CellPress

Review

Fibroblasts Lead the Way: A Unified View of 3D Cell Motility

Ryan J. Petrie* and Kenneth M. Yamada*

Primary human fibroblasts are remarkably adaptable, able to migrate in differing types of physiological 3D tissue and on rigid 2D tissue culture surfaces. The crawling behavior of these and other vertebrate cells has been studied intensively, which has helped generate the concept of the cell motility cycle as a comprehensive model of 2D cell migration. However, this model fails to explain how cells force their large nuclei through the confines of a 3D matrix environment and why primary fibroblasts can use more than one mechanism to move in 3D. Recent work shows that the intracellular localization of myosin II activity is governed by cell–matrix interactions to both force the nucleus through the extracellular matrix (ECM) and dictate the type of protrusions used to migrate in 3D.

Trends

Primary human fibroblasts can transition between three distinct mechanisms of migration in 3D extracellular matrix.

The degree of actomyosin contractility and cell–matrix adhesion helps to dictate the mode of cell migration.

The modes of migration are distinguished, in part, by the intracellular localization of myosin II and the type of protrusion used by the cell to migrate.

The mechanism by which a cell moves its bulky nucleus through the fibrillar matrix also governs intracellular pressure and the type of protrusion used to migrate.

Moving from 2D to 3D Environments

The ability of cells to navigate diverse 3D environments is essential for many aspects of multicellular life. For example, immune cells patrol structurally diverse tissues to detect and fight infections, while fibroblasts move through the dermis to sites of tissue damage, where they remake the matrix and help to restore the barrier function of the skin. Conversely, the inappropriate 3D migration of metastatic cancer cells can be lethal. Discovering the molecular mechanisms driving 3D fibroblast migration could improve our understanding of normal wound healing, as well as fibroblast-mediated pathologies, such as tissue fibrosis or tumor progression and metastasis. Additionally, by learning how normal, primary human cells move in 3D, we could establish whether the motility mechanisms used by single invading cancer cells are abnormal. Such cancer-specific mechanisms of 3D movement might then be targeted therapeutically to reduce metastasis, while leaving the movement of untransformed cells, such as fibroblasts, relatively unaffected.

Ideally, cell movement should be studied in a physiologically relevant 3D tissue. The discovery that primary fibroblasts can crawl out of tissue explants and onto rigid 2D tissue culture surfaces enabled the pioneers of the field of cell behavior to infer underlying molecular mechanisms [1,2]. The imaging of dynamic cell movements, along with biochemistry and genetics helped to establish the mechanistic basis of primary fibroblast motility as a conceptual cycle of four steps, known as the cell motility cycle [3,4].

Together, the steps of the 2D cell motility cycle generate directional lamellipodial movement (Figure 1B). First, polarized signaling by phosphatidylinositol (3,4,5)-trisphosphate (PIP3) [5] and the small GTPases Ras-related C3 botulinum toxin substrate 1 (Rac1) [6] and Cell division control protein 42 (Cdc42) [7] direct actin nucleating proteins, such as Arp 2/3 [8], to help polymerize branched actin filaments (F-actin) against the plasma membrane to initiate protrusion of a lamellipodium [9]. Second, integrin receptors in the protruding plasma membrane bind matrix ligands on the 2D surface and cluster to form small nascent adhesions [10]. Third, Ras homolog gene family, member A (RhoA) and the formin family of actin nucleators, such as Protein diaphanous homolog 1 and 2 (mDia1 and 2), help assemble actin stress fibers to connect the

Laboratory of Cell and Developmental Biology, National Institute of Dental and Craniofacial Research, National Institutes of Health, Bethesda, MD 20892, USA

*Correspondence. petrier@mail.nih.gov (R.J. Petrie), kyamada@mail.nih.gov (K.M. Yamada).

 http://dx.doi.org/10.1016/j.tcb.2015.07.013
Published by Elsevier Ltd.

CellPress

Key Figure

Three Distinct Mechanisms of Fibroblast Migration

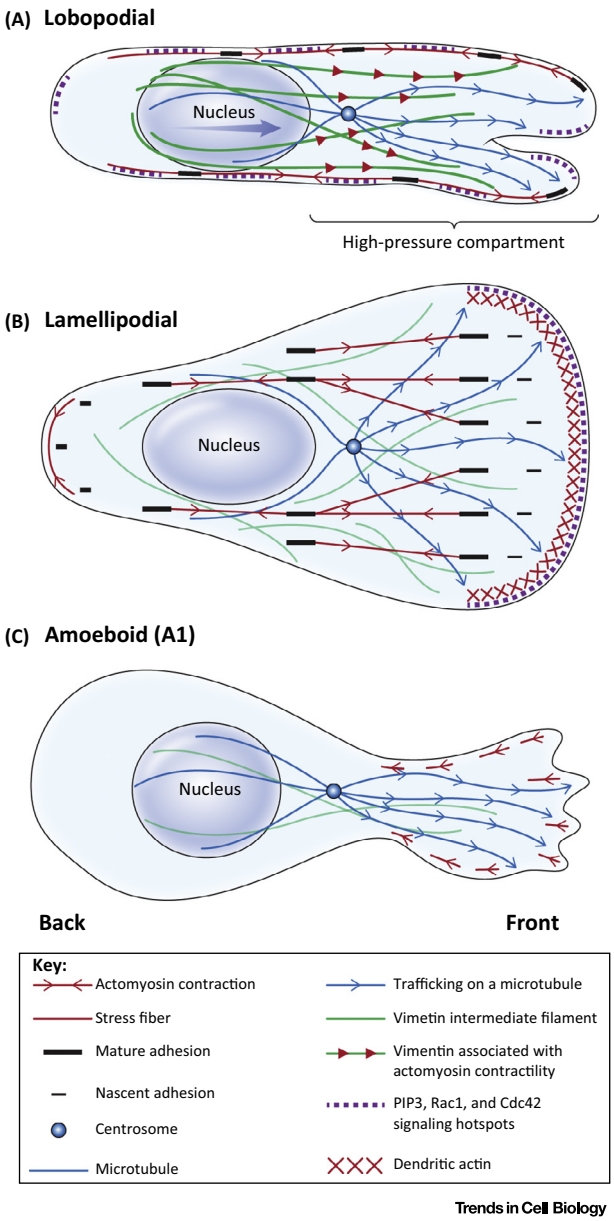

Figure 1. (A) High-pressure 3D migration. In lobopodial cells, polarized myosin II acts through vimentin filaments and the nucleoskeleton–cytoskeleton linker protein nesprin 3 to pull the nucleus forward and raise intracellular pressure. This high pressure causes the membrane to protrude and allows new cell–matrix adhesions to form. We speculate that connections are then made to link the new adhesions to older adhesions in the cortex, and to the lamin-based nucleoskeleton. Myosin II-independent forces bring the cell rear forward as cell–matrix adhesions disassemble. In lobopodial fibroblasts, the nucleus can act as a piston, physically separating the cell into two compartments and raising the pressure in front to produce lamellipodia-independent protrusion. While Ras-related C3 botulinum toxin substrate 1 (Rac1), Cell division control protein 42 (Cdc42), and phosphatidylinositol (3,4,5)-trisphosphate (PIP3) signaling are nonpolarized in these polarized cells, microtubules might provide polarity in response to matrix topography. (B) 2D and 3D lamellipodia-based movement. Membrane protrusion by actin polymerization allows the formation of new membrane–matrix contacts. Actomyosin contractility throughout the cell strengthens these adhesions and increases cellular tension without increasing intracellular pressure. Adhesions disassemble at the back of the cell, and actomyosin contractility retracts the trailing edge to help the cell body glide forward. Polarized signaling by Rac1, Cdc42, and PIP3 coordinates protrusion and adhesion formation. Microtubules deliver additional polarity cues to the front of the cell, along with membrane and lipid components. (C) Adhesion-independent 'amoeboid' fibroblast 3D motility. When cells are not strongly adherent to the substrate, myosin II-driven retrograde flow of actomyosin occurs only in the leading protrusions and likely leads to a relative uniform distribution of myosin II in the cell cortex. These cells are unable to generate productive forward movement on a 2D surface. However, when these cells are compressed between two surfaces, the resulting friction is sufficient to translate force, presumably from the retrograde flow of the cortical cytoskeleton, into forward movement of the cell. Box 1 (main text) discusses how the physical structure of the matrix can help determine 3D migration mechanisms.