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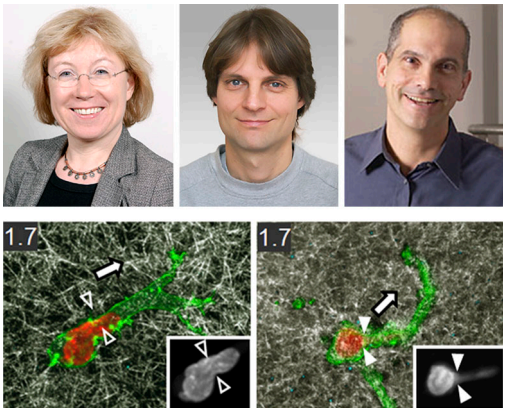
Testing the limits of cell migration

Migrating cells are restricted by their ability to squeeze their nuclei through pores in the extracellular matrix.

Focal Point



(Top row, left to right) Katarina Wolf, Peter Friedl, Stephen Weiss, and colleagues (not pictured) collaborate to explain how the physical properties of collagen matrices limit cell migration. (Bottom row) In the absence of protease activity, a tumor cell (green) can deform its nucleus (red) to migrate through the relatively large pores of a matrix formed from bovine dermal collagen (left). The nucleus can't be squeezed through the much smaller pores of a matrix assembled from rat tail collagen (right), causing the cell to arrest unless matrix metalloproteinases can enlarge the pores by cleaving collagen fibers.

PHOTOS COURTESY OF KATARINA WOLF AND NICO LAAN (WOLF); UMC ST. RADBOUD (FRIEDL); AND UNIVERSITY OF MICHIGAN (WEISS)

When tumor cells migrate through three-dimensional collagen gels, their passage is eased by the membrane-tethered matrix metalloproteinase MT1-MMP, which degrades the surrounding extracellular matrix (ECM). Whether MT1-MMP is absolutely required for migration is unclear, however. Two groups with opposing views on the subject now come together to reveal that cells can cope without the protease as long as there are pores in the matrix large enough to accommodate the cell nucleus (1).

In 2003, Katarina Wolf, Peter Friedl, and colleagues reported that certain tumor cells, including HT1080 fibrosarcoma cells, adopted an elongated, mesenchymal shape as they moved through 3D collagen matrices, using MT1-MMP to degrade ECM along the way. When MT1-MMP was inhibited, the cells switched to a more rounded, amoeboid morphology and continued to migrate through the matrix (2). Shortly afterwards, however, Stephen Weiss' group at the University of Michigan found that MT1-MMP inhibition stopped HT1080 cells dead in their tracks (3, 4). The discrepancy appeared to lie in the different collagen preparations the two groups used in their experiments. Wolf and Friedl used collagen isolated from bovine dermis, which had been treated with the protease pepsin to reduce the number of interfibrillar crosslinks. Weiss, on the other hand, used highly crosslinked collagen extracted from rat tails.

"Other labs did side-by-side comparisons of the two types of matrix, and they found the same differences in cell behavior," says Wolf, who, along with Friedl, now works at Radboud University Nijmegen Medical Centre in the Netherlands. "But they didn't determine why."

Friedl suggested to Weiss that the two groups work on the problem together. Weiss agreed. "The pursuit of knowledge drove the collaboration," he explains. "Both groups wanted to resolve the discrepancies."

> "The pore dimensions determine whether or not a cell can move non-proteolytically."

Wolf et al. found that matrices formed from bovine dermal collagen—which permit MMP-independent migration—contained larger pores than matrices formed by the same concentration of rat tail collagen. When the researchers used increasing concentrations of bovine dermal collagen, they formed matrices with smaller pores that impeded the migration of HT1080 cells in the presence of MMP inhibitors. Eventually, the matrix pores got so small that the tumor cells couldn't move at all in the absence of MMP activity. On the other hand, MMP-impaired HT1080 cells could migrate through matrices formed from low concentrations of rat tail collagen or when collagen polymerization was delayed by low temperature, producing gels with larger pores than normal. "So the pore dimensions determine whether or not a cell can move nonproteolytically, irrespective of the collagen preparation," Friedl explains.

Pore size appears to limit migration by restricting movement of the nucleus, the cell's largest and stiffest organelle. HT1080 cells could squeeze through pores approximately 2.5 µm in diameter by deforming their nuclei into hourglass shapes. When confronted with pores smaller than this, however, cells couldn't compress their nuclei enough to fit through. At this point, the researchers agree, MT1-MMP becomes indispensable for migration because it can widen matrix pores by cleaving collagen fibers. The researchers reached similar conclusions using other, nontumor cell types, which showed different sensitivities to pore size due to variations in the size and pliability of their nuclei.

Wolf et al. identified two other factors that help cells maneuver through narrow gaps in the ECM. Integrins at the cell's leading edge attach to collagen fibers and generate traction to pull the nucleus through tight spaces, whereas actomyosin contractility, likely at the cell rear, helps push the nucleus forward. Inhibiting integrins or cell contractility reduced cells' progress through collagen gels, but enlarging matrix pore size restored migration speeds.

The next question is to determine the size of pores in collagen matrices in vivo. Weiss says this isn't completely clear, although by using intravital imaging Wolf and Friedl have observed relatively large gaps that cells could potentially navigate without the aid of proteases (5). MMP inhibitors may therefore fail to restrict the spread of cancer cells in vivo.

1. Wolf, K., et al. 2013. *J. Cell Biol.* http://dx.doi.org/10.1083/jcb.201210152.
2. Wolf, K., et al. 2003. *J. Cell Biol.* 160:267–277.
3. Sabeh, F., et al. 2004. *J. Cell Biol.* 167:769–781.
4. Sabeh, F., et al. 2009. *J. Cell Biol.* 185:11–19.
5. Weigelin, B., et al. 2012. *IntraVital.* 1:32–43.