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Collective migration and cell jamming ☆

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ABSTRACT

Our traditional physical picture holds with the intuitive notion that each individual cell comprising the cellular collective senses signals or gradients and then mobilizes physical forces in response. Those forces, in turn, drive local cellular motions from which collective cellular migrations emerge. Although it does not account for spontaneous noisy fluctuations that can be quite large, the tacit assumption has been one of linear causality in which systematic local motions, on average, are the shadow of local forces, and these local forces are the shadow of the local signals. New lines of evidence now suggest a rather different physical picture in which dominant mechanical events may not be local, the cascade of mechanical causality may be not so linear, and, surprisingly, the fluctuations may not be noise as much as they are an essential feature of mechanism. Here we argue for a novel synthesis in which fluctuations and non-local cooperative events that typify the cellular collective might be illuminated by the unifying concept of cell jamming. Jamming has the potential to pull together diverse factors that are already known to contribute but previously had been considered for the most part as acting separately and independently. These include cellular crowding, intercellular force transmission, cadherin-dependent cell–cell adhesion, integrin-dependent cell–substrate adhesion, myosin-dependent motile force and contractility, actin-dependent deformability, proliferation, compression and stretch.

1. Introduction

Metastasis and invasion, as well as development, remodeling and wound repair, all depend upon collective cellular migration. Rather than moving individually, cells tend to migrate collectively in sheets, ducts, strands and clusters (Friedl and Alexander, 2011; Friedl and Gilmour, 2009; Weber et al., 2012). Collective cellular migration is poorly understood, however, and has been highlighted as being among the 10 greatest unsolved mysteries in all of biology (Editors, 2011). Here we begin with consideration of intercellular physical forces and their role in cell biology, which in recent years has come to be called the field of mechanobiology (Discher et al., 2009), and then go on to speculate about collective phenomena viewed through a prism borrowed from recent advances in understanding dynamics of inert soft condensed matter. In particular, we address dynamic heterogeneity, cooperativity, and kinetic arrest, and then argue for a synthesis of these largely unappreciated properties into a new physical picture. Attention is restricted to the cases of the epithelial or endothelial monolayer.

The traditional reductionist view holds that cooperative cellular events are mediated at the level of the local cell–cell interaction through the agency of a spectrum of physical factors that include cell-generated forces, cell recognition, polarization, selective affinity, and differential adhesion together with gradients of morphogens and phase-gradient encoding of gene oscillations (Steinberg, 1970; Foty and Steinberg, 2005; Steinberg, 2007; Wartlick et al., 2011; Lauschke et al., 2012; Keller, 2012). Cell motility then provides the mechanical agitation that is required for the system to overcome cohesive energy barriers and thus explore various configurational possibilities before ultimately stabilizing into a favorable final state (Keller, 2012). Physical forces in question (Fig. 1) include those supported by cytoskeleton (not shown), those exerted across adhesions between the cell base and its substrate (red arrows), and those exerted across each junction between a cell and its immediate neighbors (Weber et al., 2012) (blue arrows). Since the time of D'Arcy Thompson (1942) if not earlier, physical forces such as these operating at the cellular level have been recognized as being fundamental to biological form and function, but for almost as long the forces themselves have remained virtually hidden from view.

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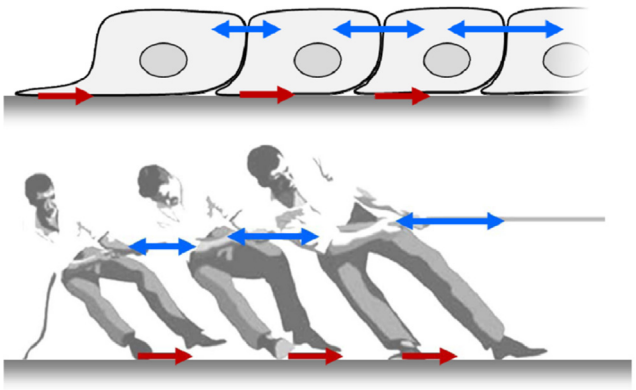

Fig. 1. Cells use a tug-of-war mechanism to integrate local tractions (red) into long-range gradients of intra- and inter-cellular tension (blue). Tension in the monolayer reflects the spatial accumulation, or pile-up of traction forces. Equivalently, the local traction force is the spatial derivative of the intercellular stress. Reprinted with permission from Trepat and Fredberg (2011).

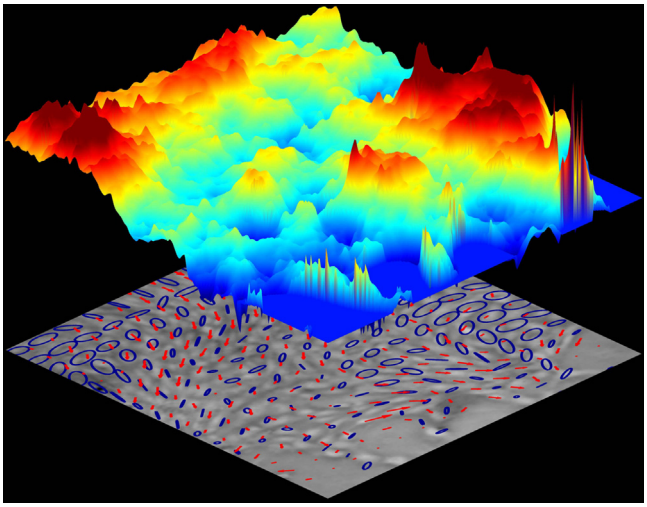

Fig. 2. Malleable cells trek a rugged stress landscape and make for a resilient monolayer. Cellular migrations (red arrows) follow stress orientations (blue ellipses) over a rugged stress landscape (colored topography denotes local tensile stress). Cell navigation on this scale– plithotaxis– is innately collective, strongly cooperative, and dynamically glassy. Reprinted with permission from Tambe et al. (2011).

2. Dynamic heterogeneity

To fill that gap, experimental methods recently developed make these hidden forces visible and even resolve forces exerted across the cell–cell junction into distinct normal (tensile) versus shear components (Ladoux, 2009; Trepat and Fredberg, 2011; Tambe et al., 2011; Krishnan et al., 2011; Angelini et al., 2010, 2011; Trepat et al., 2009). Surprisingly, even in a homogeneous monolayer these measurements reveal dynamic heterogeneities that are striking. Within the monolayer, intercellular forces fluctuate rather severely in space and in time, but are tied neither to any particular position within the monolayer nor to any particular cell (Tambe et al., 2011; Angelini et al., 2011; Garrahan, 2011) The heterogeneity is dynamic, therefore, not structural (Angelini et al., 2010, 2011; Garrahan, 2011). If at any instant the intercellular tension is mapped in relief across a homogeneous monolayer, the topography is reminiscent of neither the planes of Kansas nor the rolling hills of Vermont as much as the rugged landscape of the Himalayas (Fig. 2). The rugged peaks that define the stress landscape arise from cooperativity across clusters of roughly 10–50 cells and thereby account for the cooperative motion of cell packs; over that scale, super-cellular force chains, or force clusters, pull cohesively, coherently, and cooperatively (Tambe et al., 2011; Angelini et al., 2011).

Because the field of intercellular stress need not be isotropic, an ellipse is sometimes used to represent schematically the local state of cellular stress within the monolayer plane (Fig. 2). In that case local stress anisotropy corresponds to the departure of each ellipse from circularity, where the major axis of each ellipse corresponds to the maximal principal stress, and the minor axis corresponds to the minimal principal stress. Local principal stress orientations are defined by the orientation of each ellipse. Local tension is the sum of the two principal radii of each ellipse. Much as in a weather map, clearly evident in Fig. 2 are strong heterogeneity across the monolayer and strong local cooperativity spanning many cells.

3. Cooperativity

While the stress landscape is rugged and the associated heterogeneity is dynamic, certain systematic relationships emerge. In particular, there is a strong tendency for local cellular migration velocity (red arrows, Fig. 2) to follow the local orientation of the maximal principal stress, i.e., the orientation of the stress ellipse. This tendency, called plithotaxis, is a potent mechanism of collective cell guidance and is mediated through the agency of local intercellular stresses exerted between neighboring cells across mutual cell–cells junction (Trepat and Fredberg, 2011; Tambe et al., 2011). For example, consider the monolayer comprising epithelial breast-cancer MCF10A cells (Tambe et al., 2011), and let ϕ be the angle of the local migration velocity relative to the orientation of the local maximal principal stress, where the distribution of ϕ is represented as a rose of directions (Fig. 3). Averaged over the entire monolayer, the angular distribution of ϕ is clustered strongly around zero degrees, indicating that local principal stresses and local migration velocities are strongly aligned. When MCF10A cells overexpress the oncogene ErbB2/HER-2/neu, which promotes proliferation and leads to even more cellular crowding, the distribution of ϕ becomes even narrower, indicating that plithotaxis has become enhanced and cell guidance has become even stronger. By contrast, when MCF10A cells overexpress the oncogene 14-3-3ζ, which decreases expression of cell–cell junctional markers, the distribution of ϕ broadens, indicating that plithotaxis has become attenuated and cell guidance has been lost, and much the same loss of cell guidance is caused by calcium chelation or by E-cadherin antibodies (Tambe et al., 2011). Together, these observations suggest that plithotaxis rests on cooperativity of mechanical stresses across many cell-to-cell junctions.

4. Kinetic arrest

Dynamic heterogeneity and associated cooperativity show interesting dependencies on cellular density and other factors. As cellular density in an expanding monolayer sheet increases as a result of proliferation, and cells therefore become increasingly crowded, cooperative packs become progressively bigger and slower (Angelini et al., 2011) (Fig. 4). And as cellular crowding approaches some critical threshold, relative motion of neighboring cells slows dramatically and spatial cooperativity of these motions expands. These changes in dynamics need not be accompanied by discernible alteration in cellular structure, however. The basic notion is that with more crowding each cell can become increasingly caged by its neighbors (Tambe et al., 2011; Angelini et al.,