'Nano-sensing' drives melanoma cells' invasion

March 15 2016, by William Weir

A new study sheds light on how melanoma cells change from benign to malignant, and how the complex interaction between the cells and their surrounding environment affects outcomes of the cancer.

The transition from the radial growth patterns of benign melanoma cells to the vertical patterns of malignant cells has long been a mystery to researchers. But a study from the lab of Andre Levchenko, the John C. Malone Professor of Biomedical Engineering and director of the Yale Systems Biology Institute, has found that the cells' stiffness—determined by the specific balance of two signaling pathways—plays a major role in directing cell migration through the complex environment. Cells essentially sense and follow the nanoscale topography, a phenomenon the researchers have coined "topotaxis."

The findings, published in the online edition of the journal *Nature Materials* on March 14, could lead to new treatments and diagnostic tests, the researchers said.

Levchenko and his colleagues found that melanoma cells in the extracellular matrix (ECM)—the body's living tissue—migrate toward either dense or sparse areas of the matrix. Benign cells veer toward the dense area, where they have little room to move and stay on the surface. Malignant cells move toward sparse areas that allow them to grab onto the fibers of the matrix and more effectively spread out.

This directed migration of the cells is partly dependent on the cells'

material properties: Because they can negotiate the topography better, soft invasive cells are more capable of spreading out than stiff cells. How aggressively the cells move is determined by the chemical cues they receive. Contained in the matrix itself, these cues are processed by a network of pathways that breaks off into two branches. The direction of the cells' migration depends on which branch is dominant.

The balance of these pathways is determined by the genetic state of the cells. A mutation that causes the loss of the gene PTEN—a common genetic mutation in aggressive forms of melanoma—will alter the balance.

"We know now that we can interpret genetic changes in the context of this signaling network, which enables us to understand better why genetic changes may lead to metastatic spread," said Levchenko, who is a member of the Yale Cancer Center.

These findings also suggest avenues for reversing that invasive transition in cell behavior. It doesn't necessarily require restoring the PTEN gene, but restoring the balance of the pathways to their original state through genetic manipulations or using a set of drugs.

"In our experiments, we can take a cell that's aggressive and make it revert to a benign form and vice versa," he said. "As soon as you change the balance, the cells start moving in the opposition direction."

To study the cell behavior, Levchenko's lab is using models of the matrix made from precisely nanofabricated quasi-3D environments. More complex than the 2D environments of Petri dishes, these environments feature the complex topography and textures of ECM, but are more readily analyzed than the actual tissue.

"Here it's more controlled—we can measure cell stiffness, we can

measure activity of these pathways and networks, we can very precisely control the activity of the cells."

Levchenko also sees a potential in the findings for a less invasive diagnostic test.

"We can take cells and drop them on these nanofabricated surfaces to mimic the matrix, and depending on where they move, we can actually tell whether they're benign or malignant," he said. "That gives us an interesting possibility that didn't exist before—to characterize the degree of invasiveness based on how the cells behave."

More information: Directed migration of cancer cells by the graded texture of the underlying matrix, *Nature Materials*, DOI: 10.1038/nmat4586

Provided by Yale University