With cell-to-cell communication, more is better—up to a point

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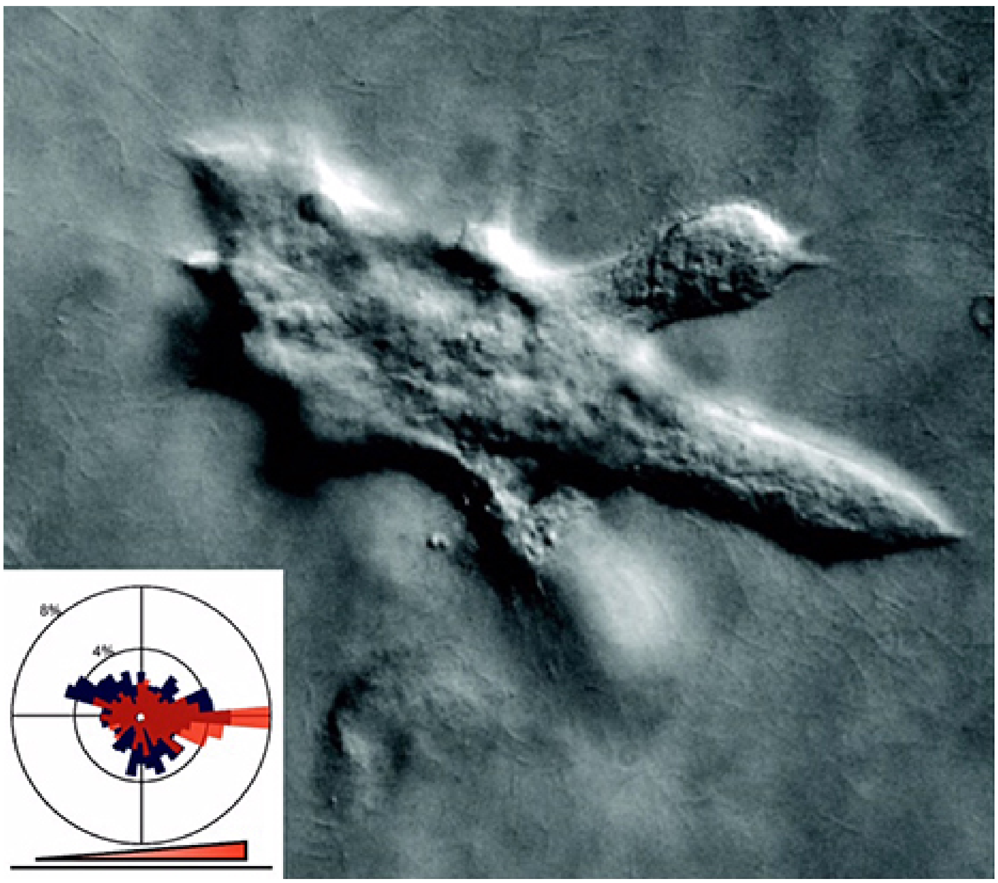

Microscopic image of an organoid exposed to epidermal growth factor, branching toward the higher concentration of EGF (toward the right side of the image).

When it comes to communicating, cells perform better in crowds. When too many work together, though, the cells end up in a game of "telephone," passing on increasingly unreliable signals.

Researchers from Yale, Emory, Purdue, and other universities looked at how cells sense the chemical and mechanical cues that determine cell behavior. Two studies with their results—which have potential implications ranging from breast cancer treatment to semiconductor manufacturing—appear the week of Jan. 18 in the journal *Proceedings of the National Academy of Sciences*.

Cells read these signals by sensing the concentration of a chemical and gravitating toward it, as if tracking a scent. "The cells want to find where there's more of this molecule," said Andre Levchenko, the John C. Malone Professor of Biomedical Engineering and director of the Yale Systems Biology Institute, one of the papers' authors. "They use the gradients as directional cues."

The studies focused on how well individual cells sense these cues compared to teams of cells. One study addressed this theoretically, while the other combined theory and experiments. The researchers placed together breast cells, which can self-organize into miniature breast tissue. The development of these small organ-like tissues, known as organoids, allowed the scientists to study how cell ensembles of different sizes sense the chemical signal's gradients. Epidermal growth factor (EGF), a substance that stimulates cell growth, was the chemical used in the experiments.

When there were very weak gradients of EGF, with only slight differences in molecular concentration, the superiority of collective decision-making among cells became clear. "The single cells could not detect those differences; it was important for the cells to be together," Levchenko said.

But the benefits of working together have a limit, he notes. The greater the number of cells that are communicating, the more the group generates its own internal noise—the cells' varying responses to cues—which can significantly jumble the communicated signal.

"They need to 'talk' to each other to interpret the signal, but talking is a noisy process," said Levchenko, comparing it to the din of a crowded party. "It's hard to hear what's happening on the other side of the room. Friends can pass on a message for you, but it gets distorted in all the noise, as in a game of 'telephone.' It's like the famous adage, but with a twist: Bigger is better, but only to a degree."

How cells communicate is crucial to many biological processes, and could have profound implications for the treatment of breast cancer. Growth factor gradients frequently guide breast cancer cells as they invade surrounding tissues, so understanding the influence of collective cell responses is critical to developing new treatments, said the researchers.

Other impacts extend beyond biology. As electronic circuits get smaller and noisier, the semiconductor industry has increasingly become interested in cellular biology, and in how coupled cell circuits can support information processing. The National Science Foundation, National Institutes of Health, and the Semiconductor Research Corporation provided funding for the study.

More information: Limits to the precision of gradient sensing with spatial communication and temporal integration, *PNAS*, www.pnas.org/cgi/doi/10.1073/pnas.1509597112

Cell–cell communication enhances the capacity of cell ensembles to sense shallow gradients during morphogenesis, *PNAS*, www.pnas.org/cgi/doi/10.1073/pnas.1516503113

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