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Mechanical forces and feedbacks in cell motility

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Cell movement is driven by a self-organized assembly of numerous actin polymers and accessory proteins surrounded by a flexible membrane. While the identity of the molecular components involved is largely known, we are still far from understanding how this enormous ensemble of molecules self-organizes into a dynamic motile cell. A great deal of work in the field has focused on the role of biochemical signaling in establishing and maintaining cellular organization. More recently, mechanical forces and feedbacks have emerged as equally important contributors to the large-scale organization of motile cells. Here we review recent progress in the field, focusing on processes related to the actin cytoskeleton and its interplay with the cell membrane.

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Introduction

Cell motility is a beautiful manifestation of biological self-organization. A typical motile cell contains $\sim 10^9$ actin proteins as well as a host of accessory molecules and motor proteins [1]. These molecular building blocks self-organize over several orders of magnitude in both the temporal and spatial domains to bridge between the rapid dynamics of individual molecules to the persistent motion of whole cells. Despite the significant progress in uncovering the molecular details of the motility process [1–3], the principles governing large-scale coordination and polarization of the motility apparatus are still not well-understood. Recent results emphasize the importance of mechanical forces and feedbacks as regulators of cellular dynamics, and highlight their central role in large-scale coordination of motile cell behavior [4••,5•,6,7•,8•]. This review focuses on the mutual interplay between mechanical forces and biochemical reactions and their role in the extraordinary self-organization processes underlying cell movement.

A motile cell is composed of different mechanical elements including the actin cytoskeleton, the cytosol, and the plasma membrane. The actin cytoskeleton is an active viscoelastic network of semi-flexible filaments which generates forces primarily by polymerization, and/or through the activity of myosin motors. The cytoskeleton maintains its non-equilibrium state by consuming chemical energy, mostly via ATP hydrolysis, which drives the activity of myosin motors, and enables cells to maintain a far-from-equilibrium concentration of actin monomers to power the polymerization motor [1,9–11]. The cytoskeleton is attached to the substrate through adhesion complexes which facilitate mechanical communication between the cell and its surroundings. These adhesions play a central role in mechanosensing and mechanotransduction which is reviewed elsewhere (see [12,13]). Most of the cell's volume is taken by the fluid cytosol. The porous cytoskeleton is embedded within this viscous fluid, forming a biphasic poroelastic material [14–16]. Finally, the cell is surrounded by a thin deformable fluid membrane composed of lipids and proteins, which is typically under tension. As discussed below, the tension in the membrane influences cell boundary dynamics and has an important role as a global coordinator of cell behavior [4••,5•,7•,8•,17–21].

Mechanical feedbacks in the cell are present at all scales, from the molecular level and up to the cellular scale [12,19,20]. Various experimental approaches have been developed to characterize these mechanical feedbacks, investigate the force-dependent behavior of cellular processes, and measure the mechanical properties of cells and their constituents (see Box 1). Here we review recent results which highlight the importance of mechanical forces and feedbacks in the motility process [19,20]. Specifically, we examine how local forces affect the activity of individual actin filaments and other accessory proteins which cooperatively determine the mechanical properties of the cell (e.g. [22,23,24•]), and how physical variables such as membrane tension provide global coupling which coordinates biochemical reactions over cellular scales [4••,5•,6,7•,8•].

Mechanical feedbacks in the actin cytoskeleton

The actin cytoskeleton is composed of many individual filaments which assemble into a variety of dynamic structures, together with different auxiliary proteins including crosslinkers, motor proteins and regulatory

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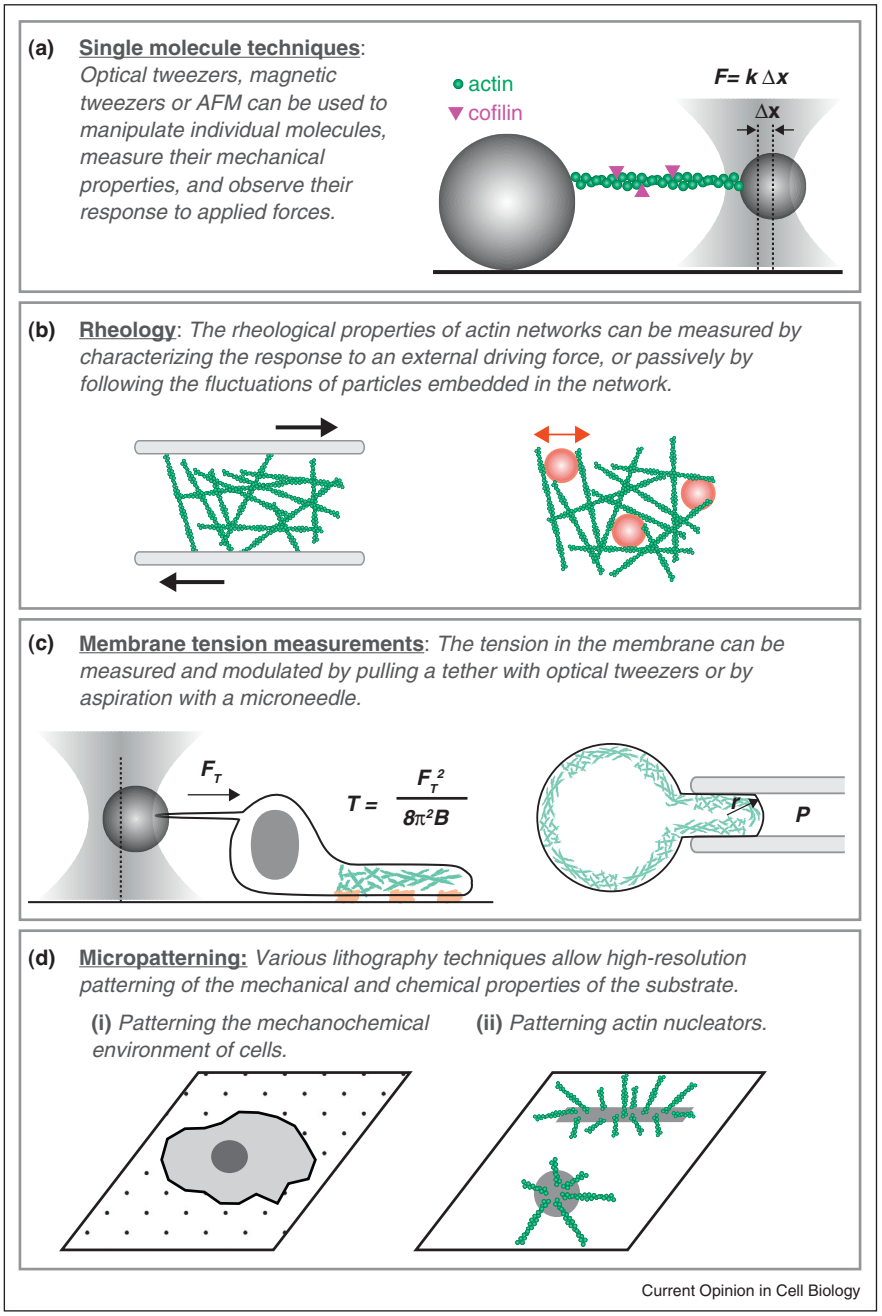
Box 1



Experimental characterization of mechanical feedbacks. A wide range of techniques has been developed to measure the mechanical properties of molecules, subcellular structures, and cells, and to characterize their response to applied forces. We present a subset of widely used techniques relevant for the study of the actin cytoskeleton and the cell membrane. **(a)** Single molecule techniques are used to measure the force-dependent behavior of individual molecules. In this example a single actin filament was stretched between a surface and a bead held in an optical trap, and the tension-dependent severing activity of cofilin was examined [23]. **(b)** The rheological properties of reconstituted actin networks can be measured using a bulk rheometer which applies sheer forces on the sample, or using passive microrheology by tracking the movements of individual beads embedded in the network [71]. **(c)** Membrane tension measurements can be done by pulling membrane tethers using optical tweezers (left) of by micropipette aspiration (right) (reviewed in [19]). **(d)** Micropatterned substrates are used in combination with time-lapse microscopy to study (i) the dynamic response of cells to controlled variations in substrate elasticity and chemical composition (reviewed in [12]) and (ii) the spatio-temporal organization of reconstituted actin networks as a function of the initial pattern of actin nucleators [43].

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