Collagen a key player in breast cancer metastasis

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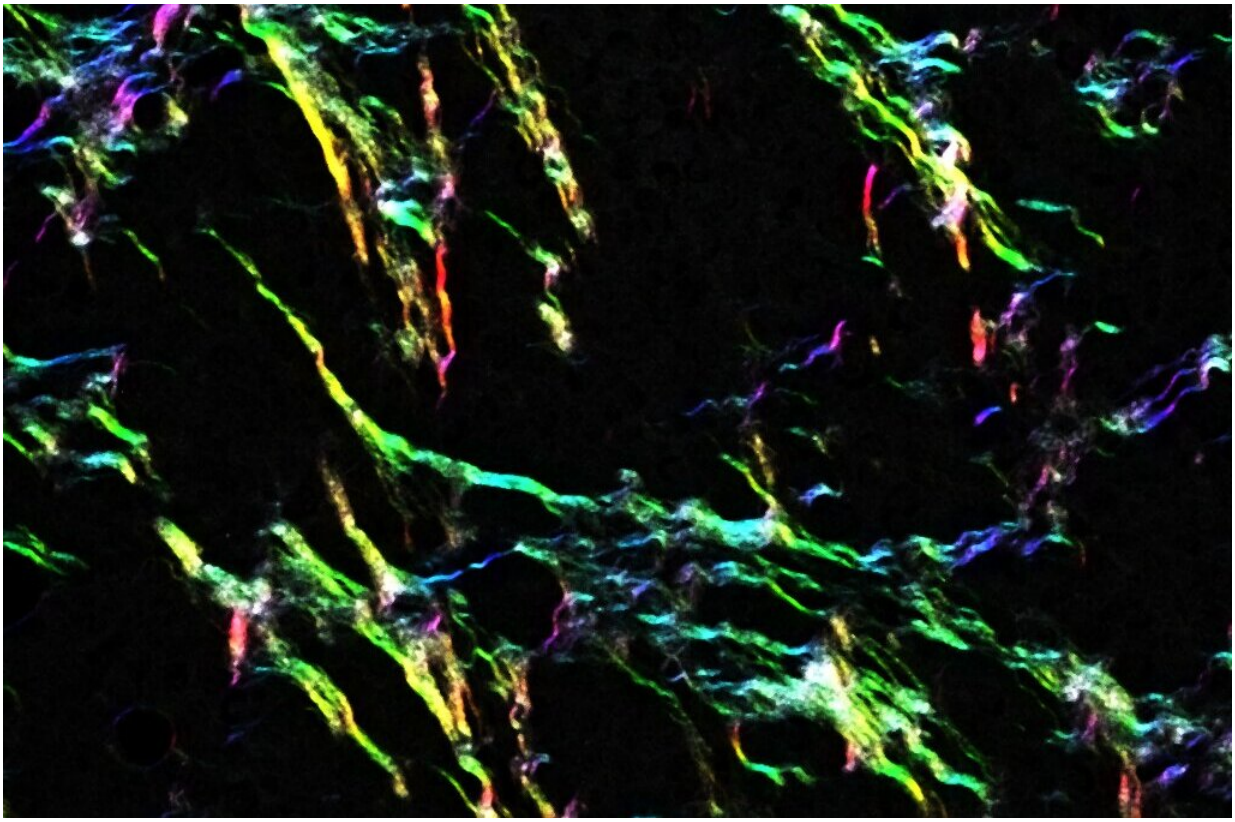


Collagen fibers running through a cancer tumor, created using a multiphoton microscope. The coloring is a visual representation of how collagen fibers are organized. Changing levels of collagen XII alters this organization; increasing collagen XII produces collagen fibers that are thicker and more aligned. Credit: Matrix and Metastasis Lab, Garvan Institute of Medical Research

Collagen type XII plays a key role in regulating the organization of the tumor matrix, reveals a new study from the Garvan Institute of Medical Research. A team of scientists led by Associate Professor Thomas Cox, Head of the Matrix and Metastasis lab, also discovered that high levels of collagen XII can trigger breast cancer cells to spread from the tumor to other parts of the body, a process known as metastasis.

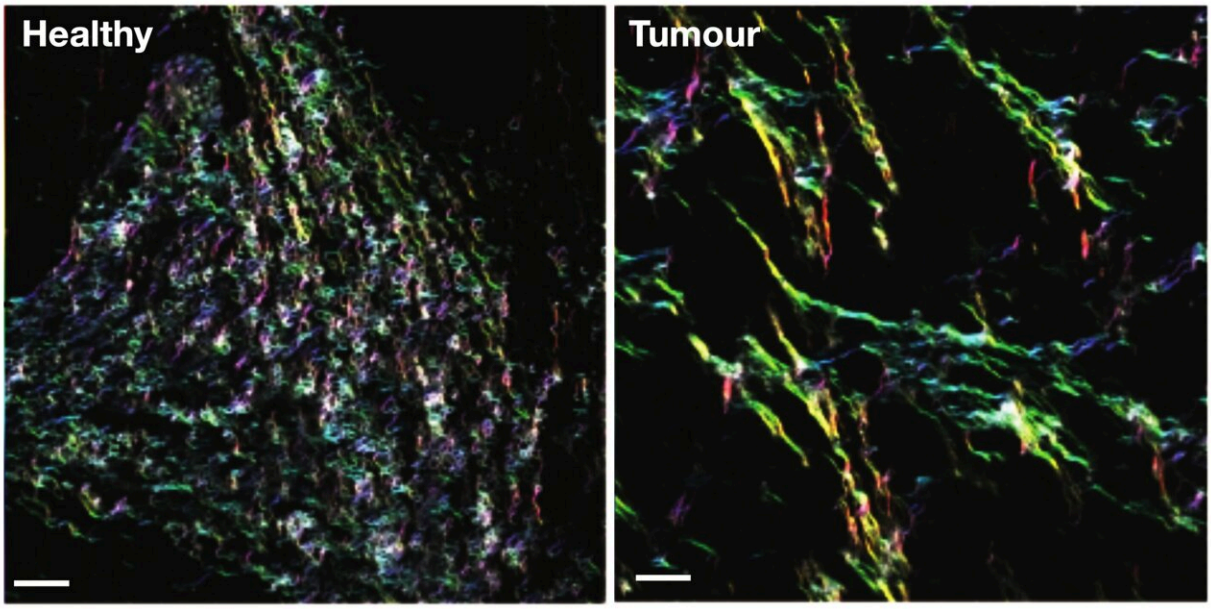
The tumor microenvironment is the ecosystem that surrounds a tumor, one component of which is the extracellular matrix. Cancer cells constantly interact with the tumor microenvironment, which affects how a tumor grows. Collagen is an important part of this tumor microenvironment, but just how it influences tumors has not been understood.

"There's still a lot we don't know about the role of the extracellular matrix in cancer metastasis. Our study shows that collagen XII plays an important role in breast cancer progression and metastasis," says senior author Associate Professor Thomas Cox.

"Imagine cancer cells as seeds, and the tumor microenvironment as the soil. By studying the soil—the extracellular matrix—we can begin to understand what makes some tumors more aggressive than others, and by extension, begin to develop new ways to treat cancer," he says.

The research also suggests that measuring the level of collagen XII in a patient's tumor biopsy could potentially be used as an additional screening tool to identify aggressive breast cancers with higher rates of metastasis, such as in the triple-negative type of breast cancer. Furthermore, collagen XII might be a possible target for future treatments.

The study is published in the journal *Nature Communications*.



The coloring is a visual representation of how collagen fibers are organized in healthy and tumor matrixChanging levels of collagen XII alters this organization; increasing collagen XII produces collagen fibers that are thicker and more aligned. Credit: Matrix and Metastasis Lab, Garvan Institute of Medical Research

Collagen XII alters tumor environment to help cancer cells invade

The extracellular matrix or 'matrix' is a 3D meshwork of around 300-400 core molecules, including several collagen proteins. This matrix provides structural and functional support to cells and tissues in all parts of the body.

In this study, the researchers cataloged how the tumor matrix changes over time and have generated a comprehensive database of these changes, which has been made freely available to researchers.

The team zeroed in on collagen XII, one of 28 types of collagen in the body. Collagen XII plays an important role in organizing other collagens and can have profound effects on the 3D structure of the extracellular matrix.

The researchers studied tumors in mouse models from the earliest pre-clinical stages of cancer, right through to late-stage tumors. They found that as the tumors developed, many matrix molecules changed, and importantly the level of collagen XII was also increased.

"Collagen XII seems to be altering the properties of the tumor and makes it more aggressive," says first author Michael Papanicolaou, from Garvan. "It changes how collagens are organized to support cancer cells escaping from the tumor and moving to other sites like the lungs."

The team then used genetic engineering to manipulate production of collagen XII, and looked at the effects of metastasis to other organs. They found that as levels of collagen XII increased, so did metastasis. These findings were then confirmed in human tumor biopsies, which showed that high levels of collagen XII are associated with higher metastasis and poorer overall survival rates.

Further research will focus on studying more human samples, and investigating possible therapeutic pathways.

More information: Michael Papanicolaou et al, Temporal profiling of the breast tumour microenvironment reveals collagen XII as a driver of metastasis, *Nature Communications* (2022). DOI: 10.1038/s41467-022-32255-7

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