Thousands of tiny anchors keep our cells in place—and now we know how

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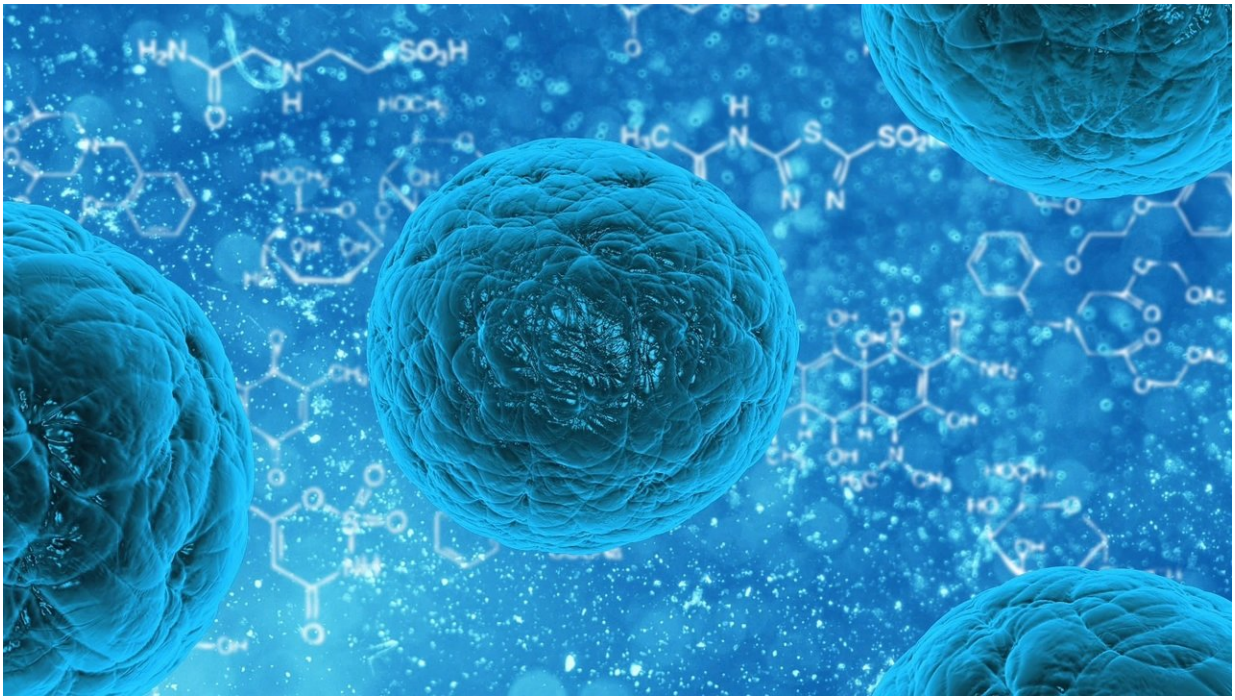

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Most of the cells in our bodies—be they bone, muscle or pancreas cells—are locked into the right place with the help of tiny anchors (called 'focal adhesions'). These strong anchors use protein chains to link the cell to collagen, the protein that gives structure to our body.

The anchors help the cells stay put and, for the most part, resist

disruptions to their environment—but if a cell morphs into a cancer cell, the chain can break, letting the cancer spread to other parts of the body.

Now, for the first time, a team of UNSW Sydney scientists have found the specific protein (or link) in the chain responsible for upholding the connection.

The findings, published today in *Nature Materials*, build on our understanding of cell mechanics—and could help give new directions for cancer research.

"We've identified the protein that's essential for these attachments to function," says Ms Maria Lastra Cagigas, lead author of the study and Scientia Ph.D. candidate at UNSW Medicine & Health.

"If these attachments fail, the cell could be more prone to moving and invading tissues, like cancer."

Scientists already knew that cancer weakens cells' anchors in some way, but they didn't know exactly how this happens.

One of the reasons it's been so hard to study this is the miniscule size of the anchor's chain: it's only a few nanometres thick—about 1/10,000th the size of a human hair.

The team used specialized 3D cryo-electron microscopy—a powerful imaging technique that uses an electron microscope to create high-resolution images of cells—to identify tropomyosin as the key protein in the chain holding the anchor in place. Cryo-electron microscopy is currently the most powerful technique to look at proteins inside cells, and its development won the Nobel Prize in Chemistry in 2017.

"This is the first time we can actually see in detail what the anchor's

chain looks like," says Professor Peter Gunning, co-senior author of the study. The team made the findings at UNSW's Mark Wainwright Electron Microscope Unit, and are the first in the world to use this technique to look at these tropomyosin chains.

"It's completely new technology."

The researchers identified tropomyosin's role in the anchor's chain by comparing normal cells with cells from bone cancer patients, along with cancer cells created in the laboratory.

They then tried putting the tropomyosin back into the cancer cells—surprisingly, the anchors managed to attach again.

"Looking into the future, we want to learn if we can leverage this knowledge to reduce the invasion of cancer cells," says Ms Lastra Cagigas.

"In the short term, we could use this information to find out if a cancer has a predisposition to metastasize, which means to move throughout the body.

"In the long term, we could look into it as a potential target in cancer treatment."

Prof. Gunning and co-senior author Professor Edna Hardeman, who have been researching this field of science for 40 years, say it's a milestone in understanding cell mechanics.

"It's been a real pleasure to watch this work develop," says Prof. Gunning, who was recently presented with the 2020 President's Medal from the Australian and New Zealand Society for Cell and Developmental Biology (ANZSCDB) for his contribution to research

into cell mechanics.

"It reinforces what has essentially been a lifetime's work for us: understanding the principles of the architecture of cells."

A potential drug target

Around 30 percent of the body is made up of collagen, which forms what's called 'the matrix'.

"The matrix is like a scaffold present in our bones, ligaments, muscles, and skin. It's almost everywhere in the body," says Ms Lastra Cagigas. "Other than the cells that move through our body, like those in blood, the collagen matrix forms the home for most cells—including cancer cells."

Pancreatic cancer is one of a few cancers that can modify this matrix for its own benefit by creating a 'barrier' around the tumor. This barrier works as a defense mechanism, making it harder for cancer treatments like chemotherapy and immunotherapy to kill the cancer cells.

The tumor forces pancreatic cancer-associated fibroblasts (or PCAFs) – cells around the tumor that are anchored by chains—to build this defense barrier. But now that scientists have identified the proteins in the cell's anchor and chain, they can explore these proteins as future targets for therapies that could loosen that barrier.

"We've identified that the type of protein involved in the chain, tropomyosin, is druggable," says Prof. Hardeman.

"This means it's possible to develop small molecule inhibitors, or drugs, that can actually attack these proteins."

Prof. Hardeman says it's likely that these potential future drugs would be

delivered alongside cancer treatments, so the drugs can temporarily destabilize the barrier while the cancer treatments do their work.

Looking ahead

While the findings are encouraging, Prof. Gunning says it doesn't mean suitable drugs will be available for use in the next few years.

"We have an understanding of the biology, but to go from that to treating a patient is difficult to predict," he says.

"We can see what the path looks like, but we are less sure of the timeline."

It's more likely that in the near future—potentially the next two or three years—the protein in the chain, tropomyosin, may help scientists predict which cancers are likely to spread more quickly.

"As we build on the underlying mechanisms of cancer and expand our markers of cancer cell biology, our discovery adds a missing link to the development of a personalized diagnosis for cancer," says Prof. Gunning.

More information: Correlative cryo-ET identifies actin/tropomyosin filaments that mediate cell–substrate adhesion in cancer cells and mechanosensitivity of cell proliferation, *Nature Materials* (2021). DOI: 10.1038/s41563-021-01087-z , www.nature.com/articles/s41563-021-01087-z

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