Mechanical Forces in Cell Biology

Important for : cell shape, movement of intracellular components, whole cell motility, and tissue integrity

Key components of the Force Generating Machinery

Intracellular	Actin Filaments: non-covalent, polymers of actin	
	Microtubules:	tubulin
	Intermediate filaments:	vimentin, desmin
Plasma membrane	Cell Adhesion molecules: integrins	
Extracellular	Extracellular matrix proteins: collagen, laminin, fibrillin	

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The Intracellular Cytoskeleton - Proteins to filaments :

Actin → Actin Filaments
Tubulin → Microtubules

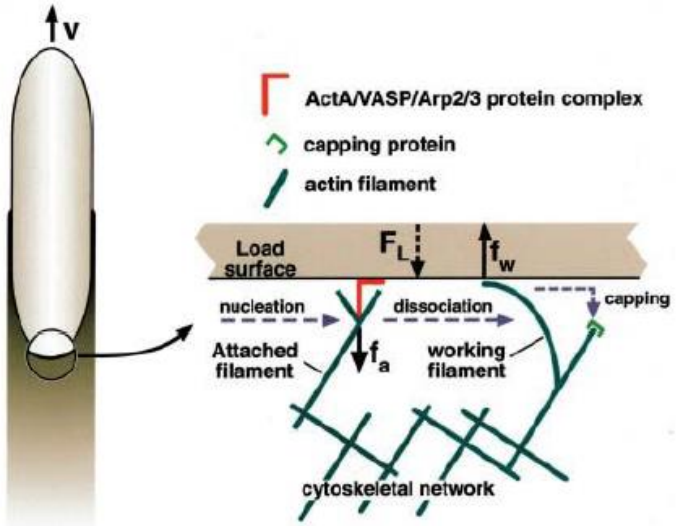
Filaments assemble from monomers in a vectorial manner

Filaments are dynamically unstable as they are continuously being formed at one end by addition of monomers and "dissolving" at the other end due to shedding of monomers -- a process called *treadmilling*

Monomeric actin (and tubulin) have bound ATP (and GTP, respectively)
Upon association into a polymer, the nucleotide is hydrolyzed with ADP (or GDP) remaining bound to actin (or tubulin)

Intermediate filaments provide rigidity to maintain the shape of the cell

Force generation - Elastic Brownian Ratchet Model



Mogliner & Oster, Biophys J. 84:1591 (2003)

Movement of the bacteria listeria, used as a prototype to study force generation

- Dependent on force generated by actin filament polymerization at the plasma membrane
- Back end anchored in cytoskeleton

Transient attachment of growing filament to the membrane

Growing filaments push membrane forward

Attached filaments provide resistance to forward movement

Relationship between force and velocity for a single filament is governed by the equation:

$$V = V_{\max} \exp[-f_w l / k_B T] - V_{dep}$$

V_{max} -- free polymerization velocity (no resistance)
F_w -- force excerted by working (growing) filament
l -- length by which the filament grows when when one action monomer is added
$K_B T$ -- thermal energy
V_{dep}-- Free depolymerization rate (no resistance)

At steady state movement with a constant rate

$$V = V_{max} \exp[-l(f_b v\omega^2(v)(\kappa/\delta_0)+(F_L\kappa/n))/k_BT] - V_{dep}. \quad (11)$$

We introduce the following four dimensionless parameters, which determine the model's behavior:

$\varepsilon_1 = (f_b l/k_B T)(\kappa/\delta_0)$: work done per working filament in breaking an attachment.
$\varepsilon_2 = (V_{max}/V_0)$: free polymerization velocity.
$\varepsilon_3 = (V_{dep}/V_0)$: free depolymerization velocity.
$\varepsilon_4 = (F_L l/k_B T)(\kappa/n)$: work performed on the load per working filament.

Using these definitions, Eq. 11 can be rewritten in the dimensionless form:

$$v = \varepsilon_2 \exp[-\varepsilon_1 v\omega^2(v) - \varepsilon_4] - \varepsilon_3. \quad (12)$$

An analytical model of how actin polymerization at the plasma membrane drive the movement of the bacterium

Where $v \equiv V/V_o$
and V_o is velocity at which the attachment bond stretches to its length over the lifetime of the bond

Mogliner & Oster, Biophys J. 84:1591 (2003)

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Movement of filament is controlled by motor proteins
Motor proteins bind to cytoskeleton filaments

Myosin Motors

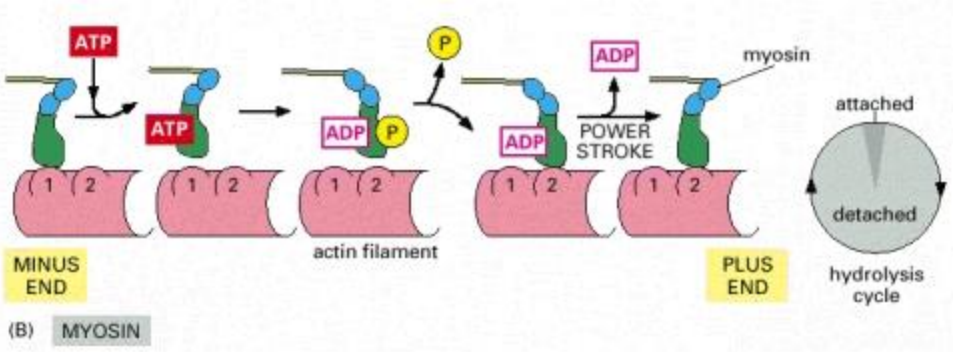

Fig 16-59 Molecular Biology of the Cell
Alberts *et al*. 4th Edition

Myosin uses energy from ATP hydrolysis to move along actin filaments, thus generating force

This intracellular force can move actin filaments, organelles and other cargo within cells

Motor proteins also contribute to whole cell motility.

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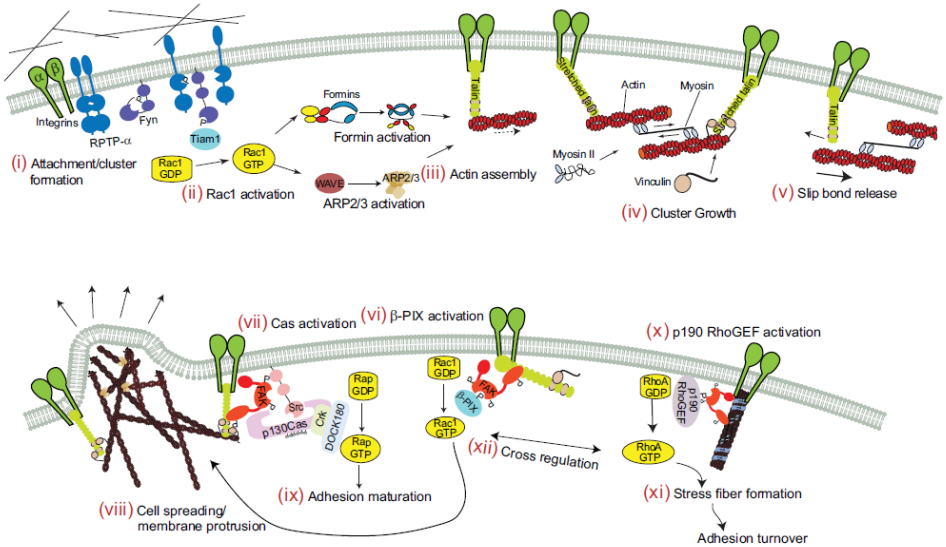
How is force sensed?
Mechanotransduction



Roca-Cusachs et al J Cell Sci 125: 3025 (2012)

1. Interactions between ECM, integrins and actin filaments deforms ECM and generates force

2. Force activates channels, receptors, phosphatases, tyrosine kinases by altering their structure

3. In turn, these activated signaling proteins or calcium regulate GEF/GAPs to modulate G proteins that transmit signals to cytoskeletal regulators

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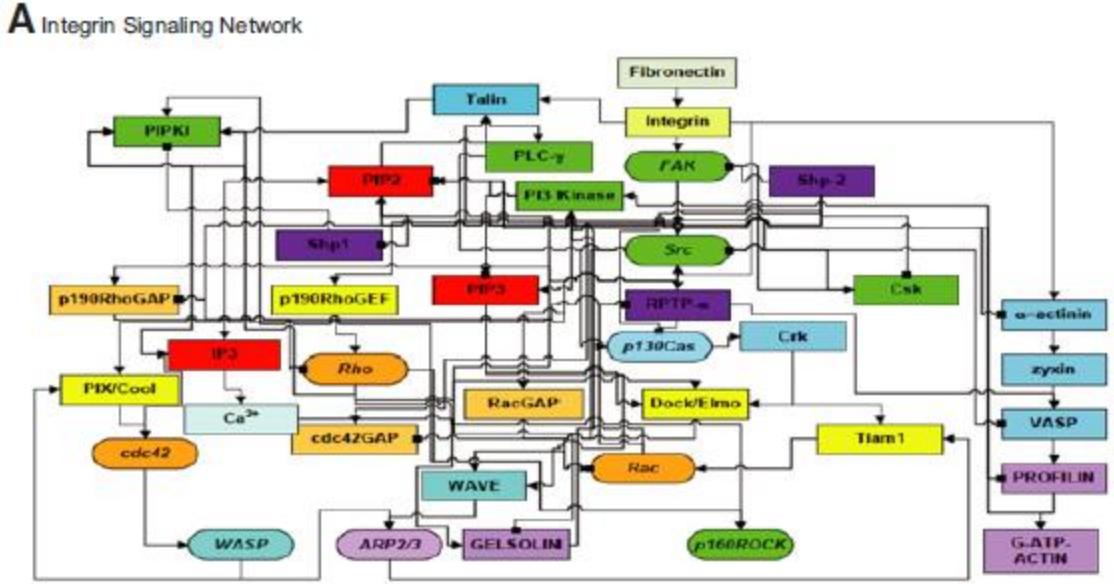
Regulation of Cytoskeleton by Biochemical Signaling and Controlled Cell Movement



A relatively elaborate network controls signal flow from integrin to key regulators that modulate actin filament growth and branching to drive cell movement.

Rangamani *et al*. Biophys J. 100; 845 (2011)

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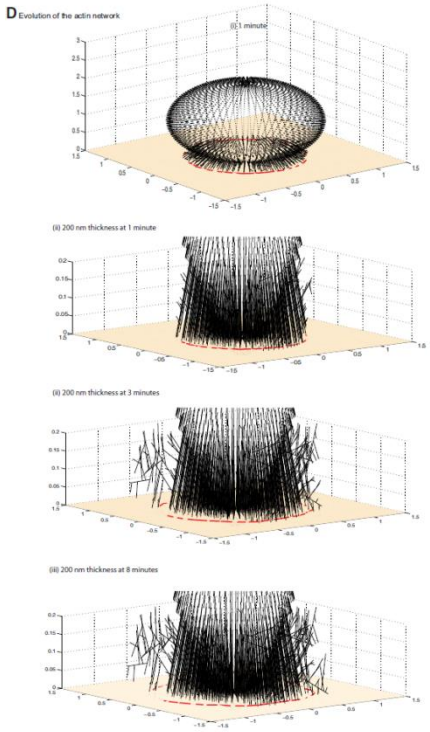
Regulation of Cytoskeleton by Biochemical Signaling and Controlled Cell Movement



The filament growth process can be modeled computationally using a hybrid model that combines

deterministic modeling of the signaling reactions

with

stochastic modeling of actin filament network growth and cell spreading

Rangamani *et al*. Biophys J. 100; 845 (2011)

Lecture 4A – Take Home Points

- Interactions between specific proteins lead to formation of filaments and other structures that are capable of generating mechanical forces
- Force generation within cells can be analytically modeled
- Interaction of molecular motors with filaments are involved in force generation
- Force generation by actin filaments is regulated by cell signaling networks, and conversely force signals can be sensed (*mechanotransduction*) by these same networks
- Hybrid models can be used to study how signaling networks regulate cell spreading through control of force generation