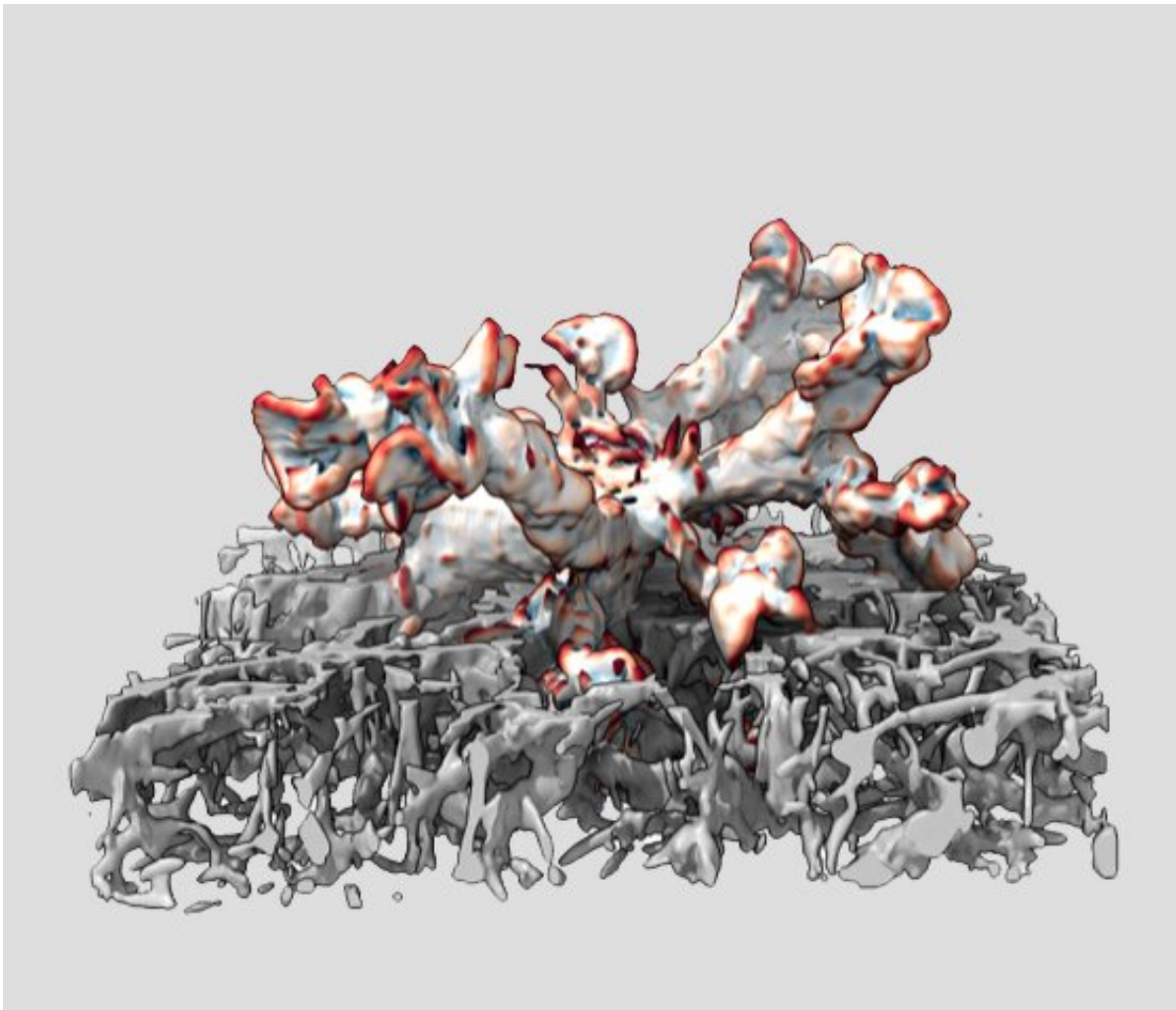


Leukocytes use their nucleus as a ruler to choose path of least resistance

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A leukocyte embedded in a 3D collagen network. Imaged by light sheet microscopy; imaged by Meghan K. Driscoll, University of Texas Southwestern Medical Center, Dallas, USA Credit: Meghan K. Driscoll

How do mobile cell types like leukocytes or metastatic cancer cells reach their place of action during immune surveillance or cancer dissemination, respectively? The research group around Michael Sixt at IST Austria has now shown that leukocytes use their nucleus as a ruler to screen their surroundings for the largest pores—and thereby find the path of least resistance.

Certain [cell types](#) continuously crawl through the body to reach their place of action. For instance, all leukocytes—the white blood cells of the immune system, cover a cumulative distance of more than 100,000 km per hour. On their journey, these migratory cells have to find their way through a three-dimensional maze crowded with other cells and extracellular matrix. Certain cell types—[mesenchymal cells](#) like fibroblasts—move forward by digesting the tissue they come up against, thus leaving behind a tunnel as a wake of devastation.

Leukocytes, on the other hand, show an amoeboid way of movement that allows them to move around 100 times faster. Also, they do not digest or remodel their environment (if they did, they would perforate the body with more than 2 million kilometers of tunnels per day). How these extremely fast cells navigate through the dense meshwork of interstitial connective tissue fibers without harming other cells has been of great interest to cell biologists.

Professor Michael Sixt and his team—including first author Jörg Renkawitz, have now determined how leukocytes manage to choose the path of least resistance when navigating through complex environments.

Nucleus measures pore size and helps leukocytes to move full speed ahead

To understand the mechanism behind this selective form of cell movement, the researchers built an obstacle course for leukocytes in

reconstituted tissue in which the cells could choose between differently sized pores while following global directional cues such as chemotactic gradients. What they observed was that whenever the amoeboid cells had a choice, they used the bigger pores, i.e. the path of least resistance.

In further tests, the scientists found that the cells facilitate this active directional movement by pushing their [nucleus](#) very much to the front of the cell so it can serve as a kind of mechanical gauge or ruler. In other words, as the cell is moving forward, it applies cytoskeletal forces to insert its nucleus into several adjacent pores to measure pore sizes. Michael Sixt says, "The usual organelle to steer a cell is the actin-rich leading front, which explores the environment. Unexpectedly, we found that this is not what determines the path of a [leukocyte](#). Instead, it is the nucleus that guides the cell through the bigger pores. This makes sense, as the nucleus is the most bulky part of the cell, and also sensitive to damage."

Microtubules make sure that cells are not fragmented when passing through pores

Whenever the cells successfully push their nucleus through a pore, they have to retract the nucleus-free protrusions, which are still inserted in the other pores, to avoid becoming entangled or even fragmented. To tell the protrusions to retract, the [microtubules](#) disappear from these protrusions as soon as the microtubule organizing center (which always follows the nucleus) passes through a [pore](#).

This disappearance of the microtubules triggers actomyosin contraction, and the cell finally retracts the remaining protrusions. When the researchers actively destroyed the microtubules, the cells entangled because the supernumerary protrusions had not retracted, kept moving forward through other pores and migrated in many directions.

Ultimately, the cell fractured into pieces and died.

"Our findings are based on the analysis of leukocytes. Yet, most probably, the mechanisms are the same for any other amoeboid cell types involved in developmental, immunity or regeneration processes. Also, the mechanism might help to explain how cancer [cells](#) move from one part of the body to another to form metastases and, most importantly, how to stop them from doing so," Michael Sixt concludes.

The results of this study are reported in *Nature*.

More information: Nuclear positioning facilitates amoeboid migration along the path of least resistance. *Nature* [DOI: 10.1038/s41586-019-1087-5](https://doi.org/10.1038/s41586-019-1087-5) , www.nature.com/articles/s41586-019-1087-5

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