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Mechanics of the F-actin cytoskeleton

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ABSTRACT

Dynamic regulation of the filamentous actin (F-actin) cytoskeleton is critical to numerous physical cellular processes, including cell adhesion, migration and division. Each of these processes require precise regulation of cell shape and mechanical force generation which, to a large degree, is regulated by the dynamic mechanical behaviors of a diverse assortment of F-actin networks and bundles. In this review, we review the current understanding of the mechanics of F-actin networks and identify areas of further research needed to establish physical models. We first review our understanding of the mechanical behaviors of F-actin networks reconstituted in vitro, with a focus on the nonlinear mechanical response and behavior of "active" F-actin networks. We then explore the types of mechanical response measured of cytoskeletal F-actin networks and bundles formed in living cells and identify how these measurements correspond to those performed on reconstituted F-actin networks formed in vitro. Together, these approaches identify the challenges and opportunities in the study of living cytoskeletal matter.

1. Introduction

Since the discovery of actin in non-muscle cells, it has been postulated that spatiotemporal regulation of the mechanical behaviors of the filamentous actin (F-actin) cytoskeleton networks may regulate cellular shape change and force generation in cell migration and division Pollard, 1976; Clarke and Spudich, 1977; Stossel, 1978. Perhaps the simplest idea is that a transition between fluid-like (solution) and solid-like (gel) behavior of cytoskeletal F-actin networks could regulate the direction of cellular protrusions. In homogeneous networks of F-actin formed with a single cross-linking protein *in vitro*, such "sol–gel" transitions have been observed by changing cross-linker and F-actin concentration and modulating F-actin length Wachsstock et al., 1994; Janmey et al., 1990; Janson et al., 1991. F-actin networks formed *in vitro* demonstrate a broad diversity of mechanical behaviors that, in principle, could be harnessed to regulate the mechanical properties of cells over a variety of time and length scales.

However, the F-actin cytoskeleton in adherent animal cells can hardly be considered as a homogeneous network undergoing 'sol–gel' transitions (Fig. 1). A myriad of actin-binding proteins work in concert to regulate the kinetics of F-actin assembly and the organization of F-actin networks Vale and Kreis, 1999. Typically, a unique molecular signature and dynamic structure is found in F-actin networks in different regions of the cell and are temporally regulated during cell migration and division Le Clainche and Carlier, 2008; Naumanen et al., 2008. While it is widely appreciated that an intact F-actin cytoskeleton is essential for regulation of cell shape change and the generation of mechanical forces, the mechanical behaviors of the living F-actin cytoskeleton are largely unknown. Moreover, an understanding of how the mechanical behavior of the F-actin cytoskeleton is modulated during physiological behaviors such as cell adhesion, migration and division remains far from complete.

Since this understanding will only come from an integration of measurements performed *in vitro* with those inside live cells, we review the recent work in both these fields and identify potential intersections for future research.

2. Mechanics of F-actin networks in vitro

Isotropic, three-dimensional networks of F-actin can be formed *in vitro* by polymerizing F-actin in the presence of cross-linking proteins (Fig. 1). Although the structure of these networks is quite different from those found in many live cells, these systems have served as models with which to identify basic mechanisms of mechanical response of F-actin networks. Here, we briefly discuss

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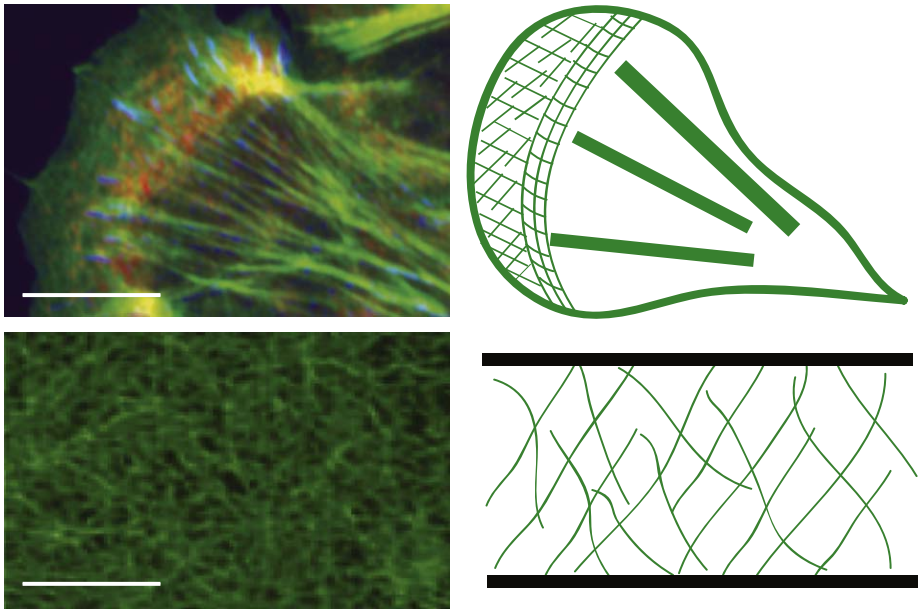

Fig. 1. Fluorescent Images (left) and schematics (right) of F-actin networks observed in living cells (top) and in vitro (bottom). F-actin (green), a focal adhesion marker (blue, paxillin) and myosin-II (red) are indicated in the image of the cell; in vitro network is stained for F-actin using fluorescent phalloidin. Cell schematic indicates the lamellipodium (green cross-hatches), lamella (thin gridded lines), stress fibers (thick lines) and cortex (surrounding boundary). By contrast, F-actin networks in vitro are homogeneous networks. Scale bar is 10 μm in both images. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

two ubiquitous features of the mechanics of F-actin networks: linear viscoelasticity and nonlinear elastic response. We also discuss recent advances in understanding the physics of 'active' F-actin networks where chemical energy is harnessed to establish asymmetric structure and generate local forces Fletcher and Geissler, 2009.

2.1. Linear viscoelastic response

Simple elastic materials are described by a linear stress–strain relationship that relates the deformation (strain) of a material to the force per unit area (stress) exerted; the ratio between the stress and strain is called the elastic modulus. By contrast, in a Newtonian fluid, an applied stress results in a constant deformation rate; the ratio between the stress and strain rate is a measure of viscosity. Generally, networks formed from biopolymers often show mechanical properties that are in between that of a pure fluid or elastic solid and, thus, are said to be 'viscoelastic' Gardel et al., 2008a, b. The viscoelastic response often depends on the time scale of the measurement as a result of different length scales associated with internal stress relaxation Lieleg et al., 2008.

Permanent cross-linking of F-actin eliminates much of the viscous response by restricting the ability of cross-linkers to unbind from actin filaments at long time scales MacKintosh et al., 1995a, b; Gardel et al., 2004; Tharmann et al., 2007a, b. F-actin networks formed with relatively static cross-links, such as scruin Gardel et al., 2004, rigor-state heavy meromyosin (HMM) ($K_d \approx 10^{-8}$ M) Tharmann et al., 2007a, b; Marston and Weber, 2002 and biotin–avidin ($K_d \approx 10^{-15}$ M) MacKintosh et al., 1995a, b are predominately elastic solids and exhibit a very large degree of tunability, ranging from 0.03 to >300 Pa as a function of cross-linker concentration Gardel et al., 2004.

Most physiological cross-linkers are dynamic on physiological time-scales and have a finite binding affinity to F-actin Wachsstock et al., 1994; Lieleg et al., 2008; Lieleg and Bausch, 2007. For instance, α-actinin ($K_d \approx 10^{-6}$ M) has a dissociation rate around $1\,s^{-1}$ Wachsstock et al., 1993. When compared to static cross-linkers, the lower affinity cross-linkers will decrease, but not completely eliminate, the elastic behavior of the network. An increase in the dissociation rate of cross-linkers shifts the frequency dependent viscous response to higher frequencies Wachsstock et al., 1994. Such modifications to the binding and unbinding rates to actin tune the timescale of the viscoelastic response for F-actin networks Lieleg et al., 2008; Lieleg and Bausch, 2007; Ward et al., 2008. Because cross-linker unbinding allows for rearrangements that play a significant role in viscous response in F-actin networks, it is hypothesized that cross-linker unbinding and rearrangement could enable stress relaxation through cytoskeletal networks at long times to accommodate cell shape change while maintaining a rigid network in response to short timescale perturbations. However, future work is required to delineate these behaviors in live cells.

2.2. Nonlinear elastic response

For most F-actin networks, the mechanical response becomes nonlinear at large stress or strain, such that the stiffness depends on the magnitude of the applied stress or strain MacKintosh et al., 1995a, b; Gardel et al., 2004; Storm et al., 2005; Xu et al., 2000. Quite generally, sparse (low F-actin density) networks with a small degree of cross-linking are observed to soften at large strains Gardel et al., 2004; Head et al., 2003a, b; Wilhelm and Frey, 2003. In contrast, dense (high F-actin density) networks with a high concentration of cross-links are observed to stiffen at intermediate strains followed by a dramatic softening at larger strains Gardel et al., 2004; Head et al., 2003a, b; Wilhelm and Frey, 2003.

Qualitatively, the nature of this stress-stiffening response is similar for networks formed with different actin cross-linking proteins, including α-actinin, filamin, scruin, HMM Gardel et al., 2004; Tharmann et al., 2007a, b; Esue et al., 2009 as well as non-physiological cross-links formed through biotin–avidin bonds MacKintosh et al., 1995. The critical strain at which the onset of stiffening occurs is typically on the order of 5–30% and is dependent on the type of cross-linker, linear elastic modulus

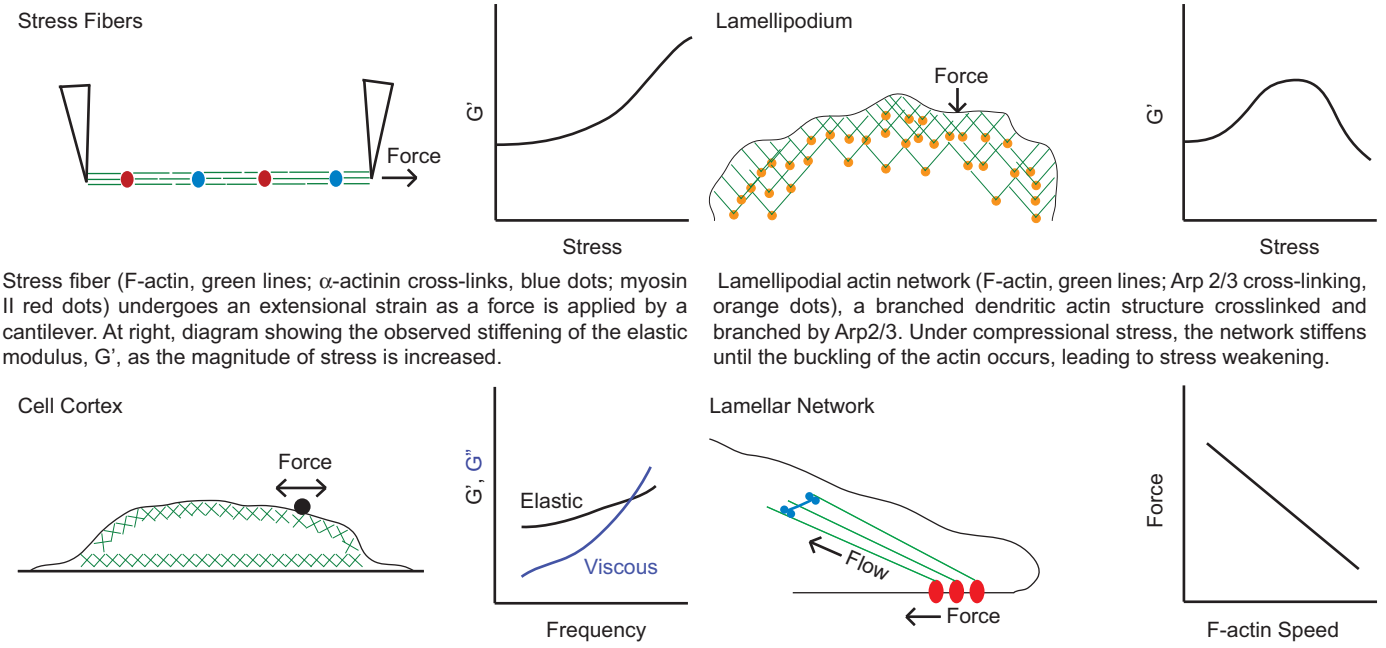

Fig. 2. Schematic diagrams of four distinct F-actin cytoskeletal networks discussed here showing the geometry of force application (black arrow) for the mechanical measurement of elastic modulus (G′) or viscous modulus (G″). For the lamellar network, force arrow indicates cell-generated force measured in the underlying extracellular matrix.

and measurement time scale. Typically, the shear elastic stiffness increases by about a factor of two; however, for F-actin networks cross-linked with filamin A, the stiffness can increase by nearly a factor of 100 Gardel et al., 2006a, b. Here, the elastic properties of the cross-linking proteins themselves is thought to dominate the network's elastic properties Gardel et al., 2006a, b; Broedersz et al., 2008; Kasza et al., 2009.

Recent experiments suggest that living cells may capitalize on this tunability to modify its viscoelastic properties in response to a stimulus. Physiological networks of F-actin shortened with gelsolin and cross-linked with filamin A demonstrate tremendous stress-stiffening at strains of approximately 30% Gardel et al., 2006a, b. By incorporating motor proteins within the network, this stiffening is observed in the absence of externally applied stress (Koenderink, unpublished). This suggests that, when attached to a resistive substrate, motor-containing F-actin networks may operate in a state of 'pre-tension' and that the stiffness of this network could be modulated by the level of myosin activity Wang et al., 2002. The regulation of myosin activity, which occurs through phosphorylation of its regulatory light chain, can occur at much faster than the time scales required for transcriptional regulation of actin-binding proteins. In this way, a cell may be able to tune its stiffness quickly in response to fast strain.

2.3. 'Active' F-actin networks

F-actin networks within the living cell operate far from chemical equilibrium, and chemical energy, in the form of ATP or GTP, is harnessed to control the assembly, architecture and mechanical properties of F-actin networks in a myriad of ways including the regulation of F-actin assembly, affinity of cross-linking proteins, and activity of myosin-II. Thus, a major challenge for the future is to extend current knowledge of the mechanics of F-actin networks in chemical equilibrium to those driven far from equilibrium to form 'active' F-actin networks Fletcher and Geissler, 2009.

Perhaps the best studied model system is the actin-based motility of the pathogen Listeria monocytogenes Cameron et al., 2000 where the minimal necessary proteins required for motility has been identified and motility has been recapitulated *in vitro* Carlier et al., 2003; Akin and Mullins, 2008. Briefly, the localization of ActA drives the preferential assembly of F-actin into a branched dendritic network. The polymerization of semi-flexible F-actin filaments is harnessed to generate forces Footer et al., 2007 sufficient for displacement of the sphere. Within the actin filament, ATP is hydrolyzed to ADP and becomes susceptible to filament severing by the protein cofilin. Thus, in this system chemical energy in the form of ATP is utilized to provide a sufficient available pool of actin monomers required for force generation. By directing the assembly of a similar network formed from cytoplasmic extracts at the surface of the tip of an atomic force microscopy, properties of this dendritic network under compression have been measured and showed a transition between stress-stiffening and softening behavior under increased strain (Fig. 2) Chaudhuri et al., 2007.

Reconstitution of active contractile F-actin networks, as a model for the cellular cortex, has been of interest for sometime. Initial experiments sought to explore the importance of network gelation, via cross-linking proteins, on the contraction driven by myosin-II motors Janson et al., 1991; Janson et al., 1992. These experiments identified that a minimal amount of cross-linking was required for macroscopic network contraction whereas further increasing the density of cross-linking proteins inhibited contraction Janson et al., 1991; Janson et al., 1992. More recent

experiments have further characterized the range of concentrations of cross-linkers and motor proteins over which contractility is observed. These experiments estimate the force generated by this contraction to be on the order of 100 pN per F-actin bundle Bendix et al., 2008. Recent models have made predictions for the upper limit of tension generated by actomyosin gels Carlsson, 2006.

3. Mechanics of F-actin networks in cell migration

In living cells, the F-actin cytoskeleton encompasses a variety of different structures that are essential for many different aspects of cell physiology. For each process, the F-actin cytoskeleton has a distinct molecular composition and structure, which suggests that the mechanical properties of these networks may be tuned for a specific aspect of cellular physiology. Here we focus on F-actin structures involved in different steps of cell migration, including those essential for cell protrusion (lamellipodia and filopodia), adhesion (lamella and stress fibers) and shape change (cortex). However, the role of F-actin mechanics in other cellular processes, such as endocytosis, trafficking and cell division are other rich areas of study.

3.1. Mechanics of lamellipodial actin networks

The initial step in cell migration is the protrusion of the leading cell membrane created by a branched, dendritic array, similar to that formed in listeria-based propulsion, called the lamellipodium. Here, it is thought polymerization of F-actin generates mechanical forces to change leading edge cells shape. Adhesions to the extracellular matrix can occur within the lamellipodium, forming small, myosin-II independent focal adhesions through which the lamellipodial F-actin networks exert low traction stresses, of the order of 20 Pa, on the extracellular matrix Gardel et al., 2008a, b. Depending on the type of technique utilized, the forces associated with cell protrusion have been measured to be quite weak (a few pN per micron) Bohnet et al., 2006 or significantly stronger (several hundred pN per micron) Prass et al., 2006. Filopodia, a protrusive organelle also driven by F-actin polymerization, consists of tightly bundled F-actin and exert significantly less stress than lamellipodial networks Cojoc et al., 2007. These variations in the absolute force generated by protrusion may arise from differences in geometry or timescale of the measurement, which may probe the effect of cellular adhesion to a varying degree. Additional experiments have shown that myosin-II driven networks proximal to the lamellipodium apply additional tension through this network that promotes the assembly of cellular adhesions Giannone et al., 2007. Since migrating cells may need to exert significant stress to invade surrounding extracellular matrix, future work to understand the origins of stall stress for various protrusive organelles could have a significant impact on our ability to control cell migration.

3.2. Mechanics of the lamellar actin network

Proximal to the leading edge lamellipodium, adhesions to the extracellular matrix form and delineate a transition to a myosin-II containing F-actin network termed the lamella. Here, the F-actin network is transported from the leading edge towards the cell center in a myosin-II-dependent process termed ‘retrograde flow’. Many characteristics of retrograde flow can be captured by modeling the F-actin network as an active polar gel Kruse et al., 2006.

Understanding how retrograde flow in the lamella is harnessed for efficient cell protrusion has been of interest for many decades. Measurements have shown that increased rate of cell protrusion occurs when retrograde flow decreases Lin and Forscher, 1995; Jurado et al., 2005, suggesting that adhesions to the extracellular matrix act as a ‘molecular clutch’ to modulate interactions between the F-actin cytoskeleton and the immobilized extracellular matrix (Fig. 2) Mitchison and Kirschner, 1988. When the clutch is engaged, focal adhesion proteins bind strongly to actin and transmit forces to the extracellular matrix via their attachment to integrins. When disengaged, focal adhesions bind weakly to actin and contractility allows fast retrograde flow of actin and slippage past the focal adhesion. However, traction force experiments revealed a biphasic relationship between F-actin speed and traction force Gardel et al., 2008a, b. Near the cell edge where F-actin speed is fast, F-actin speed and traction force are inversely related, consistent with a simple molecular clutch. However, at larger focal adhesions farther from the cell edge where F-actin motion is overall slower, F-actin speed and traction stress follow a direct relationship. More recent experiments and modeling have shown that such a slip clutch could additionally act as a mechanical sensor Wang, 2007; Chan and Odde, 2008. Future work is required to determine how the F-actin retrograde flow is utilized, in concert with mechanosensitive focal adhesions to enable adherent cells to sense the mechanical properties of their surrounding extracellular matrix.

3.3. Mechanics of stress fibers

In some cell types, the lamellar network is further organized into contractile bundles that form parallel or perpendicular to the cell edge Cramer, 1999; Cramer et al., 1994. Contractile F-actin bundles form from contraction of the lamellar network Verkhovsky and Borisy, 1993; Verkhovsky et al., 1995 and *de novo* assembly Naumanen et al., 2008; Hotulainen and Lappalainen, 2006; Senju and Miyata, 2009. Typically, one end of a stress fiber terminates at a point of adhesion to the extracellular matrix or another cell while the other end typically becomes woven into the F-actin cortex near the nucleus. It is likely that the contractile F-actin networks linked to cellular adhesions determine the magnitude of forces transmitted to outside the cell as well as the mechanical response of the cell to stresses and strains applied to these adhesions. A wide variety of contractile F-actin networks with different architectures and organization of F-actin polarity are found near cellular adhesions and, it is likely that differences in the mechanical behavior determine the precise nature of the force transmission to the extracellular matrix.

Stress fibers are a specific type of contractile F-actin bundle characterized by repeating units of myosin-II motor proteins and α-actinin, reminiscent of the sarcomere structure in muscle cells. The spacing between myosin-II along the stress fiber can change over time, indicating a dynamic structure with non-uniform elasticity and forces Peterson et al., 2004. For instance, if the stress fiber becomes severed or detached its length contracts in a myosin-II-dependent fashion Kumar et al., 2006; Deguchi et al., 2006. If myosin-II activity is enhanced, the spacing between the myosin-II decreases near the peripheral regions, but expands near the central regions, suggesting a non-uniformity in the mechanical properties of these bundles. Atomic force microscopy measurements have shown that the stiffness of the stress fiber is approximately 12 kPa and that the modulus is constant for strains up to 12% Lu et al., 2008. When myosin-II cross-linking and enzymatic activity is perturbed by pharmacological treatment with blebbistatin, the elastic modulus decreases to 8 kPa. Thus,

myosin-II plays an important role in determining the linear stiffness of stress fibers.

Moreover, the stiffness of blebbistatin-treated stress fibers becomes highly strain sensitive, with the modulus increasing by 60% for strains between 1% and 10% (Fig. 2) Lu et al., 2008. Nonlinearity in the elastic properties of stress fibers have been confirmed by tensile tests, which have shown that the tensile elastic modulus increases from 1.45 MPa at low strains to 104 MPa at strains near 200% Deguchi et al., 2006. The nonlinearity of the stress–strain relationship for stress fibers is strikingly similar to those that have been observed *in vitro* and suggest the importance of nonlinear elasticity in the determination of force transmission.

Interestingly, the rupture force of stress fibers has been measured to be close to 370 nN, nearly a 100-fold larger than the typical amount of force exerted at a cellular adhesion site. Instead, the magnitude of traction stresses is consistent with the amount of force required to extend the length of the stress fiber by 20%; consistent with the idea that stress fibers within the cell exist in a pre-strained state and that nonlinear elastic behavior of stress fibers determines the interplay between intracellular strain and traction stress exerted to the extracellular matrix.

Stress fibers have been modeled as viscoelastic cables, possessing an elastic component and a viscous dissipative element from filaments gliding past each other, in addition to active contractile units from myosin motor protein activity Achim and Ulrich, 2007; Stachowiak and O'Shaughnessy, 2008. Future work to identify how the mechanical behaviors of actomyosin structures regulate the assembly and mechanical properties of stress fibers will provide new insight into the regulation of cellular adhesion and migration.

3.4. Mechanics of the cell cortex

The F-actin cortex is a thin, membrane-bound F-actin network that regulates cell shape. The F-actin cortex also utilizes myosin-II contractility to remodel and generate tension along the cellular periphery. Such contractility can describe the convex shape attained by a variety of adherent cells, including fibroblasts and B16 melanoma cells, and a modified Laplace law model which considers the contractile properties of the actin cortex can predict the radius of curvature of the convex arcs Bischofs et al., 2008. Models assuming only a 2D cable network of a specified lattice geometry and a distribution of focal adhesions can predict finite forces at adhesions Paul et al., 2008. Myosin-II generated tension within the actin cortex is also observed to inhibit local cell protrusion. Inhibition of this tension by perturbations to myosin-II or mechanics of the extracellular matrix can enhance local protrusive activity, such as that observed in angiogenesis or neuronal growth Fischer et al., 2009.

When the F-actin cortex detaches from the cell membrane, a rounded structure known as a 'bleb' occurs. Cellular blebbing is observed to occur during apoptosis, but also during cell division and certain types of cell migration. In non-apoptotic blebs, the diameter of the bleb expands after initial formation for approximately 30 s, reaching sizes of between 1 and 2 μm Charras et al., 2006; Charras et al., 2008. After expansion, assembly of a new F-actin cortex at the membrane, coupled with myosin-II contractility drives the retraction of the bleb. During this retraction phase, the bleb's stiffness increases fivefold due to the stiffness of the newly reattached actin cortex Charras et al., 2008. These experiments also suggest that the blebs are an indicator of a high intracellular pressure, on the order of 100 Pa Charras et al., 2008. Further experiments are needed to assess implications of this high pressure on cytoskeletal dynamics and cellular physiology.

A myriad of techniques have been developed to measure the mechanical response of cellular cortex by indenting, shearing or extending the exterior cell membrane through integrin-mediated (or non-specific) adhesion to a micron- or nano-scale probe (Fig. 2) Kasza et al., 2007. A primary component of this response is the F-actin cortex, although other contributions from the soluble and insoluble cytoskeleton cannot be neglected. These measurements have shown that the cortex is a viscoelastic solid, displaying a broad spectrum of mechanical relaxations reminiscent of glassy materials Bursac et al., 2005, and consistent with the broad spectrum of relaxations observed for 3D in vitro F-actin networks Gardel et al., 2006a, b. The elastic modulus at 0.1–1 Hz can range from a few hundred Pa for neutrophils and neurons to several thousand Pa for fibroblasts. Moreover, for many adherent cells, the cortical stiffness varies monotonically with the stiffness of the extracellular matrix: stiffer extracellular matrices promote the generation of a stiffer cortex Solon et al., 2007. Similarly, the cortical stiffness increases linearly with the magnitude of cell-generated traction stress or stress applied to the cortex, similar to the nonlinearity observed in *in vitro* F-actin networks Kasza et al., 2007. While viscoelastic models of the F-actin cortex can explain many of the observed measurements of the cellular cortex, recent measurements have identified additional slow propagations which are better described by poroelastic models of F-actin deformation and cytoplasm flow Rosenbluth et al., 2008.

4. Outlook

Advances in molecular biology and biochemistry have enabled rapid progress both in the control over F-actin cytoskeletal networks formed in live cells and the ability to reconstitute F-actin networks *in vitro*. Thus, future work to integrate physical measurements and models of *in vitro* F-actin networks with observations and measurements of cellular networks will provide a coherent foundation to understand how the dynamics and mechanics of individual macromolecules give rise to the complex, adaptive F-actin cytoskeleton in adherent cells.

The ultimate goal in the field of F-actin cytoskeletal mechanics is to develop predictive physical models to characterize the mechanics of cellular physiology, including adhesion, migration and division. These models will provide insight to the key physical parameters that govern the mechanics of each of these processes and an understanding of how macromolecular interactions give rise to shape change and force generation at the cellular level. While some of these parameters could be ones we have developed to characterize equilibrium materials such as viscosity and elasticity, other behaviors may require the development of new parameters to describe non-equilibrium materials. This insight will open up new opportunities to control and modulate aspects of cellular physiology that rely specific mechanical response of the F-actin cytoskeleton.

Conflict of interest statement

None

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