The dance of the cells: A minuet or a mosh?

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The physical forces that guide how cells migrate—how they manage to get from place to place in a coordinated fashion inside the living body—are poorly understood. Scientists at the Harvard School of Public Health (HSPH) and the Institute for Bioengineering of Catalonia (IBEC) have, for the first time, devised a way to measure these forces during collective cellular migration. Their surprising conclusion is that the cells fight it out, each pushing and pulling on its neighbors in a chaotic dance, yet together moving cooperatively toward their intended direction.

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Until now it was known that cells could follow gradients of soluble chemical cues, called morphogens, which help to direct tissue development, or they could follow physical cues, such as adhesion to their surroundings. Fundamental studies of these and other mechanisms of cellular migration have focused on dissecting cell behavior into ever smaller increments, trying to get to the molecular roots of how migration occurs. In contrast, the HSPH team worked at a higher level—the group level—and focused upon the forces that cells exert upon their immediate neighbors, to begin to resolve the riddle of collective cellular migration.

Collective cellular migrations are necessary for multicellular life; for example, in order for cells to form the embryo, cells must move collectively. Or in the healing of a wound, cells must migrate collectively to fill the wound gap. But the migration process is also dangerous in situations such as cancer, when malignant cells, or clumps of cells, can migrate to distant sites to invade other tissues or form new tumors. Understanding how and why collective cellular migration happens may lead to ways to control or interrupt diseases that involve abnormal cell migration.

The laboratories of Jeffrey Fredberg, professor of bioengineering and physiology at HSPH, and his colleague Xavier Trepat, a researcher at IBEC, are the only ones in the world that can now measure the forces within and between complex cellular groups. "We're beginning for the first time to see the forces and understand how they work when cells behave in large groups," said Trepat.

To do this, the researchers invented a measurement technology called Monolayer Stress Microscopy, which allows them to visualize the minute mechanical forces exerted at the junctions where individual cells are connected. Their studies led to discovery of a new phenomenon, which they named "plithotaxis," a term derived from Greek "plithos" suggestive of throng, swarm or crowd.

"If you studied a cell in isolation, you'd never be able to understand the behavior of a cell in a crowd," said Dhananjay Tambe, the first author and a research fellow at HSPH. Instead, the researchers studied groups of cells living in a single thin layer—a monolayer—and precisely measured the forces each cell was experiencing as it was navigating within the group. The findings surprised them.

"We thought that as cells are moving—say, to close a wound—that the underlying forces would be synchronized and smoothly changing so as to vary coherently across the crowd of cells, as in a minuet," said co-first author Corey Hardin, a research fellow at Massachusetts General Hospital. "Instead, we found the forces to vary tremendously, occurring in huge peaks and valleys across the monolayer. So the forces are not smooth and orderly at all; they are more like those in a 'mosh pit'—organized chaos with pushing and pulling in all directions at once, but collectively giving rise to motion in a given direction," he said.

"This new finding has the potential to alter, in a fundamental way, our understanding of mechano-biology and its role in the basic processes that underlie the function of monolayers in health and disease," said Fredberg. He also predicted the new report would be interesting for both physicists and biologists, and might even spur new research collaborations between the two disciplines.

The study findings should provide a better understanding of cell migration as it occurs in embryonic development—how the human body gets put together soon after fertilization, say the researchers. The findings may also help to explain how cancer cells migrate in the deadly process called metastasis.

More information: "Collective Cell Guidance by Cooperative Intercellular Forces," Dhananjay T. Tambe, C. Corey Hardin, Thomas E. Angelini, Kavitha Rajendran, Chan Young Park, Xavier Serra-Picamal, Enhua H. Zhou, Muhammad H. Zaman, James P. Butler, David A. Weitz, Jeffrey J. Fredberg, Xavier Trepat, *Nature Materials*, online May 22, 2011.

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