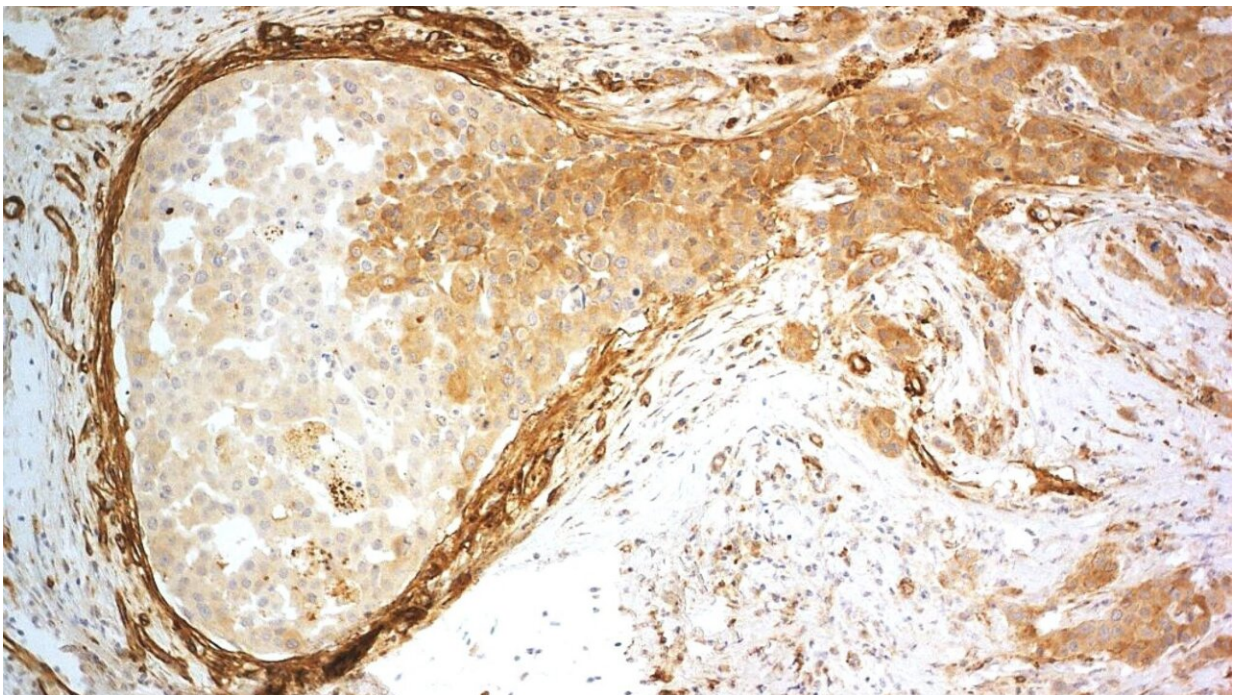


Significant discovery in breast cancer research: Inhibiting collagen XVIII function weakens cancer cells

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A microscopic image of a breast cancer sample, in which collagen XVIII is stained in brown within the cancer cells spreading into the surrounding tissue and in the blood vessels bordering the tumor nest. Credit: Devarajan et al. *J Clin Invest* 133(18):e159181, 2023

Researchers at the University of Oulu have made a discovery in breast

cancer research. They demonstrated that the extracellular matrix protein collagen XVIII significantly promotes breast cancer progression and metastasis. Additionally, they showed that inhibiting the function of this collagen improves the efficiency of certain commonly used targeted therapies for breast cancer. These findings are significant as they may lead to the development of more effective and entirely new cancer drugs.

[The research](#) was published in the *Journal of Clinical Investigation*.

The [extracellular matrix](#) consists of proteins and carbohydrates produced by cells and regulates cell behavior and function. In cancer tissues, the extracellular matrix is known to control [cancer growth](#) and metastasis, as well as treatment response and drug resistance.

Collagens are the most common proteins in the extracellular matrix, with 28 different types known in humans. Collagen XVIII is present in the [basement membrane](#), a specialized form of the extracellular matrix. The basement membrane is thin, sheet-like matrix where cells adhere to and which regulates cell division, movement, and differentiation.

Inhibiting collagen function enhances the efficacy of cancer drugs

By studying collagens in mouse and cell models of breast cancer, researchers discovered that [collagen](#) XVIII regulates the signaling of certain growth factor receptors in [cancer cells](#). Collagens were not previously known to function in this way.

"We identified a completely new mechanism of action for collagen XVIII. We demonstrated that it regulates epidermal growth factor receptor signaling in cancer cells. Inhibiting collagen XVIII significantly enhanced the effectiveness of drugs that target specifically these

receptors, such as Herceptin, an established drug for human breast cancer," says Dr. Raman Devarajan, the key investigator of the study.

Furthermore, the researchers demonstrated that collagen XVIII supports cancer stem cell characteristics. Cancer stem cells sustain cancer cell growth and metastasis and are more resistant to drugs and radiation than other cancer cells. "We found that by inhibiting collagen XVIII we can even reverse [drug resistance](#)," Devarajan added.

Collagen as a new marker for breast cancer

Next, researchers investigated the expression of collagen XVIII in over 700 human breast cancer samples in collaboration with researchers from Umeå and Uppsala Universities and by utilizing open patient databases.

They found that increased production of collagen XVIII in breast cancer cells was associated with a poor prognosis for the disease. Elevated levels of collagen XVIII were observed in the tissue and blood samples of patients with aggressive breast cancer. Thus, collagen XVIII can be considered a new marker for [breast cancer](#).

This research is part of a broader research project in which the researchers of the University of Oulu are investigating the significance and functions of collagens in healthy individuals and in various diseases, including breast, lung, skin, and blood cancers.

"Our longstanding work to understand the functions of these collagens in cancers is now yielding significant results," says Associate Professor Ritva Heljasvaara, who leads the research group at the Faculty of Biochemistry and Molecular Medicine, in collaboration with Professor Taina Pihlajaniemi.

"Several collagens are known to promote cancer, but their detailed

mechanisms of action are poorly understood. Collagens have not been reported to increase [epidermal growth factor receptor](#) signaling, which is activated in several different cancers," Heljasvaara explained.

The research team aims to further investigate the interaction between collagen XVIII and growth factor receptors, which is crucial for developing new drugs that disrupt the signaling between the extracellular matrix and cancer cells.

The published research findings are significant and increase the understanding of the extracellular matrix's role in cancer tumors and the complex interactions between the extracellular matrix and growth factor receptors. They suggest that targeting the extracellular matrix could have important clinical relevance, especially when conventional drugs alone are not effective.

More information: Raman Devarajan et al, Targeting collagen XVIII improves the efficiency of ErbB inhibitors in breast cancer models, *Journal of Clinical Investigation* (2023). [DOI: 10.1172/JCI159181](https://doi.org/10.1172/JCI159181)

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