Cell 'hands' to unlock doors in health research, drug design, and bioengineering

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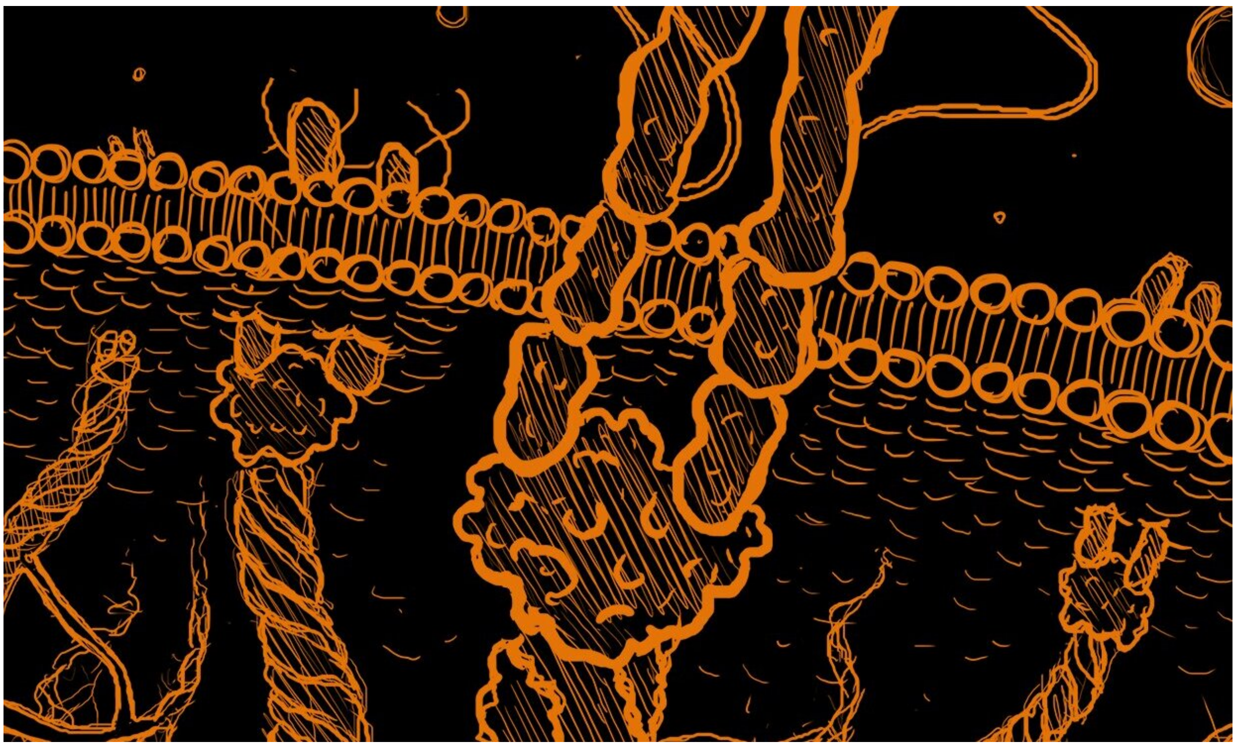

Syndecan-4 connecting the cell inside with the space outside - a prime position to communicate inside and outside signals. Credit: 3DforScience - Visuals for Bio&Health, Imperial College London

The protein, called syndecan-4, combines with fellow cell membrane proteins, called integrins, to form protruding 'hands' that sense the environment outside the cell.

Both proteins sit in the cell membrane, with one end pointing inside the cell and the other outside. They are therefore in a prime position to sense conditions outside the cell and convert signals to biochemical messages that change conditions inside the cell. In doing so, they're able to drive some of the cellular processes behind cancer and other diseases.

The early-stage research, conducted by a team at Imperial College London, Queen Mary University of London, and Tampere University in Finland, could present a new research pathway and drug target for certain cancer types.

Lead researcher Dr. Armando del Río Hernández, of Imperial's Department of Bioengineering, said: "Our findings could have immediate implications in the fields of cell and developmental biology, and lead to developments in several diseases including cancer and fibrosis."

The paper is published today in *Nature Materials*.

Helping hands

Syndecan-4 exists in nearly every human cell and is already known for its role in cardiovascular disease. However its potential roles in cancer biology and drug development have thus far been overlooked.

To study syndecan-4 the research team, led by Dr. del Río Hernández, used biophysical, cell biology, and computational techniques.

The team found that activating these cellular 'hands' triggers a pathway with key roles in disease development, involving a cellular protein called the yes-associated protein (YAP).

YAP triggers some of the typical hallmarks of cancer. It reduces cells' ability to programme their own death, in a process called apoptosis. Cells initiate apoptosis when they age or malfunction, so halting apoptosis allows diseased, even cancerous, cells to spread. YAP also controls the development of blood vessels—a hallmark of cancer as tumour growth requires extra blood flow.

They also found that syndecan-4 helps cells respond to movements outside themselves, by creating tension in the cytoskeleton—the 'scaffolding' within cells. This makes cells stiffen, which activates an enzyme called PI3K that regulates additional hallmarks of cancer.

It does this by converting the movements outside the cell into biochemical signals which, the researchers found, 'tune' the way the cells respond to tension and movement.

Dr. del Río Hernández said: "The way cells interact with their environment could inform how we engineer tissues and mimic human organs for drug design. Syndecan-4 could now play a fundamental part in this endeavour."

Co-lead author Dr. Stephen Thorpe of Queen Mary University of London said: "As syndecan-4 is expressed on almost all of our cells, the mechanisms we've uncovered could be targeted to alter any number of diseases and biological processes."

Professor Vesa Hytönen of Tampere University said: "Better understanding of cellular mechanosensing opens possibilities to develop treatments for conditions like cancer and fibrosis."

Onward pathways

Next, the research team will further investigate syndecan-4's links to specific diseases like pancreatic cancer.

Dr. del Río Hernandez said: "Our next approach will involve syndecan-4 as a key contributor in disease. We hope this will lead to new insights into disease mechanisms."

More information: Syndecan-4 tunes cell mechanics by activating the kindlin-integrin-RhoA pathway, *Nature Materials* (2020). DOI: 10.1038/s41563-019-0567-1 , nature.com/articles/s41563-019-0567-1

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