New insight into the crosstalk between cancer cells and their environment

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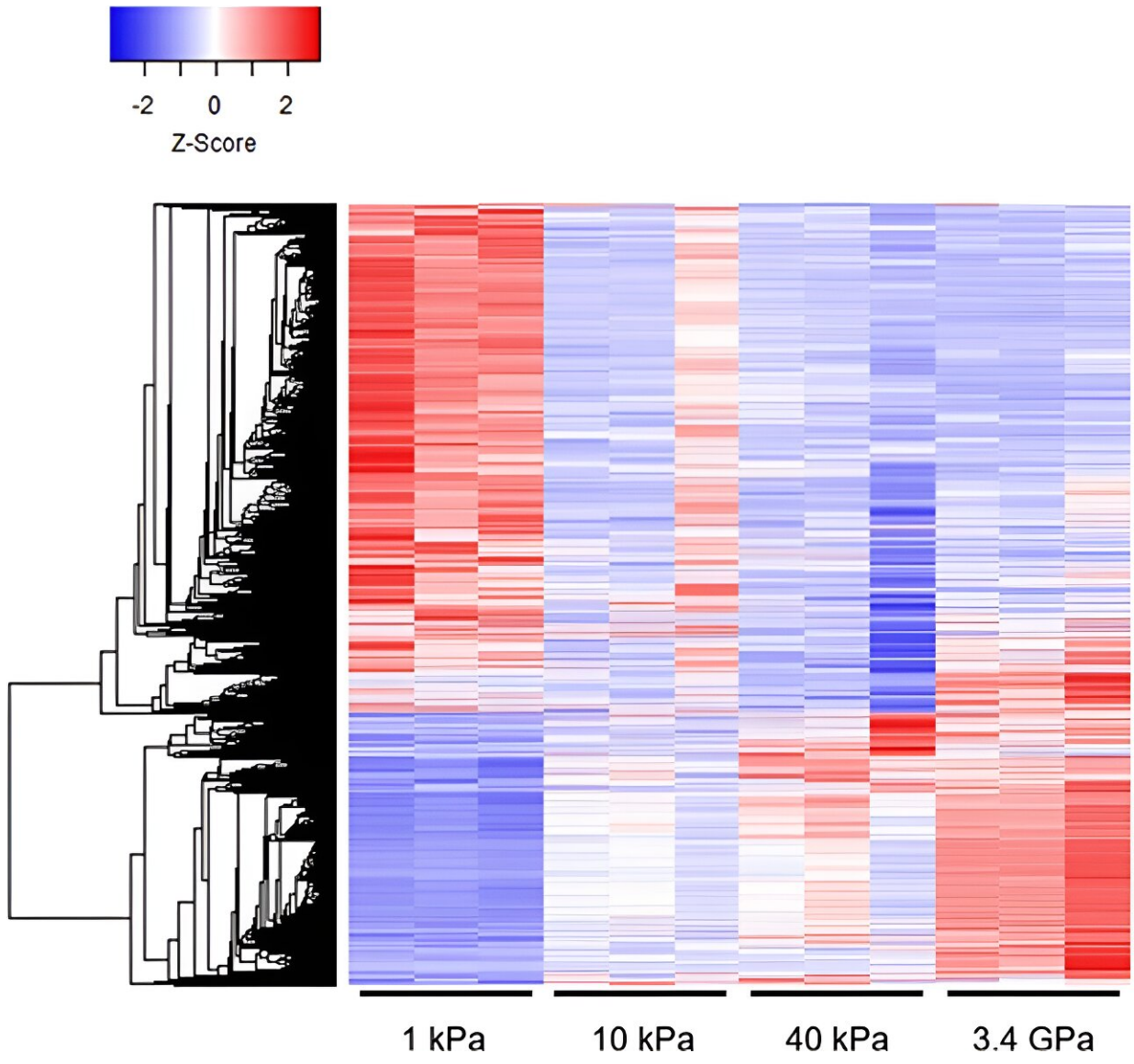

CAFs undergo significant gene expression changes when grown on substrates of

increasing stiffness. Hierarchical clustered heatmaps showing the relative expression levels of differentially expressed genes based on RNA-seq. Rows represent genes which are hierarchically clustered using the average-linkage clustering method. Columns represent the samples, showing three biological replicates of CAFs grown at 1 kPa, 10 ka, 40 kPa, and 3.4 GPa of stiffness. Credit: *Scientific Data* (2023). DOI: 10.1038/s41597-023-02233-9

Most solid tumors become stiff as the cancer progresses. Although researchers recognize that the environment around the cancer cells influences their behavior, it is unclear how it does so. In a new paper, published in *Scientific Data*, researchers from the University of Illinois Urbana-Champaign have collected gene expression data in response to mechanical stiffness in tumors. Their work can help guide our understanding of the crosstalk between cancer cells and their surroundings.

Historically, researchers have focused on how cancer cell genes change their expression over time. Based on this information, scientists have developed several therapeutic strategies, and yet over 600,000 people die every year in the US alone.

"We haven't made as much progress as we would have liked against cancer," said Bashar Emon, a postdoctoral researcher of mechanical science and engineering in the Saif (M-CELS/RBTE) lab. "Even with all the advances, the patient survival rate has not improved proportionately, when you consider how much research and funding has gone into studying cancer."

As a result, there has been a recent push to understand the tumor environment holistically. Cancer cells are surrounded by non-cancerous stromal cells, the most abundant of which are the cancer-associated

fibroblasts. Although researchers have recognized that CAFs play a role in metastasis, they do not understand which signals are involved in the process.

"In this paper we focused on the tumor microenvironment because it becomes stiffer with time and we know that CAFs can sense this change," Emon said. "We wanted to understand how they convey this information to cancer cells."

The researchers cultured human colorectal CAFs on gels that had increasing stiffness ranging from 1 kPa to 40 kPa. "One kPa is very soft, like Jell-O whereas 40 kPa is firmer, like rubber erasers. Imagine pressing your finger against a layer of Jell-O or rubber; one should feel like a normal tissue, while the other one is more like a tumor," Emon said.

After isolating and sequencing the RNA from the CAFS, the researchers were able to compare which genes were being expressed differently in response to the increasing stiffness. Furthermore, they were also able to decipher changes in signaling molecules and pathways, and observe which biological functions were being affected.

"A gradient of increasing pressures from 1 kPa to 40 kPa created dramatic changes in gene expression, indicating that these CAFs were able to sense changes in stiffness and adapt. Comparing 1 kPa to 40 kPa, which are similar to the pressure inside a solid tumor, showed differentially expressed genes and molecules that may be relevant for cancer progression," said You Jin Song, a graduate student of cell and developmental biology in the Prasanth lab.

The study looked at CAFs whereas other groups have looked at how cancer cells respond to different pressure conditions. In future studies, the authors would like to grow the two types of cells together and see

how the crosstalk manifests. "Our study was a necessary step in this direction because we need to first understand the individual responses of each cell type before we study their interactions," Song said.

"The importance of our paper lies in the fact that it is an unbiased experiment that monitored the expression of several genes simultaneously. It could be a good resource for other researchers who want to see whether the genes that they are interested in change in response to stiffness," Song said.

More information: Bashar Emon et al, Mechanosensitive changes in the expression of genes in colorectal cancer-associated fibroblasts, *Scientific Data* (2023). DOI: 10.1038/s41597-023-02233-9

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