levels of mutation and poorer outcomes for patients with breast cancer, but a causal connection had not been established between this enzyme and the development of therapy resistance. By using both clinical data and mouse models, Harris, Yee and colleagues were able to show that APOBEC3B is responsible for the reduced response to tamoxifen therapy in breast cancer.

The findings open a new door for improving the effectiveness of tamoxifen in treating breast cancer by discovering ways to prevent APOBEC3B from mutating the cancer cell's DNA. Because APOBEC3B has been implicated as a major cause of mutations in bladder, lung and other cancer types, the results could potentially be applied to boosting the success of therapies against other tumors as well.

"It's not just breast cancer," Yee said. "In treatment of all metastatic cancer, patients will eventually develop resistance and progress. What are the mechanisms of resistance? [APOBEC3B] is proving to be a major driver of resistance and something we're continuing to actively investigate."

The big challenge now is to try to identify exactly how APOBEC3B alters a cell's DNA to induce tamoxifen resistance. "We know how it mutates DNA, but we don't know exactly which genes are

mutated to confer tamoxifen resistance," Harris said. "If it turns out APOBEC3B mutates a known pathway, such a result may point to additional therapies."

More information: "The DNA cytosine deaminase APOBEC3B promotes tamoxifen resistance in ER-positive breast cancer", *Science Advances*, DOI: 10.1126/sciadv.1601737 , advances.sciencemag.org/content/2/10/e1601737

Provided by University of Minnesota

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