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Review Article

Cell and tissue mechanics in cell migration

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ABSTRACT

Migrating cells generate traction forces to counteract the movement-resisting forces arising from cell-internal stresses and matrix adhesions. In the case of collective migration in a cell colony, or in the case of 3-dimensional migration through connective tissue, movement-resisting forces arise also from external stresses. Although the deformation of a stiffer cell or matrix causes larger movement-resisting forces, at the same time a larger stiffness can also promote cell migration due to a feedback between forces, deformations, and deformation speed that is mediated by the acto-myosin contractile machinery of cells. This mechanical feedback is also important for stiffness sensing, durotaxis, plithotaxis, and collective migration in cell colonies.

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Introduction

Cell migration involves cell deformation and – as the space occupied by the migrating cell moves along – also deformations of the surrounding tissue. Depending on the mechanical properties of the migrating cell and the tissue, these deformations are coupled to a buildup of mechanical stresses that resist cell migration. To overcome resisting stresses, the migrating cell or the cells in the surrounding tissue need to generate mechanical forces. The interplay between driving and resisting forces, deformations, movements, and how they depend on the mechanical properties of cells and tissue, is the topic of this review.

Passive mechanics of cells

Passive mechanical properties describe the relationship between mechanical stress (force per unit area), mechanical strain (gradient of the deformation field), and its time derivatives. Passive mechanical properties can be measured by applying a mechanical stress to a material, and observing the resulting deformations, or vice versa by applying a prescribed deformation and observing the resulting stresses. In the case of a Hookean linear elastic solid, the ratio between stress and strain is given by the elastic modulus. In the case of a Newtonian fluid, the ratio between shear stress and strain rate is given by the viscosity. Cells are neither purely elastic nor viscous but are visco-elastic, implying that mechanical stresses relax, or decay, over time when a constant deformation is applied (stress relaxation), or that deformations increase over time when a constant stress is applied (creep response) [1]. Such behavior is often described by a network of elastic springs and viscous dashpots. Each combination of a spring with a dashpot shows an exponential creep or stress relaxation response. However, a spring-dashpot description fails in the case of cells because stress relaxation or creep responses are time scale invariant, meaning that they are spread out in time over many orders of magnitude according to a power-law. Power-law responses require a very large number of (physically meaningless) spring and dashpot elements for an adequate description [1,2], and therefore the traditional method to describe mechanical behavior by a superposition of exponential response functions needs to be abandoned in the case of cells.

Instead, power-law behavior offers a much simpler and physically more meaningful approach to describe cell mechanics. The creep response $J(t)$ of the cell (this is the ratio of cell strain $\gamma(t)$ and applied stress σ) is captured with only two parameters: $J(t)=J_0(t/t_0)^b$, with time usually normalized to $t_0=1$ s. The prefactor J_0 is the creep compliance at $t_0=1$ s and corresponds, apart from a negligible correction factor (the Gamma function $\Gamma(1-b)$), to the inverse magnitude of the cell's dynamic shear modulus G^* evaluated at a radian frequency $\omega_0=1$ rad/s [3]. The power-law exponent b reflects the dynamics of the force-bearing elastic structures of the cell that are deformed during the measurement process. A power-law exponent of $b=0$ is indicative of a purely elastic solid, and $b=1$ is indicative of a purely viscous fluid. In cells, the power-law exponent usually falls in the range between 0.1 and 0.5 [4].

Power-law behavior has a number of important implications for the migrating cell. First, a power-law exponent around 0.25 means that cells are predominantly elastic. Second, migration-resisting mechanical stresses in such a material decay much slower than exponentially, but given sufficient time, they become small. For example, a cell with an effective stiffness of 1 kPa when measured at a frequency of 1 Hz would exhibit an effective stiffness of around 300 Pa when measured at a frequency of 0.01 Hz. Consequently, movement-impeding forces arising from deformations of cell-internal and external structures become increasingly weaker as the speed of the movements decrease. Whether power-law behavior holds at even smaller frequencies is currently debated [5], as such measurements are difficult to interpret because the cell may start to respond to the probing forces of the measurement apparatus, and active processes such as cell traction forces and cell movements begin to dominate the measurements. The separation of active from passive mechanical processes is non-trivial at the level of single cell. However, active cell processes, in particular contractile properties, have been studied at the tissue level long before single cell measurements became feasible.

Tissue mechanics

Tissue consists mostly of cells and extracellular matrix biopolymers such as collagen, elastin, laminin, perlecan and other proteins and proteoglycans. These non-cellular components have often a much higher elastic modulus than cells, typically on the order of tens of kPa, although there are large differences among different tissue types, depending on the amount and structure of the extracellular matrix. For example, brain tissue with a shear modulus of around 1 kPa [6] consists predominantly of cells and has only a relatively small extracellular matrix content. In contrast, cartilage with an elastic modulus in the range of 1 MPa [7] consists mostly of extracellular matrix with only a few cells.

These stiffness values refer to the bulk properties of the tissue, with the tacit continuum-mechanical assumption that the material is homogeneously distributed. However, the extracellular matrix usually has a filamentous structure, with matrix fibers and fibrils that form a 3-dimensional meshwork, often with enough space in between these fibers for cells to pass through. The migration-resisting forces from the extracellular matrix can

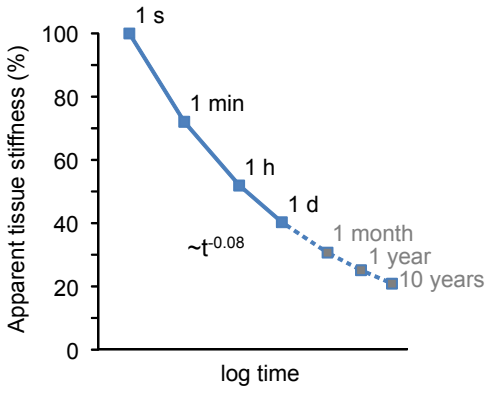

Fig. 1 – Creep and stress relaxation behavior of the extracellular matrix leads to a continuous decline of the apparent stiffness. Here, a power-law exponent of 0.08 was assumed. Within 1 h, the stress required to maintain a given matrix deformation has declined by approximately 50%.

therefore be uncoupled from the bulk properties so that both mechanical and structural information are necessary to predict the steric hindrance that the extracellular matrix imposes on the migrating cell [8].

Apart from their higher elastic modulus, extracellular matrix biopolymers exhibit power-law mechanical responses similar to cells [9], with power-law exponents typically below 0.1—closer than cells to an ideal elastic solid. Consequently, tissue as a combination of cells and extracellular matrix also shows power-law stress relaxation and creep [10]. The steric hindrance that a migrating cell encounters therefore depends on the duration of the force with which the cell attempts to penetrate the tissue (Fig. 1).

A notable exception from power-law behavior is muscle tissue with low matrix content, where the mechanical response is largely dominated by the molecular interactions of actin and myosin filaments [11]. Hence, the creep, stress relaxation and frequency response of muscle reflects mostly acto-myosin bridge kinetics [12]. Furthermore, muscle cells can change their elastic modulus by over 2 orders in magnitude, from around 10 kPa in the relaxed state to around 200 kPa in the fully activated state [13]. This is because each actin-myosin bridge that forms during muscle contraction not only adds to the total force but at the same time acts as a cross-linker and adds to the total stiffness.

Active mechanics

Most non-muscle cells are rich in actin and myosin and can generate substantial contractile forces. If a cell is attached to the extracellular matrix, these contractile forces generate an internal stress, called cytoskeletal pre-stress (so called because it is already present before any additional external stress is applied e.g. by a measuring apparatus). The pre-stress cannot be directly measured but it can be inferred from the tractions that cells exert on their surroundings [14].

As in muscle cells and for similar reasons, the cytoskeletal pre-stress causes adherent cells to stiffen. In fact, the relationship between pre-stress and stiffness is strictly linear, apart from a small additional baseline stiffness [14,15]. This linear coupling of stiffness and contractile force creates a conflict-of-interest for the migrating cell: in order to migrate through dense tissue, the cell needs to adhere, contract, and thereby pull itself forward. At the same time, the contractile machinery increases cytoskeletal prestress and thereby increases cell stiffness. A high cell stiffness, however, impedes cell deformations and movements. This, in a nutshell, is also the conflict that ordinary skeletal muscle faces during shortening: the maximum shortening velocity decreases with increasing force [16] because of the growing internal resistance that is an unavoidable consequence of force generation [17,18]. The relationship between force and shortening velocity is empirically summarized by the Hill-curve [16], and mechanistically explained by acto-myosin filament sliding and acto-myosin bridge kinetics [17]. Although the Hill curve is strictly valid only for quick-release experiments, the empiricism of the Hill-curve also holds for the velocity of cell shortening against an external load during the adhesion and spreading process of non-muscle cells [18].

Apart from cell-internal pre-stress and stiffness, a cell that is migrating relative to contracting – and hence stiff – neighboring cells feels their stiffness too, just as if these neighboring cells were a stiff extracellular matrix, with the only difference that adhesion and trans-cellular force transmission to neighboring cells occurs not via integrin-type cell–matrix adhesions but via cadherin-type cell–cell adhesions. A stiff surrounding, however, does not necessarily impede cell migration, as explained below.

Mechanical basis of durotaxis, plithotaxis, and mechanotransduction

Cells respond to external forces as well as to the mechanical properties of their surroundings in many different ways (such as stiffening or softening, maturation or disassembly of focal adhesions, calcium influx, shape changes, changes in tractions, altered gene expression) through a large range of mechanisms (integrin activation and reinforcement, activation of putative force sensors, stretch-activated channels, protein unfolding, activation of signaling pathways), as reviewed elsewhere [19]. Here, we focus on three striking responses of cells to the stiffness of their surroundings: With higher stiffness, cells spread more and contract stronger, but migrate more slowly [19,20]. Although receptor activation and biochemical signal transduction processes undoubtedly contribute greatly to these responses [21], we will in the following discuss purely mechanical mechanisms.

Why do cells adhere and spread? The simplest explanation draws an analogy to a wetting process, whereby the cell or cell aggregate acts like a liquid drop with a given cohesiveness (or surface tension) and adhesiveness [22]. The surface tension

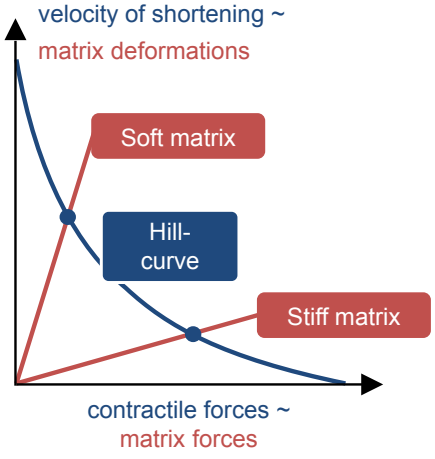

Fig. 2 – Different spreading and migration behavior of cells attached to soft versus stiff substrates is a consequence of the inverse relationship between the maximum shortening velocity and force generation due to the internal resistance and reaction kinetics of force-bearing cytoskeletal structures. It follows that cells on a stiff substrate generate larger forces and migrate more slowly compared to cells on a soft substrate. Note that the velocity vs. force curve (Hill-curve, blue) and the matrix deformation vs. matrix force relationship for stiff and soft matrices (red) can be superimposed in the same diagram only if cell–matrix contacts remain stable during a contraction cycle. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

originates from acto-myosin driven cortical tension and, in the case of cell aggregates, also depends on cell–cell adhesiveness [23].

Why do cells spread more on stiff substrates and generate larger traction forces? It holds both for muscle and non-muscle cells that acto-myosin forces are highest only for low or zero velocities and break down during fast movements [18]. A soft substrate will respond to large forces with a large and fast deformation. Under this condition, however, the cell is unable to maintain a large force and therefore will spread less (Fig. 2). Stiffness-dependent spreading partially explains also why cells tend to migrate along the stiffness gradient towards the stiffer region of a substrate in a process called durotaxis [20].

Why do cells migrate more slowly on stiff substrates? And why do cells migrate in the first place? A net translocation of the cell occurs when the cell-generated forces are not balanced by the substrate, giving rise to a net traction force [24]. In fact, every newly formed or newly dissociated adhesion site disturbs the traction force equilibrium, and as a consequence, the cell moves in response until the tractions summed over all cell–matrix adhesions vanish [25]. If we consider that these processes occur randomly in space, then the cell undergoes diffusive migration [25] with a speed that scales inversely with the number of engaged cell–matrix adhesion sites. A stiffer substrate with a larger cell spreading area and consequently a larger number of cell–matrix adhesions per cell would therefore result in a slower migration speed.

Unlike water droplets, however, cells often assume a pronounced anisotropy and polarity during spreading on stiffer substrates. Moreover, migration is not a random process. Instead, the cell employs a specialized structure – the lamellipodium – to establish new adhesions at the leading edge and to probe the surroundings for suitable migration directions. Outward movements of the lamellipodium are driven by actin polymerization forces that can be quite substantial (a single actin filament can generate pushing forces of several pN, similar in magnitude to the pulling forces generated by myosin motors [26]). In principle, actin polymerization forces in the lamellipodium can be transmitted to the extracellular matrix through nascent contacts. However, high-resolution traction force measurements show appreciable tractions only at focal adhesion sites in the lamella, suggesting that traction forces by actin polymerization are dwarfed by acto-myosin generated traction forces [21,27].

A polarized cell necessarily shows a polarized footprint of tractions that also determines the cell migration direction. This apparent directional correlation between tractions and migration is secondary, however, because it is not the total tractions that drive cell migration but rather the net tractions, i.e. the imbalance of tractions. A point-in-case is the migration of fish keratocytes where the cell's traction dipole and migration direction are orthogonal [28]. Moreover, despite large tractions and their fluctuations, the magnitude of the net tractions can be exceedingly small to cause appreciable movements of an isolated cell attached to a flat 2D substrate because the liquid drag is the only unavoidable resisting force from the environment. In contrast, the self-imposed friction between the cell and the matrix due to cell–matrix adhesions is many orders of magnitude higher than the liquid drag. By definition, all traction forces generated by the cell are counterbalanced by equally large friction forces with the matrix. Strong adhesions and large tractions, however, are only needed for cell spreading, endocytosis, shape stability, or resistance against fluid shear stress, but they are not needed for—and rather hinder—cell migration on a flat 2D matrix [24].

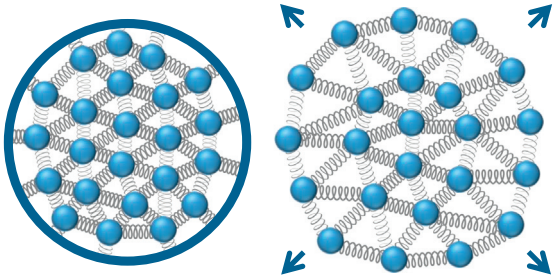

Fig. 3 – Collective migration in a cell sheet and the outward directed movement of "leader" cells during a wound healing or cell spreading assay arises from the viscoelastic interaction of cells with their neighbors and the matrix, similar to the mechanical (repulsive) interactions of densely packed particles after the mechanical constraint has been released. Friction between the particles with the matrix, due to matrix adhesion, leads to larger tractions and hence larger outward movements at the boundaries compared to the center. The same principle also applies to attractive interactions between actively migrating cells that exert tension on their neighbors [38].

The situation is reversed for cells migrating through a dense 3D biopolymer network that imposes a much larger resistance against deformations and movements [8]. Adhesion and traction forces are now important in that they allow the mesenchymally migrating cell to pull itself through the network and push interfering fibers away. Indeed, a strong directional correlation between traction forces, cell polarization and orientation, and cell migration has been reported for single tumor cells in a 3-dimensionsional biopolymer fiber matrix [9].

Essentially the same basic physical principles apply to cell migration in a sheet of cells. Here, the net force driving cell migration arises from an imbalance both of cell–matrix and cell–cell tractions [29]. Appreciable movement-resisting forces now arise from viscoelastic interactions with neighboring cells, which causes an alignment of movements in particular near cell-free boundaries (Fig. 3). Viscoelastic interactions with neighboring cells present the simplest mechanism to account for such coordinated movements among neighboring cells in a cell sheet, or for the outward-directed movement of cells at the edge of a cell colony during a wound healing assay [30,31]. Because the contractile stresses generated by one cell are transmitted across cell–cell junctions to the adjacent cells, these stresses align, as does the contractile machinery of adjacent cells even when the outlines of the individual cells do not [32]. When cell–cell adhesions are strong, especially when cell matrix adhesions become weaker in response [33], such stress alignment can span multiple cell diameters [32,34,35]. Here again, it is not the stresses themselves but their imbalance that cause cell movements. Because stress imbalance tend to be highest in the direction of the highest principal stress, cell movements tend to follow the direction of stress anisotropy. This effect has been termed plithotaxis [32] and, together with viscoelastic interactions of neighboring cells, contributes to long-range coordinated movements in cell colonies and cell sheets [30,36,37].

Summary

Cell adhesion and migration behavior as well as cell responses to forces and mechanical matrix properties can be understood to a surprisingly large extent by considering only a few basic mechanical principles. Of course, such a simplistic physical approach is necessarily incomplete and cannot account for mechano-chemical signal transduction, gene regulation and cell differentiation processes, or epithelial–mesenchymal transition in response to mechanical stimuli [39–46]. However, simple physical principles are still at work even when exceedingly complex biological mechanisms seem to dominate cell behavior, and should therefore not be ignored.

Acknowledgments

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