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The symphony of cell movement: how cells orchestrate diverse signals and forces to control migration

Editorial overview

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Carole Parent is a Senior Investigator at the Laboratory of Cellular and Molecular Biology at the National Cancer Institute in Bethesda, MD. Her research interests are centered on understanding how cells detect and respond to external chemotactic signals and, in particular, how the relay of chemotactic signals from cell-to-cell impacts single and group cell migration under physiological and pathological conditions.

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Orion Weiner is in the Cardiovascular Research Institute and the Department of Biochemistry & Biophysics at the University of California at San Francisco. He seeks to understand how signaling networks generate cell polarity, motility and other complex behaviors. Towards this end, his lab is developing tools for manipulating cell signaling with light as well as new techniques for interrogating how physical forces and biochemical signals interact to orchestrate cell polarity.

Many cells rely on directed movement to properly interact with their surroundings. Directed migration is essential for single celled organisms to hunt and mate and for multicellular organisms to regulate development, wound healing and immune cell surveillance. To reach their proper destination, cells must coordinate multiple processes, including protrusions, adhesions and retractions and integrate distinct guidance cues that range from soluble chemoattractants and chemorepellants to adhesive cues, electric fields and physical forces. This issue of *Current Opinion in Cell Biology* will highlight our current understanding of the events that regulate directed cell migration. Starting with a description of how external cues are transduced into intracellular signals that regulate protrusion, adhesion and retraction, we continue with discussions on the role of mechanotransduction and the forces associated with it during migration. Finally, a view on how cell motility is regulated in complex 3-dimensional (3D) and intravital settings is provided.

We begin with [Insall](#), who suggests that directional migration is best understood from a pseudopod-centered view, and that chemotaxis is an inevitable outcome of guidance cues interfacing with a self-organized motility machine. Under this view, cells do not have an internal ‘compass’ that tells them which direction to go, but directional guidance emerges nonetheless by external cues biasing self-organizing pseudopods. [Jin](#) sets up the challenge of how cells read and respond to gradients during chemotaxis. In prokaryotes, the machinery and logic of gradient sensing, adaptation, signal amplification and motility are relatively well understood, but how eukaryotic cells accomplish these behaviors is only just emerging. [Zhang et al.](#) explain how mathematics are becoming an integral element of both the experimental and theoretical components of modern cell biology. Mathematics enable the extraction of quantitative information from microscopic images and help build migration models that predict behaviors, which may not be obvious through experiments or intuition alone. The next generation of cell biologists should be as comfortable with Matlab as they are with microscopes.

The signal transduction cascades regulating cell movement do not only rely on biochemical events such as protein phosphorylation and GTP/GDP exchange as their sole currencies. Physical forces such as membrane tension and substrate stiffness are also key information carriers in these cascades. How physical forces act as inputs and integrators of cell movement is a recurring theme in this issue and represents a focus of the next three reviews. [Roca-Cusachs et al.](#) describe the parallels between chemotaxis (directed migration in response to chemical cues) and mechanotaxis (directed migration in response to mechanical cues) and explain how both

of these involve an interplay between physical and chemical signals. [Shah and Keren](#) explain how mechanical forces and feedbacks enable the rapid dynamics of individual molecules to be integrated into the large-scale organization of migrating cells. [Ricca et al.](#) break down mechanotransduction on the basis of the type of input stimuli and the nature of the cell response. Passive inputs such as substrate stiffness require cells to expend energy to sense, whereas active inputs such as cell strain could be sensed without energy expenditure. Similarly, cells can respond to mechanical inputs either through passive material outputs, such as by undergoing viscoelastic deformation, or actively by executing biological programs such as transcriptional changes.

Migrating cells need protrusive fronts to push them along and contractile backs to bring up their rears. Protrusive structures such as lamellipodia are comprised of branched actin networks. [Scita et al.](#) provide an overview of some of the key signaling molecules that specify where and when these actin structures are assembled. [Svitkina](#) presents a high-resolution ultrastructural view of actin organization during cell protrusion, adhesion, endocytosis and other actin-based processes. However, actin-rich protrusions are not the only way to move a cell forward: [Paluch and Raz](#) introduce blebs, which are cell protrusions driven by hydrostatic pressure and lack filamentous actin during their initial extension phase. Some cells, such as zebrafish germ cells, move primarily with blebs, others such as fish keratocytes move with only actin based lamellipodia, and other cells such as metastatic cancer cells use a combination of the two. Next we move to the back of migrating cells where the textbook view is that myosin II-based motors power retraction. [Cramer](#) presents emerging evidence showing that myosin II is not the only game in town. Actin filament depolymerization, actin filament crosslinking and protrusive-based changes in membrane tension also contribute to retracting the trailing edge during cell migration.

The next review focuses on establishing the role of intermediate filaments during migration. Intermediate filaments are remarkable given their diversity and tissue-specific regulation. While their involvement in regulating the micromechanical properties of cells has been known for many years, their impact on cell migration is just beginning to be understood. [Chung et al.](#) provide a timely review on the topic, focusing on vimentin and keratin, which play key roles in a broad array of physiological and pathological processes. Because intermediate filaments directly regulate signaling effectors they can mediate effects on the cytoskeleton as well as on cell-cell and cell-substrate adhesion during migration.

Integrins have the ability to transduce forces exerted from the extracellular matrix (ECM) into cellular biochemical signals that regulate the cytoskeleton. These forces are

important in many physiological processes and in disease states such as cancer metastasis. The next four reviews describe the recent progress that has been made in deciphering the molecular mechanisms that mediate mechanotransduction. [Ross et al.](#) provide an update on the mechanisms by which ligand-integrin-cytoskeleton linkages are regulated by force, with a special emphasis on the role of talin, filamin A and zyxin, as well as the role of ion channels in lateral membrane tension sensing. [Plotnikov and Waterman](#) discuss the molecular events that mediate stiffness sensing, or durotaxis. Here again, the authors describe how integrin-based focal adhesions play an important role by acting as rigidity sensors linking local stiffness to myosin contractility, actin assembly and focal adhesion dynamics. [Jacquemet et al.](#) provide an overview on how the trafficking of integrin and syndecan receptors is important during 3D cell migration. Finally, [Glukhova and Streuli](#) present an in-depth description of the role of the ECM-integrin pathway during normal and malignant breast biology. They provide a fascinating view on how integrins regulate mammary stem cells, ductal and alveolar development and how they contribute to tissue disorganization during malignancy and metastasis.

The final three reviews focus on the role of ECM organization in relation to cell migration. While studying cell migration in 2-dimensional (2D) environments remains key in motility research as it provides an easy and reliable way to assess motility behaviors under a variety of complex conditions, it is essential to know if these behaviors are conserved in *in vivo*-like environments. [Doyle et al.](#) provide a valuable review on this topic. Surveying studies that mainly focus on fibroblasts, they compare and contrast the migration behaviors of cells in 1 dimension (1D), 2D and 3D and highlight the role of ECM composition, stiffness and topography on the migration response. [Lam and Huttenlocher](#) discuss the migration behavior of leukocytes during interstitial migration, mainly focusing on intravital studies in zebrafish and mouse. They approach the topic by describing our current understanding on how external chemical cues are transduced into intracellular signals, leading to highly polarized responses and effective migration in complex 3D spaces. Lastly, [Alexander et al.](#) discuss how recent advances in intravital microscopy have enabled the monitoring of cancer progression in a dynamic fashion, something that has only recently become feasible. Studies using this experimental paradigm are giving rise to novel concepts on how tumor cells are disseminated during metastasis. Furthermore, this approach is poised to provide pre-clinical applications in the identification of specific and effective treatment against tumor invasion.

In summary, this issue of *Current Opinion in Cell Biology* provides an up-to-date account of our understanding of how physical forces and biochemical signaling events

interact to guide cell movement. While the field is starting to uncover the basic building blocks of a migrating cell, that is, the machinery that builds cell protrusions and retractions and how they are regulated by external chemical and adhesive cues, we are just scratching the surface in

our understanding of how these processes are controlled within 3D surroundings and within a tissue. Indeed, the tools to enable such a feat are emerging and will eventually lead to a molecular understanding of cell migration in physiological and pathological conditions.