

Cell dynamics in development, tissue remodelling, and cancer

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Cell dynamics is essential for development, tissue remodelling, and cancer progression. Traditionally, studies of cell dynamics have focused on the biochemical signals that control these processes; however, it has become evident that mechanical cues are also important in regulating cell dynamics. This issue provides an update of new and exciting developments in the field of cell dynamics and covers a broad range of experimental approaches to study diverse aspects of cell migration, cell polarity, and cell-cell and cell-substrate interactions.

Mechanobiology of collective cell migration

Cell migration is indispensable for many biological processes, such as embryonic development, organogenesis, immune response, wound healing, and cancer metastasis. Cell migration can occur in single isolated cells or in clusters of cells during collective cell migration. The review by **Khalilgharibi and colleagues** summarizes the mechanical properties of cellularized aggregates, which can be described in terms of elastic springs and viscous dashpots, combined in different serial or parallel configurations. The authors conclude that actomyosin and intermediate filaments are the most important determinants of cellular mechanical properties. One example of collective migration behavior is gap closure of epithelial tissues, which is reviewed by **Begnaud and colleagues**. The two main mechanisms involved in gap closure are a purse-string of actomyosin cables and cell crawling into the gap driven by protrusion extension, both of which generate mechanical forces during wound repair that are transmitted to the adjacent cells and to the substrate. The complexity of wound healing in vivo is reviewed by **Shaw and Martin**, who describe the cell lineages that require reprogramming, such as keratinocytes that re-epithelize the tissue, dermal fibroblasts that populate damaged connective tissues, immune cells that control infections, and endothelial cells that re-establish blood supply. Re-establishing blood circulation is necessary to supply oxygen and immune cells into the wound.

The development of blood vessels has been an intense area of research in recent years, and **Kutys and Chen** review the effects of mechanical forces during this process. The mechanical forces involved in vasculogenesis include both extrinsic and intrinsic stresses. Recent investigations have developed 3D microfluidic devices in which endothelial cells are seeded in 3D vascular networks, which are able to recapitulate in vivo force-driven endothelial behaviors and can identify novel cellular behaviors and molecular functions. Although many cellular structures have been described as mechanosensors in vascular biology, some of the most important are cell-cell junction structures, such as adherens junctions. Other kinds of cell-cell junctions that are essential to maintain the mechanical integrity of the tissue and to regulate its remodelling are tight junctions. **Balda and Matter** review the role of tight junctions as regulators of tissue remodelling. The authors describe

the molecular components of tight junctions, emphasizing the effect of loss of these proteins on different cellular and physiological processes.

Chemotaxis drives directional cell migration

Chemotaxis refers to the directional migration of cells towards external, soluble factors along a gradient, which is generated by a localized source that releases the attractant and a sink that absorbs it. **Tweedy and colleagues** review recent evidence that challenges this mechanism, discussing several examples that show that a self-generated chemoattractant gradient is more common than initially thought. They predict where more examples of this robust and efficient mechanism for directing cell migration are likely to be found. Chemotaxis plays an important role in development, such as for example the migration of germ cells as reviewed by **Barton and colleagues**. The authors describe that translocation of germ cells during development is a complex process that involves several steps, including moving passively with underlying somatic cells, traversing epithelial barriers, and responding to environmental chemoattractants during active migration. Another example where a complex array of chemoattractants is essential for directional migration during development is the neural crest. **Szabo and Mayor** review the molecular and mathematical models that have been proposed to explain the directional migration of neural crest cells in embryos. The authors propose an integration of different models for neural crest migration based on a recent cell behavior called “chase and run,” in which a population of cells (leaders) produces a chemoattractant towards the trailing cells, but when these two populations interact, they become repolarized in a cell contact-dependent manner.

Diversity of cell migration

Recent studies have revealed a remarkable diversity and plasticity of the mechanisms by which cells can migrate in local environments that differ in composition, architecture, and physical properties such as stiffness. This plasticity can involve rapid changes in the structure and function of the leading edge of migrating cells. For example, cells protrusions can switch from actin-based lamellipodia to filopodia, or even to pressure-based lobopodia. **Swaney and Li** describe recent studies that reveal a surprising level of plasticity in the modes of cell migration driven by Arp2/3 actin-based cellular protrusions; these changes depend on the type of matrix or physical environment and intracellular regulators of actin, with alterations in cancer. **Petrie and Yamada** extend this notion of diversity in response to matrix environments to additional modes of 3D cell migration, highlighting key roles for cell adhesion, Rho GTPases, actomyosin contractility, and mechanisms for squeezing the nucleus through different types of matrix environments.

Cell-matrix adhesion dynamics

The next four reviews explore additional facets of the rapidly expanding field of cell interactions with the extracellular matrix mediated by integrin receptors. These transmembrane receptors mediate dynamic two-way interactions between cells and their adjacent matrix; the extracellular matrix can rapidly modulate a wide range of signalling and other cellular functions, and conversely, cells remodel the matrix. **Vega and Schwarzbauer** review ways in which fibronectin and its major integrin receptor collaborate with growth factors and cadherins in various dynamic interactions that govern tissue morphogenesis and subsequent differentiation. Recent examples include roles of such interactions in heart, cartilage, and gland formation.

Striking alterations in extracellular matrix can occur near human tumors, where stiffened matrix around a tumor can provide the first sign of cancer. The mechanisms of this “desmoplastic” response are reviewed by **Alexander and Cukierman**, who explore how dynamic, reciprocal cell—matrix interactions can drive cancer progression. They then consider ways to disrupt these interactions as potential new approaches to cancer therapy.

Integrins play particularly prominent roles in angiogenesis. **Demircioglu and Hoidalva-Dilke** review the current status of clinical attempts to target a particular integrin implicated in tumor angiogenesis, emphasizing the need to consider drug timing, dosage, and effects on signalling. They note that future clinical approaches could include targeting intracellular integrin interactions, regulation, and autocrine signalling.

Another class of cell-matrix interactions in disease occurs in bacterial infections involving biofilms. Comparisons of the dynamics and local heterogeneity of bacterial biofilm matrix versus mammalian matrix reveal a number of mechanistic parallels and differences in cell signalling and in roles of matrix physical properties. **Koo and Yamada** review these advances, emphasizing approaches and concepts from one field that could accelerate research progress in the other.

Epithelial polarity and cytoskeletal regulation

Polarity is a fundamental property of epithelial cells. **Ahmed and Macara** review the functions and regulation of proteins known to govern the apical-basal polarity of epithelial cells, particularly by transcription factor networks and selective degradation of specific polarity proteins. They highlight opportunities for further elucidation of the complex gene networks and posttranslational networks regulating cell polarization. The molecular regulators and mechanisms that determine cell polarity in *Drosophila* and their roles in signalling, cell division, and other processes have been characterized in impressive depth, but new findings reviewed by **Flores-Benitez and Knust** reveal a variety of

mechanisms for regulating polarity complexes. For example, expression of different isoforms of proteins encoded by the same gene or switching of interactions between the various polarity complex proteins can regulate polarity. In other cases, transient recruitment of new components to polarity protein complexes or post-translational modifications of existing components by selective phosphorylation or dephosphorylation of specific components can also regulate polarity.

Besides polarity, other prominent features of epithelial cells include their distinctive cell shapes and importance of cell-cell junctions. As reviewed by **Braga**, new findings provide insight into the important roles of integrated and reciprocal functions of the actin cytoskeleton and Rho-family GTPase signalling to regulate cell junctional plasticity responsible for the morphology and tissue architecture of epithelial cells. Key elements include a variety of specific protein-protein interactions, cytoskeletal scaffolding for signalling proteins, and focal signalling.

Prospects

These reviews provided by leaders in the rapidly expanding field of cell dynamics highlight the remarkably diverse and sophisticated mechanisms used by cells during development, tissue repair and remodelling, homeostasis, and disease. We predict many more exciting advances in the very near future based on recent technical advances that permit detailed cell- and tissue-specific characterization and experimental manipulation of gene and protein regulation, new protein-protein interactions, and dynamics of cell and tissue movements.