The forces of attraction: How cells change direction

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Many cell types in higher organisms are capable of implementing directed motion in response to the presence of certain chemical attractants in their vicinity. A team led by Dr. Doris Heinrich of the Faculty of Physics and the Center for NanoScience (CeNS) at Ludwig-Maximilians-Universitat (LMU) in Munich has developed a novel technique to expose an ensemble of living cells to rapidly varying concentrations of chemoattractants.

"Using this novel experimental approach, we investigate with high temporal and spatial resolution how living cells react to rapid changes in concentration gradients of chemoattractants. This gives us a new means of studying how such changes are detected and transduced by the cell's signaling pathways," says Heinrich. The work is also of clinical significance, since directed migration of cells is essential for embryonic development and for immune responses. The researchers have even used their system to build a chemotactic trap that allows them to immobilize cells by exposing them to rapidly changing patterns of chemoattractants. (*PNAS* Early Edition 27 June 2011)

The term "chemotaxis" refers to the ability of many cell types in higher organisms to detect and respond to concentration gradients of specific compounds by migrating toward or away from the source of the gradient. "We investigate how cells follow concentration gradients of a chemoattractant and change their migration direction after a change in the external stimulus. We have developed a so-called microfluidic gradient generator, which allows us to rapidly alter the direction of the

gradient such that the cells are repeatedly stimulated to reverse their direction of migration," says Börn Meier, who is the first author on the new study.

Each cell migrates along a gradient by crawling in the direction of the source of a chemoattractant. This cell locomotion is in turn based on the ongoing reorganization of the cytoskeleton, a network of fibers made up of the protein actin within the living cell. In response to the presence of a chemoattractant, actin filaments are assembled at the front of the cell, causing the membrane to extend protrusions called pseudopodia in the direction of migration. Previous studies have shown that this reorganization is controlled by the localized accumulation of signal molecules in response to the binding of the chemoattractant to specific receptors on the cell surface. "It is however very difficult to detect the underlying changes in the spatial and temporal distributions of the biochemical agents involved. In order to achieve this, very precise control over the shape and the direction of the chemoattractant gradient must be obtained," says Heinrich. The new gradient generator provides this control, and promises to facilitate deeper insight into the signal pathways that control chemotaxis. In the new study, the investigators describe two different ways in which cells can reorient in response to changes in the gradient. Depending on the conditions, cells can either execute a U-turn, or they can go into reverse by disassembling the actin cytoskeleton at the prior leading edge of the cell, and switching the site of filament formation to the opposite end. Such reorganization of the actin cytoskeleton requires the participation of a large number of proteins, The research team is especially interested in determining the spatio-temporally changing distributions of these factors during the course of the entire process.

The new technique even makes it possible to vary the direction of the gradient field at such a high rate that, although the cell can respond to each switch by activating its internal signaling machinery, it does not

have time to reorient the actin network appropriately before the gradient changes again. The net result is that the cell remains in its initial position, immobilized in a chemotactic trap.

In a further experiment cells were exposed to varying gradients of chemoattractant in the presence of drugs that are known to affect the chemotactic signal cascades in the cells. The team was able to show that one particular inhibitor has a drastic effect on the pattern of cell motion. As Heinrich emphasizes, "Our experimental setup will give us new insights into complex intracellular signalling pathways of fundamental relevance for many areas of biological research, including cell and developmental biology, biochemistry and medicine."

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