Stochastic variations of migration speed between cells in clonal populations

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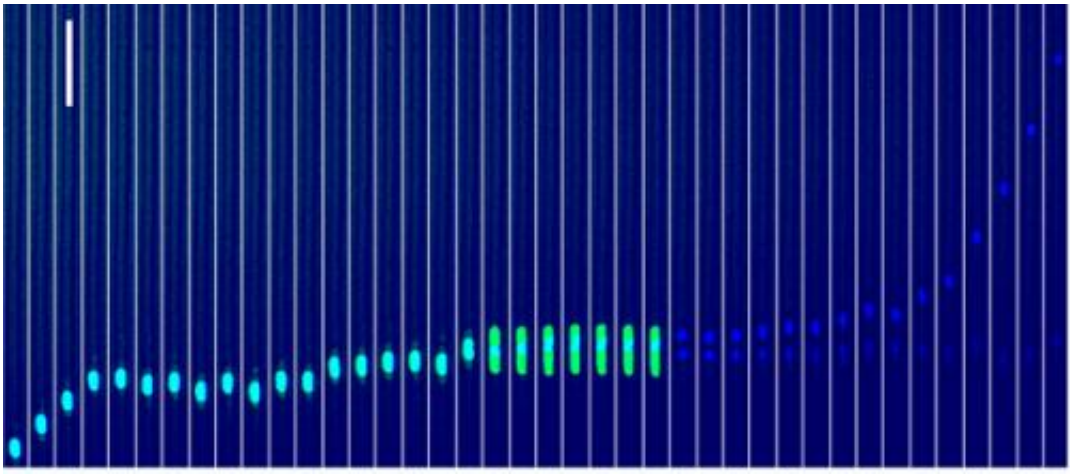

A temporal array of fluorescence images captures the migration of a cell through a microfluidic channel before and after division. The "mother" cell appears in light blue up to the time of division when it appears mostly green and its migration stops completely. The two "daughter" cells after division appear in darker blue. One of the daughter cells moves fast after division, while the other moves significantly slower. Vertical bar is 100 μm. The time between consecutive images is 20 minutes.

Microfluidic tools for precision measurements of cell migration speed reveal that migratory speed of individual cells changes stochastically from parent cells to their descendants, while the average speed of the cell population remains constant through successive generations.

A team of researchers at the Massachusetts General Hospital and Harvard Medical School in Boston has developed technologies for precision measurement of cell migration speed before and applied the new tool to study the variations of migration speed in population of cancer cells. This tool enabled comparisons between successive generations of cells with single cell resolution. One interesting finding from this study was that the speed of migration, maintained relatively constant throughout the life of a cell, is not inherited from the mother down to the daughter cells. Instead, the characteristic migration speed of each cell changes randomly through successive generations. This finding comes as a surprise, considering that the average migration speed of the larger cell population does not change through multiple cycles. This finding is important in the context of cancer treatment, where treatments are sought to slow down the invasion of cancer cells.

"Our finding suggests that a factor may exist which determines the characteristic speed of a cell and that factor is set at random levels in the new cells after cell division." says Daniel Irimia, M.D., Ph.D., of the Massachusetts General Hospital in Boston and senior author on this paper. "These measurements could not be performed today with any of the traditional tools for cell migration. Transwell assays could only compare population averages and lack single cell resolution. Wound healing assays have single cell resolution, however the results are confounded by frequent interactions between moving cells. Other more recent microfluidic devices are also hampered by the noise of measuring cell migration on flat surfaces, when the direction of migration changes frequently interfering with the velocity measurements."

Inside the microfluidic device, each cell is assigned one channel-track along which the cell will migrate for several hours. An automated microscope takes images every 20 minutes at multiple locations in the microfluidic device, and multiple devices at once, allowing for the tracking of dozens of cells in one experiment. Interestingly, each cell

that migrates through the channels maintains its migration speed throughout its lifetime. Only some of the cells divide while in the channels, and those are scrutinized closely. To better visualize the cells through the division cycle, the researchers took advantage not only of fluorescent dyes, but also of a recently developed Fucci fluorescent marker. Using this marker, the green fluorescence of the nucleus increases progressively in cells in the growth phase and turns off after the division. "We optimized the design of the device such that most of the channels have only one cell traveling through at a time, and calculated the length of the channels such that we could observe each cell for an average of 12 hours" says Jun Yan, Ph.D., the lead author on this paper.

The team from the Massachusetts General Hospital plans to use the microfluidic devices in synergy with some more sophisticated molecular biology tools and identify the control factors of cell migration speed. "Identifying this factor could provide an interesting target for drugs to modulate how fast or slow cells move" says Dr. Irimia. In cancer, this could help slow down the migration of cancer cells, to delay their invasion and metastasis. After injuries of healthy tissues, we would like to accelerate the migration of healthy cells that move to close the wound.

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