Cells guided on their journey

The formation of complex organs, tissue repair and metastasis all require a coordinated regulation of the shape and movement of groups of cells. The mechanical means of communication between cells is crucial to understanding collective cell motions — so how can cells transmit physical forces within cell sheets?

Benoit Ladoux

How living cells are able to sense their environment and adequately respond remains one of the more puzzling issues in cell biology. This is particularly important in the context of embryonic development where a specific and complex architectural organization of biological tissues is defined. Embryonic cells adhere, migrate, segregate and differentiate in a selective and coordinated fashion. As histogenesis proceeds, specific cellular junctions are formed, which contribute to the mechanical cohesion of tissues and act as platforms that make communication between cells possible. Furthermore, dysfunctions in cell adhesion frequently lead to the loss of tissue homeostasis, which has serious physiopathological consequences such as tumour development and metastasis. It is thus important to understand how cells can establish and regulate precise contacts with adjacent cells, and how this depends on their physiological state and position in the embryo or tissue.

In 1917, D'Arcy Thomson published a treatise On Growth and Form in which he suggested that morphogenesis could be explained by forces and motion — in other words by mechanics1. For a while this idea took a back seat in favour of genetics and chemical communication within cell assemblies, but it has recently been revisited and it has been suggested that mechanical forces are important in the organization, growth, maturation and function of living tissues.

Within living tissues, local tension changes can occur during the addition or removal of cells, cell movements linked to morphogenesis, tissue repair or tumour invasion. Therefore, contacts between cells, or between cell and extracellular matrix (ECM), are subjected to force fluctuations and adjust to changes in tension2. Cell migration is commonly understood as the movement of individual cells, and this idea has led to a well-established model whereby cells move by the extension and adhesion of a leading edge pointed in the direction of migration, and the retraction and loss of adhesion of the trailing edge3. Here, the transmission of nanonewton-scale contractile forces required for the translocation of the cell body is generated at the points of contact with the surrounding substrate4 (Fig. 1a). Besides this well-established mode of cell migration, detailed knowledge obtained over the past 30 years suggests that at least one additional mechanism is important for cell translocation within tissues: the movement of cell groups, sheets or strands consisting of multiple cells connected by cell–cell junctions5. The regulation of such a migration mode, although ubiquitous in development, tissue repair and tumour invasion, has been largely unexplored and has awaited experimental models to decipher important steps of force transmission during collective cell migration.

Xavier Trepat and colleagues6, reporting on page 426 of this issue, have used traction force microscopy to investigate how physical forces regulate the motion of epithelial cell sheets. These sheets represent a convenient in vitro model to describe many aspects of the migratory behaviour of cell groups. By culturing epithelial cells on flexible gels, researchers can analyse the traction forces exerted at the cell–substratum interface by looking at the deformation pattern of embedded particles that act as markers4. To determine the transmission of forces...
within an advancing cell sheet, Trepat and colleagues have analysed the radial expansion of cell colonies as a function of time. Surprisingly, they find that large traction forces are observed many cell rows behind the leading edge, suggesting a mechanical cooperation from cell to cell over large distances within the cell sheet. As their results indicate long-range force transmission, this finding will undoubtedly fuel debates in the field, especially on the question of the push or pull mechanism that could drive collective migration (Fig. 1b).

When thinking about cells moving as a cohesive tissue, an important issue is the extent to which mechanical stress propagates within multicellular cohorts to control migration behaviour. Various in vivo and in vitro situations26 suggest that extrinsic cues can drive the movement of tissues, not by acting directly on all members of the group, but rather by instructing smaller numbers of peripheral leader cells that in turn seem to be responsible for the guidance of naive followers. But it remains an open question whether the global motion is coordinated by ‘leader’ cells pulling on cells behind or by internal pressure due to cell division and proliferation that would expand cell sheets outwards. Additionally, other mechanisms could involve submarginal cells that extend ‘cryptic’ lamellipodia several rows behind the wound margin of epithelial cell monolayers and thus could collectively drive cell-sheet movement27.

The direct measurement of physical forces within advancing epithelial cell monolayers provides some evidence to discriminate between these various plausible mechanisms. First, mapping the traction forces in directions normal to and parallel to the front edge at different locations underlines that large traction forces exerted by cells on the substrate are observed far away from the leading edge. Moreover, both traction distributions show non-Gaussian behaviours with exponential tails, independent of the distance from the edge. It further suggests that cells within the sheet share a common mechanical behaviour with a long-range force transmission. The idea of leader cells moving outwards, normal to the edge, ‘dragging’ passive followers behind them, is not sufficient to explain this complex mechanical process.

The propagation of physical forces depends on cell interactions not only with the substrate but also with neighbouring cells. This implies a ‘tug of war’ between both types of adhesion10. Physical signals from the substrates tend to induce a migration of cells away from each other, whereas a stronger mechanical input from cell–cell interactions would drive them towards each other. Thus the importance of cell–cell junctions in the force transmission requires a cell sheet to transmit physical forces in a cooperative way. Consistent with these arguments, Trepat et al.8 show that the average traction stress exerted by cells on the substrate in the direction perpendicular to the edge is not concentrated at the leading edge but decays slowly with the distance from the edge over several cell diameters, keeping values larger than zero. By applying Newton’s third law at various distances from the leading edge of the cell sheet, they are able to use the mechanical force balance to calculate the accumulated stress within the cell sheet. They show that this stress transmitted through cell–cell junctions increases as a function of the distance from the edge. These combined findings clearly demonstrate that guidance within tissues is due to a cohesive and coordinated movement, and that the growth of the epithelial cell sheet is induced by a global state of tensile stress (Fig. 1c).

Interestingly, such a tensile stress rules out the possibility of the build-up of an internal pressure due to cell proliferation that would push neighbouring cells outwards.

A remaining question is how such a tensile state is modulated by external cues, such as the stiffness of the environment. As collective cell migration and traction forces are affected by substrate rigidity11,13, one would expect to observe changes in the value of the tensile stress with the stiffness, providing important information about the reciprocal modulation of tension induced by cell–cell and cell–ECM adhesions. The study by Trepat et al. opens a promising possibility of testing the impact of mechanical stress on tissue remodelling and repair by dissecting the respective contributions of local and global forces.

Benoit Ladoux is at the Laboratoire Matière et Systèmes Complexes (MSC), Université Paris Diderot, and CNRS, UMR 7057, Paris, France. e-mail: benoit.ladoux@univ-paris-diderot.fr

References

TOPOLOGICAL INSULATORS

The next generation

Spin–orbit coupling in some materials leads to the formation of surface states that are topologically protected from scattering. Theory and experiments have found an important new family of such materials.

Joel Moore

Topological insulators are materials with a bulk insulating gap, exhibiting quantum-Hall-like behaviour in the absence of a magnetic field. Such systems are thought to provide an avenue for the realization of fault-tolerant quantum computing because they contain surface states that are topologically protected against scattering by time-reversal symmetry. However, topological phases in condensed matter generally behave like ‘hothouse flowers’; they are beautiful but fragile and, until now, were thought to be impossible to create without extremes of temperature and magnetic field. This conventional wisdom may be overturned by a pair of papers in this issue1,2, which show that a certain class of three-dimensional topological insulator material can have protected surface states and display other topological behaviour potentially up to room temperature without

© 2009 Macmillan Publishers Limited. All rights reserved