Cells migrate *en masse* to generate and renew tissue — but inadequate resolution and incompatible timescales obscure the mechanism behind this migration. A unique approach reveals that stress mediates collective motion by propagating in a wave from the leading edge to the population centre.

Manuel Théry

We need not delve far into our early development to appreciate the critical role of collective cell migration. At two weeks, the cell monolayer that makes up our entire embryo folds back on itself during the process of gastrulation — separating layers of cells fated for different functions in adulthood, and mapping out the future growth of our form. A few of our cells move out of the monolayer, causing a local deformation that triggers a collective migration along the outer side of the embryo (Fig. 1a). But the exact mechanism supporting such multicellular migration has so far remained obscure.

The production and spatial distribution of mechanical forces during individual cell migration has been comparatively well characterized. Now, writing in *Nature Physics*, Xavier Serra-Picamal and colleagues report an innovative approach for probing the mechanical rules governing collective migration, which were previously hidden by the complex fluctuations of cellular forces. Their technique has enabled them to precisely quantify the development of intercellular forces in a cohort of migrating cells, revealing the observation that stress propagates in a wave, from the moving front to the centre of the group.

Cell motion is slow — on the order of micrometres per hour — and dominated by friction. At the cell scale, inertia is negligible compared with viscous drag, and forces in moving cells sum to zero. By contrast, the dynamics regulating the spatial organization of the intracellular cytoskeleton is faster — on the order of micrometres per second — and is known to be responsible for the oriented cell deformation and propulsion. It is therefore difficult to relate fast internal reorganization to slow global deformation to formulate an exact description of the physical mechanism regulating cell migration. Furthermore, it seems that cells can migrate by exerting either pulling forces and/or pushing forces on their microenvironment. The scenario gets even more complicated when several cells interact with each other.

Multicellular migration can be studied by assembling colonies of cells, bound together by cell–cell adhesions, which expand by outward migration of the cells on the periphery. However, a complete description of the mechanical forces is compromised by the fact that, although forces exerted on the underlying substrate may be measured, the forces between adjacent cells are difficult to gauge.

Members of the same research team previously developed a method to infer these forces in large multicellular aggregates from measurement of the traction forces on the substrate. In the study, these traction forces were associated with every cell in the colony rather than being restricted to those at the front. This showed that the collective movement was not supported by pulling forces exerted specifically by the leader cells at the front. Moreover, cells seemed to exert strong traction and intercellular forces throughout the colony. The transmission of mechanical constraints from cell to cell generated local correlations in the

**Figure 1** Multicellular migration mechanics. **a**, The collective movements of cells during gastrulation give rise to the first two distinct layers dictating our body plan. Green arrows show cell migration in the original layer towards the invagination streak and red arrows show the cell migration in the newly formed layer away from it. **b**, Pulling forces exerted by the front cell stimulate traction forces on the substrate, and each cell counterbalances these forces by applying force to the cell behind it — effectively transmitting the mechanical signal generated by the release of the leading edge throughout the cell population. **c**, Central cells (purple) initially lengthen in response to pulling forces, then suddenly recover their rest shape via fluidization (blue star), only to become elongated again. These shape changes mediate the observed contraction waves.
orientation of forces. However, these forces fluctuated in space and time in response to many parameters, such as local cell density, misaligned cell movement and stochastic internal activities. The distribution of forces within the cell group was dominated by dynamic heterogeneities spanning only a few cells. How these mechanical dynamic heterogeneities were able to support global cell cooperation during collective movement remained mysterious.

Examples of reproducible organizational processes are few and far between in cultured cells, even though the same cells order readily in vivo. This artefact is thought to stem from a lack of geometrical boundary conditions, because the deterministic rules guiding intracellular organization or force distribution in multicellular groups are only reproducible under defined geometrical boundary conditions. One way to overcome this limitation in migrating cells involves controlling the geometry such that the initial conditions, when relaxed, trigger oriented migration.

In their new study, Serra-Picamal et al. have combined this spatio-temporal control of cell group migration with a quantification of mechanical forces. Force fluctuations persisted in the system, but by controlling the geometry, the authors were able to project two-dimensional force distributions into one dimension, and calculate the local average force field at any given moment. Repeating over several time points enabled them to quantify and visualize the temporal variations of the averaged force field.

The investigation revealed that the original intercellular stress generated close to the free group edge propagates backward as the edge moves forward (Fig. 1b). For a given cell within the group, the study shows that the pulling force exerted by the front cell towards the free edge is not the sole propelling force. Instead, it stimulates traction forces on the cell substrate along the direction of intercellular forces. These traction forces are internally counterbalanced by each cell applying force to the cell immediately behind it, and thereby, the mechanical signal triggering forward cell migration is transmitted throughout the group.

Using their accurate force-quantification method, involving thousands of cells, migrating in geometrically controlled conditions, Serra-Picamal et al. also revealed important individual cell-mechanical properties critical to eventual dynamic large-scale force patterning. They found that the cells along the midline, subject to increasing isotropic stress as the group extends, initially manage to sustain the stress and simply deform. But above a critical stress, these cells suddenly relax and recover their rest shape (Fig. 1c). Cytoskeletal reinforcement and the idea of a positive feedback loop generating force production in response to external stress are well-known cell behaviours. But force-induced relaxation has been underappreciated by other researchers using precise tools to probe single cells.

Previous work by the same team shows that cell cytoskeleton can fluidize without reinforcing in the specific case of short symmetric external stretch. Now, the authors have proposed that such a fluidization could be responsible for the observed relaxation at the group centre. This would support the reiteration of wave propagation throughout the group, and the consequential formation of alternate stripes of stress accumulation.

This new piece of work demonstrates that local movement could have reproducible mechanical consequences hundreds of micrometres away from the moving edge, through the propagation of stress waves. It is tempting to speculate that such waves occur during embryonic gastrulation. As cell contraction has been shown to direct stem cell fate, alternating stripes of contraction could be a robust way to structure the newly formed cell layers and specify complex geometrical differentiation patterns.

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References


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DARK MATTER

Supersymmetry wimps out?

Supersymmetric particles are prime candidates to make up the dark matter of the Universe — yet the lack of evidence for them so far from the Large Hadron Collider could force a rethink.

Alexander Merle and Tommy Ohlsson

Less than 20% of the matter in the Universe can be accounted for by known particles: what constitutes the major part is unknown or ‘dark’. Proposed by the Swiss astronomer Fritz Zwicky in 1933, the existence of dark matter has since been established by a body of observations that includes galaxy rotation curves, measurements of the cosmic microwave background radiation and gravitational lensing. Possible explanations such as a modified law of gravity (known as MOND) or the existence of many heavy Jupiter-like objects (called MACHOs) have been ruled out or at least strongly constrained, and the most plausible solution seems to be that dark matter is particle-like.

Particular dark matter is often designated by the acronym WIMP, for ‘weakly interacting massive particle’: massive to account for the gravitational effects of dark matter, and weakly