Epithelial monolayers as active materials

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Status. Cells are able to sense and react to their mechanical environment. Their various organelles form a mechanosensitive system that connects external mechanical cues to the gene expression. Furthermore, several functions of animal cells are mechanical in nature. Examples include controlling their shape during cytokinesis [232], migrating individually or collectively [233], or cohesively adhering to each other in epithelial tissues [234]. All these functions ultimately depend on the architecture and dynamics of the structural, force-bearing, elements in cells, which include the cytoskeleton, adhesive structures, the plasma membrane and the cytosol. The cytoskeleton is a composite structure of rheological components including microtubules (elastic), intermediate filaments (strain-stiffening coiled-coils), and actin networks (active viscoelastic gels). Cells and cohesive tissues can thus be seen as materials or structures. However, unlike inert engineering materials or structures, cells and tissues are constantly renewing the materials from which they are built and are actively generating forces, all of which requires chemical energy input [232].

Here, we focus on epithelial monolayers, which are very simple yet very important animal tissues. They consist of cohesive and highly organized cells that adhere to each other and often to an underlying matrix to form a barrier that lines internal and external organ surfaces, controls transport of gas or nutrients, and protects us from pathogens or desiccation. Moreover, epithelial mechanics is also important to shape embryos during development [235] and in diseases including cancer [236]. Epithelial tissues are subjected to mechanical deformations of various magnitudes and at different time-scales. For instance, as we breathe, cell monolayers in our lungs undergo areal stretches of more than 10% over seconds, whereas during blastocyst expansion in developing mammals, the trophectoderm undergoes a several-fold increase in area. Despite the fact that epithelial monolayers are active materials performing crucial mechanical tasks during adult life and development, the quantification of their mechanical response to stretch remains very limited, and how these tissues control tension, which if excessive could lead to tissue fracture and loss of function as barriers, remains poorly understood. Next, we review recent work on the characterization of the mechanical behaviour of epithelial monolayers under stretch and highlight initial steps and challenges in connecting tissue-scale mechanics with the architecture and dynamics of sub-cellular cytoskeletal networks (figure 36).

Current and future challenges. Epithelial mechanics has been studied in various contexts, identifying a variety of mechanisms, cellular and supra-cellular, by which they respond to stretch. These include changes in the topology of the junctional network such as cell division, cell extrusion, and other types of network rearrangements, notably T1 transitions

[235]. The fluid or solid rheology of epithelial monolayers has been linked to unjamming/jamming transitions dictated by the ease of undergoing a T1 transition leading to cell intercalation and flow. However, at shorter time-scales of minutes up to hours, epithelial tissues accommodate stretch by cellular deformation [235]. Focusing on this regime, only a handful of quantitative *in vitro* experiments have been able to measure the stress–strain relationship of epithelial monolayers. Charras and co-workers [237, 238] have probed free-standing monolayers through creep and stress relaxation experiments at various time-scales and stretch/stress magnitudes. Casares *et al* [234] stretched adherent cultured cell monolayers on a flexible substrate while measuring tissue tension using traction force microscopy during stretch-unstretch manoeuvers. Latorre *et al* [239] developed a microscopic bulge test in which epithelial monolayers were stretched up to areal strains of 300% by transmural pressure forming 3D domes. These tests have unveiled, even in the seemingly simple case of frozen junctional network, a wealth of dynamical rheological behaviours, which we summarize below.

Under sudden stretch application, epithelial tissues initially build-up tension, which is then partially relaxed over time-scales of 10 s of seconds [238] to a few minutes [234]. Upon unstretch or compression, tissue tension rapidly drops, and then partially recovers within a comparable time-scale [234]. In free-standing monolayers, sudden compression leads to formation of folds that can transiently flatten or stabilize depending on the unstretch magnitude [238]. These mechanisms have been interpreted as supra-cellular analogues of 'reinforcement' and 'fluidization' responses previously reported at the single-cell level [234], and have been understood with minimal rheological models. When subjected to a sudden tension in a creep testing setup, suspended epithelial tissues exhibit complex rheology behaving as viscoelastic solids at lower tensions and as complex fluids at higher tensions [237]. The equibiaxial stretching of suspended epithelial monolayers in bulging epithelial domes [239] has shown the ability of monolayers to reversibly undergo extreme deformations (up to 300% areal strains) at nearly constant tissue tensions. The measured tensional plateau was accompanied by heterogeneous cellular strain distribution, with coexistence of superstretched (~1000% areal strain) and barely stretched cells in a tissue with nearly uniform tension. These are hallmark features of superelasticity, a phenomenology associated prominently with superelastic nickel–titanium alloys, which in epithelial tissues were shown to be of an active origin.

As discussed earlier, all these mechanical behaviours should depend on the structural components of cells and their dynamics. The turnover time-scales of adhesion molecules (~10 s of minutes) are significantly longer than those of cortical components including actin filaments (~min), myosin motors and crosslinkers (~s) [238]. Consequently, at intermediate time-scales of a few minutes to hours, the junctional network of the tissue is conserved and epithelial mechanics is dictated by mechanical behaviour of the cell cytoskeleton, and more specifically the actomyosin cortex. The cortex is a 50–200 nm thin meshwork of crosslinked actin filaments anchored beneath the cell membrane [232]. The cortex is
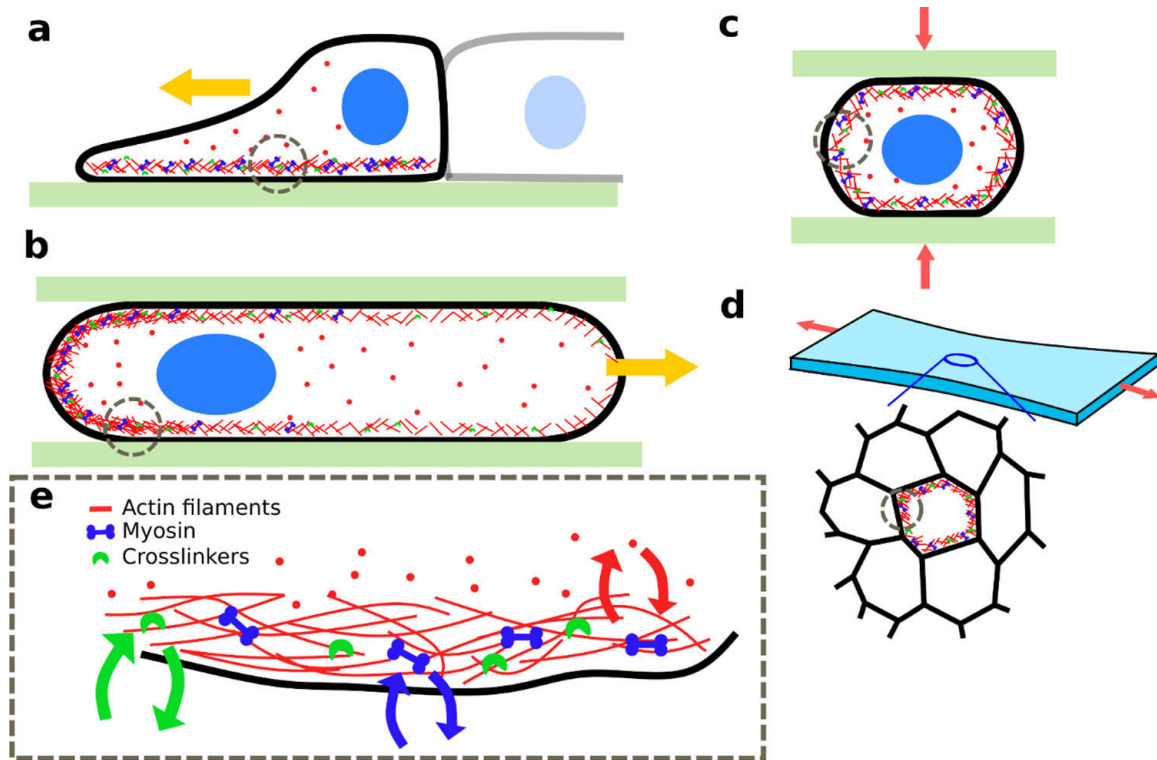
Figure 36. The active viscoelastic rheology of the actomyosin cortex, controlled by architecture, power input and turnover dynamics on the subcellular level (e) plays a dominant role in (a) mesenchymal and (b) amoeboidal cell migration, (c) cellular mechanics and (d) epithelial tissue rheology.

highly dynamic due to constant turnover of crosslinkers and actin filaments. Moreover, the pulling action of myosin motors powered by ATP hydrolysis collectively leads to effective contractile tensions. On a mesoscopic level, the active viscoelastic phenomenology of the cortex is captured by active gel theories grounded on non-equilibrium thermodynamics [240]. In principle, the tissue-scale phenomenology reviewed in the previous paragraph should be a consequence of the mechanics of the actin cortex. However, this connection between subcellular dynamics as described by active gel theories and tissue rheology has been lacking.

The predominant approach to theoretically understand epithelial monolayers is through vertex models, which represent the monolayer as a polygonal tessellation. The motion of vertices is governed by the mechanical forces arising from a work or pseudo-energy functional [241]. The mechanical forces have contributions from effective contractile tensions, cytoplasmic pressure, and cell-substrate interactions. The out-of-equilibrium nature of tissue mechanics is hidden in the cortical tensions, which can be assumed to be constant in a steady state. However, going beyond quasi-steady states and looking ahead, tissue-level dynamical vertex models based on out-of-equilibrium active gel theories of the actin cortex could help us establish a link between various molecular mechanisms, possibly tuned by cells, and the emergent epithelial phenomenologies. For instance, such a framework would help us understand how stress relaxation time-scales, tensional homeostasis, creep behaviour or transient buckling depend on the turnover of cross-linkers, the actin architecture and polymerization dynamics, or myosin activity. Such a theory would allow us to make specific predictions about how molecular

mechanisms affect tissue rheology, which can be tested by biochemically perturbing cytoskeletal dynamics while measuring forces and deformation on tissue scales.

As an initial step in this direction, Latorre *et al* [239] explained active-superelasticity of epithelial tissues by explicitly accounting for cytoskeletal mechanics in vertex models. The classical vertex model was augmented with cortical turnover to account for stretch-induced cortical dilution due to limited amount of actin monomers ready for polymerization and re-stiffening from intermediate filaments at large stretches. The enhanced vertex model captured active-superelastic phenomenologies, including the tensional plateau, the sudden increase in strain variance amongst cells, and the extreme strain heterogeneity at later stages.

At the centre of this conceptual framework, active gel models should reflect the physics of the actin cytoskeleton. Various studies have shown that active gel models employing a simple description of cortical network architecture through actin density fields and nematic order parameter can capture the hydrodynamics of actomyosin gels. Yet recent work on living cells and reconstituted actomyosin gels have highlighted our lack of understanding of how actin network architecture, connectivity, and dynamics is controlled molecularly, and how this affects the effective material properties of the active gel [242–244]. To this end, increasingly realistic discrete models of the actomyosin cortex combined with super-resolution microscopy may help establish this connection between scales.

Concluding remarks. Up to now, we have focused on the actin cortex as the major determinant of epithelial mechanics.

However, at longer time-scales, tissue rheology depends on the ability of the junctional network to remodel, which ultimately depends on the dynamics of adhesion molecular complexes and adaptor molecules linking them to the cytoskeleton. How these ingredients integrate to control tissue mechanics remains a largely open question. Besides connecting sub-cellular mechanisms to in-plane tissue rheology, a similar connection could help us understand the collective migration of cohesive tissues or their 3D morphogenesis. In the coming years, an integration of experimental examination and theoretical modelling of tissues at various scales—from the dynamics of molecules to tissue mechanics—has the potential to provide a quantitative framework to understand epithelial mechanobiology during physiology, disease and development, and control it in epithelial technologies such as organs-on-a-chip.

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