CELL MIGRATION

Switching to 3D

Cell migration on two-dimensional (2D) surfaces is well characterized; in the 2D cell migration model, cells repeatedly extend lamellipodia (actin-rich protrusions) at the leading edge, adhere to the substrate and then retract the trailing edge. This migration mode relies on highly polarized signalling that involves the second messenger phosphatidylinositol-3,4,5-trisphosphate (PtdIns(3,4,5)P_3) and the RHO family members RAC1, CDC42 and RHOA, which are all enriched at the leading edge to coordinate cell protrusion. By contrast, the mechanisms underlying 3D migration *in vivo* are not well understood; Petrie *et al.* now show that cells can switch between lamellipodium-based and lobopodium-based migration in 3D matrices, and that this depends on both the degree of polarization of intracellular signalling and the physical properties of the extracellular matrix (ECM).

The authors first observed that many human fibroblasts migrating in dermal tissue explants formed large blunt, cylindrical protrusions called lobopodia.

They then went on to study cell migration in two *in vitro* models of the 3D ECM, namely cell-derived matrix (CDM) and collagen, to define the mechanistic basis of lobopodium-dependent cell motility. CDM has the same mechanical properties as dermal explants as it is stiff and linearly elastic (that is, it does not undergo strain-induced stiffening), whereas collagen is soft and nonlinearly elastic (with a strain-stiffening behaviour). Fibroblasts migrating in CDM formed lobopodia, whereas they formed multiple protrusions tipped with small lamellipodia when placed in collagen. Interestingly, lobopodium-dependent migration was specific to the 3D ECM, as cells displayed the characteristic lamellipodium-based migration when placed on 2D CDM surfaces. Importantly, when collagen or CDM were treated to modify their elastic properties from linear to nonlinear, and vice versa, cells switched their type of migration, which suggests that the elastic properties of the matrix dictate the mode of 3D migration.

> “the elastic properties of the matrix dictate the mode of 3D migration”

Next, the authors imaged the localization of PtdIns(3,4,5)P_3, and of the active forms of RAC1 and CDC42, in fibroblasts that migrated using lobopodia in 3D CDM. They observed that these signalling molecules were not polarized towards the leading edge, but were instead distributed in patches around the cell perimeter. By contrast, PtdIns(3,4,5)P_3, RAC1 and CDC42 were concentrated at the leading edge of the small lamellipodia during migration in 3D collagen. Thus, signalling polarization is not required for lobopodium-based migration.

Finally, small interfering RNA (siRNA)-mediated knockdown of RAC1 or CDC42 did not affect lobopodium-mediated cell motility, indicating that RAC1 and CDC42 are dispensable for lobopodia formation. By contrast, knockdown or chemical inhibition of RHOA, its effector ROCK or the ROCK target myosin II induced a switch from lobopodium-based to lamellipodium-based migration in 3D CDM. Thus, RHOA, ROCK and myosin II are required for lobopodium-based migration.

This work identifies two modes of integrin-dependent 3D migration *in vitro*; whether migrating cells other than fibroblasts use lobopodia, and in which physiological conditions, awaits further confirmation.

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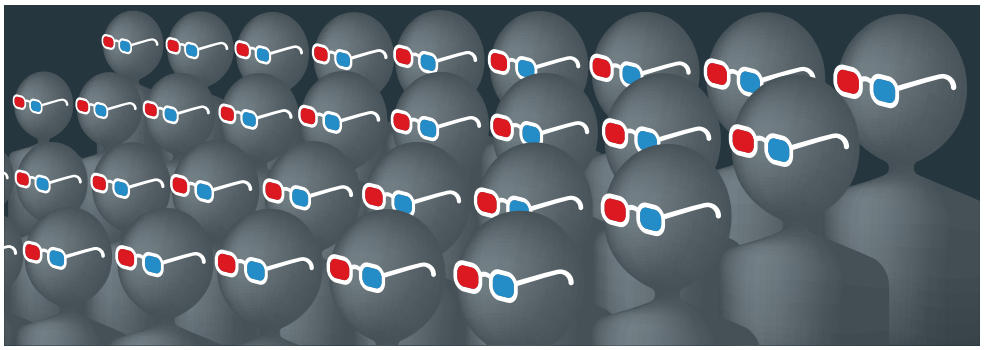

Vicky Summersby/NPG

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