Cell

# Cell Migration, Freshly Squeezed

Matthew D. Welch[1,*]
[1]Department of Molecular and Cell Biology, University of California, Berkeley, Berkeley, CA 94720, USA
*Correspondence: welch@berkeley.edu
http://dx.doi.org/10.1016/j.cell.2015.01.053

**Migrating cells exhibit distinct motility modes and can switch between modes based on chemical or physical cues. Liu et al. and Ruprecht et al. now describe how confinement and contractility influence motility mode plasticity and instigate a mode termed stable bleb migration in embryonic and tumor cells.**

Crawling cell migration arose early in the evolution of eukaryotes and is exhibited by diverse eukaryotic lineages (Fritz-Laylin et al., 2010). In multicellular animals, cell migration is crucial in development, tissue maintenance, and immunity. Cell migration gone awry can also contribute to disease, for example, during cancer invasion and metastasis (Friedl and Alexander, 2011). The migration behaviors of animal cells are heterogeneous and differ depending on cell type, developmental stage, local environment, and disease state. In this issue of *Cell*, studies from the Piel group (Liu et al., 2015) and Heisenberg group (Ruprecht et al., 2015) uncover how the plasticity of cell migration behaviors is impacted by the strength of adhesion, physical confinement (squeezing between two surfaces), contractility, and chemical cues.

To make sense of the heterogeneity of migration behaviors, the migration modes of single cells have been divided into two broad categories—mesenchymal and amoeboid—based on cell morphology, mechanism of force generation, cytoskeleton organization, and characteristics of the cell-substrate interaction (Figure 1) (Friedl and Wolf, 2010). The mesenchymal mode, exemplified by fibroblasts, is typified by slower velocity, irregular shape, strong cell-substrate adhesion, prominent actin stress fibers, and actin-rich leading edge structures, including lamellipodia and filopodia (Gardel et al., 2010). The amoeboid category is characterized by a faster velocity, rounder shape, weaker cell-substrate adhesion, and the absence of stress fibers (Lämmermann and Sixt, 2009). Distinct amoeboid motility modes, however, employ different leading edge structures. Immune cells typically form actin-rich pseudopods at their leading edge (Figure 1, pseudopod mode), for which protrusion is driven by local actin assembly. Other cells—zebrafish primordial germ cells, for example—instead form actin-deficient blebs at their leading edge, for which protrusion is driven in part by contraction at the rear by actin and myosin II (Figure 1, bleb mode) (Paluch and Raz, 2013). There is plasticity between motility modes, and cells can switch between modes, depending their environment (Friedl and Wolf, 2010).

To investigate the effects of adhesion strength and physical confinement on cell migration plasticity, Liu et al. (2015) systematically vary the strength of adhesion and degree of confinement of a fibroblast cell line that normally migrates in the mesenchymal mode. They observe that, under conditions of low 2D adhesion and high 3D confinement (Figure 1), fibroblast cells switch from mesenchymal to one of two higher-velocity amoeboid motility modes, a so-called mesenchymal-to-amoeboid transition (MAT). Cells migrating in the A1 mode have a round cell body and small leading edge resembling a pseudopod or lamellipod. Unexpectedly, cells migrating in the A2 mode have an unusually long and ellipsoid cell body and leading edge. Examination of numerous other cell lines shows that many favor one mode or the other, but some exhibit both modes. Notably, transformed and tumor cells, as well as leukocytes, prefer the A2 mode. These findings suggest that individual cell lines exhibit migration mode plasticity and that adhesion strength and confinement are key parameters in controlling migration behavior.

At the molecular level, Liu et al. (2015) find that the ability of tumor cells to switch to the A2 mode depends on diminished activity of proteins that contribute to cell-substrate adhesion. Moreover, conditions of high contractility generated by myosin II favor the A2 mode, whereas conditions of low contractility favor the A1 mode. The driving force for the A2 mode is linked to global retrograde flow of actin and myosin II in the central region of the cell, whereas the A1 mode is linked to retrograde flow only in the leading edge. In A2 cells, the result of more global cortical flow of actin and myosin II is the accumulation of these proteins at the cell rear and the formation of a stable bleb at the leading edge that is largely devoid of actin. Mathematical modeling also predicts the appearance of this stable bleb in a regime of high contractility. In a previous study, cells migrating with a stable bleb-like protrusion dependent on myosin II function were observed in *Dictyostelium discoidium* treated with quinine, although the physiological significance remained unclear (Yoshida and Inouye, 2001). The Liu et al. (2015) study advances this earlier work by examining physiologically relevant environmental factors that influence migration plasticity and stable bleb migration and by providing a mechanistic description of motility.

In a companion study, Ruprecht et al. (2015) examine the migration modes of primary germ layer progenitor cells isolated from zebrafish embryos. They find that cells plated on a 2D substrate undergo amoeboid blebbing or mesenchymal motility, depending on the germ layer origin of the cells and the extracellular matrix composition of the substrate. However, if cells of various origins are treated with serum or the serum component lysophosphatidic acid (LPA), they switch to a rapid amoeboid motility

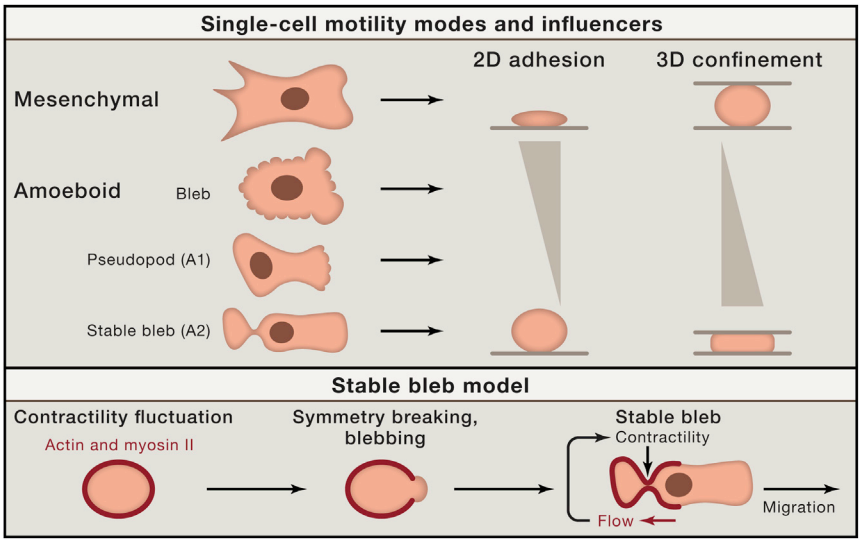


**Figure 1. Motility Modes, Influencing Parameters, and the Initiation and Maintenance of Stable Bleb Motility**

Motility modes include mesenchymal motility, or various forms of amoeboid motility characterized by blebs, pseudopods, or stable blebs. These are influenced by environmental factors, including the strength of adhesion to the substrate, or the extent of physical confinement and contractility. The formation of a stable bleb is theorized to involve fluctuations in cortical contractility, followed by symmetry breaking and the formation of a bleb. Cortical flow of actin and myosin II toward the cell rear then enhances contractility in this location, stabilizing the formation of a single bleb at the front and generating force that drives migration.

mode characterized by the formation of a single stable bleb, similar to the A2 mode described by Liu et al. (2015). Spatial confinement of zebrafish cells in the absence of serum also induces stable bleb formation and migration. Furthermore, for both LPA-induced and confinement-induced stable bleb migration, myosin II accumulate at the rear of the cell, and myosin-II-driven contractile activity is required. These results, together with those of Liu et al. (2015), indicate that stable bleb motility is observed in primary cells and cell lines isolated from various animal species.

To understand how cortical contractility contributes to stable bleb motility, Ruprecht et al. (2015) develop a mathematical description of this process. Their model predicts that local fluctuations in cortical contractility at the cell periphery are amplified by external cues or physical confinement, causing symmetry breaking and initial polarization (Figure 1). Cell polarization is then enhanced and stabilized by positive feedback between cortical flow of actin and myosin II toward the cell rear and the formation of a cortical contractility gradient that reinforces flow. In support of this model, they observe coupling of cortical flow of actin and myosin to stable bleb migration. Thus, the theoretical model and experimental evidence suggest that contractility itself is sufficient to initiate stable bleb motility.

They then examine the incidence of stable bleb motility in zebrafish embryos in response to contractility. Cells expressing a constitutively active variant of the Rho family G protein RhoA (to enhance cortical contractility) exhibit similar shape, migration behavior, and cortical actin and myosin II flows as stable bleb cells in vitro. Moreover, when transferred into cell culture, these cells exhibit characteristics indistinguishable from primary germ layer cells undergoing stable bleb motility. Notably, at wounding sites in embryos, which exhibit high levels of contractility, cells not expressing exogenous RhoA also assume a stable bleb motility mode and migrate from the wounding site with the rapid speed, directional persistence, and characteristics of stable bleb cells in vitro. This confirms that stable bleb motility initiates at regions of high contractility in a developing embryo.

The findings of Liu et al. (2015) and Ruprecht et al. (2015) for animal cells, along with the previous study of *Dictyostelium* amoeba (Yoshida and Inouye, 2001), suggest that stable bleb motility is a fundamental motility mode of eukaryotic cells and that it operates in a variety of contexts. These may include embryonic development, where it is speculated that this rapid and directionally persistent motility enables extrusion of cells from regions of high contractility and mediates long-range cell interactions. Moreover, stable bleb motility is prevalent in transformed and tumor cells subjected to confinement, suggesting that it may be a fundamental property related to invasion and metastasis. Future work will establish the detailed mechanisms of force generation during stable bleb motility, the contribution of this process to development and tissue maintenance, and the impact of this form of migration on cancer and other diseases.

## REFERENCES


Friedl, P., and Alexander, S. (2011). Cell *147*, 992–1009.

Friedl, P., and Wolf, K. (2010). J. Cell Biol. *188*, 11–19.

Fritz-Laylin, L.K., Prochnik, S.E., Ginger, M.L., Dacks, J.B., Carpenter, M.L., Field, M.C., Kuo, A., Paredez, A., Chapman, J., Pham, J., et al. (2010). Cell *140*, 631–642.

Gardel, M.L., Schneider, I.C., Aratyn-Schaus, Y., and Waterman, C.M. (2010). Annu. Rev. Cell Dev. Biol. *26*, 315–333.

Lämmermann, T., and Sixt, M. (2009). Curr. Opin. Cell Biol. *21*, 636–644.

Liu, Y.-J., Le Berre, M., Lautenschlaeger, F., Maiuri, P., Callan-Jones, A., Heuzé, M., Takaki, T., Voituriez, R., and Piel, M. (2015). Cell *160*, this issue, 659–672.

Paluch, E.K., and Raz, E. (2013). Curr. Opin. Cell Biol. *25*, 582–590.

Ruprecht, V., Wieser, S., Callan-Jones, A., Smutny, M., Morita, H., Sako, K., Barone, V., Ritsch-Marte, M., Sixt, M., Voituriez, R., and Heisenberg, C.-P. (2015). Cell *160*, this issue, 673–685.

Yoshida, K., and Inouye, K. (2001). J. Cell Sci. *114*, 2155–2165.