Cell communication: Wnt signaling interpreted differently depending on receiving cell and signal duration

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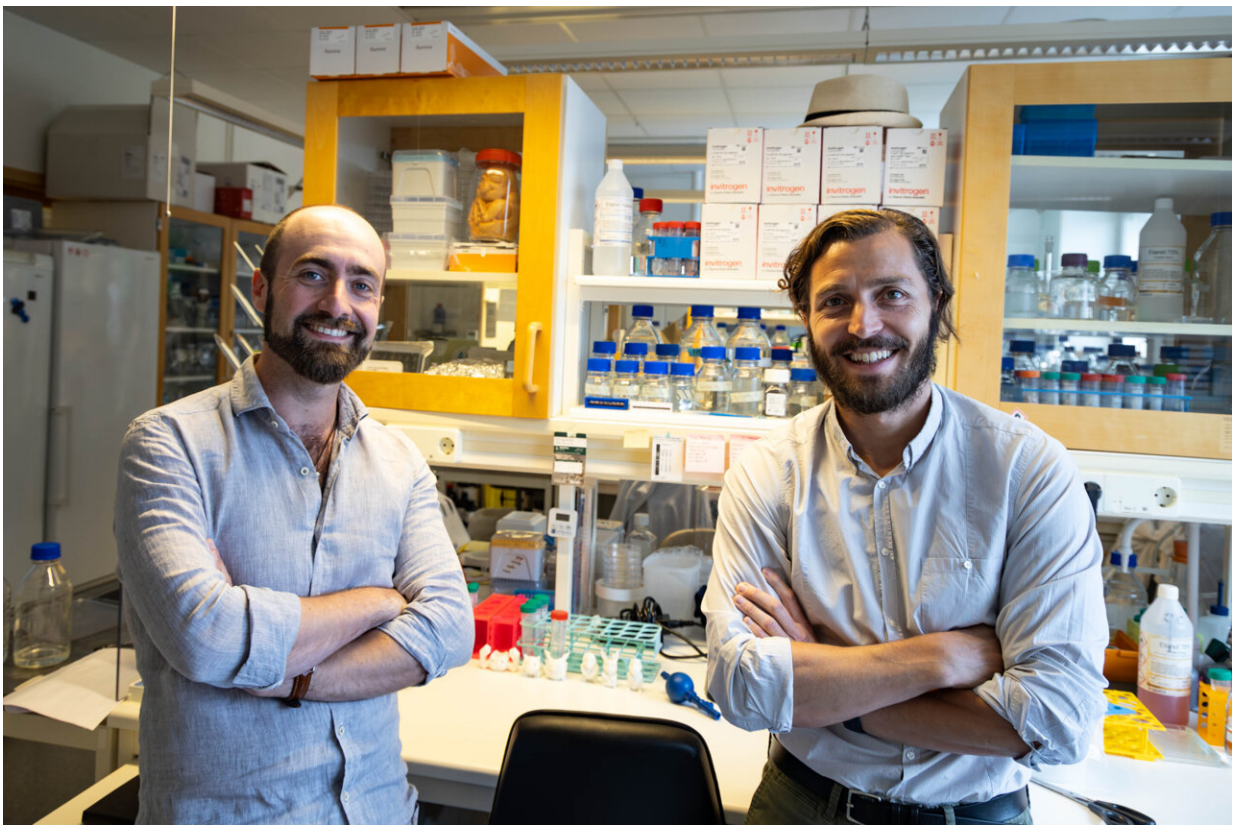

Claudio Cantù and Pierfrancesco Pagella at Linköping University. Credit: John Karlsson/Linköping University

The same message can be interpreted differently by different

individuals; also true among cells. This is shown by researchers at Linköping University who studied cell communication through Wnt signaling, which plays a decisive role in embryo development and cancer. Their findings have been published in *Cell Systems*.

The cells in our body are in constant communication. Although cell communication plays a decisive role in everything that happens in our bodies, cells have few ways to communicate with one another. Wnt signaling is one of them. It was discovered in the 1980s, through its role in the development of certain forms of cancer.

It soon unfolded that Wnt signaling also has a basic function in embryo development in a variety of organisms, from fruit flies to humans.

"At the outset of life, Wnt signaling is vital for the body to form properly, while dysregulated communication between cells may lead to cancer. A key question we are trying to answer is whether this communication mode works in a similar way in these two distinct phases," says Pierfrancesco Pagella, postdoc in the Department of Biomedical and Clinical Sciences at Linköping University.

It has long been known that when a cell sends a Wnt message to another cell, the receiving cell undergoes behavioral changes. This is achieved by activating certain genes in the genome and repressing others.

Wnt signaling has long been regarded to always activate the same groups of genes, leading to the term "Wnt target genes." But the current study upends this assumption, as the research group, led by Claudio Cantù, has shown that a signal may have radically different effects depending on its duration. In their experiments, the researchers saw that the same signal given to a specific cell type, such as embryonic stem cells, had significantly varying effects depending on the duration of the signal.

"The cell responds differently depending on whether the signal is delivered for 90 minutes, four hours or three days. It's not simply a matter of prolonging the same message," says Pierfrancesco Pagella.

Claudio Cantù and Pierfrancesco Pagella at Linköping University. Credit: John Karlsson/Linköping University

A long-standing key issue in developmental biology is: as all cells contain the same genome, how does a cell know which of all the genome's instructions to use to get its correct identity?

"I believe this discovery has uncovered a new type of cell behavior related to the 'instruction manual' of the genome. Some cells genuinely

read and utilize the information to change their identity, while others choose not to use it for that purpose. Our study reveals how this works in the context of the Wnt signaling communication mechanism. This novel phenomenon, to our knowledge, has never been previously discovered," says Claudio Cantù, senior associate professor.

What the researchers also discovered is that it has to do not only with the message, but also with the identity of the receiving cell. When the exact same signal is given to two different cell types, their immediate responses are also distinct. The researchers liken this to interpersonal communication, where the same message can be interpreted differently by different individuals.

The researchers believe that the reason behind this phenomenon is the cells' prior experiences. One of the cell types subjected to Wnt signaling is immature embryonic stem cells. These are the youngest cells, and can be further developed into all the various specialized cell types in an organism. When the stem cells in the researchers' experiment received Wnt signaling, their identity changed to resemble a specialized cell type, a behavior that the researchers refer to as "plastic."

The research team also studied how specialized cell types react to the same signaling. Despite receiving the same signal, these cells changed only temporarily, and ultimately returned to their initial state, an unexpected behavior that the team at Linköping University call "elastic."

One hypothesis that the researchers raise is that this second type of behavior, "elastic," may contribute to cancer cell aggressive behavior. The new insights into this phenomenon may come to be used in the development of new treatment strategies to impact cancer cell response to Wnt signaling. This knowledge may also lay the foundation for discoveries of exactly which genes the signal targets in different situations.

More information: Claudio Cantù, The Time-Resolved Genomic Impact of Wnt-catenin Signaling, *Cell Systems* (2023). DOI: 10.1016/j.cels.2023.06.004. www.cell.com/cell-systems/full … 2405-4712(23)00157-6

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