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Actin Cytoskeleton and Mechanotransduction

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Actin Cytoskeleton and Mechanotransduction

Mechanotransduction is a multi-step biological process by which cells sense, interpret, and respond to mechanical (i.e., physical) force through conversion to biochemical signals that elicit specific cellular responses. The responses are often mechanical in nature as they involve force generation to produce cellular protrusions and retractions which require remodeling of the actin cytoskeleton, consisting of monomeric (globular; G-) and helical polymeric (filamentous; F-) actin and actin binding proteins (ABPs)[1-3]. ABPs dynamically organize F-actin into many different structural forms such as lamellipodia, stress fibers, filopodia, podosomes, actin asters, vortices, and stars[2-4]. These different architectures serve specialized roles in the cell's multiplex response to mechanical stimulation. A primary means by which F-actin transduces these signals is through its connections to focal adhesions and adherens junctions, which coordinate contact between the cell's actin cytoskeleton and either the extracellular matrix or another cell, respectively[5-7](Fig. 1). Understanding the actin cytoskeleton's role in mechanotransduction goes beyond the basic biology underlying force-induced changes in actin-based cellular structures and functions. Diseases resulting from expression of mutant ABPs render cells unable to respond to mechanical forces physiologically[3,8-13]. In this newsletter, the role of the actin cytoskeleton in mechanotransduction is discussed.

The actin cytoskeleton functions as a mechanosensor for tension applied to cells[3]. The question is, how does the cytoskeleton respond to mechanical tension (Fig. 1)? Actin filaments in the various actin-based structures bear a mechanical load (per filament) that has been studied by a variety of microscopy techniques such as electron microscopy, Förster resonance energy transfer (FRET), atomic force microscopy, and optical traps, to name but a few[3,14]. These different actin structures are associated with specific mechanical loading that are optimized for the structure's specialized cellular functions. Mechanical loading (increased tension) of filaments alters their conformation[15] and how ABPs bind and affect filaments[3]. In the case of cofilin, a F-actin severing protein, changes in filament length affect its binding and function. Tensile forces that stretch a cell correspondingly increase the length of filaments parallel to the direction of the stretch. Under these conditions, the binding affinity of cofilin is reduced and that of myosin II is increased[16-18]. This mechanical-induced change in F-actin length and binding partners results in stabilized F-actin which can more easily form stress fibers, an essential part of a cell's mechanotransduction processes[7,16-19] (Fig. 1). Tension-induced changes in actin structural dynamics also affects the binding of actin-nucleating proteins such as Arp2/3[20]. Mechanically-induced changes in actin-based structures can also affect gene expression in at least some cell types. As more stress fibers form during mechanical stimulation, the transcriptional coactivator YAP translocates to the nucleus where it is activated. YAP is integral in Hippo signaling and mediates increased expression of genes involved in cell proliferation and differentiation. Thus, the response of the actin cytoskeleton to extracellular mechanical forces can result in processes that have both physiological and pathophysiological relevance[7,21,22].

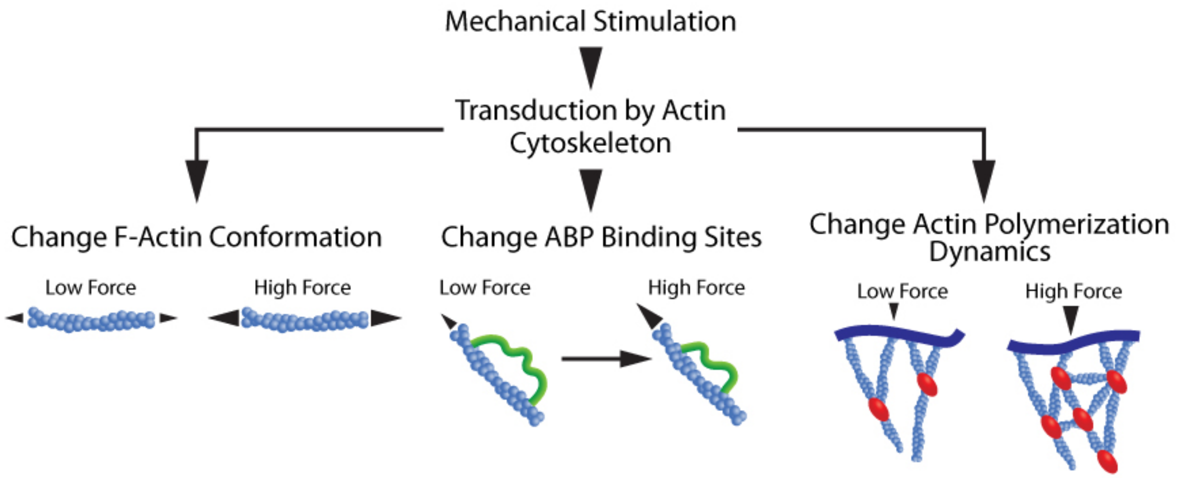

Figure 1. Actin cytoskeleton transduces mechanical forces. Mechanical loads induce a: 1. Conformational change in F-actin (left schematic); 2. Conformational change in ABPs that uncovers previously concealed binding sites (middle schematic); and 3. Alterations in ABP-mediated actin polymerization dynamics (right schematic).

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Similar to F-actin, ABPs and other actin-associated proteins directly respond to mechanical stresses (Fig. 1). Common responses include conformational changes which expose previously concealed protein binding sites. This is the case for talin, a focal adhesion-associated protein, the adherens junction protein α-catenin, and ABPs such as vinculin, filamins, myosin, α-actinin 4, and actin filament-associated protein[23-29].

Finally, actin polymerization and network assembly are modulated by mechanical forces (Fig. 1). Through force-induced changes in ABPs (see above), polymerization dynamics are altered[3]. By itself, mechanical force itself can also oppose polymerization by acting as a physical obstacle. Such changes in polymerization dynamics can alter the density and organization of filaments[3].

Summary

Actin is the quintessential cytoskeletal protein and perhaps is the protein most associated with a cell's response to varied external stimuli that results in changes to cellular shape, motility, intracellular trafficking, and force generation. Despite actin's obvious importance in physiological and pathophysiological processes and decades of focused research, challenges remain in understanding how so many different higher order actin structures exist in a cell and what their corresponding functions are in mechanotransduction. Answering these questions is technically challenging as it requires high resolution microscopy combined with applying and measuring the mechanical load on filaments. To help scientists unravel the roles of F-actin in mechanotransduction (and other cellular processes), Cytoskeleton, Inc. offers purified labeled and unlabeled actin proteins, purified ABPs, functional actin-based assay kits, and F-actin live cell imaging probes.

Actin Products

Actin Products	Amount	Cat. #
Actin Protein (>99% pure) Bovine cardiac muscle	1 x 1 mg 5 x 1 mg	AD99-A AD99-B
Actin Protein (>99% pure) Smooth muscle, chicken gizzard	1 x 1 mg 5 x 1 mg	AS99-A AS99-B
Pre-formed Actin Filaments (>99% pure) Rabbit skeletal muscle	1 x 1 mg 5 x 1 mg	AKF99-A AKF99-B
Actin Protein (>95% pure) rabbit skeletal muscle	1 x 1 mg 5 x 1 mg	AKL95-B AKL95-C
Actin Protein (>99% pure) rabbit skeletal muscle	4 x 250 µg 2 x 1 mg 5 x 1 mg 10 x 1 mg 20 x1 mg	AKL99-A AKL99-B AKL99-C AKL99-D AKL99-E
Actin Protein (>99% pure) Human platelet, non-muscle	2 x 250 µg 1 x 1 mg 5 x 1 mg	APHL99-A APHL99-C APHL99-E
Rhodamine Actin Protein (>99% pure) Human Platelet, Non-Muscle	4 x 10 µg 20 x 10 µg	APHR-A APHR-C
Rhodamine Actin Protein (>99% pure) Rabbit Skeletal Muscle	10 x 20 µg 20 x 20 µg	AR05-B AR05-C
Spirochrome SiR-Actin Kit	50 nmol	CY-SC001
Spirochrome SiR700-Actin Kit	35 nmol	CY-SC013
Acti-stain™ 488 Phalloidin	300 slides	PHDG1
Acti-stain™ 555 Phalloidin	300 slides	PHDH1
Acti-stain™ 670 Phalloidin	300 slides	PHDN1
Phalloidin (rhodamine)	500 ul	PHDR1
Profilin 1 (recombinant human no tag)	1 X 100 µg 1 x 500 µg 1 x 1 mg	PR02-A PR02-B PR02-XL2

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Actin Biochem Kits

Actin Biochem Kit	Reactions	Cat. #
Actin Binding Protein Spin-Down Assay Biochem Kit: rabbit skeletal muscle actin	30-100 assays	BK001
Actin Binding Protein Spin-Down Assay Biochem Kit: human platelet actin	30-100 assays	BK013
Actin Polymerization Biochem Kit (fluorescence format): rabbit skeletal muscle actin	30-100 assays	BK003
G-Actin/F-actin In Vivo Assay Biochem Kit	30-100 assays	BK037