Medical Xpress

Cancer cells coordinate to form roving clusters

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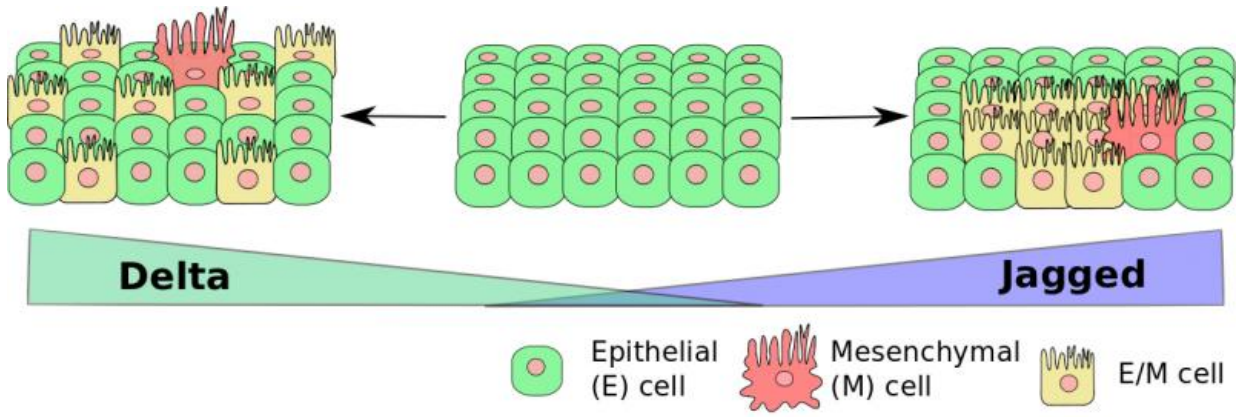

Epithelial cells normally become mesenchymal cells under the influence of a notch-signaling protein called delta, but they can become hybrid epithelial-mesenchymal cells under the influence of jagged proteins when the signaling system is hijacked by cancer, according to Rice University researchers. These hybrid cells can communicate with each other, cluster and metastasize to other parts of the body. Credit: Marcelo Boareto

Two-way communication between cancer cells appears to be key to their becoming motile, clustering and spreading through metastasis, according to Rice University scientists.

Members of Rice's Center for Theoretical Biological Physics have developed a model of how cancer cells twist a complex system of signals

and feedback loops to their advantage. These signals help the cells detach from primary tumors and form clusters that lead to often-fatal metastatic disease.

The Rice team reported in 2015 that the notch signaling pathway that involves proteins known as "notch," "jagged" and "delta" can be hijacked by cancerous cells. In normal operation, the mechanism is critical to embryonic development and wound healing and typically activates when a delta ligand of one cell interacts with the notch receptor of another. Their new paper in the Royal Society journal *Interface* advances the theory that cancer cells use these proteins, particularly jagged, to not only establish two-way signals that turn them into hybrid epithelial–mesenchymal cells but also to form mobile clusters.

"In general, our interest has been in the decision cells make by which they leave the primary tumor," said Rice theoretical biological physicist Herbert Levine. "The epithelial cells are in the primary tumor are aberrant. Still, they look like normal cells, even though they're growing where they shouldn't. But cancer only turns truly deadly when cells leave and start new growths elsewhere in the body."

Because notch signaling is such a common function, the researchers suspected it could be repurposed by rogue cells. "We've argued over the last couple of years that cells make active cell-fate decisions to become motile and leave the tumor. This paper addresses the extent to which cells coordinate their decisions with each other," he said.

The study led by Levine, Rice colleague José Onuchic and former Rice researcher Marcelo Boareto offers cancer researchers a new target to consider as they seek ways to disrupt the process of metastasis.

Notch signaling that starts in one cell triggers the transition of a neighboring cell, for instance, allowing a stem cell to reconfigure one of

its neighbors for a specific function. "You have cells that are senders and cells that are receivers," Onuchic said. "By doing that, they can differentiate. They can make their partners to be different than they are."

But in cancer, cells can act both as receivers and senders, especially when they change the primary ligand to jagged. "It turns out jagged increase is the smoking gun," he said. Not only does the higher number of jagged proteins help create these motile hybrid cells, the increase also helps the hybrids exchange information to make sure that all the cells that are able will clump into a group, he said.

"Biologists usually don't think about the differences between the ligands," Boareto said. "But there's a large difference. The main message of the paper is simple: Notch-delta signaling leads to isolated cells undergoing the epithelial-mesenchymal transition (EMT) to motile individuals, and notch-jagged leads to groups of cells undergoing EMT to motile clusters."

The researchers suspected such transitions aren't random. "Now we know they aren't just reactions to the environment," Levine said. "They're often due to cells communicating and making collective decisions." To test these ideas, he said, co-author Sendurai Mani of the University of Texas MD Anderson Cancer Center will use cancer tissue samples to quantify the presence of jagged and other related proteins over the next few years.

Onuchic said it was not surprising that cancer cells use notch pathways and probably other pathways as well. "Cancer never creates a complete new mechanism in biology," he said. "It uses existing mechanisms to fulfill its needs. Learning how that happens can provide new clues for preventing metastasis."

Even if the discovery doesn't immediately apply to therapies, it could help diagnose the severity of a tumor by quantifying its expression of notch, jagged and delta proteins. "It gives us something to measure to predict more accurately how dangerous a primary tumor is," Levine said.

More information: Marcelo Boareto et al. Notch-Jagged signalling can give rise to clusters of cells exhibiting a hybrid epithelial/mesenchymal phenotype, *Journal of The Royal Society Interface* (2016). DOI: 10.1098/rsif.2015.1106

Provided by Rice University