What's in a name? 'Death-associated protein' promotes cancer growth in most aggressive breast cancers

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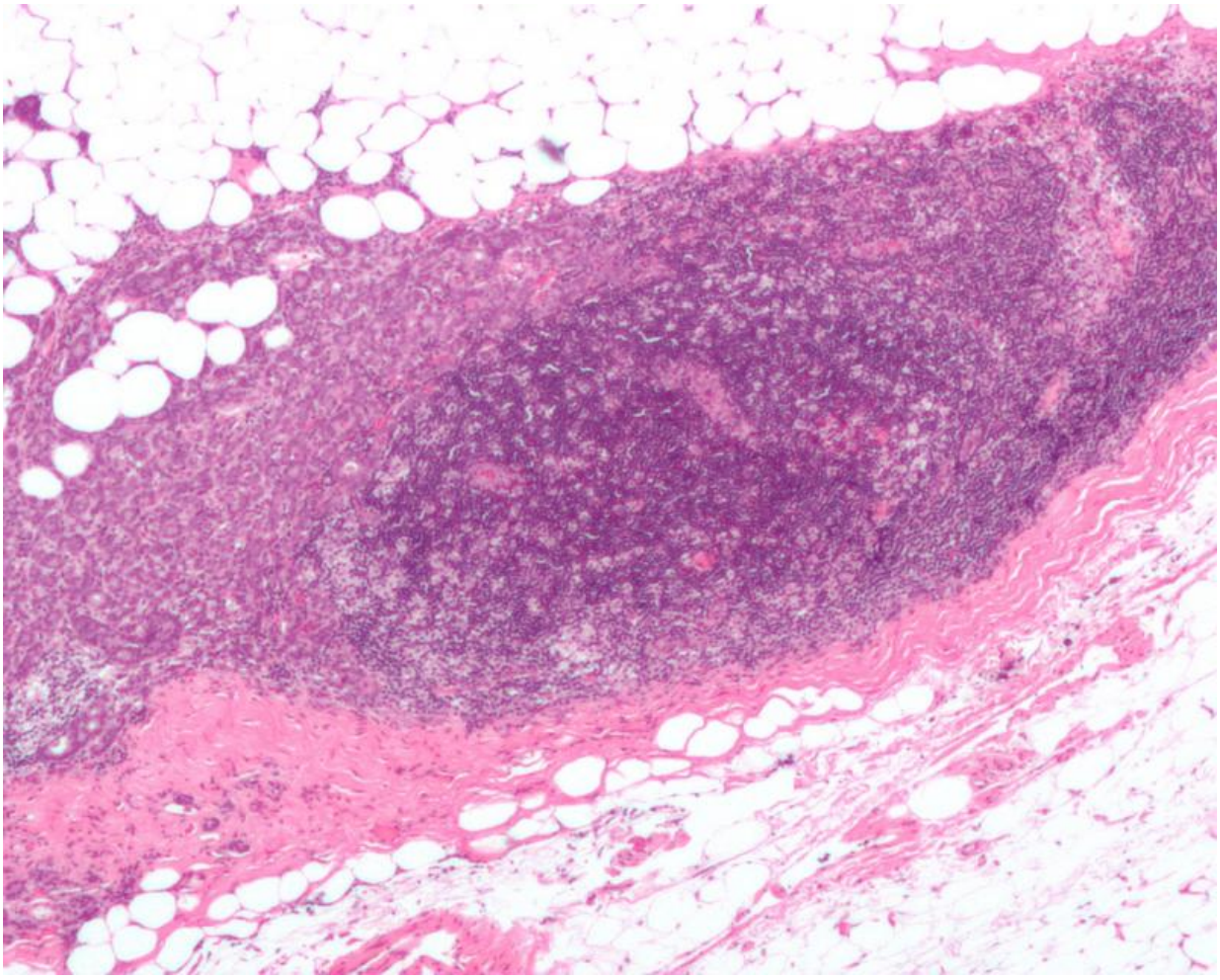

Micrograph showing a lymph node invaded by ductal breast carcinoma, with extension of the tumour beyond the lymph node. Credit: Nephron/Wikipedia

Although traditionally understood to induce death in cancer cells, researchers at The University of Texas MD Anderson Cancer Center have discovered that the DAPK1 protein is actually essential for growth in breast and other cancers with mutations in the TP53 gene. This discovery indicates DAPK1 may be a promising new therapeutic target for many of the most aggressive cancers.

As its name implies, DAPK1 (death-associated protein kinase 1) has well studied roles in activating pathways that stimulate apoptosis, or programmed cell death, in cancer cells. However, the current findings, published in *The Journal of Clinical Investigation*, report that DAPK1 functions much differently in cancers with mutations in the TP53 gene (tumor protein p53).

"This is a little studied kinase that has not been previously focused on for the treatment of cancer," says Powel Brown, M.D., Ph.D., professor and chair, Clinical Cancer Prevention, and senior author. "We discovered a yin and yang phenomenon in terms of DAPK1 function. In normal cells this protein functions as a death inducer, but in TP53 mutant cells DAPK1 acts a critical driver of cancer cell growth."

DAPK1 was identified while searching for new therapeutic targets in aggressive breast cancers, Brown explains. Breast cancers are often classified according to the presence or absence of three receptor proteins: estrogen receptor (ER), progesterone receptor (PR) and HER2.

Those tumors lacking ER (ER-negative), representing 30-40% of all breast cancers, are typically more aggressive and have a worse prognosis than ER-positive tumors. These also include triple receptor-negative breast cancers (TNBCs), which are particularly nasty. Unfortunately, there are few effective treatments for these tumors.

The researchers found that DAPK1 was significantly elevated in ER-

negative compared to ER-positive breast cancers. Higher levels of a death-associated protein in this aggressive subtype presented a conundrum that prompted further investigation.

Although DAPK1 levels did not appear directly affected by ER, higher expression of DAPK1 did correlate significantly with mutations in TP53, which are abundant in ER-negative breast cancers. This was true especially in TNBCs, 80% or more of which harbor TP53 mutations.

DAPK1 itself appears to be an indicator of poor prognosis. Patients with high levels of DAPK1 had significantly lower survival times compared to those with low levels of DAPK1, particularly in patients with TP53 mutations.

By depleting or inhibiting DAPK1 in breast cancer cell lines and mouse models, the researchers learned that cells with TP53 mutations require DAPK1 for their continued growth. Blocking DAPK1 significantly suppressed growth in TP53-mutant cells, but had no effect in those with normal TP53.

The researchers also showed that these results were mirrored in cells from other cancer types, including lung, ovarian and pancreatic, which contain mutations in TP53. As TP53 is the most commonly mutated gene across all cancer types (>50%) and is associated with a worse prognosis, DAPK1 may be a promising therapeutic target for a broad group of aggressive tumors.

"This is probably the most exciting finding," says Brown. "While a new treatment for triple-negative breast cancers would be a major advance, DAPK1 inhibitors have the potential to be used to treat many different kinds of cancers with TP53 mutations, which include the most lethal cancers without effective treatments."

This is the most active area of research in Brown's laboratory and he is eager to work on developing DAPK1 inhibitors as potential therapies. Additionally, his lab is currently testing DAPK1 inhibition in combination with various types of chemotherapy to determine if additive benefits can be achieved with other targeted therapies.

In fact, this is not the first protein Brown has identified with opposing roles dependent on TP53 mutations, with previous reports revealing similar behavior by the p38 kinase and the immune signaling protein TLR4. This seems to be a general phenomenon that can be taken advantage of for drug therapy, explains Brown, with little toxicity due to the dependence on TP53 mutations.

In the current study, the research team clarified the method by which DAPK1 promotes cancer growth. Their findings revealed that DAPK1 turns on a series of growth-stimulating proteins, collectively known as the mTOR pathway. Although they hypothesize that that loss of TP53 activity shifts DAPK1 activity towards the growth-promoting pathway, this regulation of DAPK1 by TP53 is unclear and is the focus of ongoing investigations.

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