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Adhesion-independent topography-based leukocyte migration.

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Faculty Opinions

Adhesion-independent topography-based leukocyte migration

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EVALUATION OF

Landmark

Cellular locomotion using environmental topography.

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Cells need to couple intracellular actin flows with the substrate to generate forward movement. This has traditionally been studied in the context of specific transmembrane receptors, particularly integrin adhesion receptors, which link extracellular adhesive molecules to the actin cytoskeleton. However, leukocytes and other cells can also migrate using integrin-independent strategies both *in vivo* and *in vitro*, though the cellular and environmental requirements for this mode are not fully understood. In seminal recent work, Reversat *et al*.[1] develop a range of innovative 2D and 3D engineered microdevices and probe the biophysical mechanisms underlying T lymphocytes and dendritic cells in conditions of limited substrate adhesion. They identify a physical principle of mechano-coupling between retrograde actin flow and irregular extracellular confinement, which allows the cell to generate mechanical resistance and move in the absence of receptor-mediated adhesion. Through the combined use of experiments and theoretical modeling, this work resolves a long-standing question in cell biology and establishes mechanical interaction with an irregular-shaped 3D environment which may be relevant to cell migration in a range of tissue contexts.

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Background

The mechanisms by which moving cells in different experimental and live-tissue environments contact their environments to generate migration force through their actin cytoskeleton can be diverse, with varying adhesion systems being engaged. It has previously been established experimentally that leukocytes and other cells are able to move without the need for integrin adhesion receptors[2–6]. This raised questions of whether alternative adhesion receptors generate substrate engagement with the cytoskeleton or whether the movement could also occur fully independent of adhesive interaction. A mode of adhesion-independent movement is likely important for leukocytes *in vivo*, which have to negotiate a wide range of physiological substrates and wound environments[7]. Non-adhesive migration has been proposed before and conceptualized as "chimneying", by which cells intercalate mechanically between 3D substrate interfaces; however, whether this mode of migration is truly adhesion-independent has been unclear.

Main contributions and importance

In this study, Reversat and co-workers developed the hypothesis that adhesion-independent migration is mediated by length-limited actin flux along extracellular topographic cues, which was then tested and confirmed experimentally in cells and using *in silico* modeling[1]. A new microfluidic device design was developed, which completely prevents adhesive interactions by cells but offers a range of different 2D and 3D, regular and irregular topologies. By probing T lymphoma cells in these non-adhesive environments and *in silico* modeling of cytoskeletal organization and forces, they show that retrograde actin flow can 'intercalate' with irregular substrate topology, with the force transmission depending on the relative angle of cell-substrate interface and the channel in which the cell is migrating. In spatially narrow (somewhat below the cell size) and topologically irregular 3D confinement, the movement occurred without adhesion. This secures cell migration under conditions of irregular extracellular confinement; not, however, when physical cues are smooth and retrograde actin flow loses grip and cannot translate into effective cell propulsion. A minimal mathematical model suggests that actin flow along irregular extracellular confinement drives the pressure gradients that support adhesion-independent cell migration.

The physical principle of mechano-coupling between retrograde actin flow and irregular extracellular confinement identified in this work is of fundamental importance as it provides a basic mechanism that is likely to operate in a wide range of cellular contexts.

Open questions

It remains to be elucidated under which conditions this topological mechanism is relevant and whether it applies only to leukocytes or also to other cell types. It is further unclear how this mechanism cooperates with other types of cell-substrate interactions, including high and low-affinity adhesions, or other types of topological intercalation, including the glycocalyx[8] or clathrin-based membrane wrapping around collagen fibers[9].

Migration experiments through microchannels were performed using stiff polydimethylsiloxane (PDMS); thus, it remains to be determined how the stiffness or the viscoelasticity of the surrounding microenvironment affect this motility mechanism and whether it is used in protein-based tissue environments and *in vivo*.

The mechanism identified requires that the cells are 'confined' by their environment; without confinement,

the retrograde actin flow would not be adjacent to the substrate. This raises additional questions about the role of osmolyte balance in generating the hydrostatic force to press the cell surface against the variable substrate topology. In addition, it is possible for the nucleus to act as another rigid body in confrontation with the channel topographies and enhance the mechanical force generated by the retrograde actin flow.

Conclusion

The physical principle of mechano-coupling between retrograde actin flow and irregular extracellular confinement is of fundamental importance, as it may be at work in a broad range of migratory contexts, in addition to receptor-based adhesive mechanisms.

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