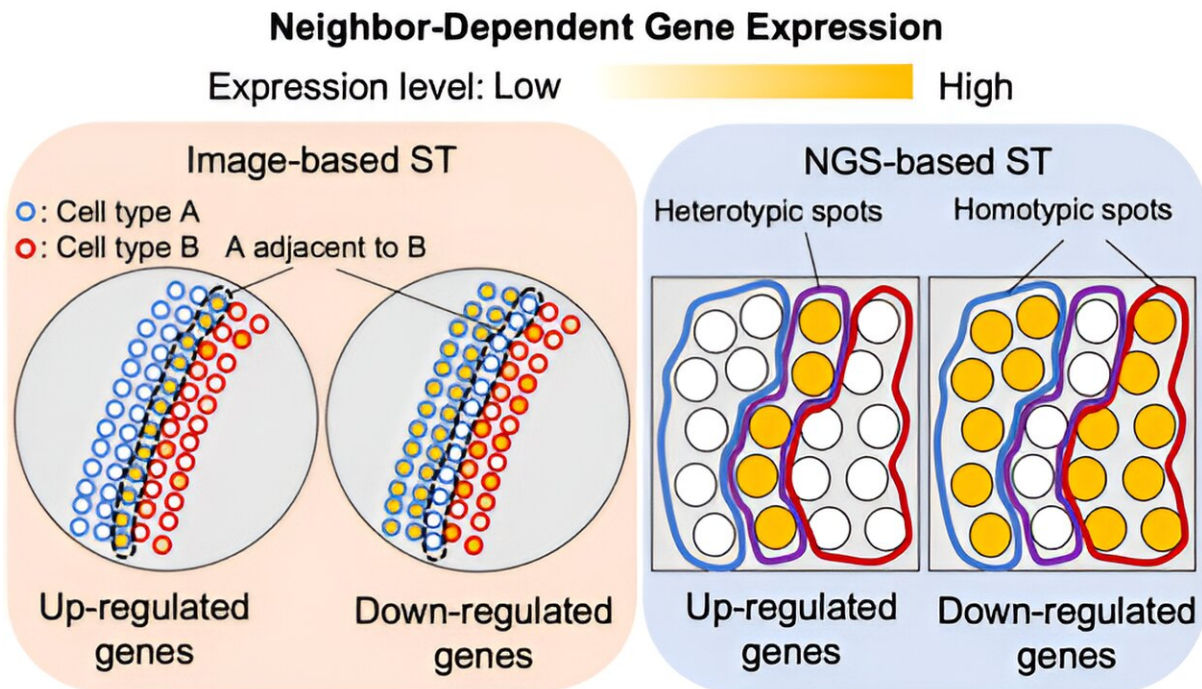


When cells touch, their genetics change: A new front in understanding cancer

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Graphical abstract. Credit: *Molecular Systems Biology* (2023). DOI: 10.15252/msb.202311670

The cells that make up our bodies are constantly communicating with each other, sometimes directly by physical touch. These interactions allow cells to respond to their neighbors, adapt to their surrounding environment and organize themselves into a fully functioning organism.

Studying how these interactions influence cells at the [genetic level](#) has historically been a challenge for the science community. However, a research team led by Virginia Commonwealth University and the University of Copenhagen has developed an innovative approach to track how neighboring cells trigger changes in each other's [gene expression](#).

Their findings, published in the [Proceedings of the National Academy of Sciences](#), could have significant implications for understanding how cancer cells and [normal cells](#) affect each other.

"This study is really a proof of principle, to show that we can use this approach to better understand how neighboring cells influence each other on a genetic scale," said Rajan Gogna, Ph.D., an assistant professor in the VCU School of Medicine's Department of Human and Molecular Genetics and one of the study's lead authors.

"To our knowledge, this is the first study of its kind to uncover the genetic changes associated with cell interactions," said Gogna, who also is associate director of cell competition and [tumor microenvironment](#) at VIMM, the VCU Institute of Molecular Medicine.

Listening in on neighbor cells

By sending each other signals, cells can initiate changes in gene expression, a process by which information encoded in our [genes](#) is used to generate the proteins that carry out various functions in the body. Neighboring cells can also influence gene expression through physical contact. This kind of communication is especially important during [human development](#), when adjacent cells are forming different kinds of organs and tissue.

"The cells in our body don't operate in a vacuum, but rather they function as a unit. The genes that are turned on within our cells very

much depend on where they're located and whom they interact with," said VIMM Director Paul B. Fisher, Ph.D., a professor in the Department of Human and Molecular Genetics and the Thelma Newmeyer Corman Chair in Oncology in the VCU Massey Comprehensive Cancer Center who was involved in this research.

"The ultimate goal of this study was to better understand how cells talk to one another and what they tell each other to do."

Scientists can use [research methods](#) like single-cell RNA sequencing to identify differences in gene expression patterns between individual cells. However, this technique can't adequately map out the location of individual cells or determine how they influence each other.

To overcome this hurdle, the researchers developed an approach that combines RNA sequencing and artificial intelligence to identify genetic signatures associated with certain neighboring cell interactions.

For this preclinical study, the researchers measured gene expression patterns in small clusters of cells. Through mathematical modeling, the team was able to identify the genetic changes that occur when certain cells are in contact with each other.

"We isolated samples containing just two or three cells, and using this strategy, we were able to pinpoint what genetic changes were caused by cells physically touching each other," Gogna said.

The researchers then tested their approach by analyzing interactions between eye lens cells and neural progenitor cells, which are found in the brain. The experiment confirmed that the model could successfully predict which genes would be turned on as a result of these cells physically touching each other.

More recently, the researchers demonstrated that this approach can also be applied to datasets from independent studies. They were able to identify genes influenced by neighboring cells in various microenvironments, such as in brain and liver tissue. The results, published in October 2023 in [Molecular Systems Biology](#), suggests that cells may have a larger genetic impact on their neighbors than previously thought.

Implications for fighting cancer

In addition to opening new doors for biological studies, the new approach could play a significant role in advancing [cancer research](#), according to the study authors.

"Our ultimate goal is to apply this method to better understand how cancer affects us. We want to understand how cancer cells interact with other cells in the body and vice versa," Gogna said. "We want to know how [cancer cells](#) develop around our normal cells and how they respond when exposed to therapies."

Fisher, who has a Master of Public Health degree, added, "This information has significant potential to define appropriate therapies to impede cancer growth and progression, as well as delineate a path to induce tumor cell death."

Normal cells are constantly exchanging signals to regulate their growth and division, and the process will often dictate when a cell needs to shut down to make space for newer, healthier cells.

Cancer cells, however, grow uncontrollably, and research has shown that many cancers take form when cell communication is disrupted. Cancer cells have also been shown to affect the behavior of normal cells. For instance, some cancers can recruit normal cells to develop [new blood](#)

[vessels](#), which in turn provide oxygen and nutrients to growing tumors.

"When developing therapies to treat different tumors, it's just as important, and sometimes more important, to think about the environment where the tumor is growing," Fisher said. "You have to account for both the tumor and its environment to more effectively stop the cancer in its tracks."

The study authors say these methods may also help the research community better understand racial differences in cancer susceptibility and survival.

Research has shown that racial disparities—largely driven by a combination of structural, economic and socioenvironmental inequities—exist in both cancer incidence and outcomes. Some studies suggest that hereditary risk for specific cancer subtypes and environmental influence on gene expression may also be contributing to these disparities.

"In addition to [cancer](#) research, the techniques developed could ultimately be used to improve our understanding of other diseases," Fisher said. "I'm looking forward to really fantastic discoveries as we go into the future."

More information: Junil Kim et al, Neighbor-specific gene expression revealed from physically interacting cells during mouse embryonic development, *Proceedings of the National Academy of Sciences* (2023). [DOI: 10.1073/pnas.2205371120](https://doi.org/10.1073/pnas.2205371120)

Hyobin Kim et al, CellNeighborEX: deciphering neighbor-dependent gene expression from spatial transcriptomics data, *Molecular Systems Biology* (2023). [DOI: 10.15252/msb.202311670](https://doi.org/10.15252/msb.202311670)

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