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CELL MIGRATION

Feeling the squeeze

Migrating cells use a multitude of resources to navigate a varying landscape of extracellular matrix (ECM). They degrade matrix locally using matrix metalloproteinases (MMPs) and use both integrin-mediated adhesion to the ECM and actomyosin-mediated contraction at the cell rear to move forward. The Weiss and Friedl groups have now teamed up to examine the relative importance of these different parameters, and find that ultimately cell migration becomes limited physically by the size of matrix pores and the ability to squeeze the nucleus through these tight spaces.

There have been inconsistent reports of how crucial MMP activity is for cell migration through the ECM. The two groups thus set out to systematically assess how cell migration varies in defined three-dimensional (3D) matrix environments and what the rate-limiting parameters are. They reconstituted 3D hydrogels consisting of matrices of varying densities and pore sizes. They then showed that although HT1080 fibrosarcoma cells can migrate in different matrices if proteolytic MMP activity is intact, inhibition of proteolytic activity rendered the cells sensitive to the pore size of the matrix. Cell migration speed correlated linearly with pore size, and this was independent of the matrix stiffness. Once the pore size was reduced below a certain point (~7 μm^2), cells lacking proteolytic activity became trapped.

A key change in cells undergoing MMP-independent migration was deformation of the nucleus. Nuclei adopted hourglass or longitudinal shapes as cells squeezed through smaller pores in the matrix; and their diameter decreased as the pore size of the matrix was reduced, until a minimum cell type-specific threshold was reached and cells were immobilized.

Cell migration requires both traction, generated by integrin-mediated adhesion to the matrix, and forward movement of the cell rear, initiated by actomyosin-dependent contractility. The authors therefore assessed how these processes affect the efficiency of cell migration under conditions in which nuclear deformation is not rate-limiting. Using antibodies or inhibitors that specifically block the function of either integrins or myosin, they showed that both of these processes modulate the efficiency of MMP-independent migration when matrix density, and thereby pore size, becomes restrictive.

Thus, cells are equipped with multiple means to enable migration through matrices of varying pore size, and this allows them to navigate a range of landscapes in the absence of proteolytic activity. But ultimately, the ability to move through restricted spaces becomes limited by their nucleus. These findings should make it now possible to better interpret the migratory behaviour of cells in a range of environments *in vivo*.

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> “ultimately, the ability to move through restricted spaces is limited by their nucleus”

ORIGINAL RESEARCH PAPER Wolf, K. *et al.* Physical limits of cell migration: control by ECM space and nuclear deformation and tuning by proteolysis and traction force. *J. Cell Biol.* **201**, 1069–1084 (2013)