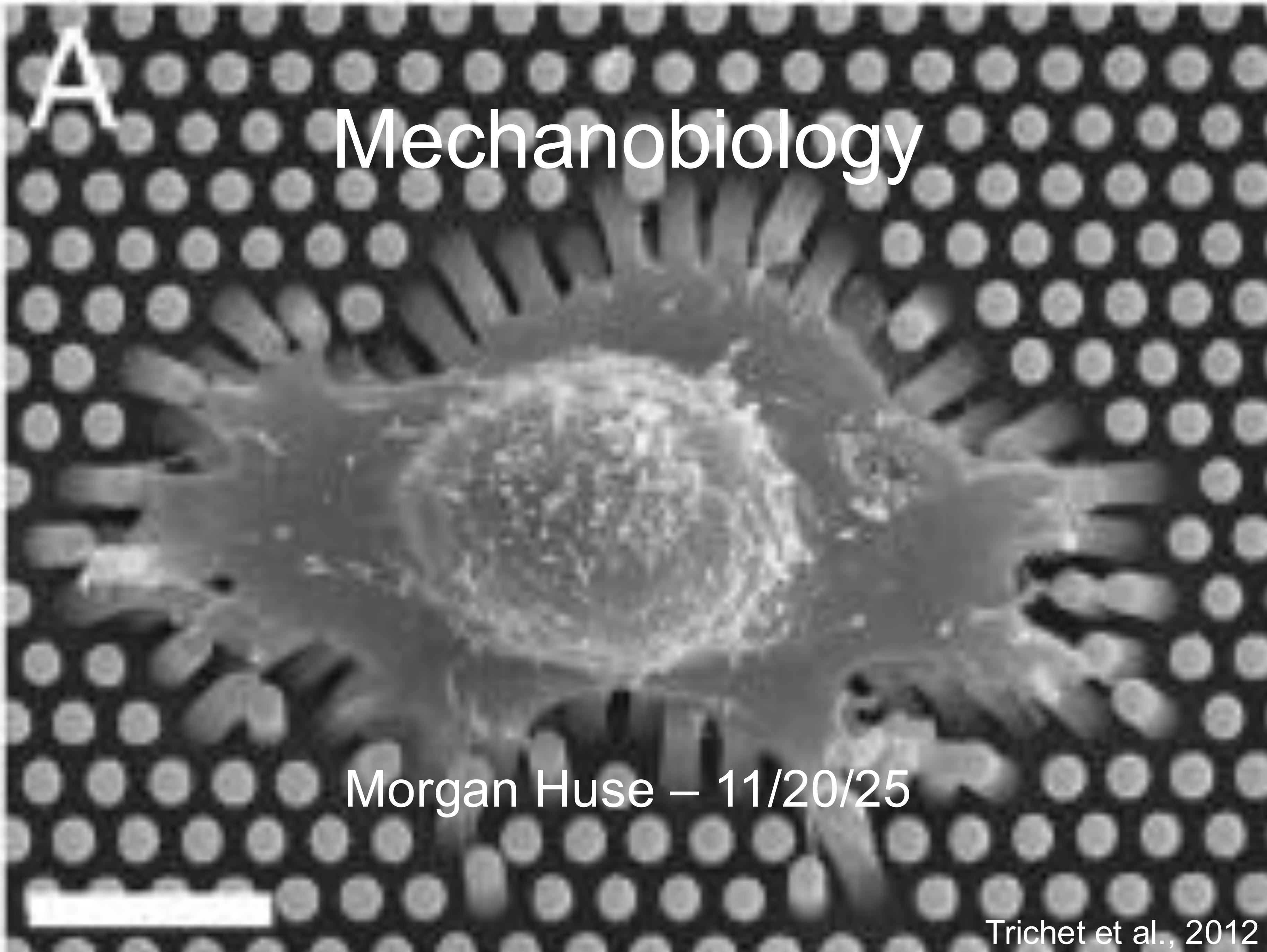
Mechanobiology

Morgan Huse – 11/20/25



Trichet et al., 2012

Lecture outline

1) The mechanical properties of cells.

2) Mechanical force exertion by cells.

3) Mechanotransduction: pathways and functions.

4) Cell motility.

5) Cell extrinsic forces.

6) Cell-cell interactions.

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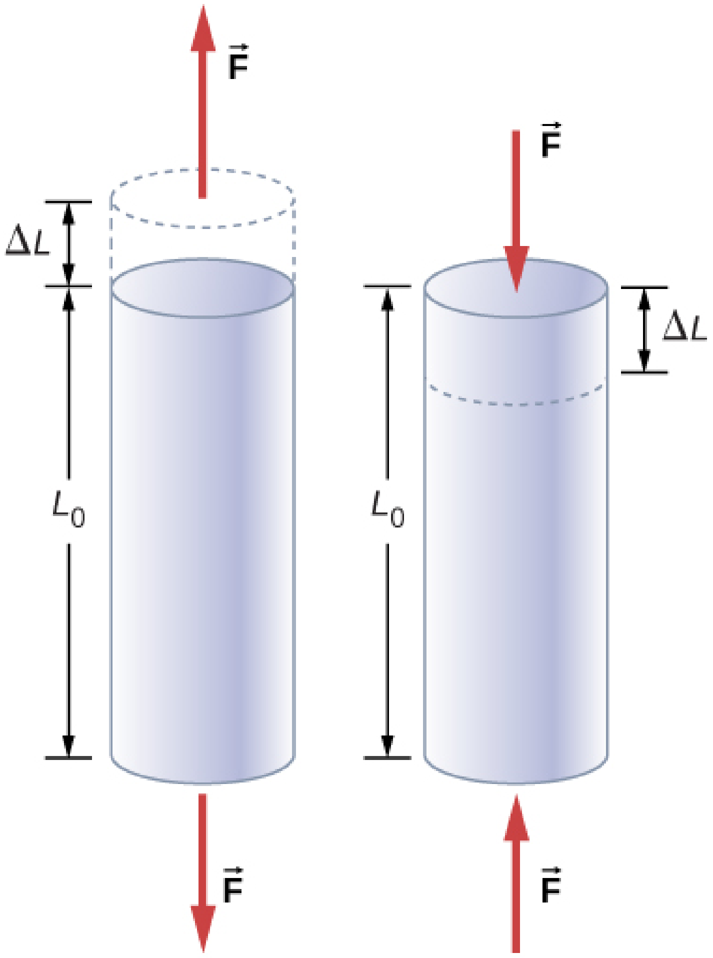
Stress and strain



Lumenlearning

Stress (force)
$\sigma = F/A$

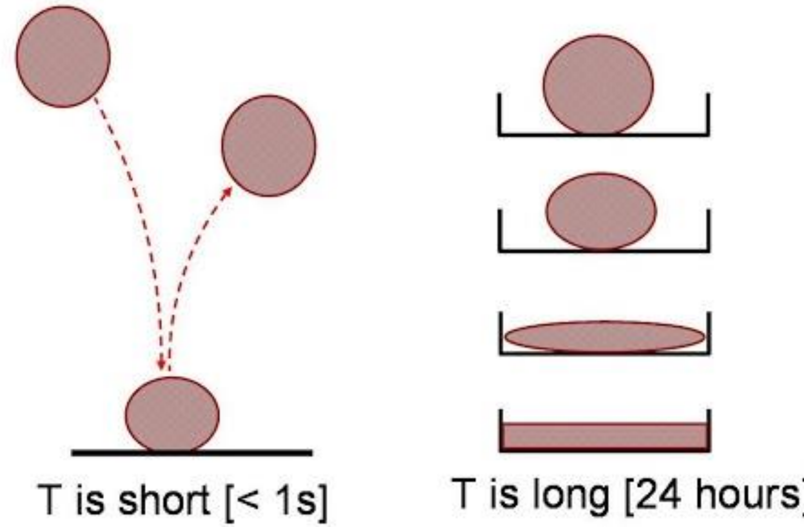
Strain (deformation)
$\varepsilon = \Delta L/L$

Modulus $E = \sigma/\varepsilon$

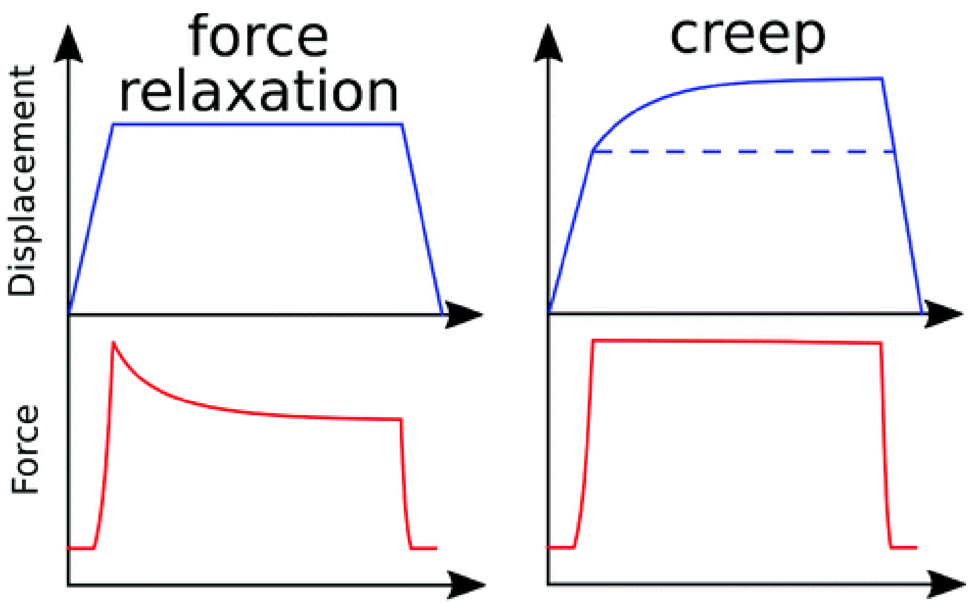
Cells are viscoelestic

Viscous materials resist shear flow linearly with time when stress is applied

Elastic materials strain when stress is applied and immediately return to their original state once stress is removed



http://www.iq.usp.br/



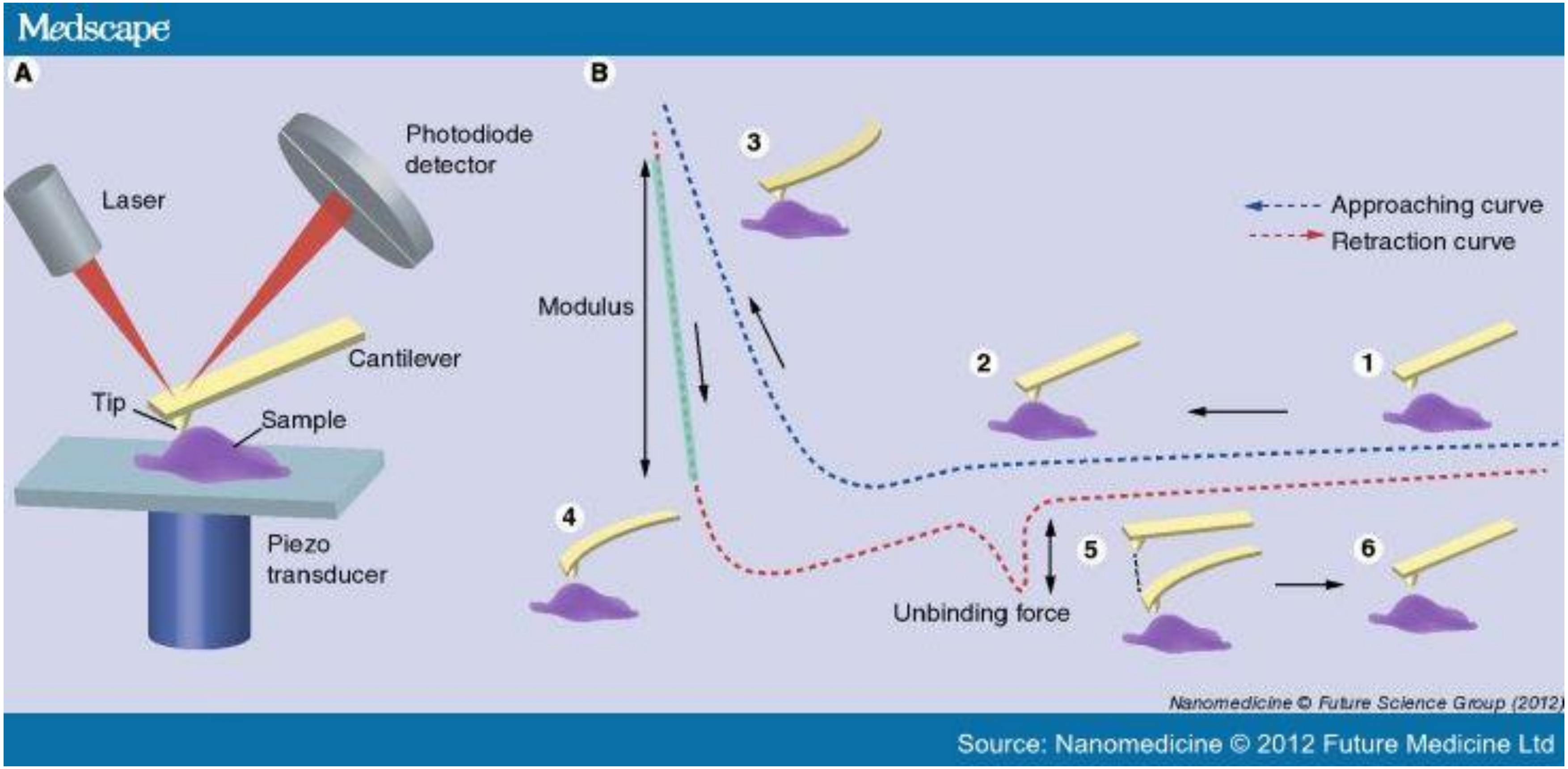
Efremov et al, 2019

Properties of viscoelastic cells

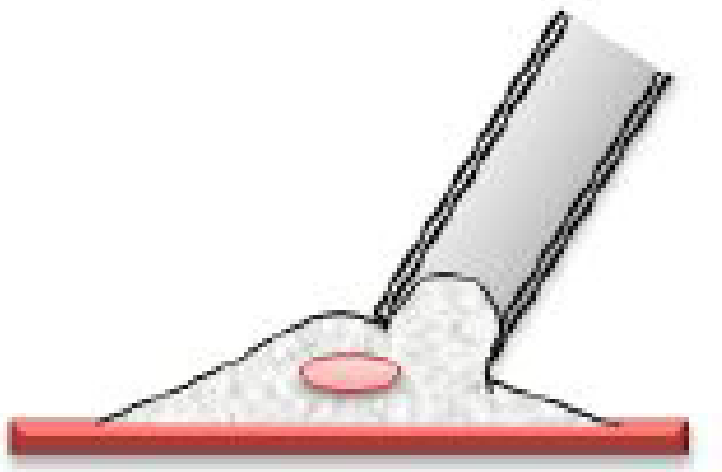
Biophysical properties – things we can measure

Cell Stiffness/rigidity/deformability: Resistance to transient deformation

Atomic force microscopy (AFM)

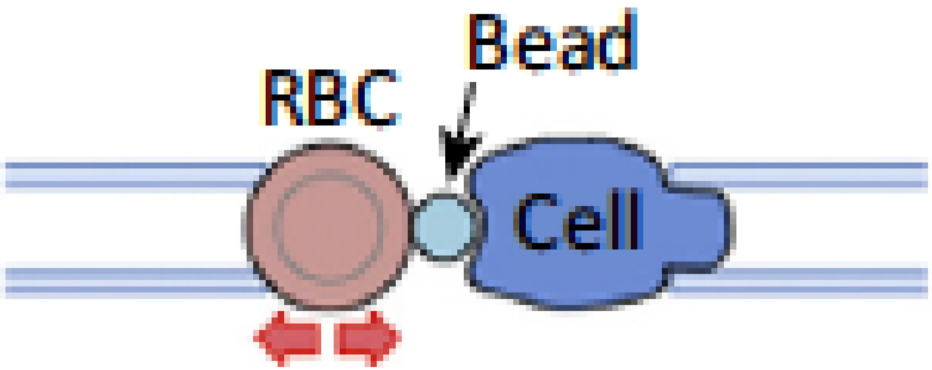


Other ways to measure deformability



Micropipette aspiration

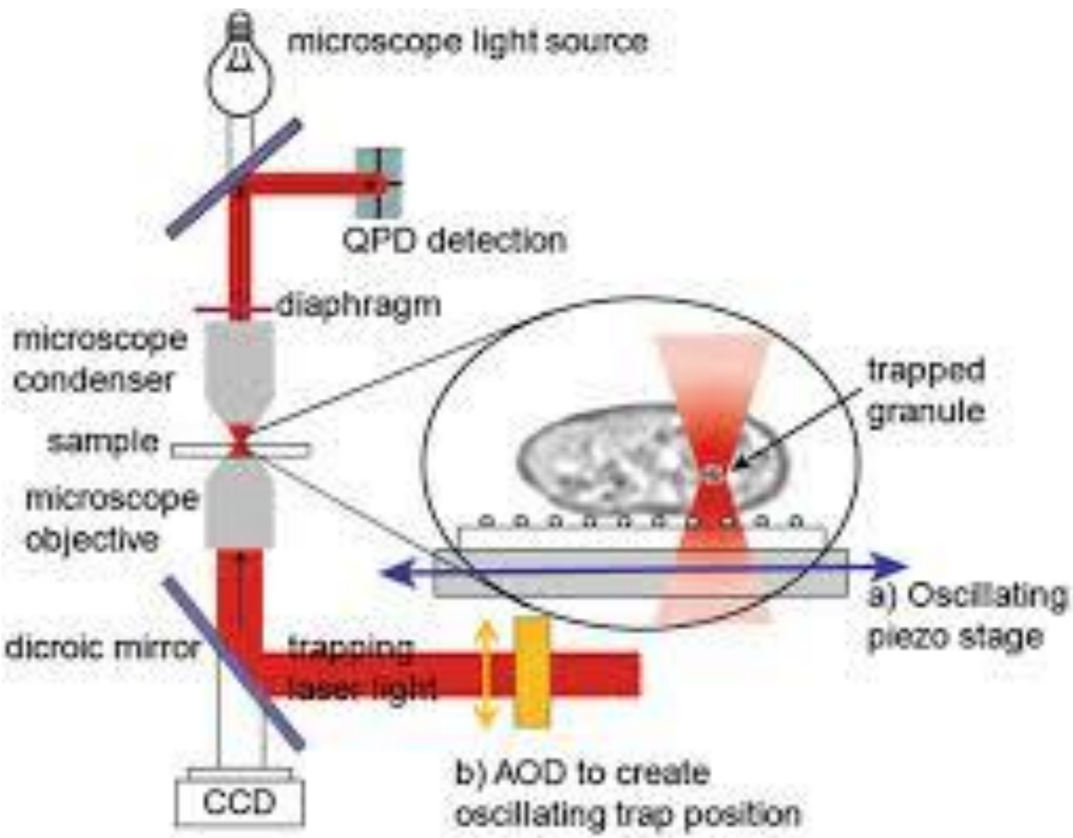
Bhat et al, 2012



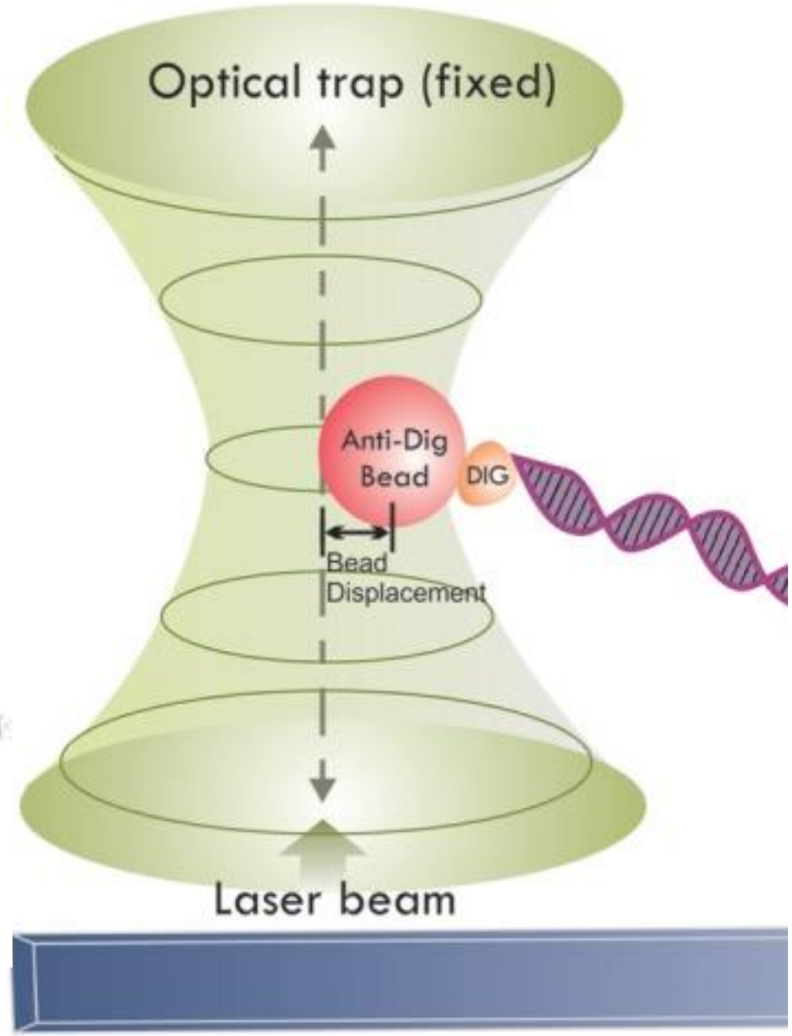
Biomembrane force probe

Basu et al, 2017

Optical trap



Ritter et al, 2017



Wang et al, 2013

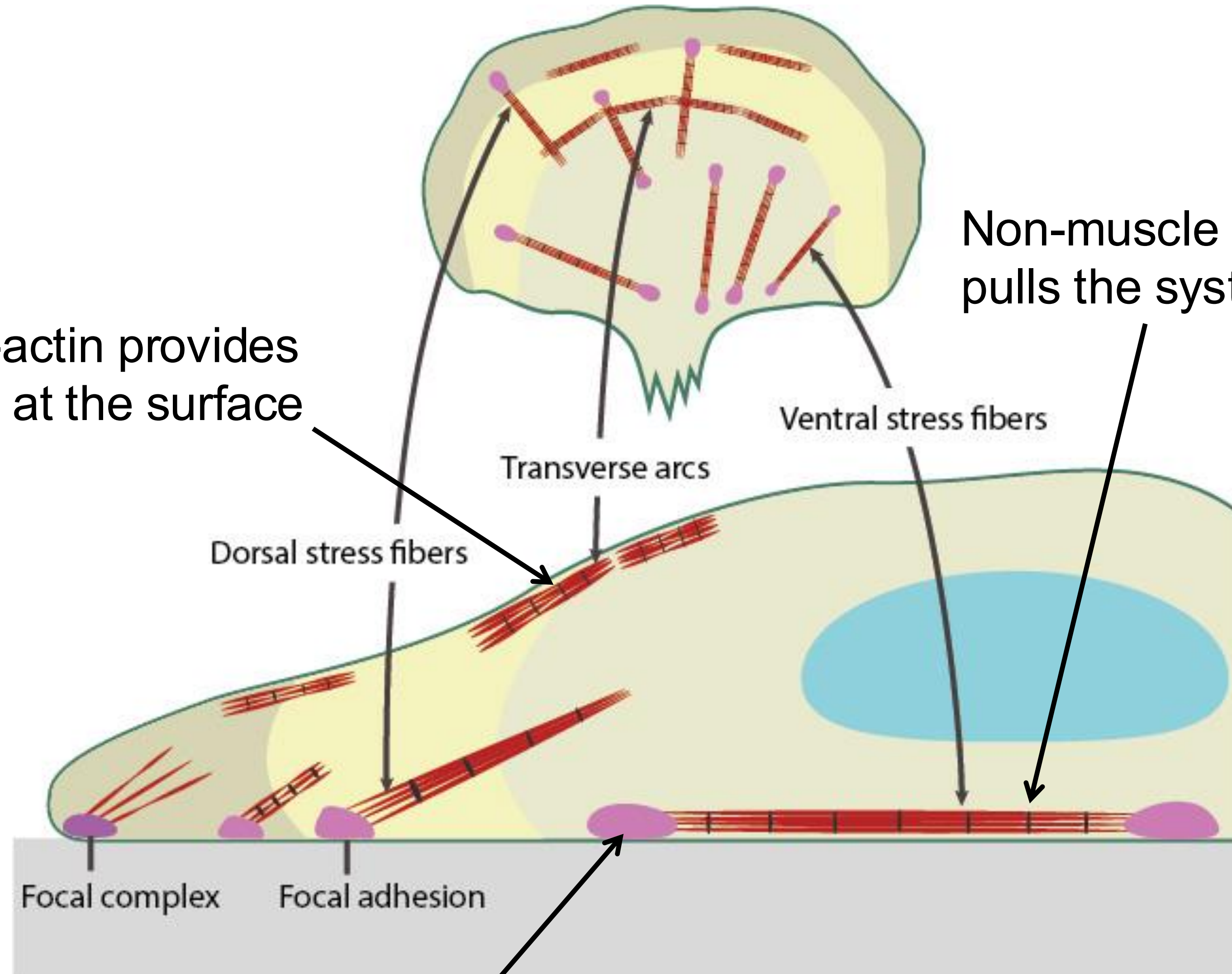
How stiffness is maintained

1) Cytoskeleton

2) Osmotic pressure

3) Cell membrane

Mechanical properties of the cytoskeleton – actomyosin system



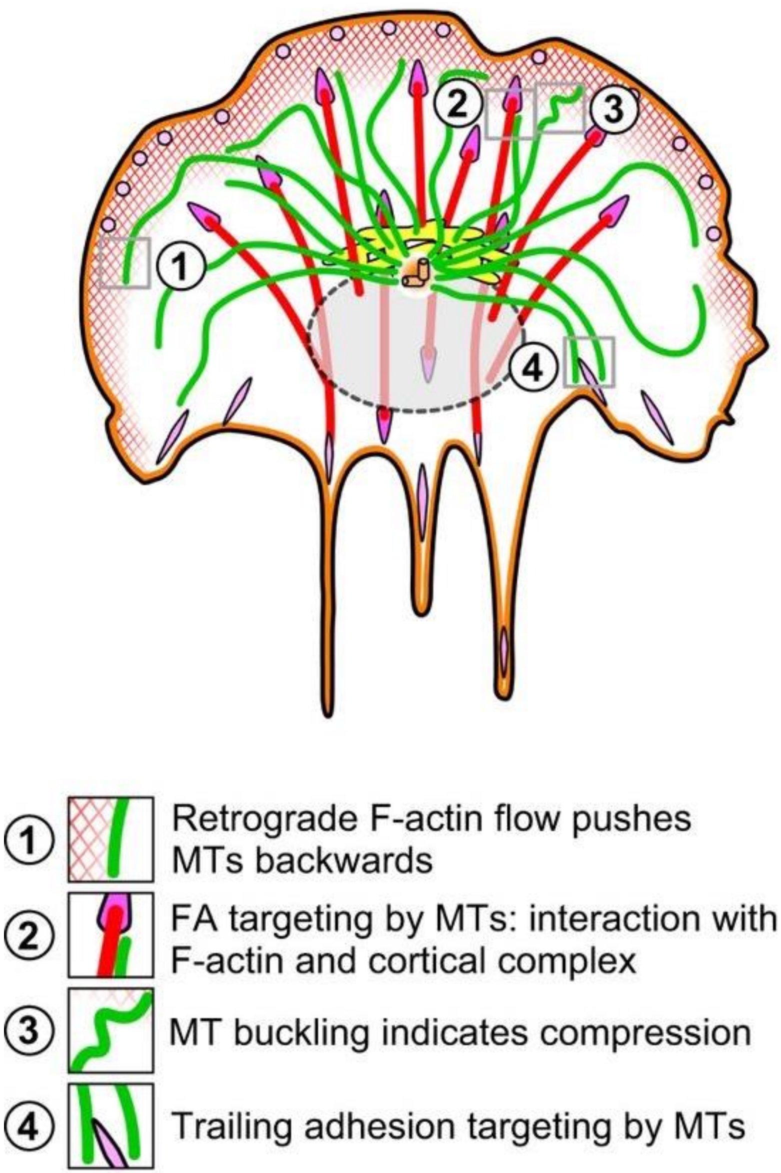
Non-muscle myosin pulls the system taut

Cortical F-actin provides resistance at the surface

Focal adhesions provide something to pull against

https://www.mechanobio.info/

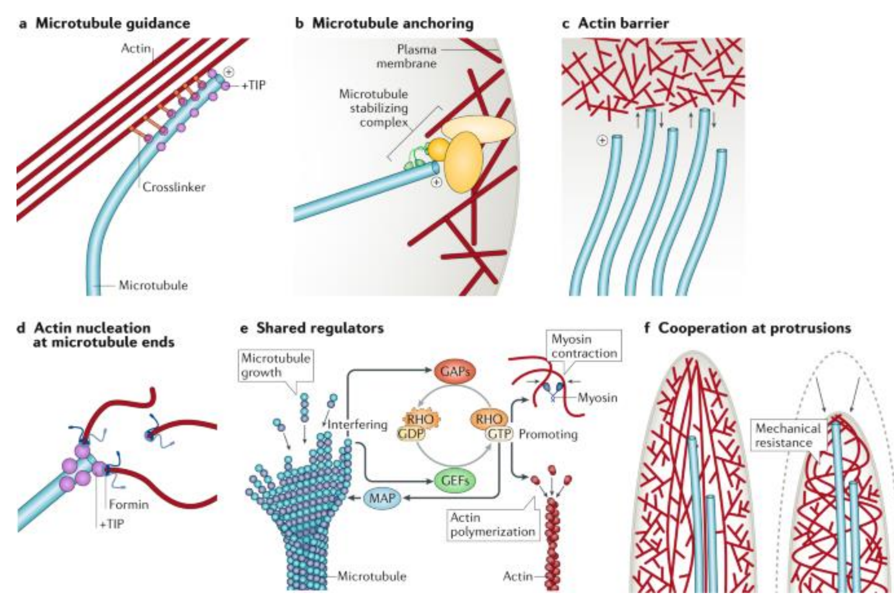
Mechanical properties of the cytoskeleton – microtubules



Microtubules resist compression

Provide safe space for cellular organelles

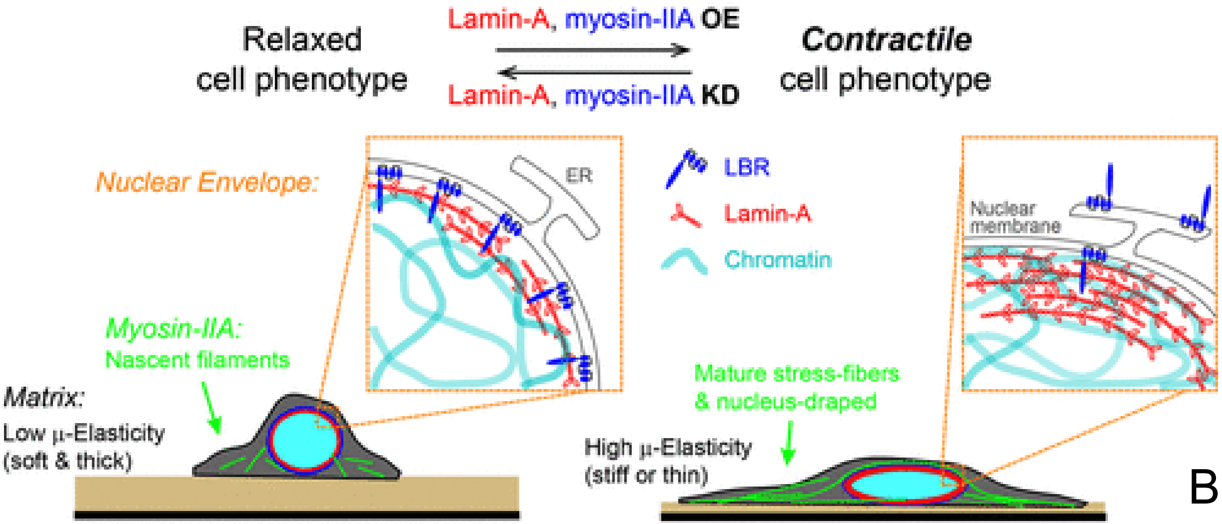
Microtubules are coupled to cortical F-actin in different ways.



Bouchet and Akhmanova, 2017

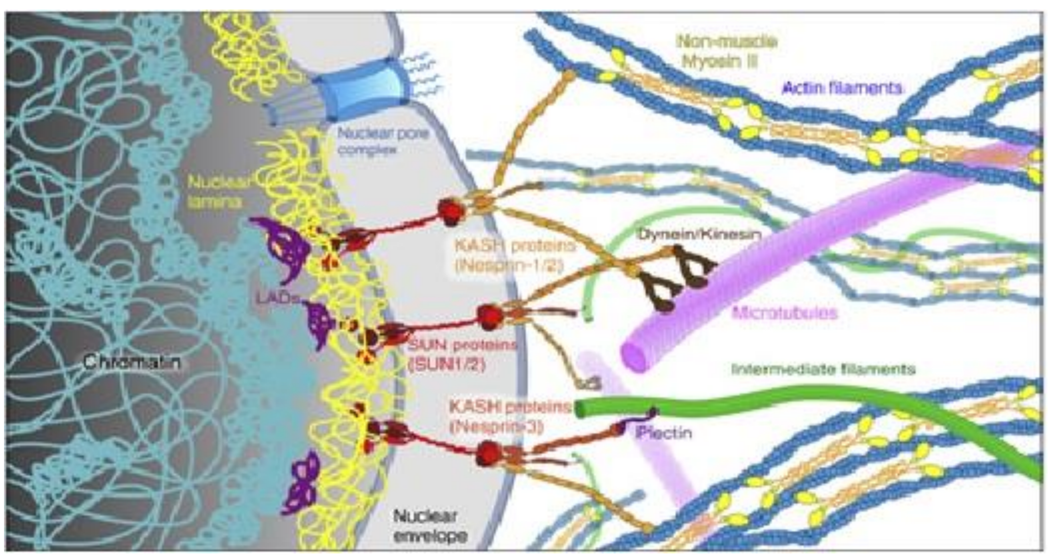
Dogterom and Koenderink, 2018

Mechanical properties of the cytoskeleton – lamins



Buxboim et al, 2017

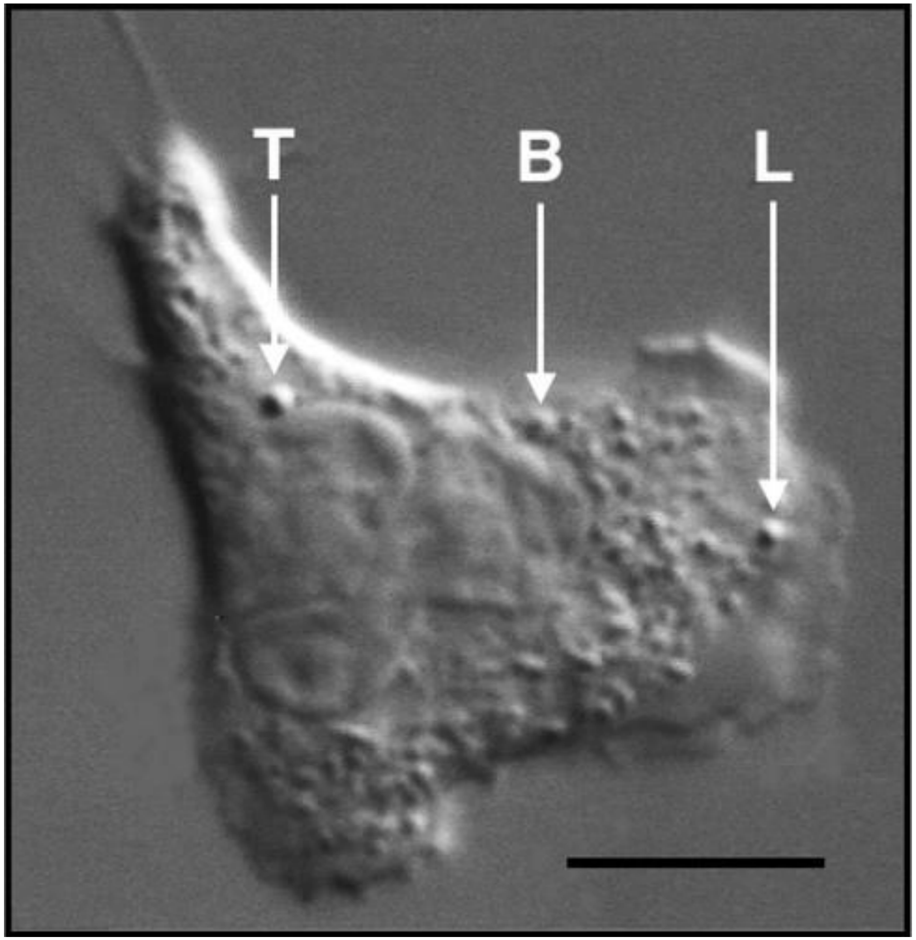
Lamins allow nucleus to resist compression



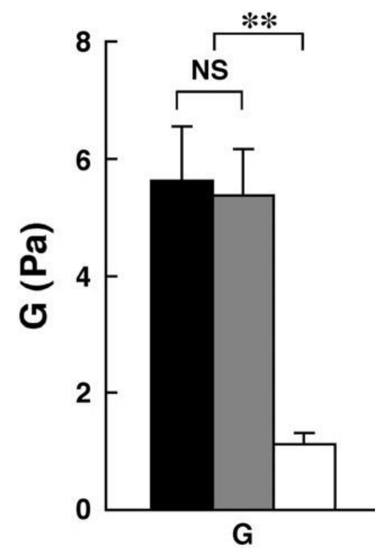
http://bam.lab.mcgill.ca/

Lamins are coupled to the cytoplasmic cytoskeleton

Cellular tension is heterogeneous



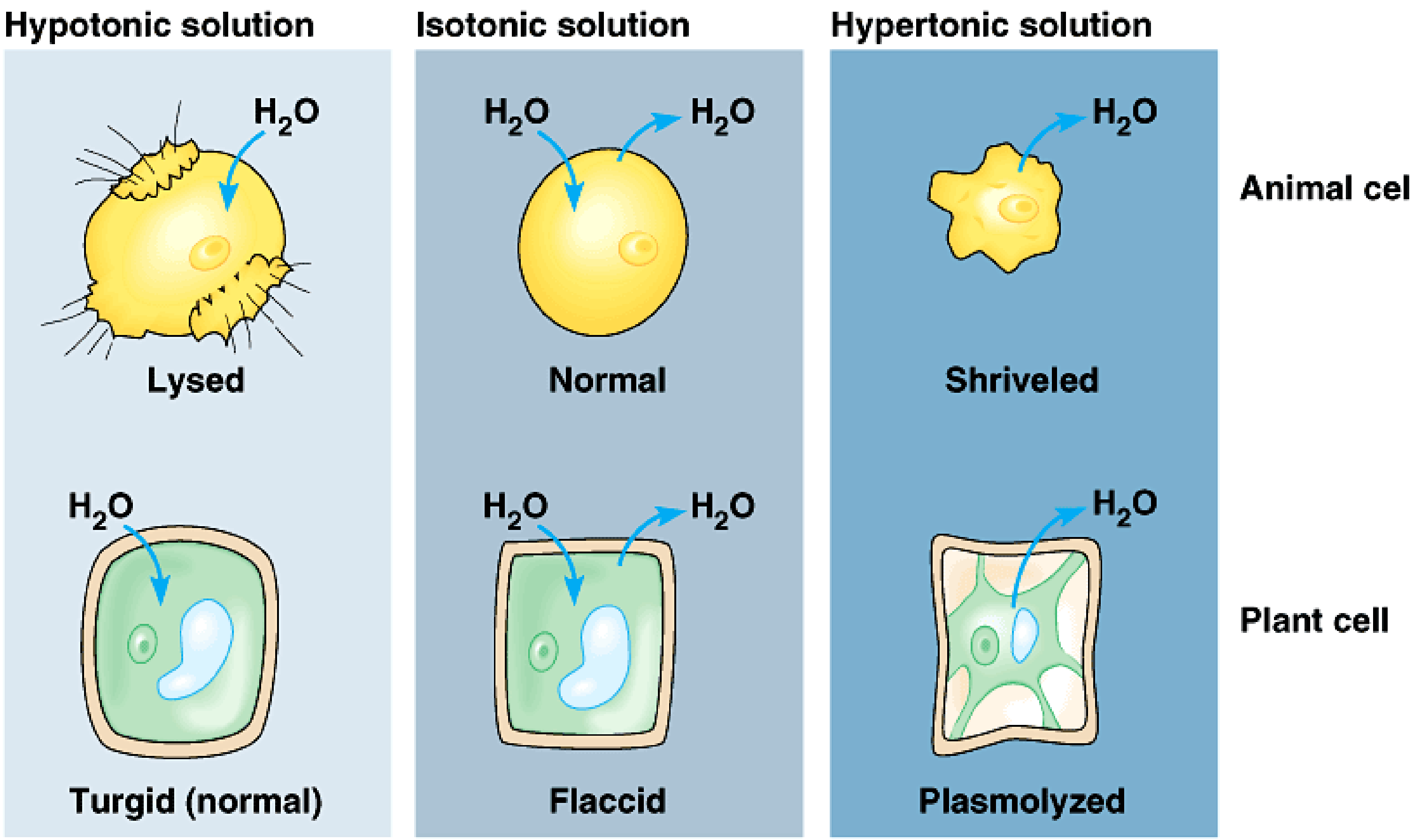
Tanai et al, 2004



Elastic modulus Stress/strain

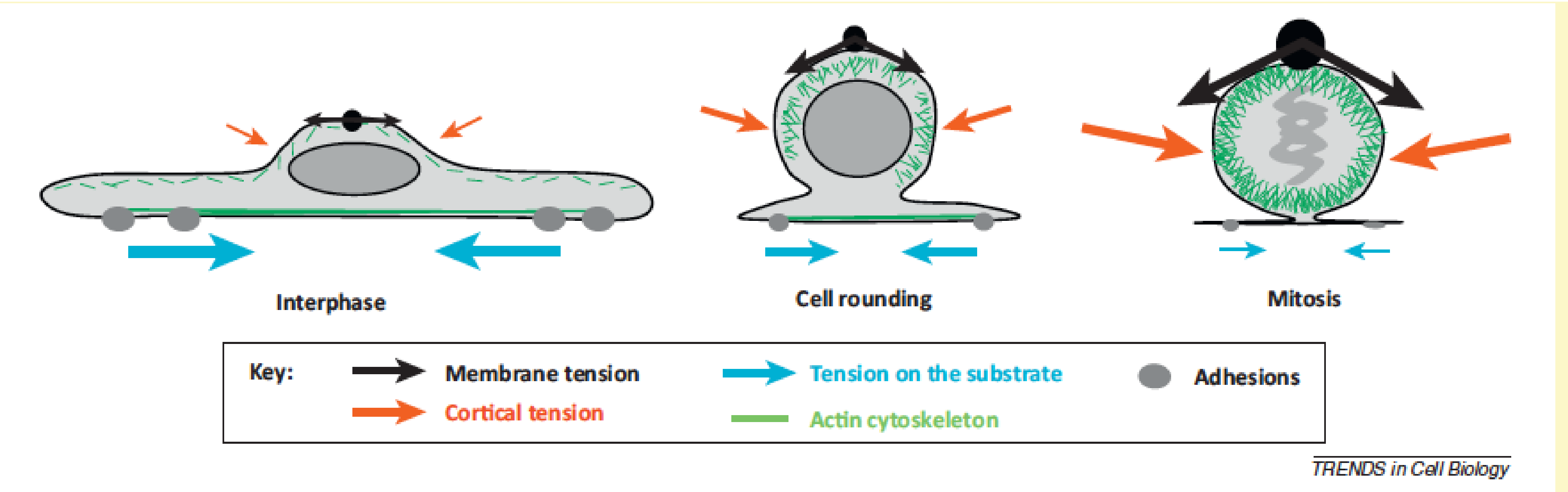
Stress = force per unit area
Strain = deformation

Osmotic pressure



Osmotic pressure is actively maintained by ion transport.
Cells will adjust to changes in tonicity

Membrane tension

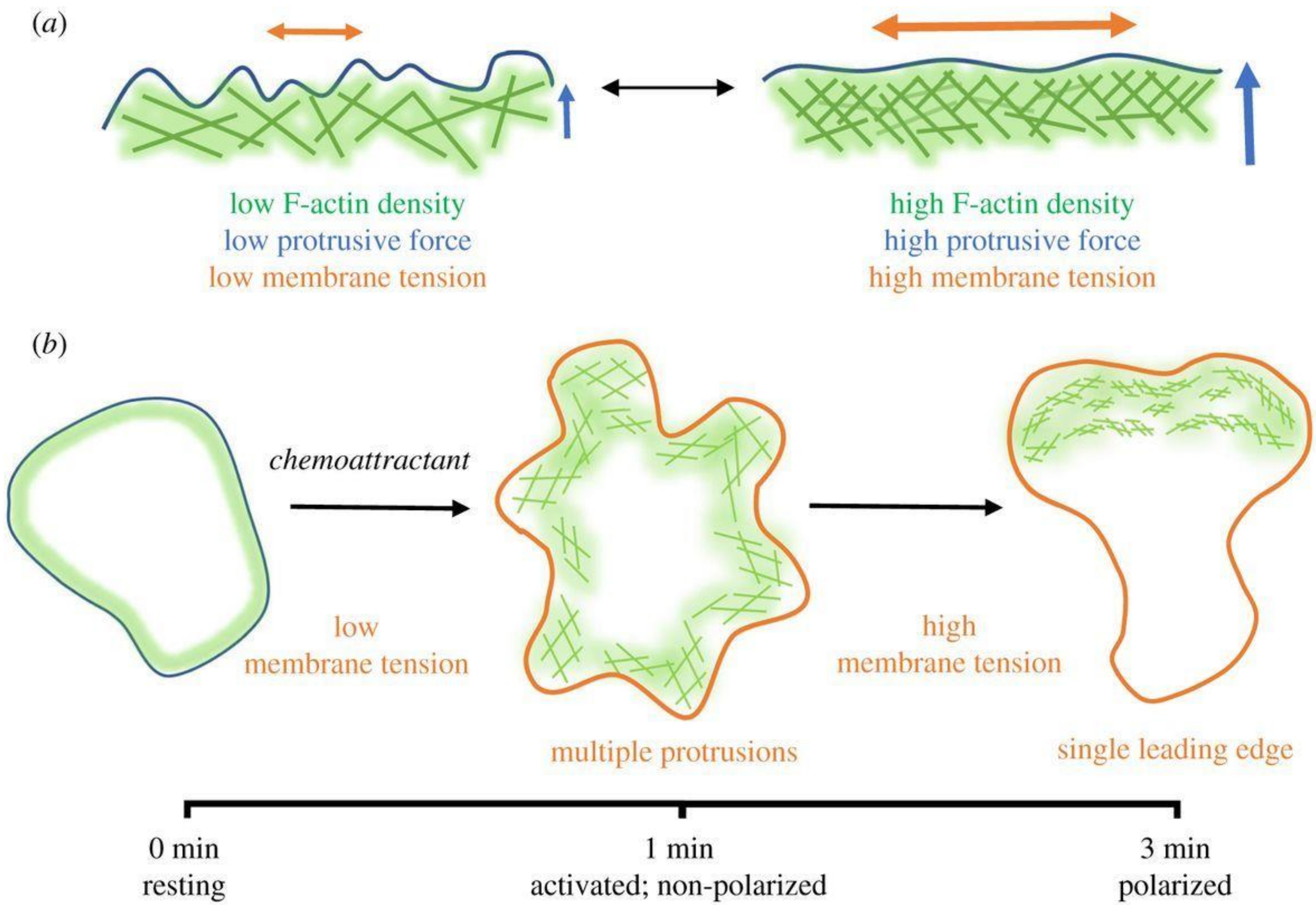


Gauthier et al, 2012

Membrane tension =
in plane tension (osmotic pressure) + membrane-cytoskeleton adhesion

Initially though to be uniform across the cell surface because tension distributes quickly across bilayers

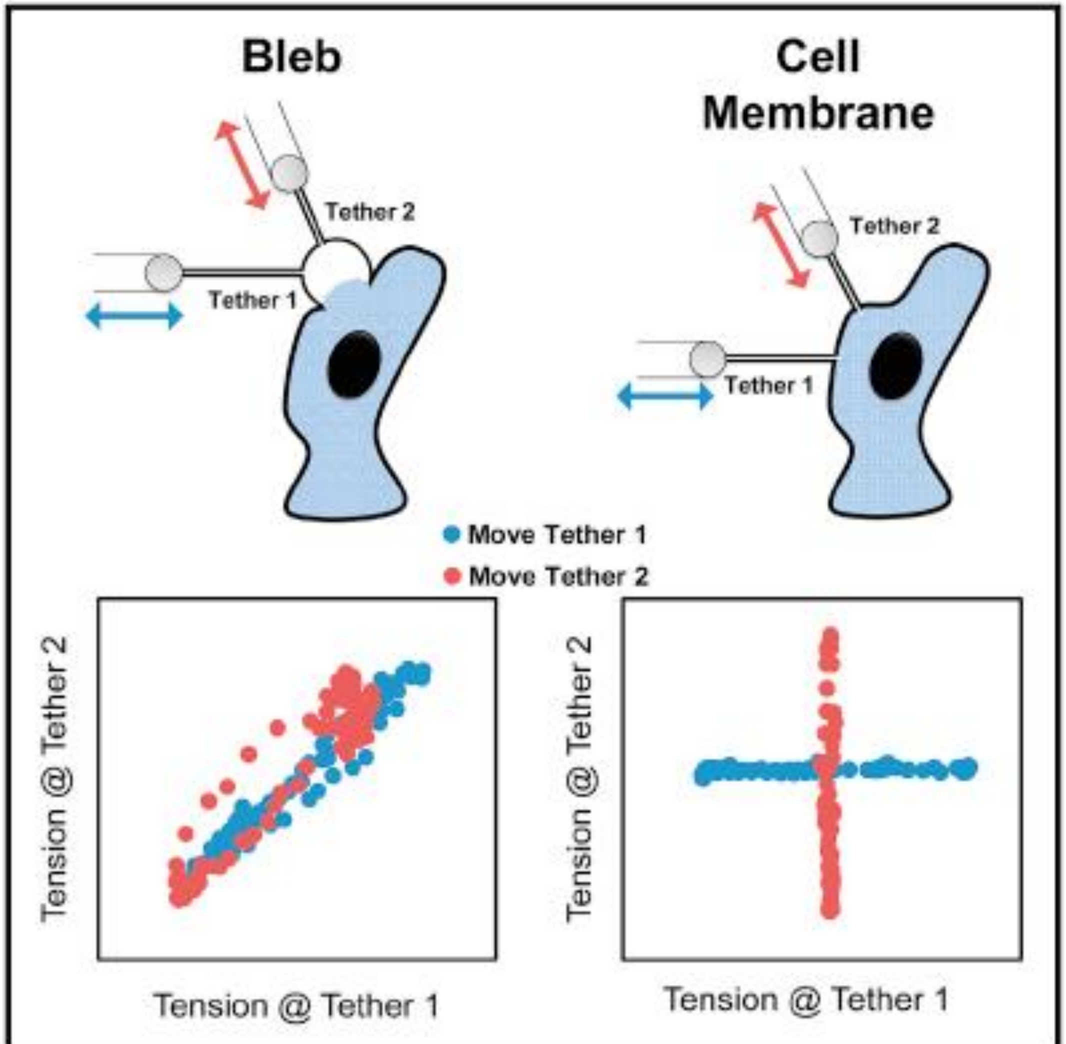
Membrane tension - a long distance regulator?



Saha et al, 2018

Membrane tension

However . . .



Shi et al, 2018

Lecture outline

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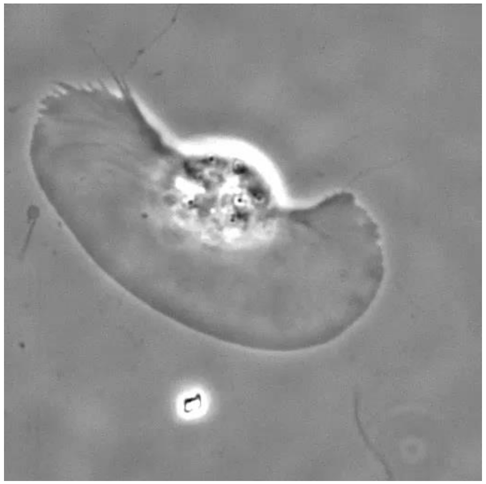
The dynamic cell

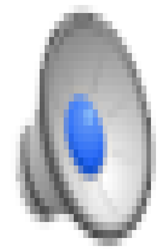
Cells also move – these movements necessarily transmit forces

Fish keratocyte



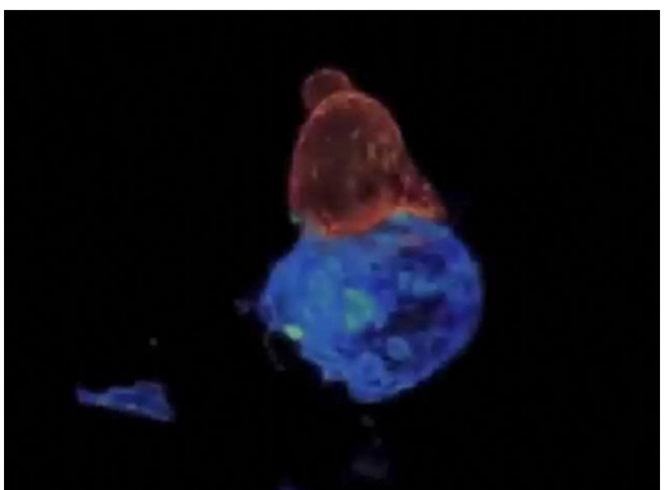
Barnhart et al, 2010

Drosophila embryo



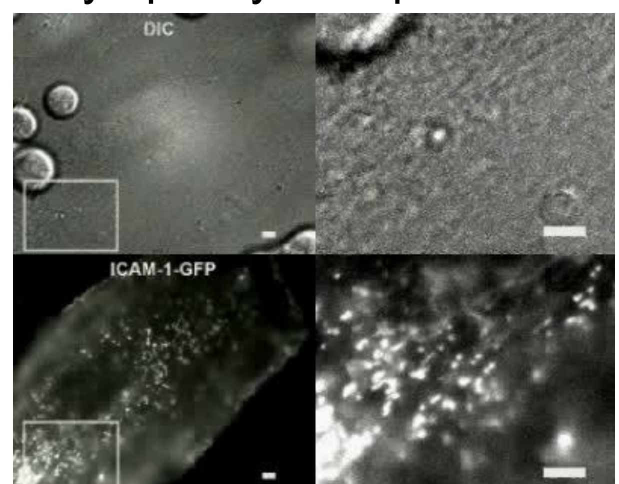
Fernandez-Gonzalez et al, 2009

T cell – tumor cell



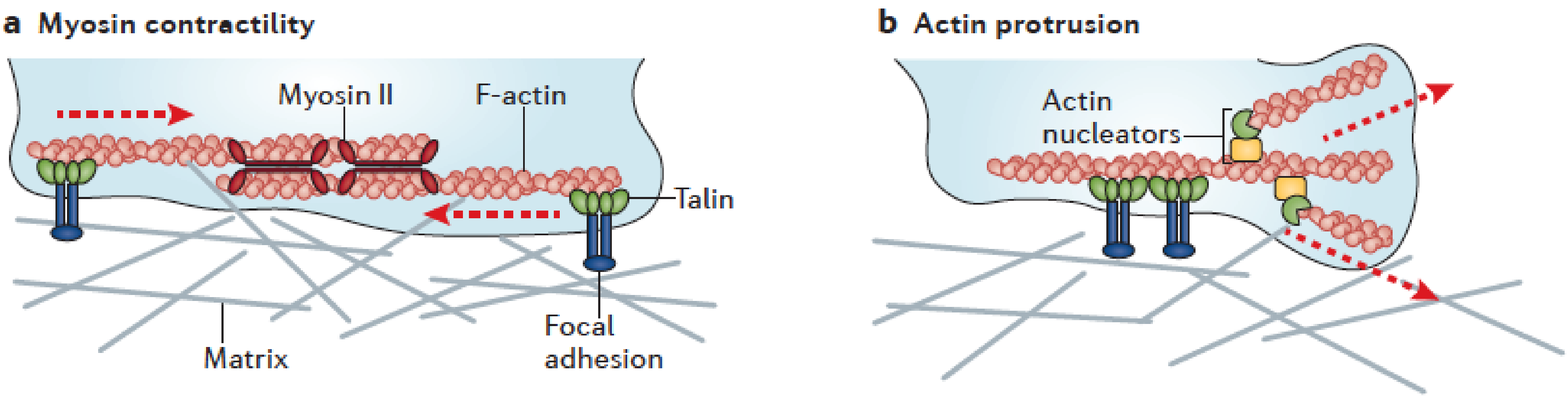
Ritter et al, 2015

Lymphocyte diapedesis



Carman et al, 2007

How cells generate force – the F-actin cytoskeleton



Contractile force

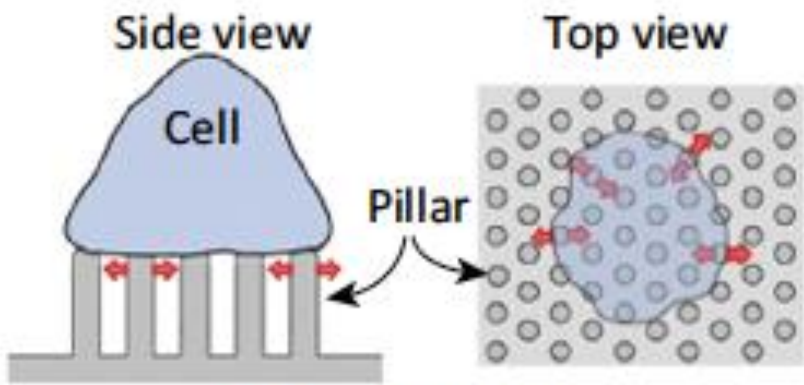
Protrusive force

Huse, 2017

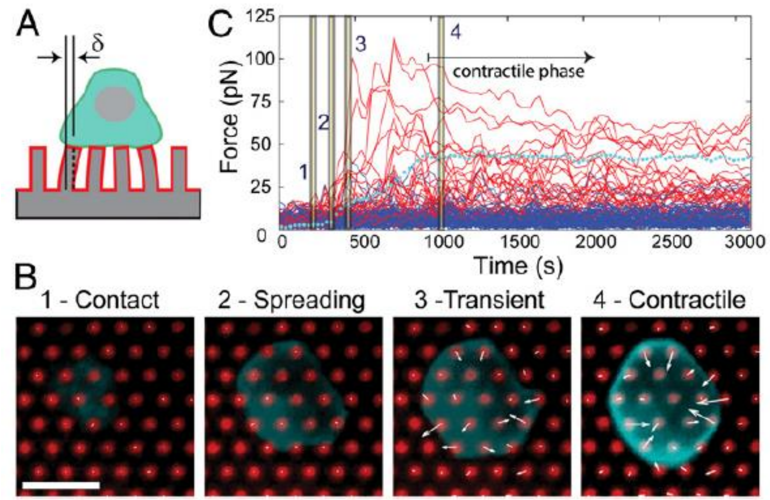
Useful for motility, manipulation of other cells, signaling

Measuring cellular forces

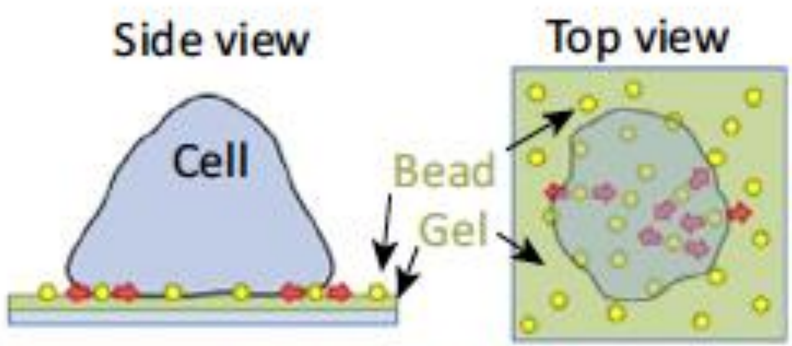
Traction force microscopy



Micropillar array

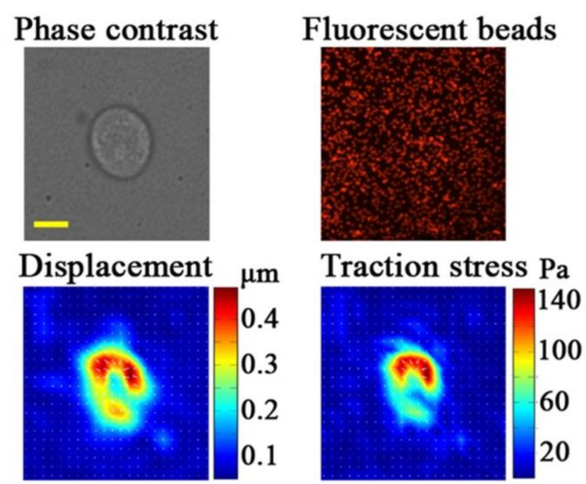


Bashour et al., 2014



Gel-based TFM

Basu and Huse, 2017



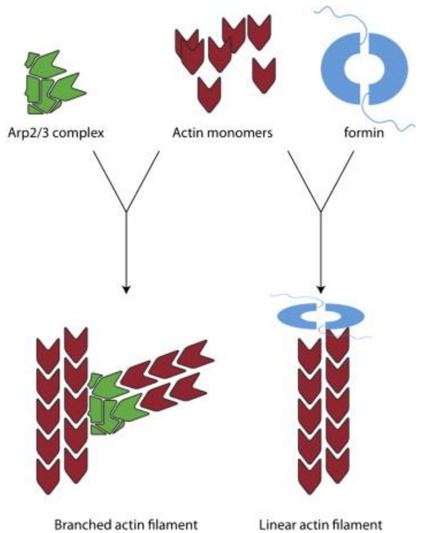
Wang et al., 2018

Components – F-actin polymerization

Actin polymerization drives cellular protrusion

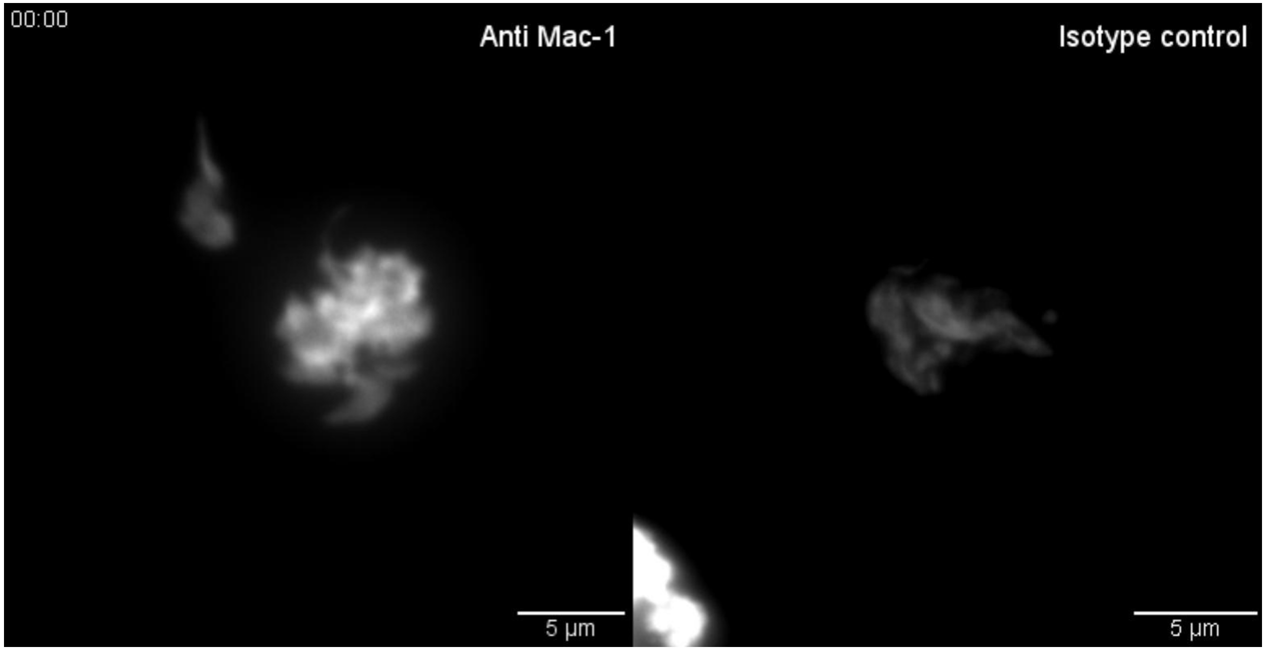
Arp2/3 complex generates branched arrays.

Formins induce linear arrays and bundles.



Insall and Machesky, 2009

Protrusion generally coupled to retraction - treadmilling



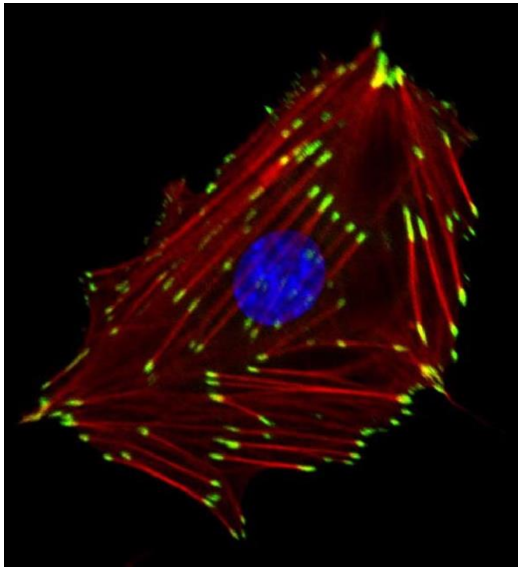
Jaumouille et al., 2019

Components – Focal adhesions

An in vitro phenomenon.

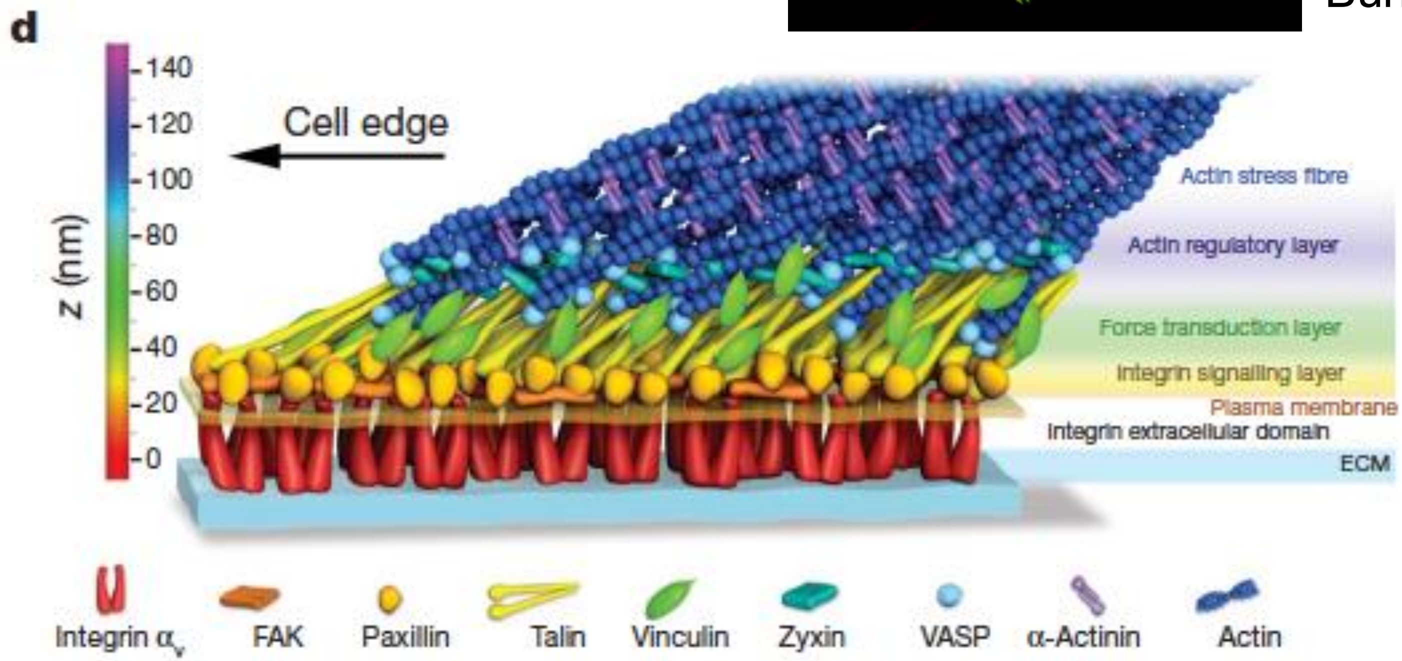
However, adhesion-like structures are observed in vivo.

A source of signals in addition to adhesive strength.



F-actin
Vinculin

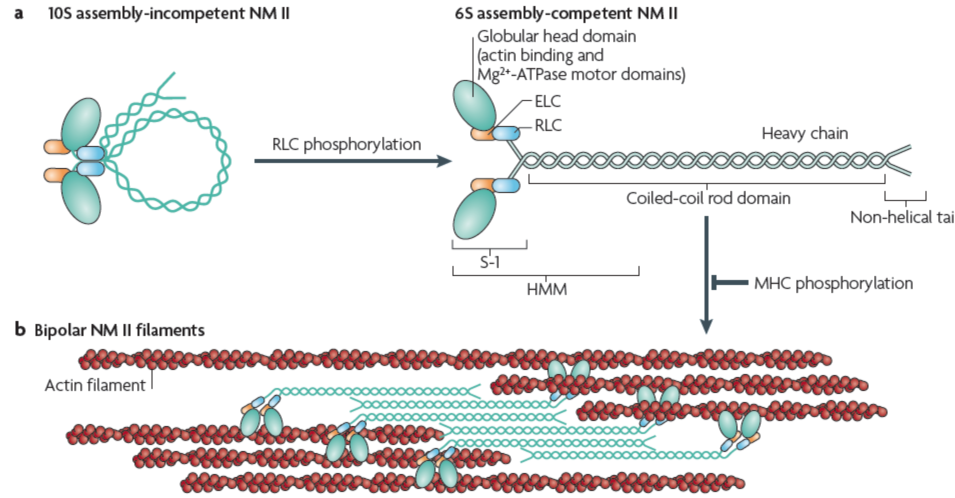
Burridge, 2017



Kanchanawong et al., 2010

Components – Myosin

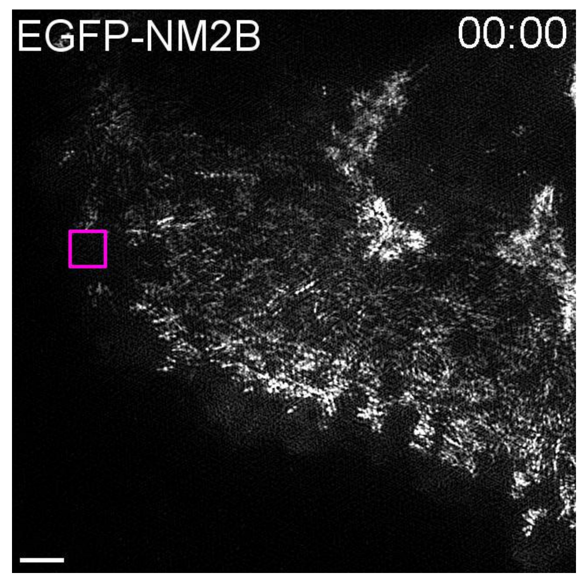
Analogous to role in skeletal muscle.



Vincente-Manzanares et al., 2009

Betzig lab, HHMI

F-actin
Myosin



Beach et al., 2017

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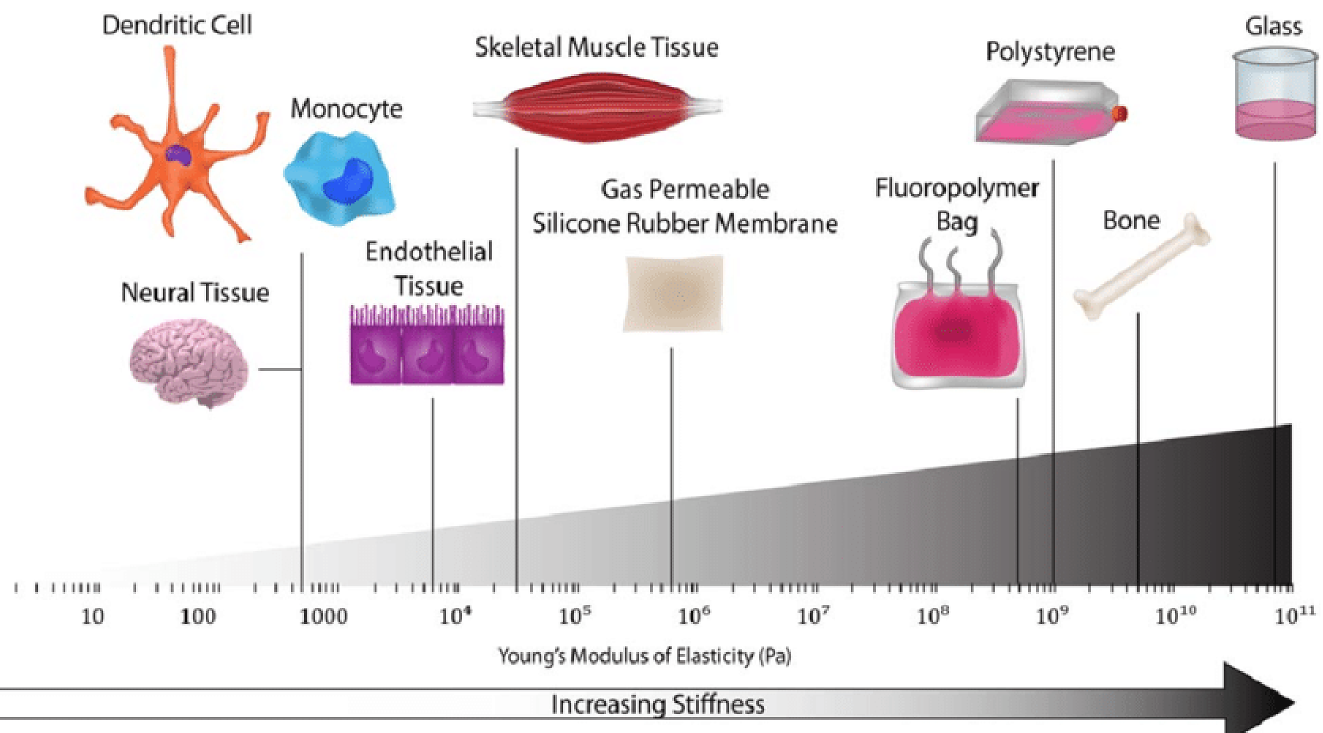
Mechanobiology and signal transduction

Mechanosensing: Cellular responsiveness to mechanical stimuli

Mechanotransduction: Conversion of mechanical stimulus into chemical signal

Enables cells to acquire mechanical information about their environment and respond accordingly. Important because mechanical environments in vivo vary widely.

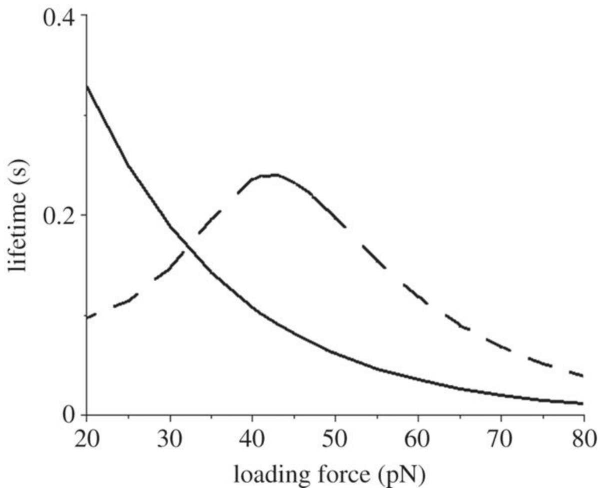


Fekete et al., 2017

Mechanotransduction – ligand binding by integrins

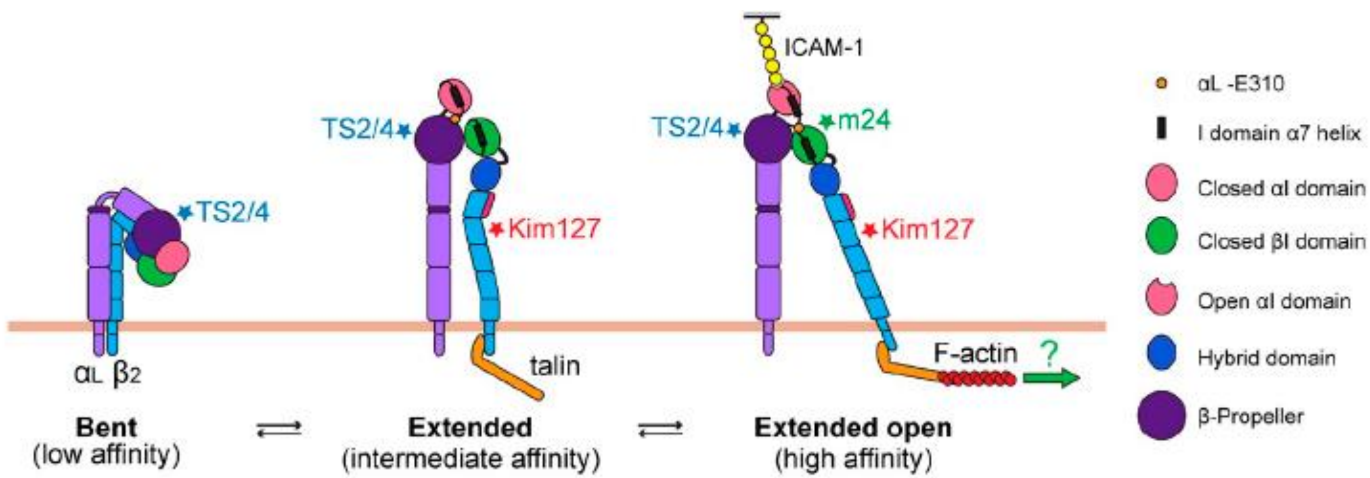
Catch bond – strength increases until optimal applied force.

Slip bond – strength decreased under applied force.



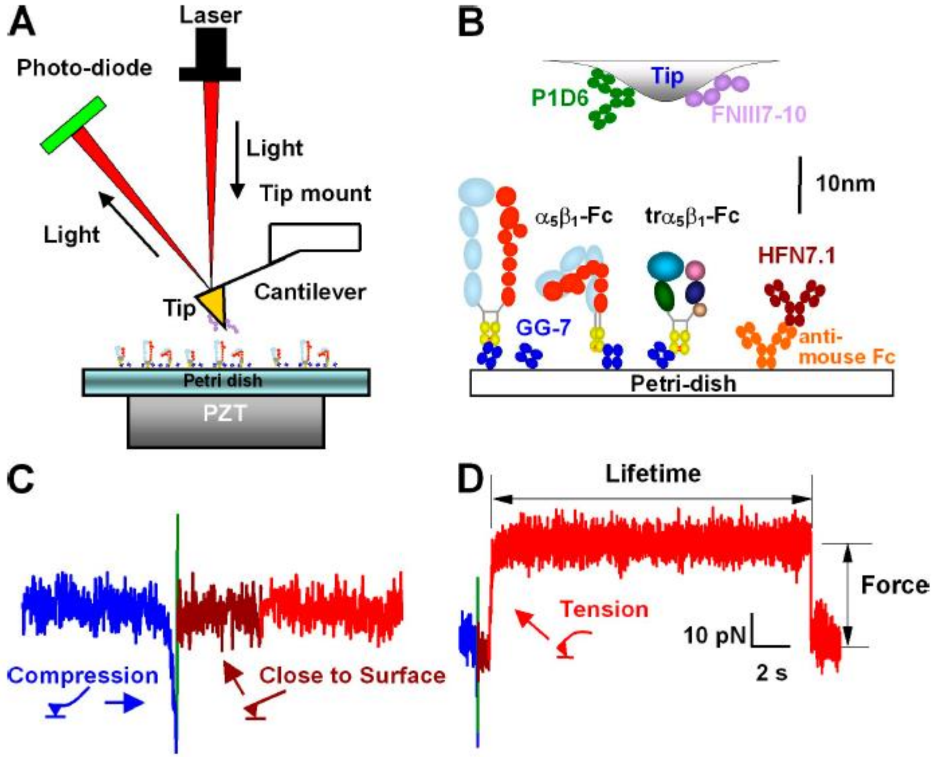
Sun et al., 2011

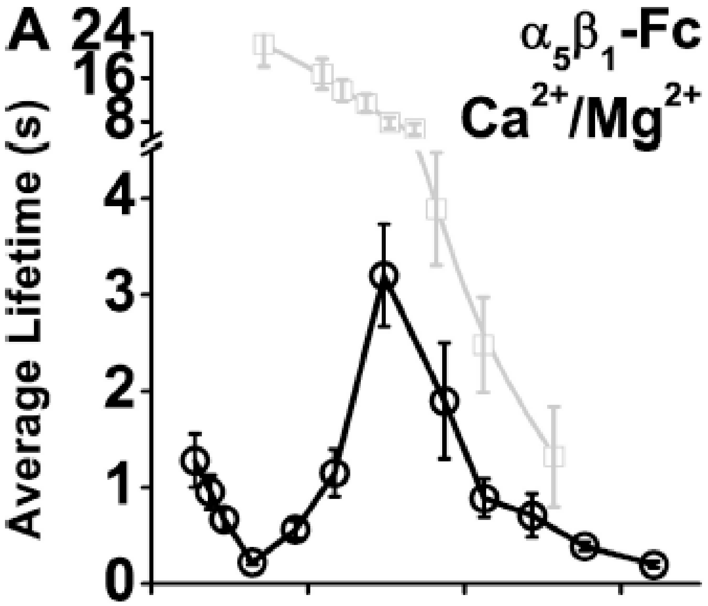
LFA1 is forms catch bonds with ICAM



Comrie et al., 2015

Mechanotransduction – ligand binding by integrins

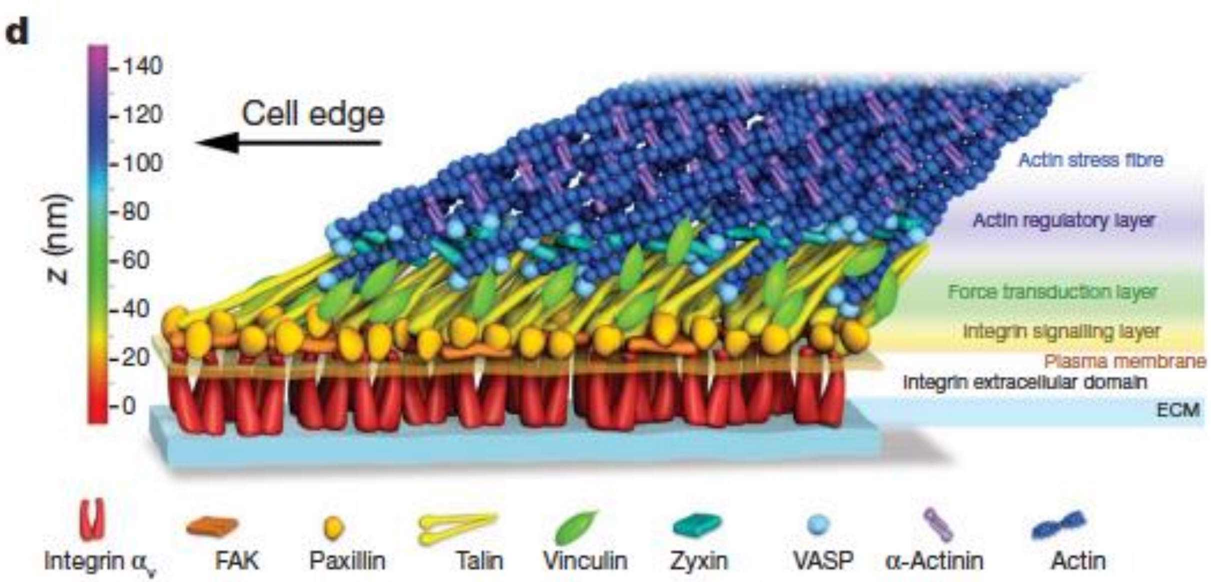




Kong et al., 2009

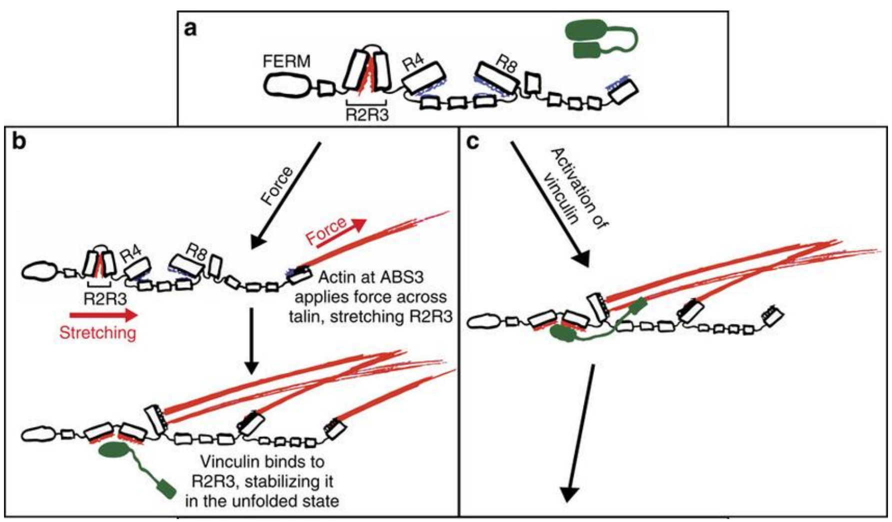
Mechanotransduction – adhesion assembly

Focal adhesion architecture



Kanchanawong et al., 2010

Talin and other adhesion proteins undergo force dependent transitions

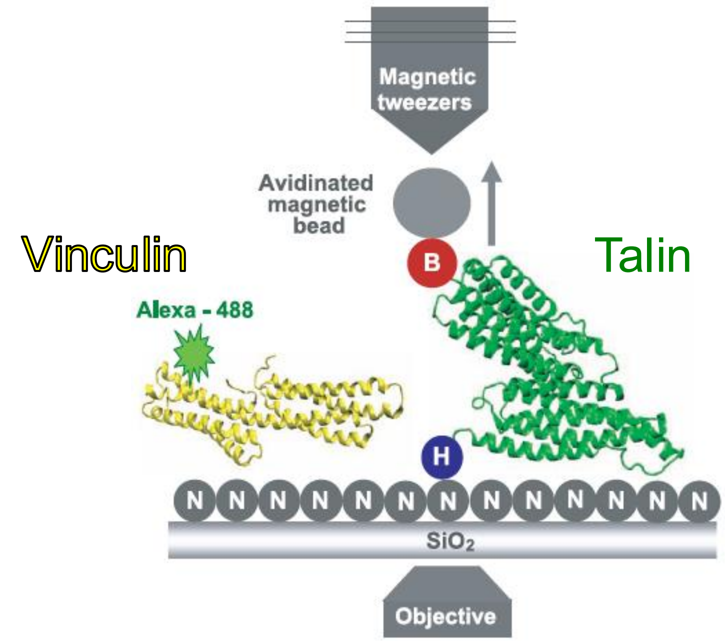


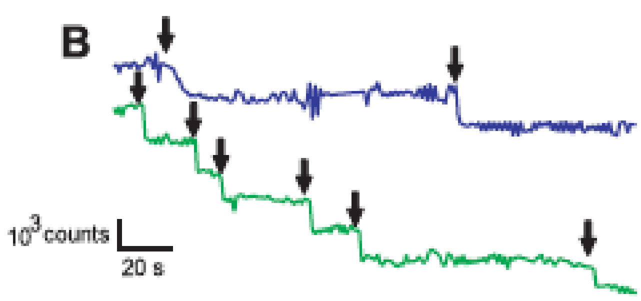
Atherton et al., 2015

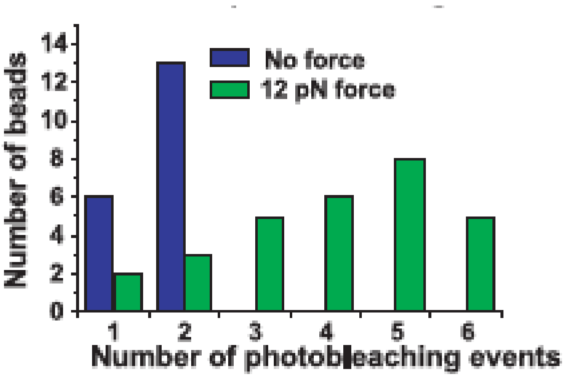
Mechanotransduction – adhesion assembly

Optical trap set up with purified proteins.

Measure binding by photobleaching of bound vinculin.







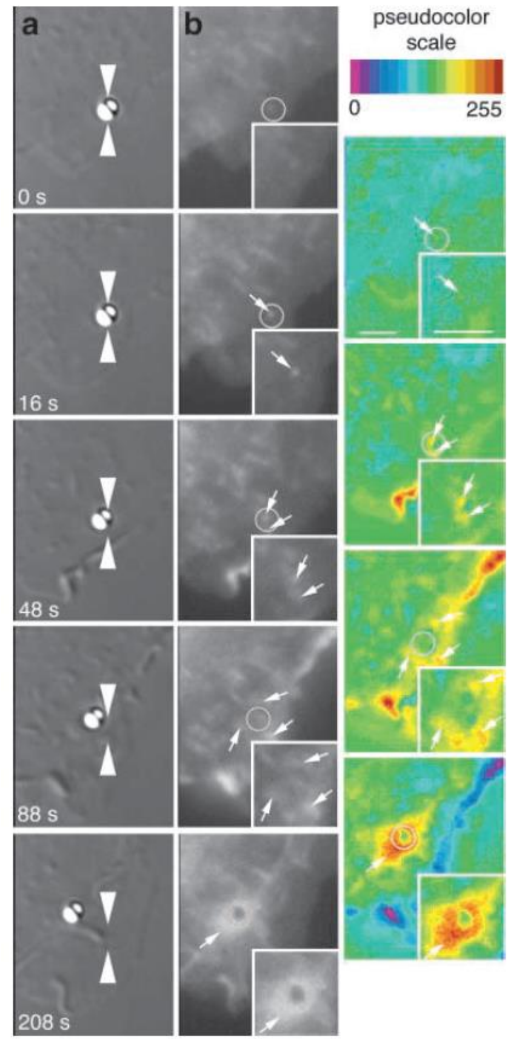
Del Rio et al., 2015

Mechanotransduction – adhesion size

Adhesions themselves are force dependent. Grow in size with pulling force.

Fibronectin covered bead, placed into contact with a cell, pulled using optical trap.

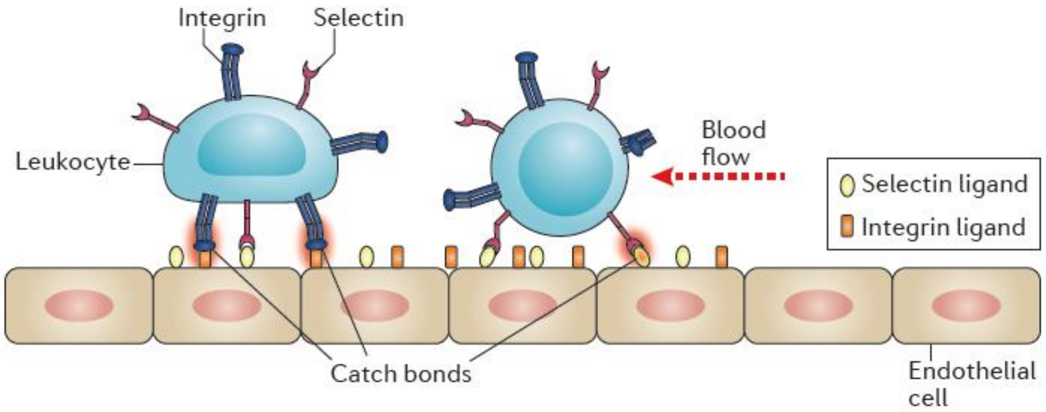
GFP-vinculin as adhesion probe.



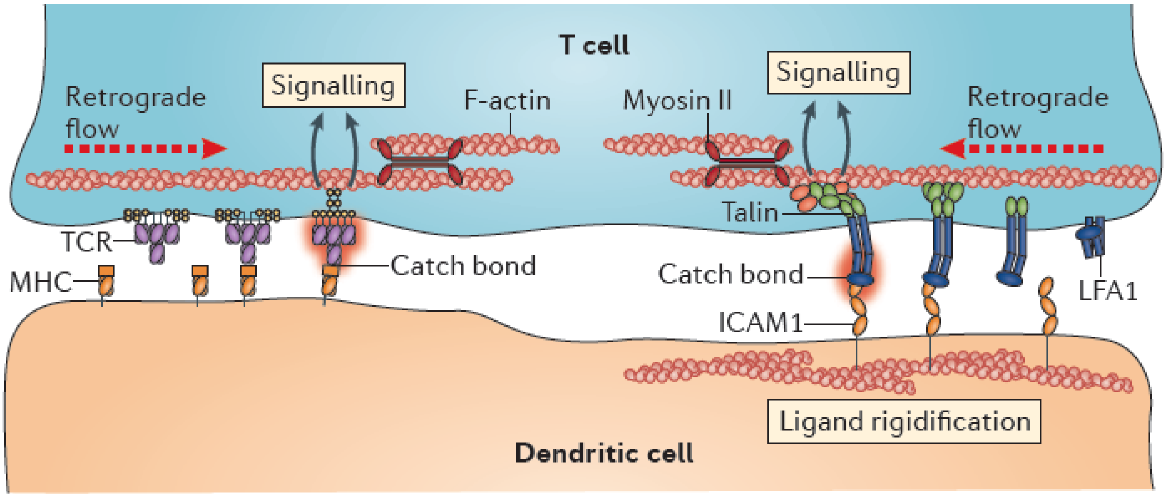
Galbraith et al., 2002

Other mechanosensitive catch bond receptors

Selectins during leukocyte rolling

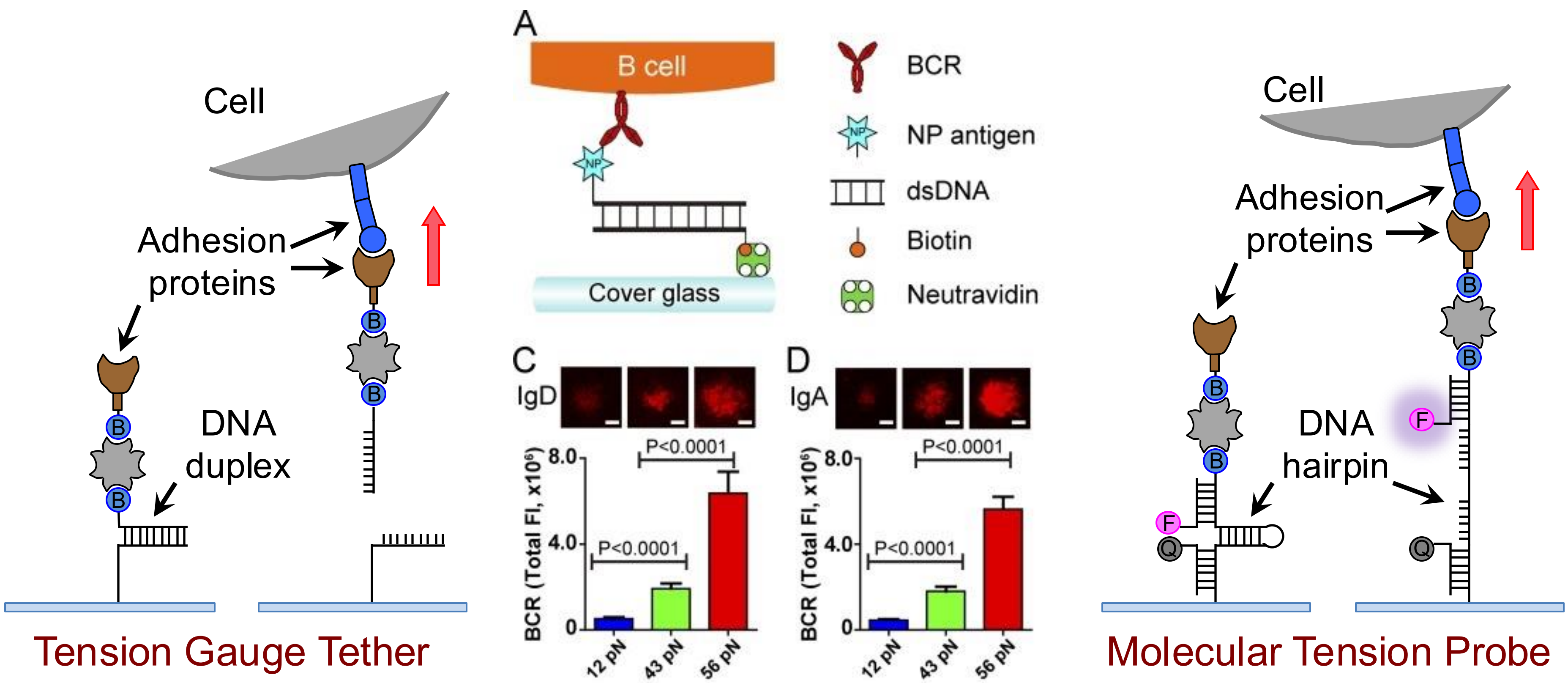


Antigen receptors in immune synapse



Huse et al., 2017

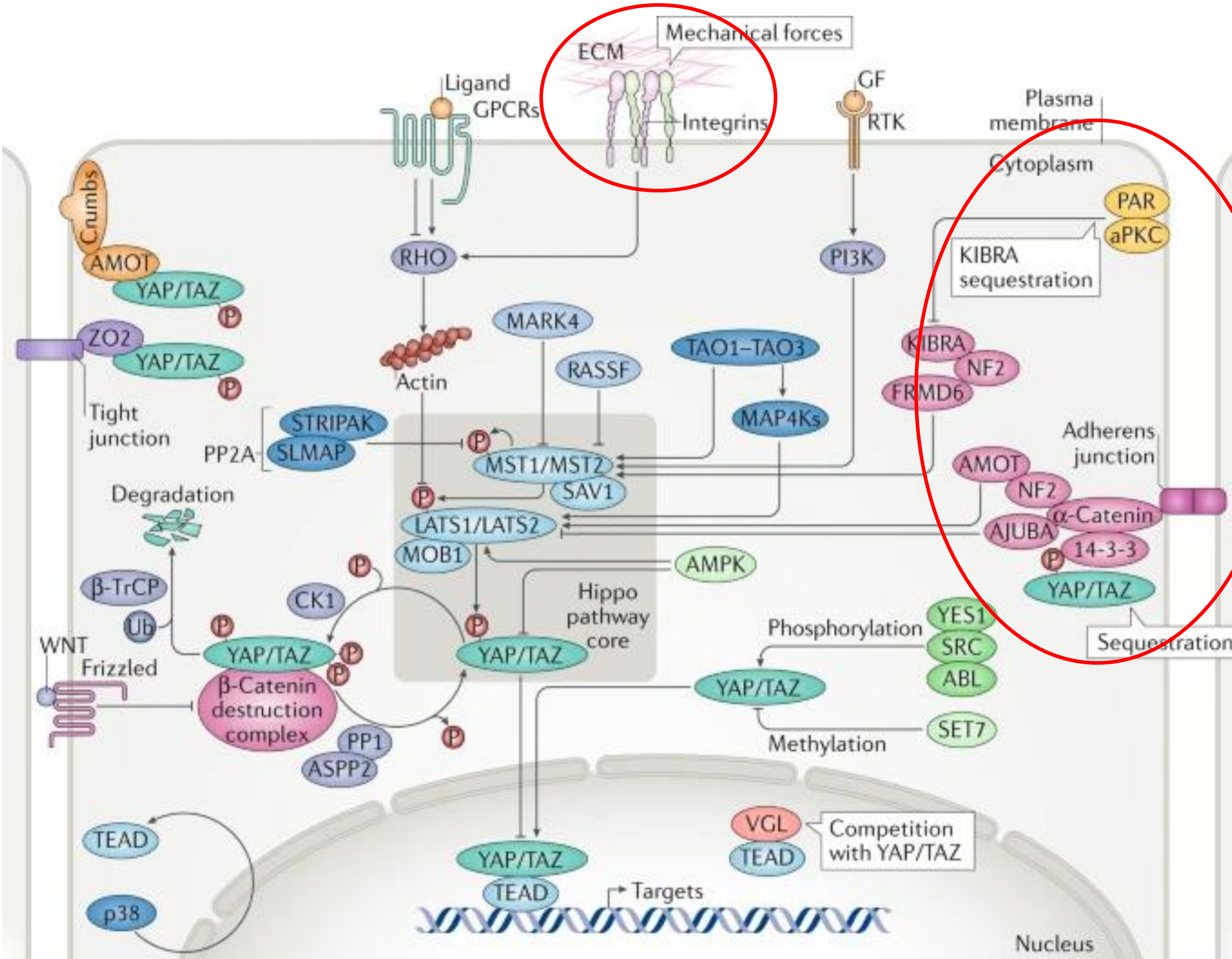
Sustained force required for full receptor activation



Wan et al., 2018

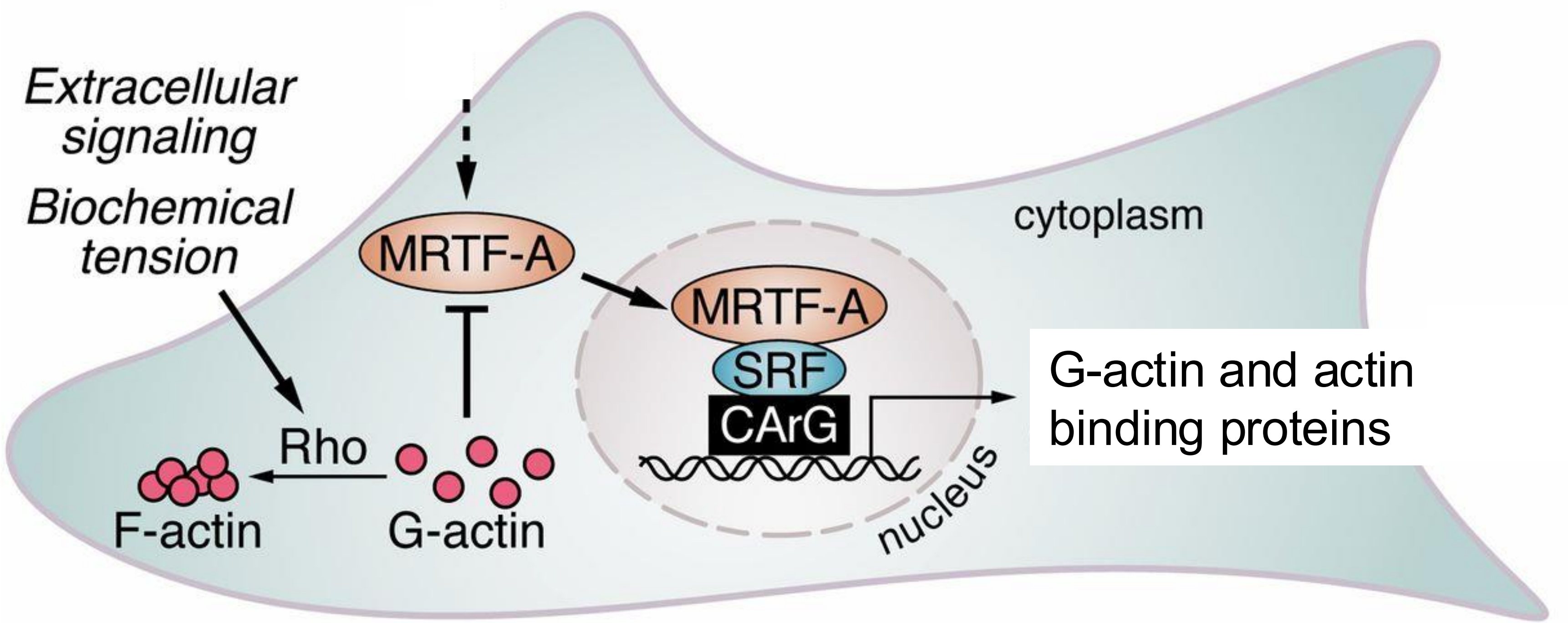
Mechanotransduction to the nucleus – YAP/TAZ

Different adhesions, different results



Moya and Halder, 2019

Mechanotransduction to the nucleus – MRTF

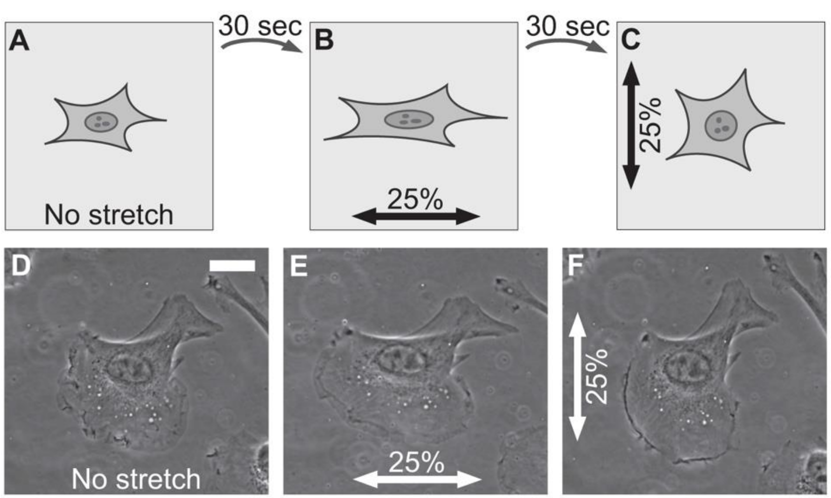


Velasquez et al., 2013

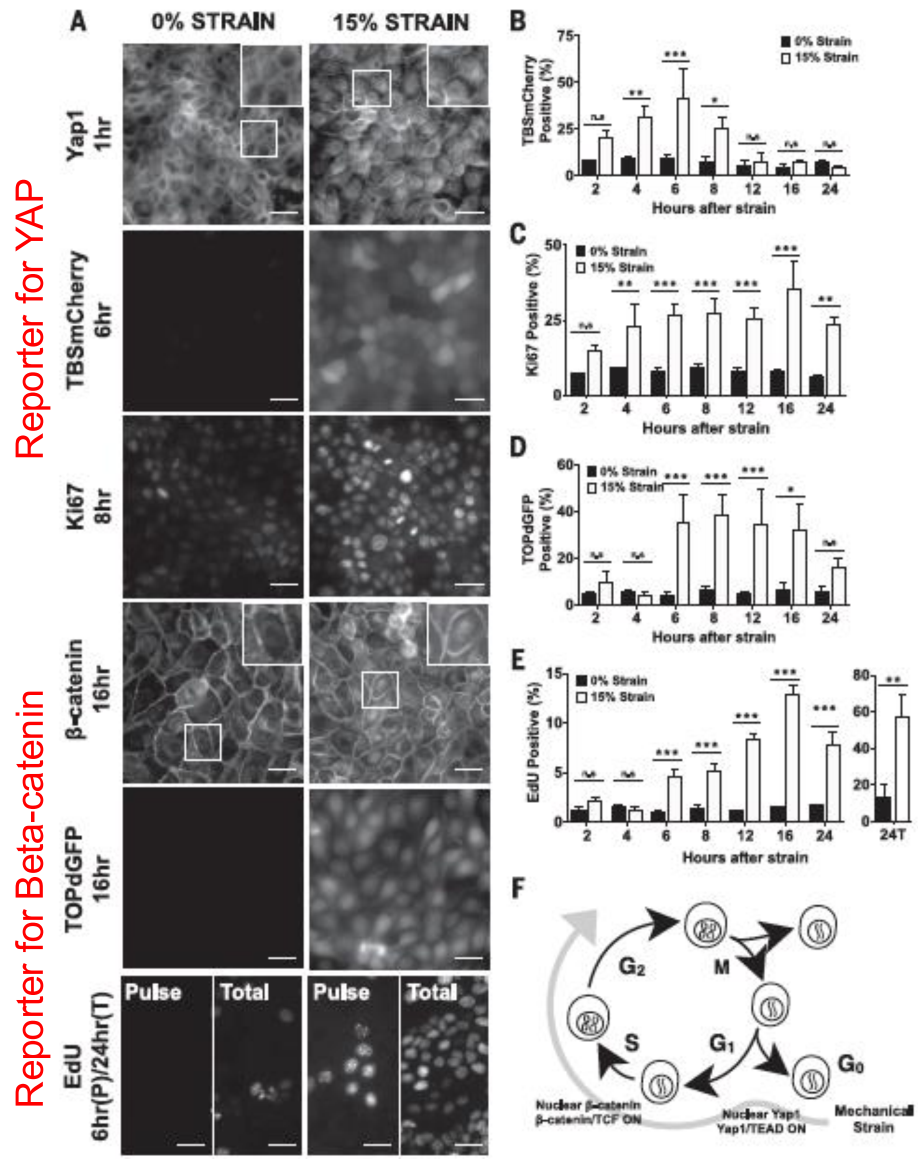
Biological consequences of mechanotransduction

Epithelial sheets on stretchable substrates.

Stretch promotes proliferation via YAP and β-catenin.



Tremblay et al, 2014



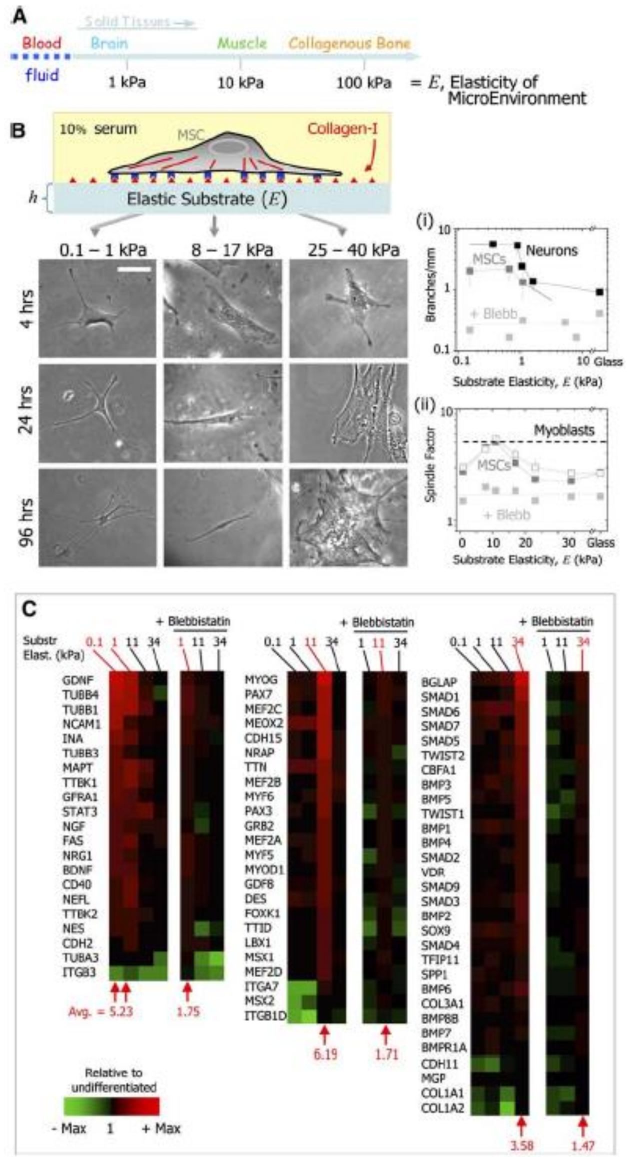
Benham-Pyle et al, 2015

Biological consequences of mechanotransduction

Mesenchymal stem cells.

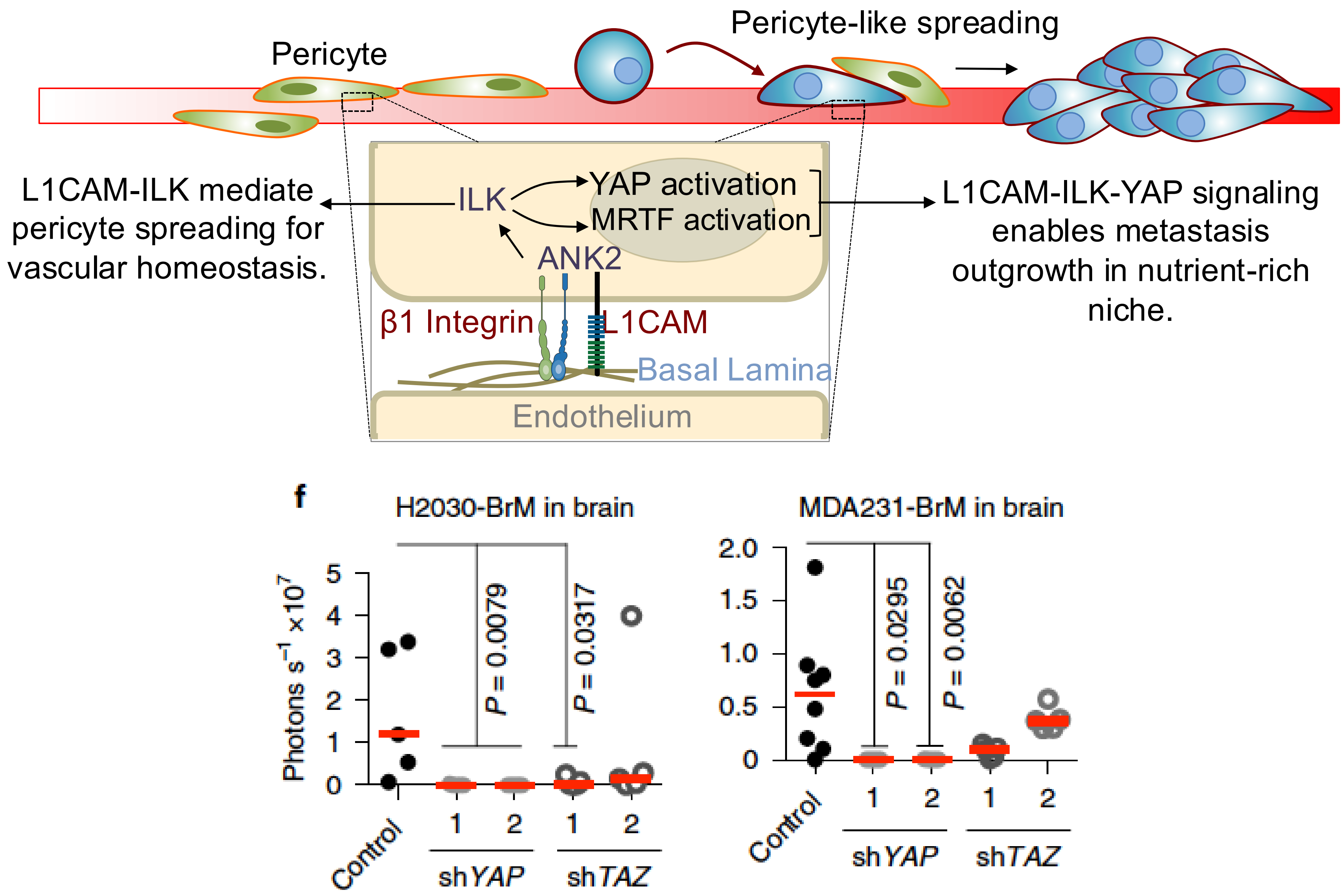
Cultured on hydrogels of different stiffness.

Stiffness determines whether the cells differentiate into neurons, muscle, or bone.



Engler et al, 2006

Biological consequences of mechanotransduction

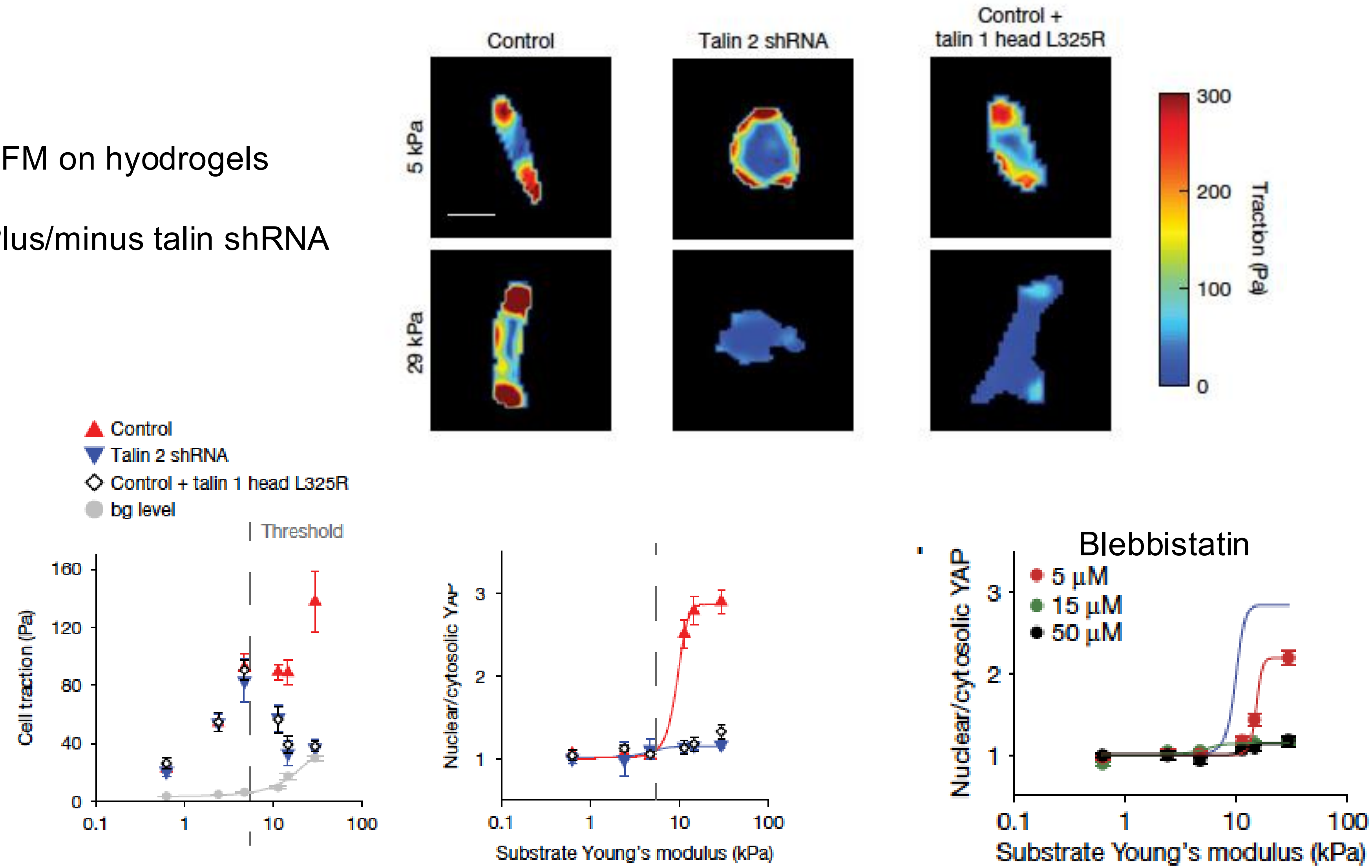


Er et al, 2018

Feedback between force exertion, mechanotransduction

TFM on hyodrogels

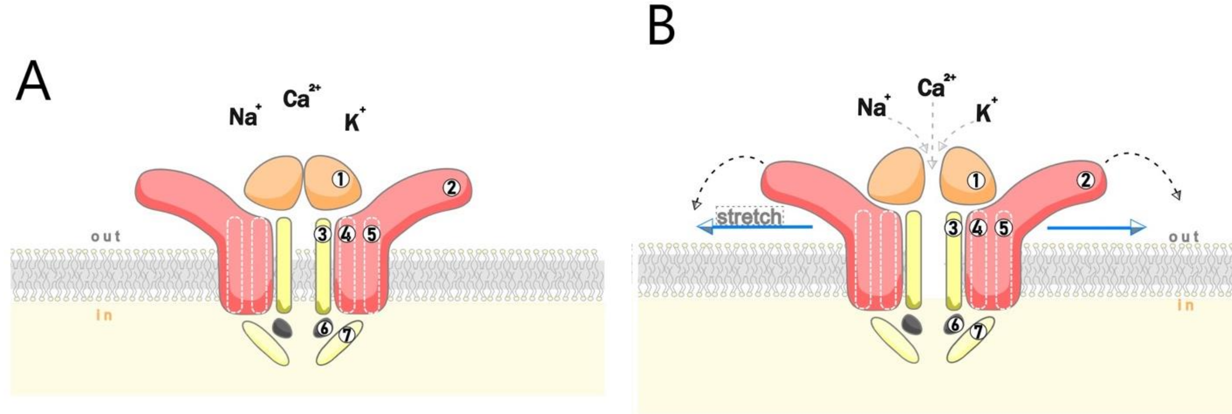
Plus/minus talin shRNA



Elosegui-Artola et al, 2016

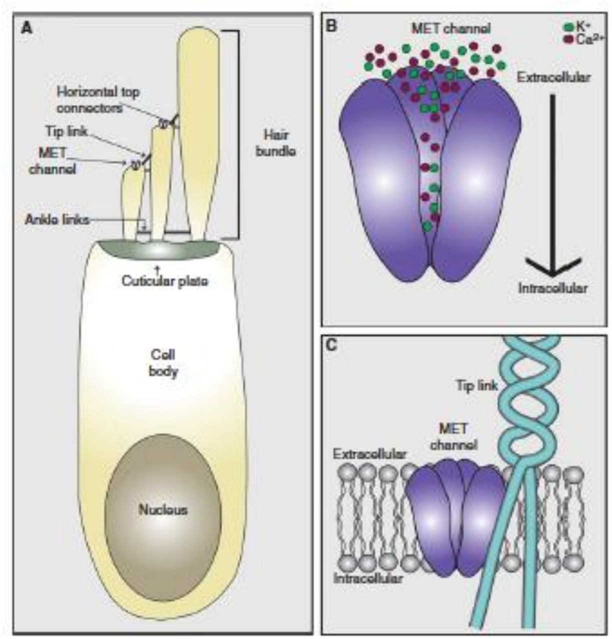
Other mechanosensing paradigms – mechanosensitive channels

Responsive to membrane tension – e.g. Piezo1



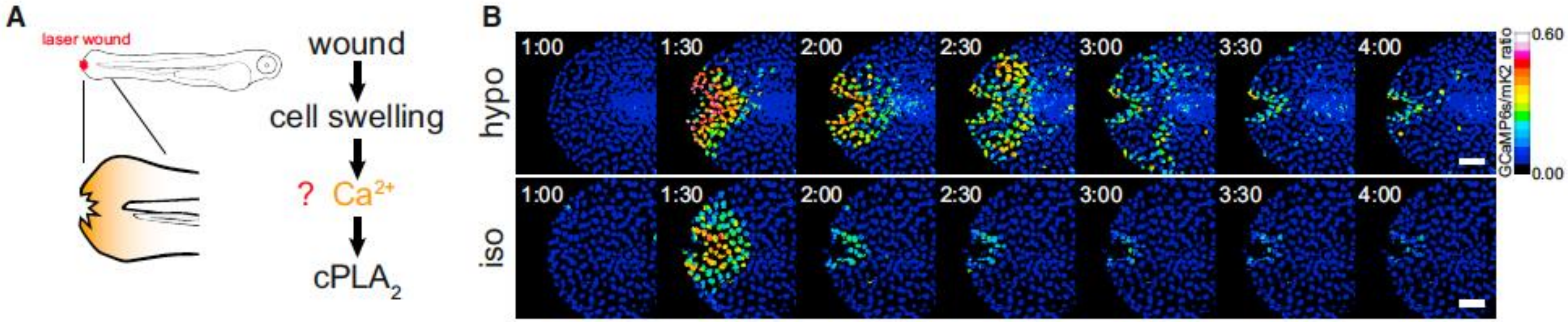
Simon Yel,wikipedia

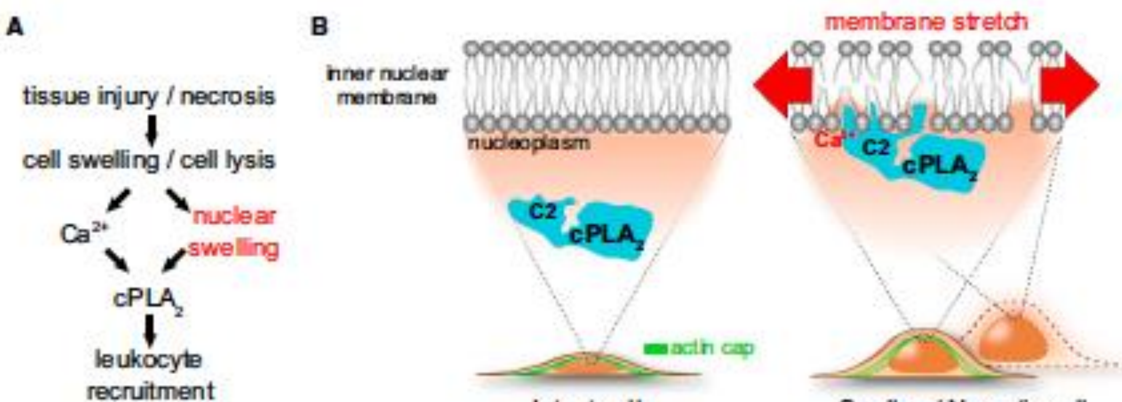
Mechanoelectrical transduction in the ear

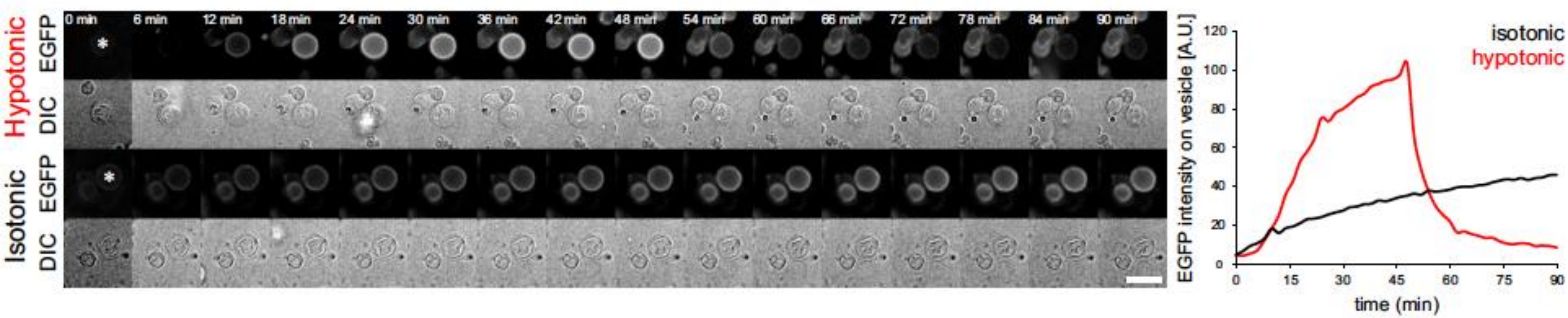


Cunningham and Müller, 2019

Other mechanosensing paradigms – mechanosensitive enzymes





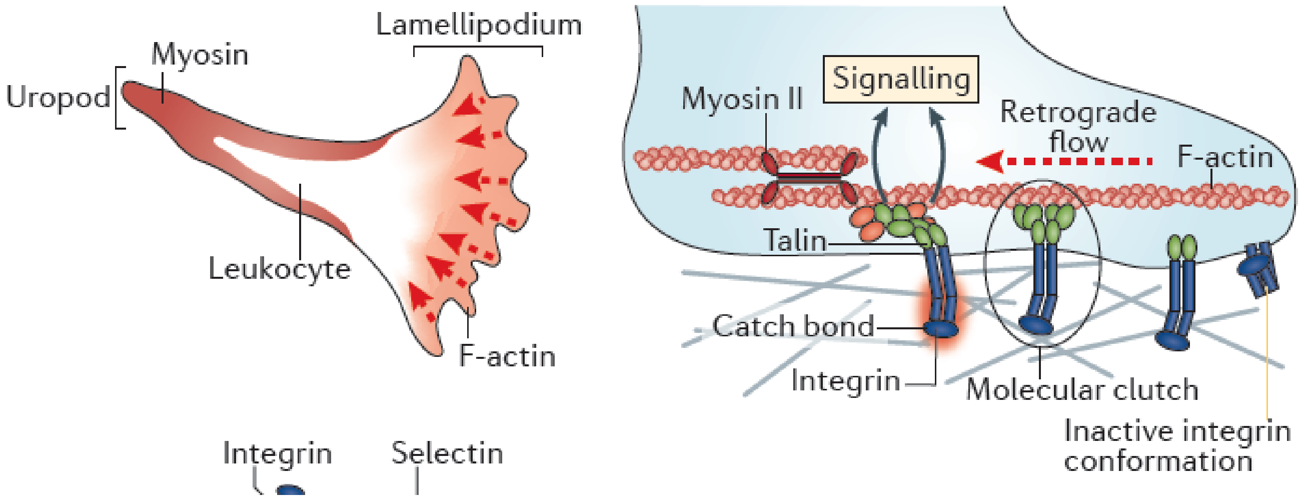


Enyedi et al., 2016

Lecture outline

1) The mechanical properties of cells.
2) Mechanical force exertion by cells.
3) Mechanotransduction: pathways and functions.
4) Cell motility.
5) Cell extrinsic forces.
6) Cell-cell interactions.

Cell motility – the mechanical clutch model

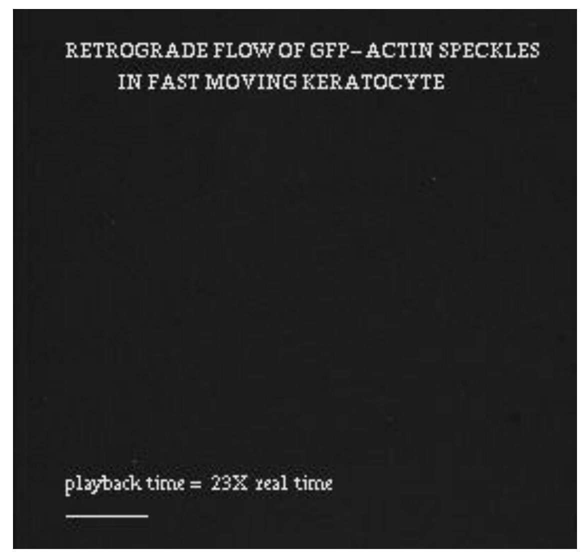


Huse, 2017

Fish keratocyte

Actin speckle microscopy

Notice that load on clutch in not 100%.
In other words, the clutch slips!



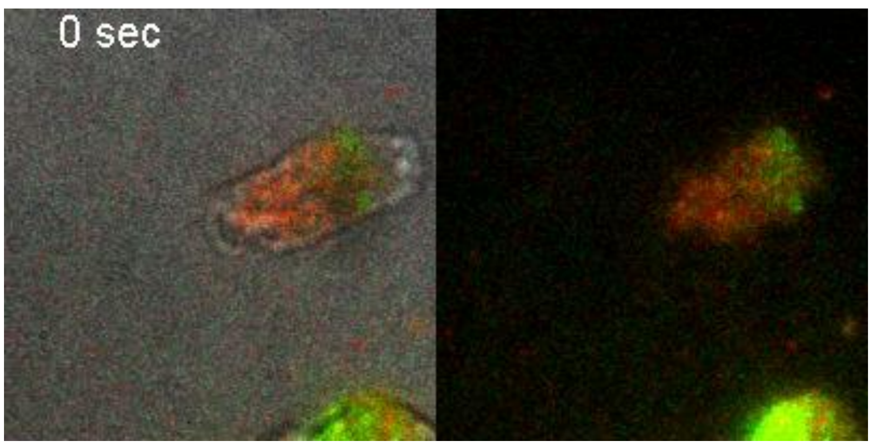
Jurado et al., 2004

Different classes of motility

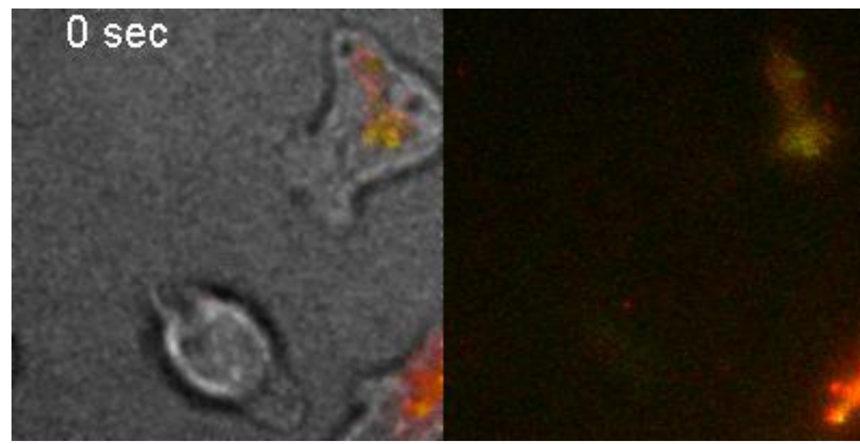
Canonical molecular clutch model developed from studies of mesenchymal cell migration in 2D environments. What about more dynamic cells (i.e. leukocytes) in 3D envrionments?

T cells exhibit both “walking” and “sliding” motility in 2D

Sliding



Walking

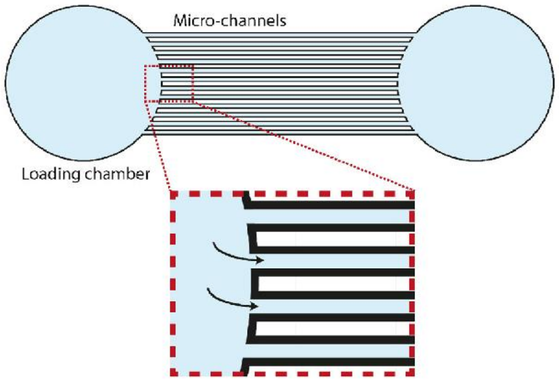


Myosin

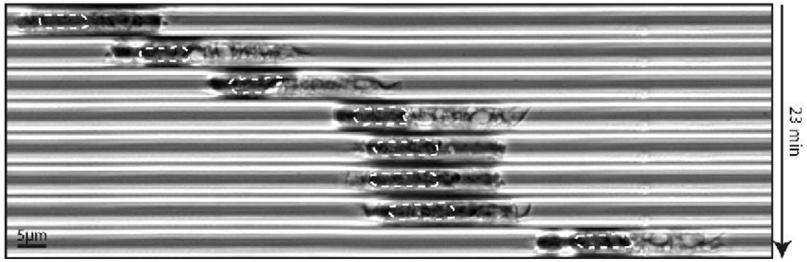
Actin

Jacobelli et al., 2009

Different classes of motility

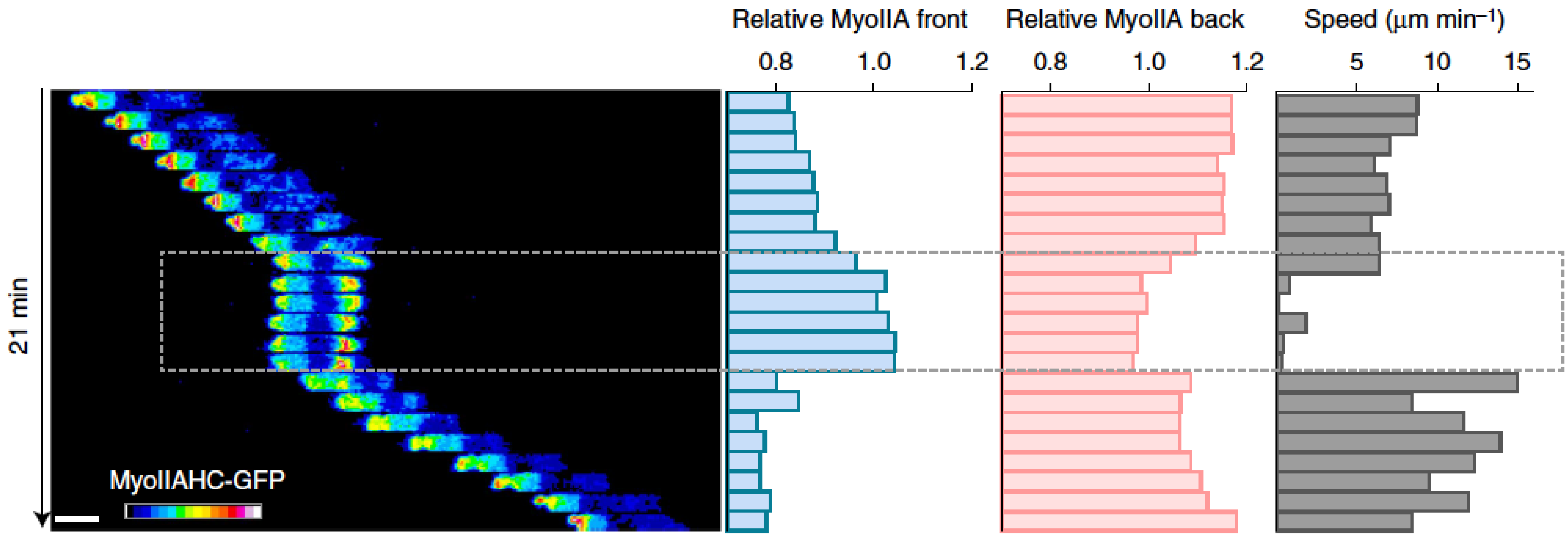


Dendritic cells in microchannels.



Vargas et al., 2015

Myosin accumulation at the back associated with forward movement.



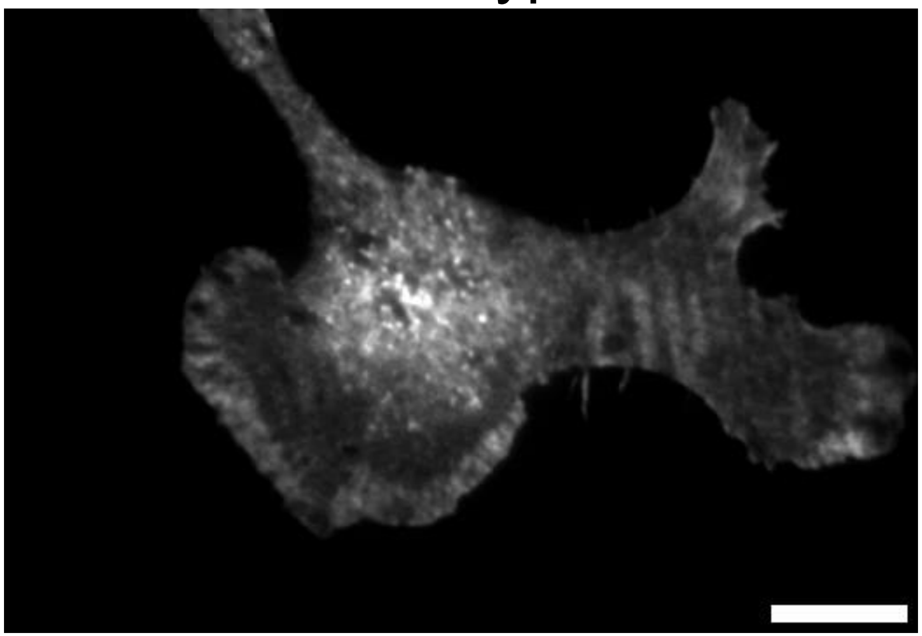
Chabaud et al., 2015

Different classes of motility

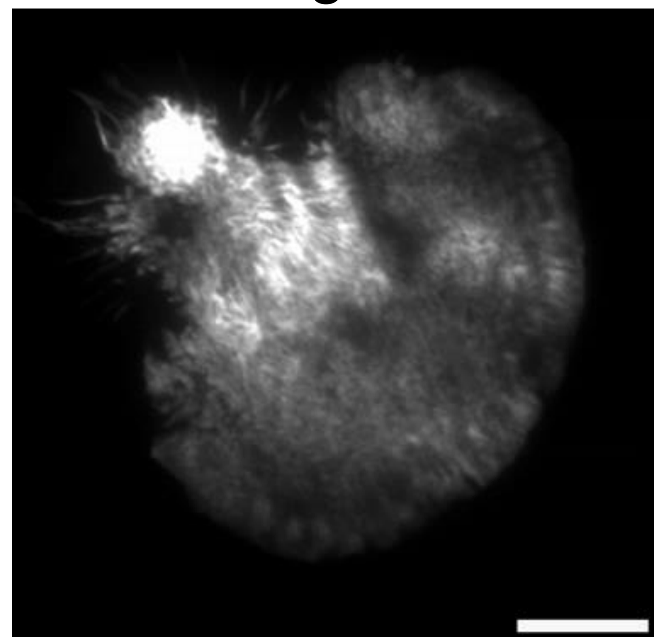
Migration is mechanically adaptive.

DCs migrating in different adhesion regimes, between coverslip and agarose pad.

Wild type



$Itg^{-/-}$

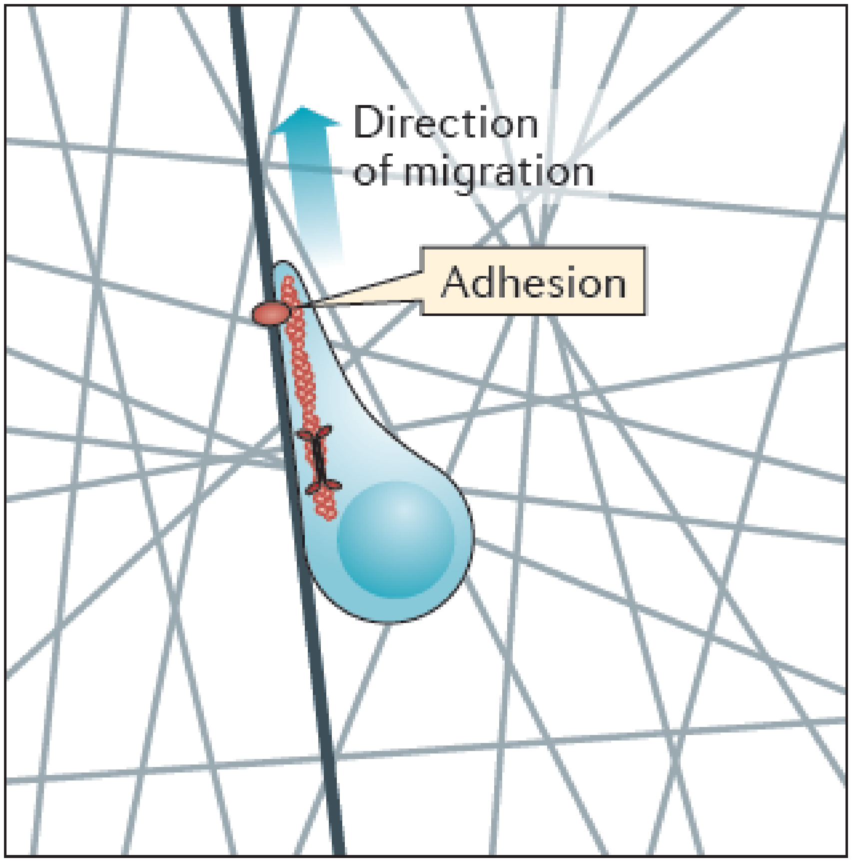


Renkawitz et al., 2009

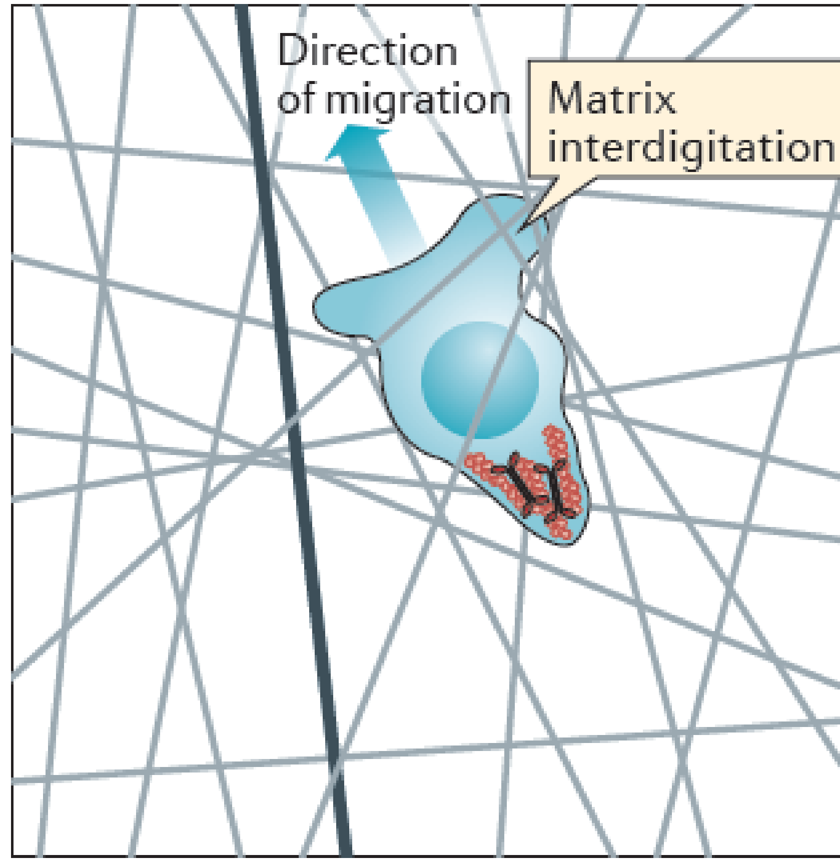
Forward progress is the same. Enhanced retrograde flow compensates for slippage.

Different classes of motility

3D environments give different options for motion.



Integrin-dependent motility

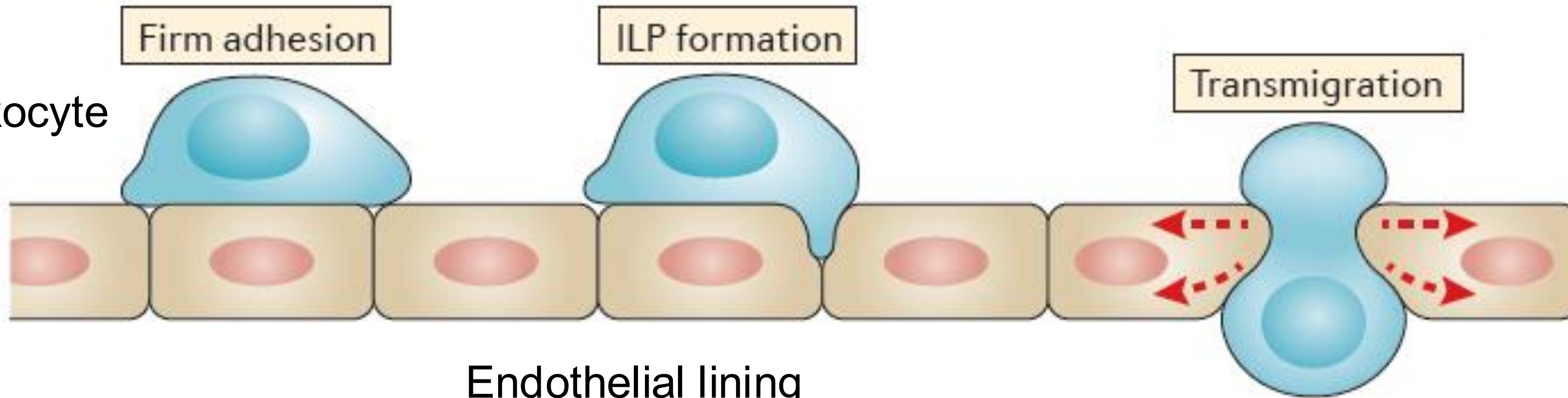


Integrin-independent blebbing motility

Huse, 2017

Motility - extravasation

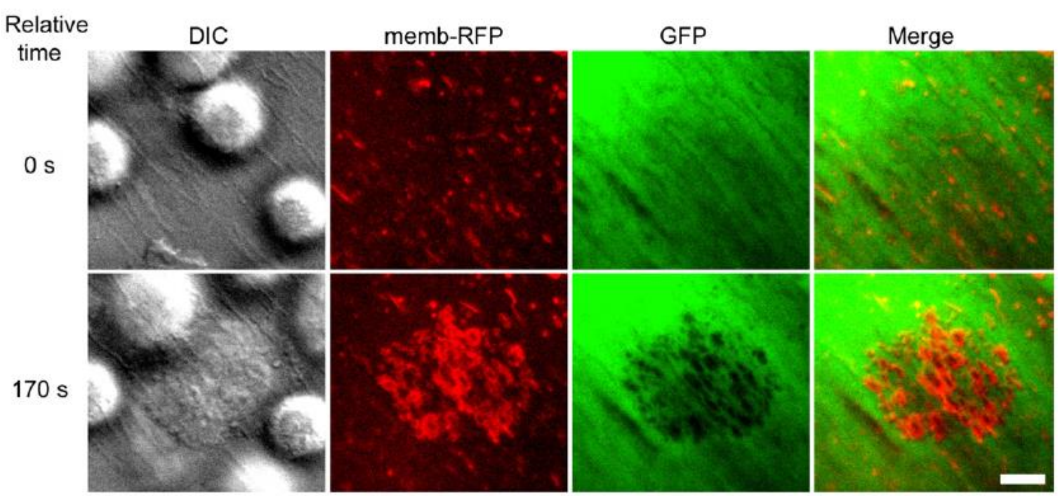
Leukocyte

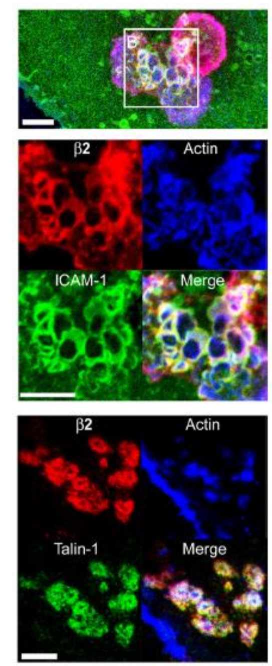


Endothelial lining

Huse, 2017

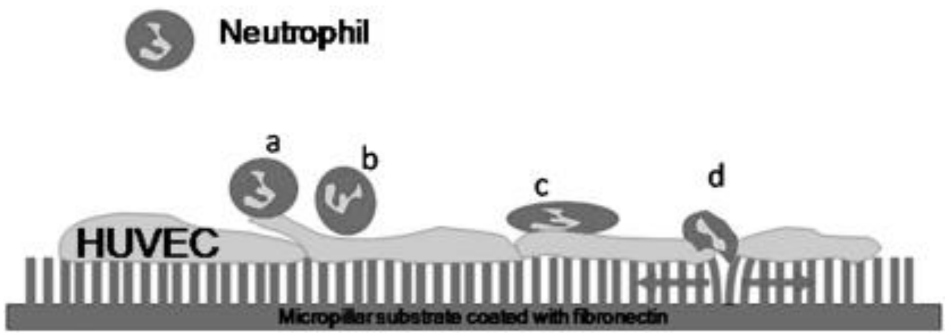
Carman. Invadopodial type pushing to “palpate” the monolayer.





Carman et al., 2007

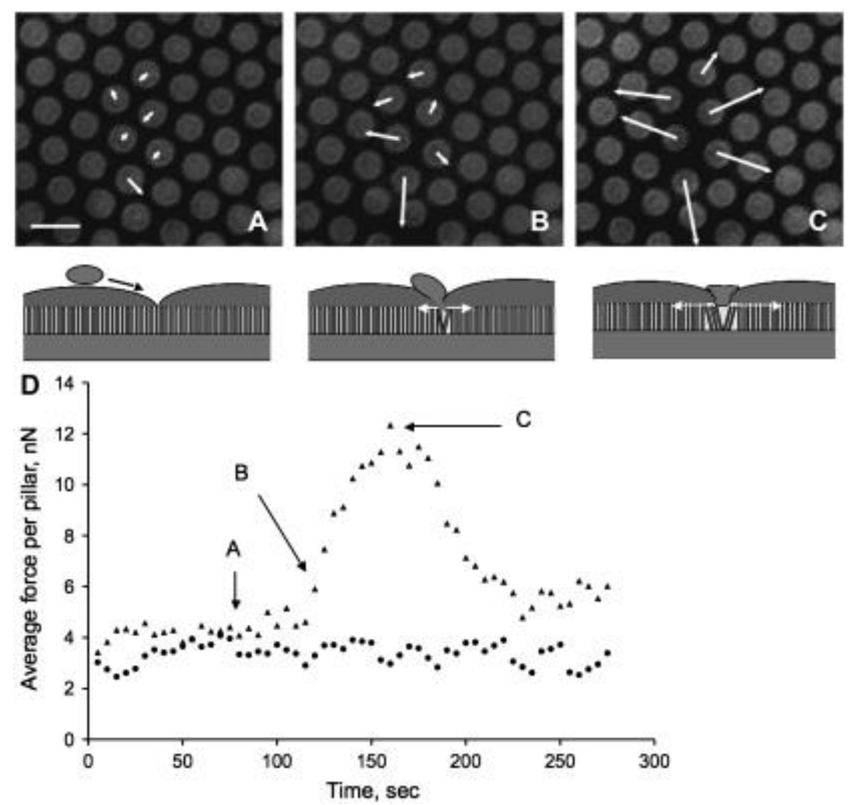
Extravasation requires nuclear squeezing



HUVEC endothelial layer grown on top of flexible micropillars.

Peak force exertion during neutrophil extravasation is associated with passage of cell body.

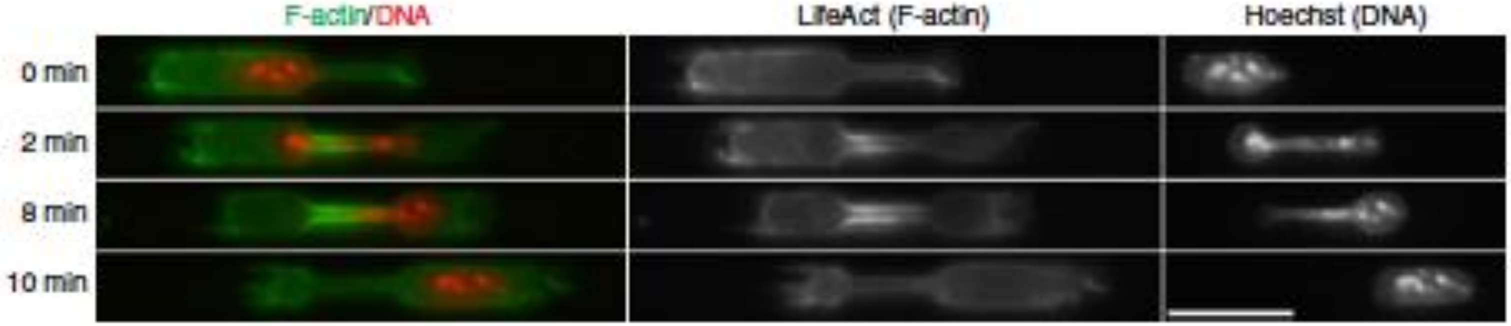
Nucleus is particularly rigid and not deformable.



Rabodzy et al., 2008

Nuclear squeezing leads to DNA damage

Actin and Arp2/3 dependent machanism for nuclear squeezing.



Thiam et al., 2016

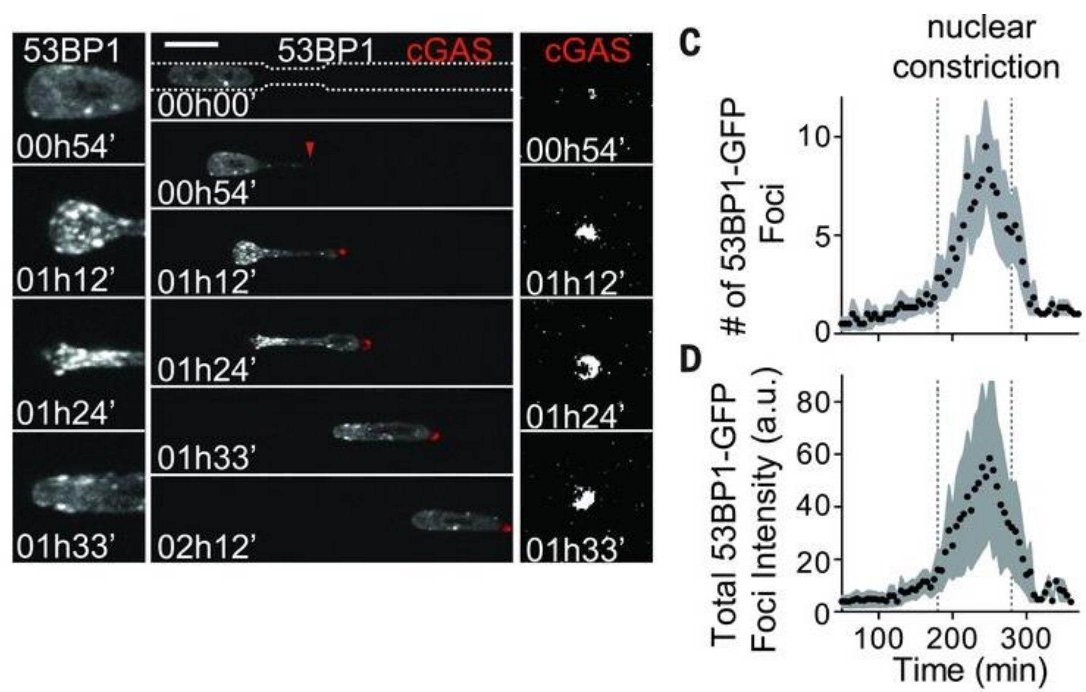
Nuclear squeezing results in DNA damage.

53BP1 – binds to dsDNA breaks.

cGAS – cytoplasmic DNA sensor.

Mechanisms for repairing damage.

Implications for cancer progression.



Raab et al., 2016

Lecture outline

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Environmental mechanics – extracellular matrix

Complex and diverse composition, which dictates its mechanical properties.

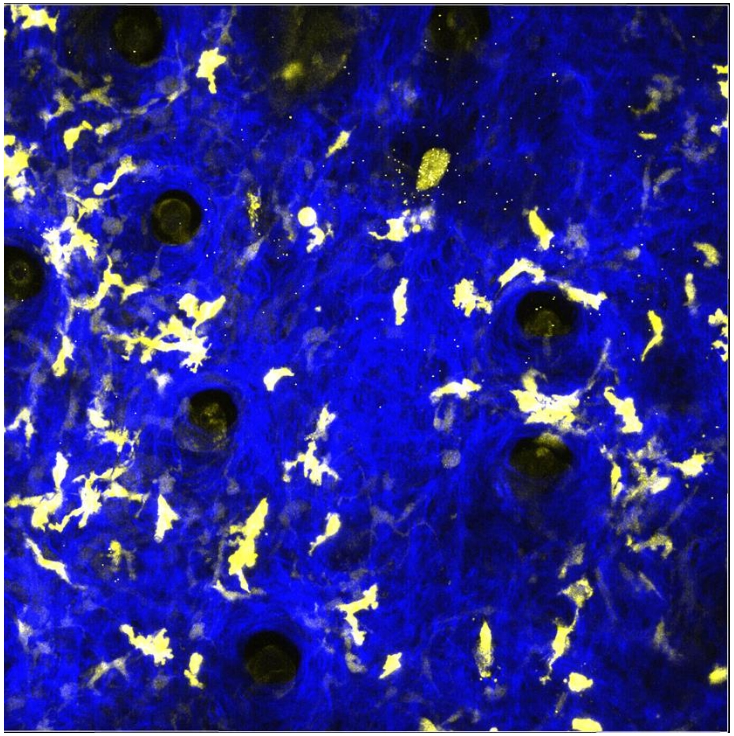
Collagen – most abundant protein in mammals. Forms long triple helix. Contains modified amino acids, in particular hydroxyproline. Physical properties depend on composition and degree of crosslinking.

Glycoproteins – glycosylated polypeptides including fibronectin and syndecans.

Hyaluronic acid – Glycosaminoglycan, extruded from cells to foor extracellular network analogous to cortical F-actin.

Laminins – Trimeric glycoproteins. Are a critical component of basal lamina.

DCs ECM

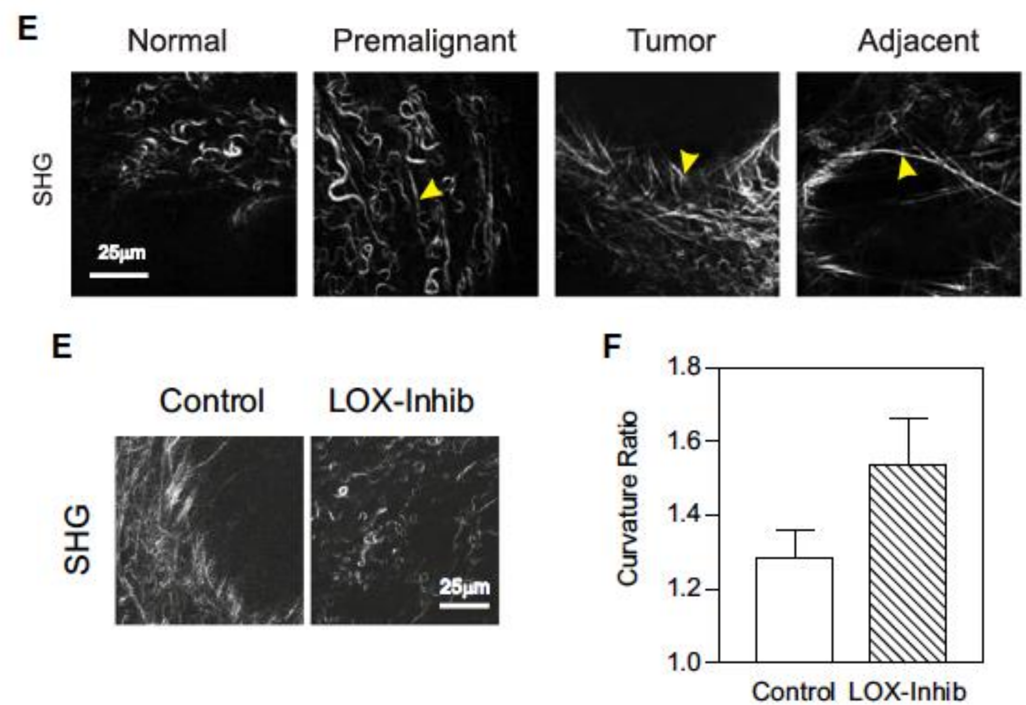


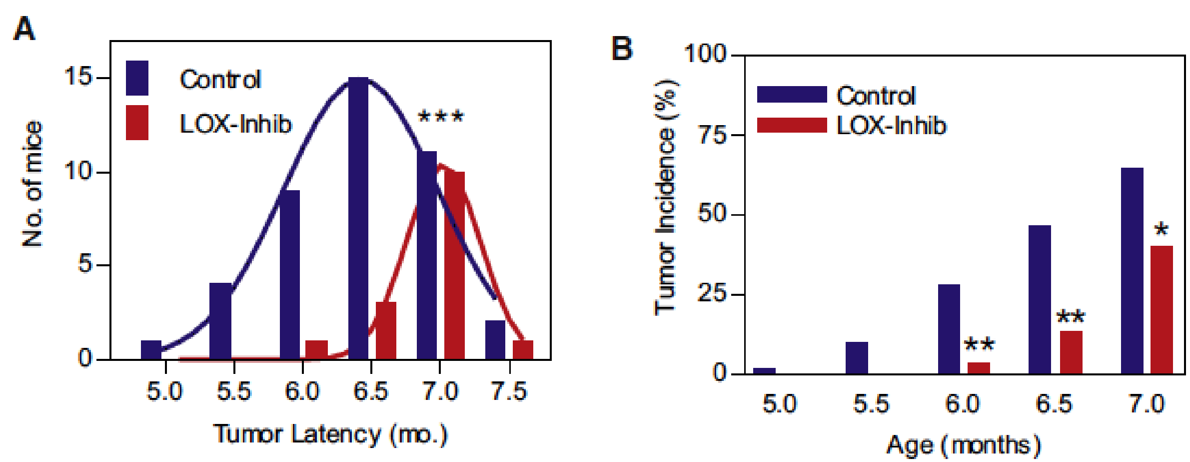
Environmental mechanics – extracellular matrix

MMTV-Neu autochthonous model of breast cancer.

LOX = lysyl oxidase, required for collagen crosslinking.

LOX inhibition normalizes collagen and suppresses tumor development.

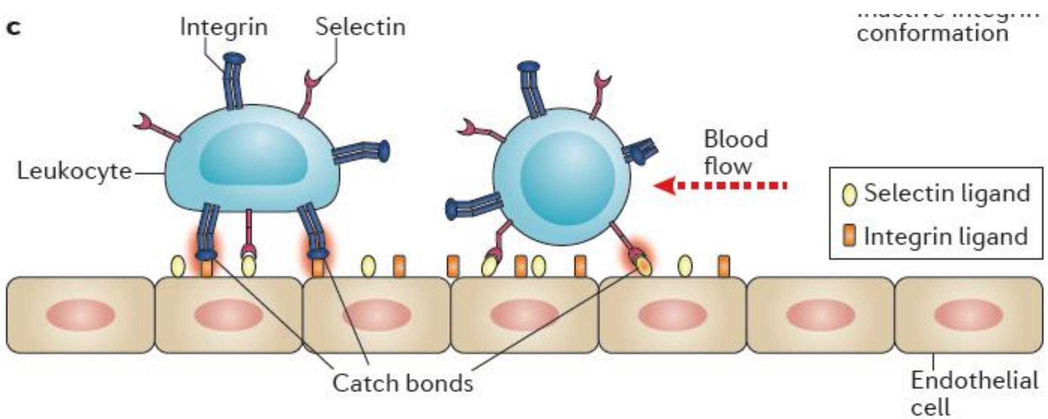




Levantal et al., 2009

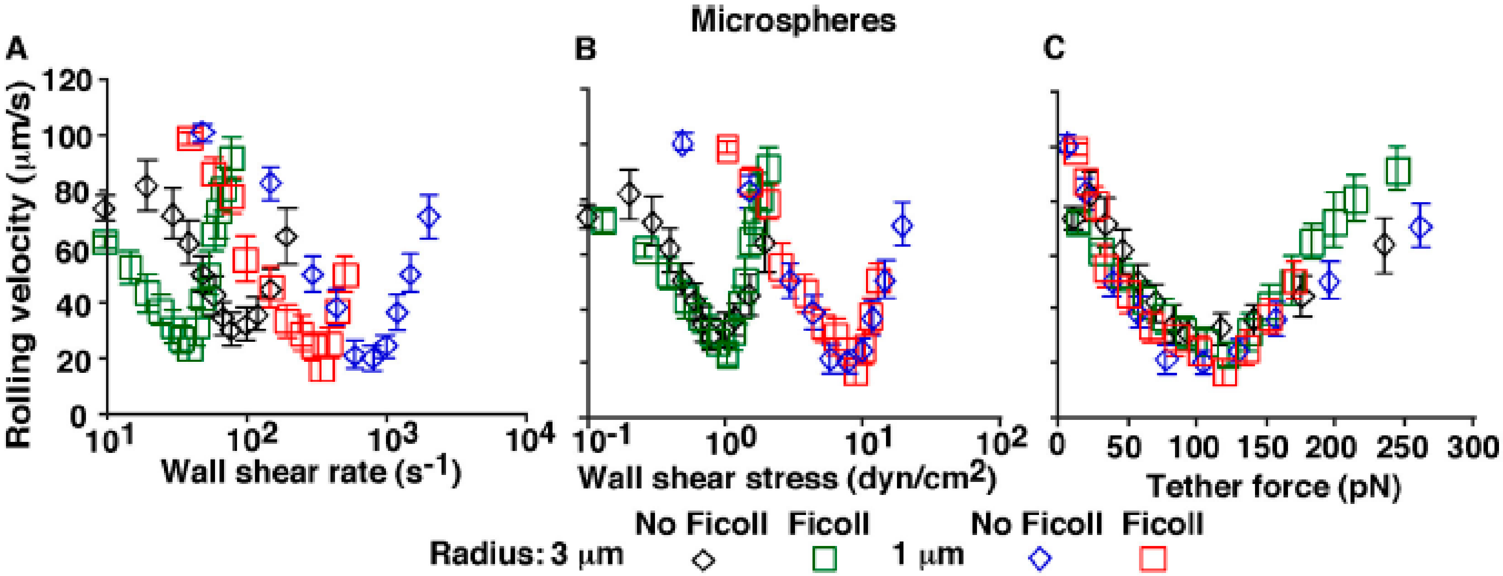
Environmental mechanics – flow

Certain adhesive proteins (selectins and integrins) have evolved to function under flow.



Huse, 2017

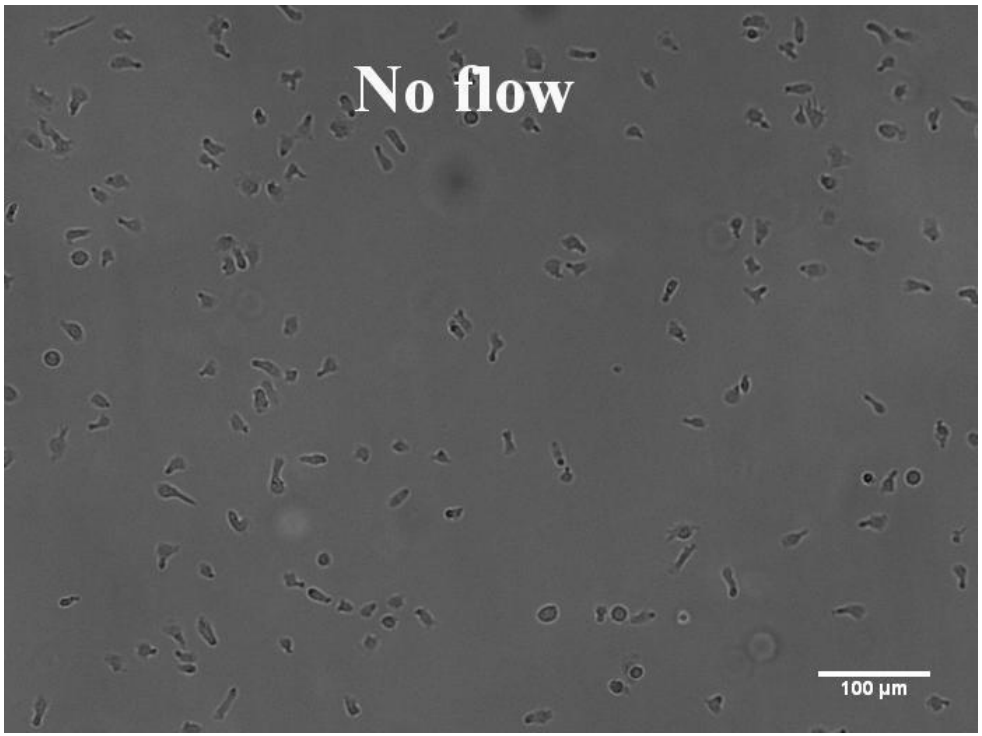
Selectin coated beads in ligand coated flow chamber. Rolling exhibits catch bond behavior.

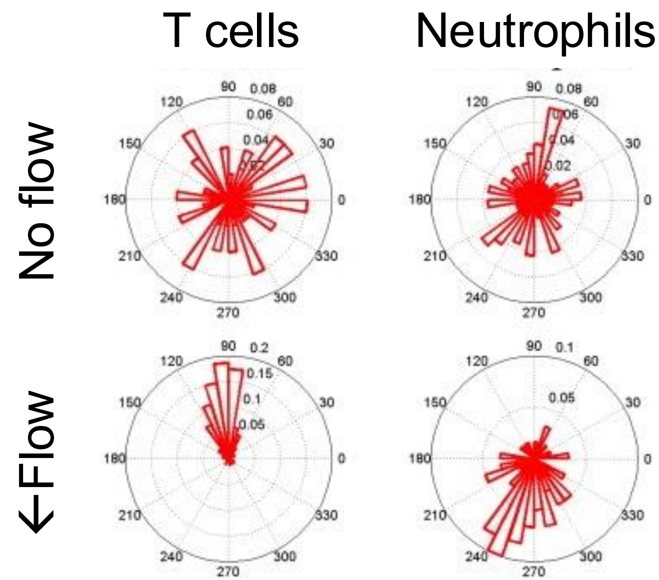


Yago et al., 2004

Environmental mechanics – flow

Leukocyte migration on integrin ligands is sensitive to the direction of flow.





T cells

Valignet et al., 2013

Lecture outline

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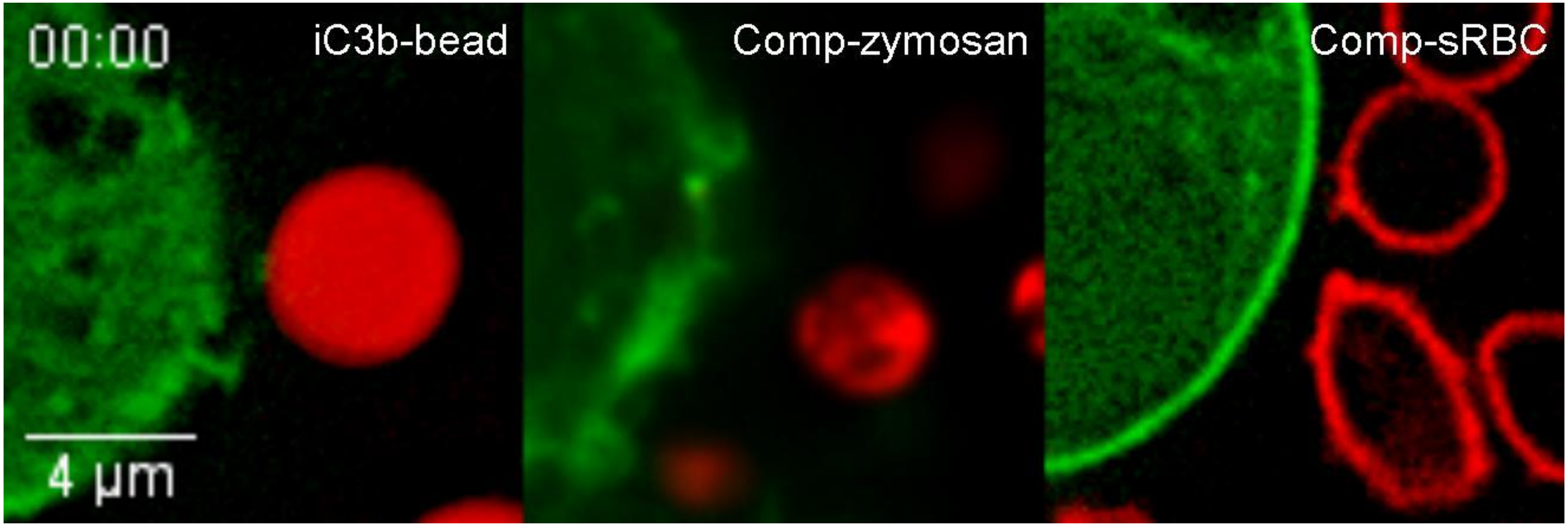
Phagocytosis

Critical for pathogen clearance but also homeostatic uptake of debris and dead cells. Must be both chemically and biophysically adaptable.

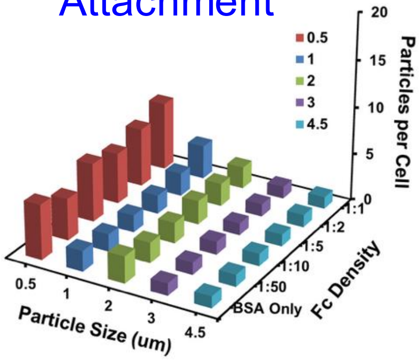


Jaumouillé et al., 2019

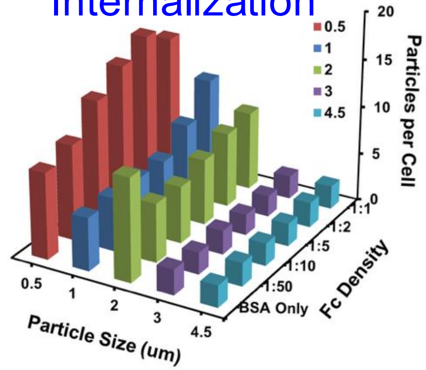
Phagocytosis

Size dependence

Attachment

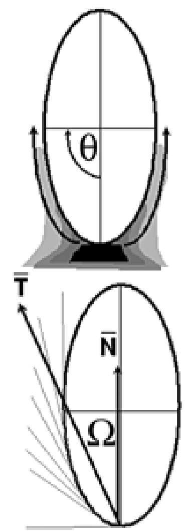


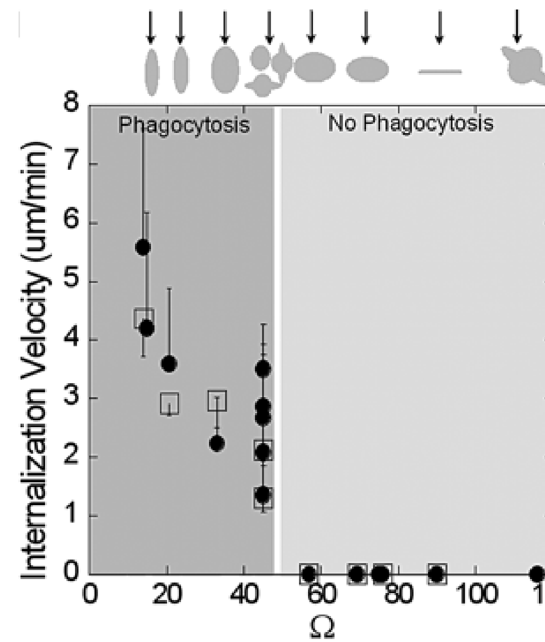
Internalization



Pacheco et al., 2013

Shape dependence

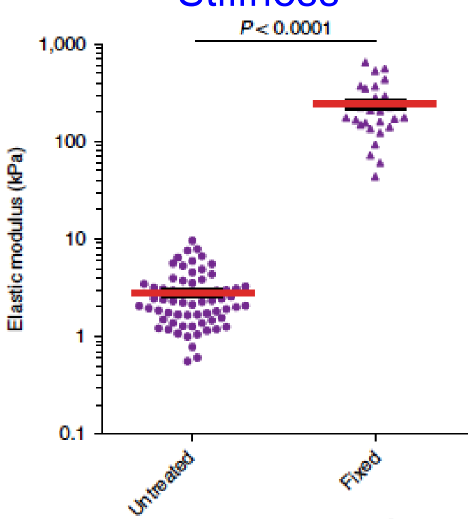




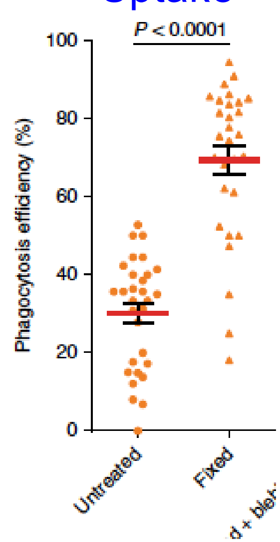
Champion and Mitragotri, 2006

Stiffness dependence

Stiffness



Uptake

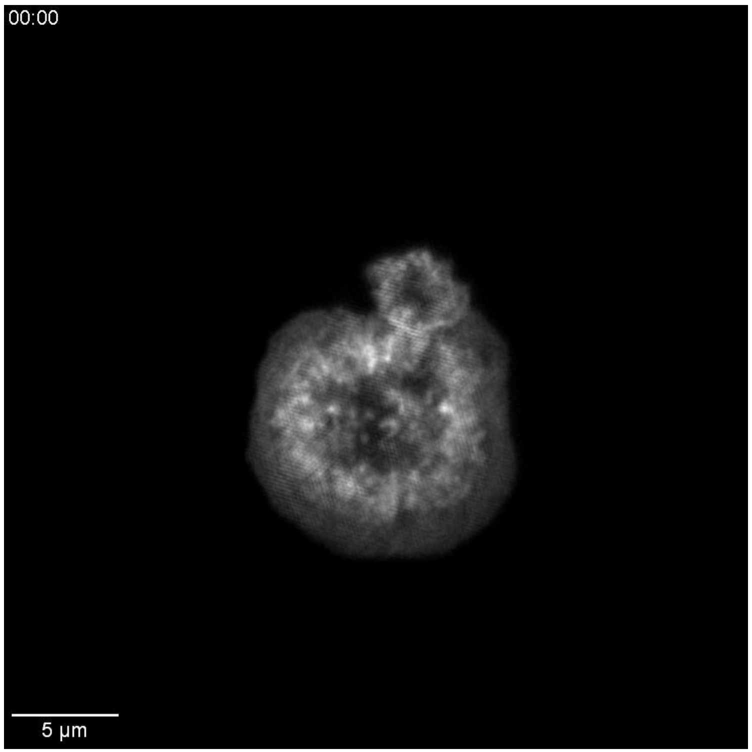


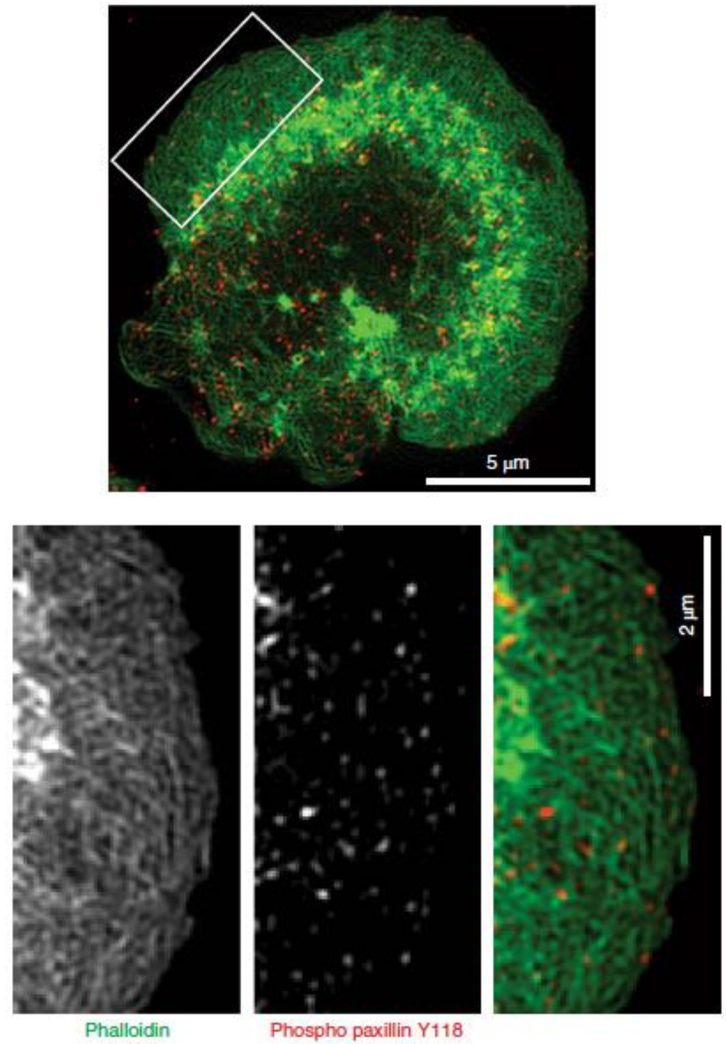
Jaumouillé et al., 2019

Phagocytosis

Clutch like adhesions are employed during phagocytosis.

Frustrated phagocytosis model.

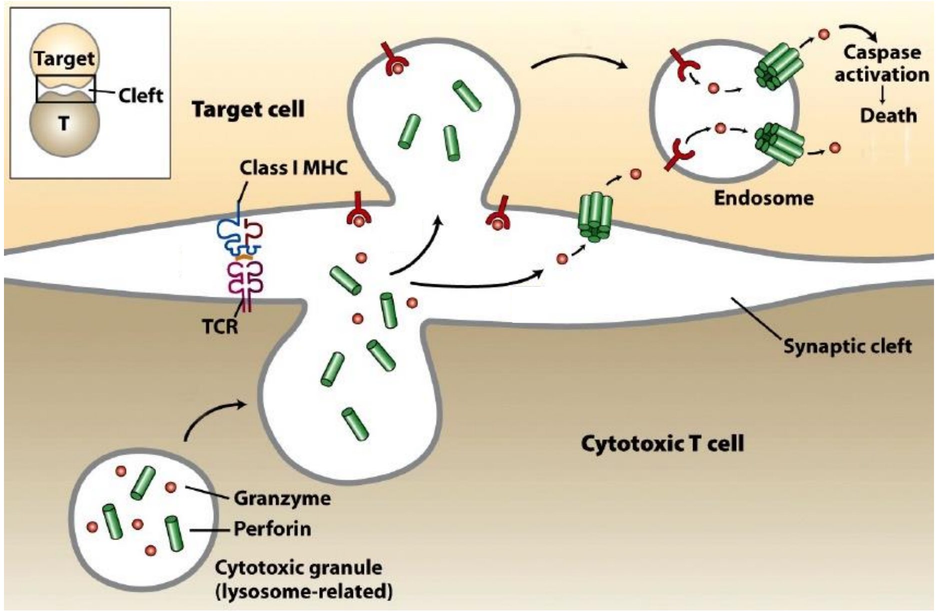




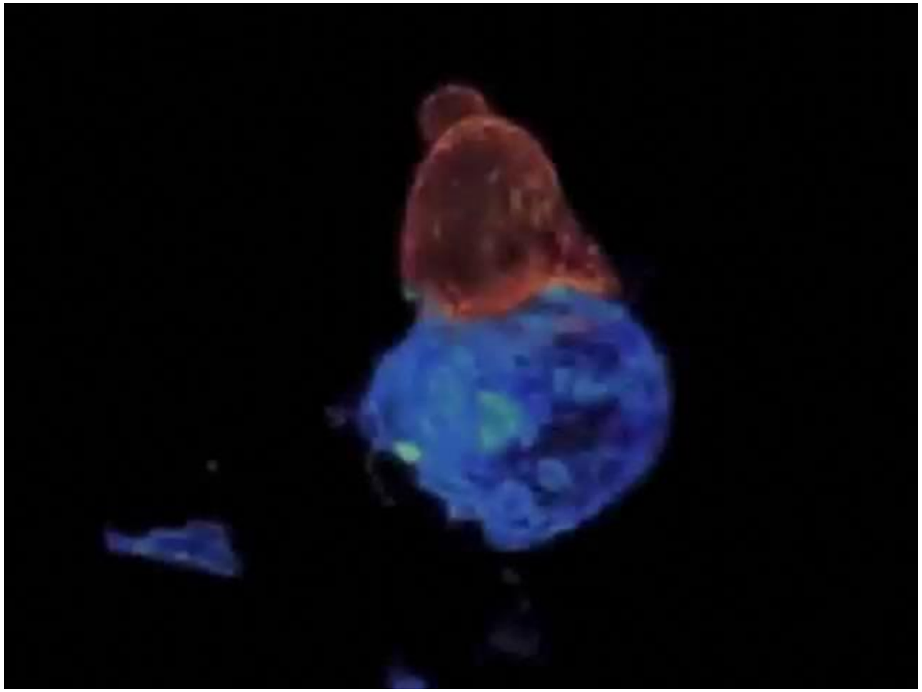
Jaumouillé et al., 2019

Immune synapse

Critical for immune responses against intracellular pathogens and tumors.
Mediated by a cellular venom (perforin and granzyme), but also highly dynamic.



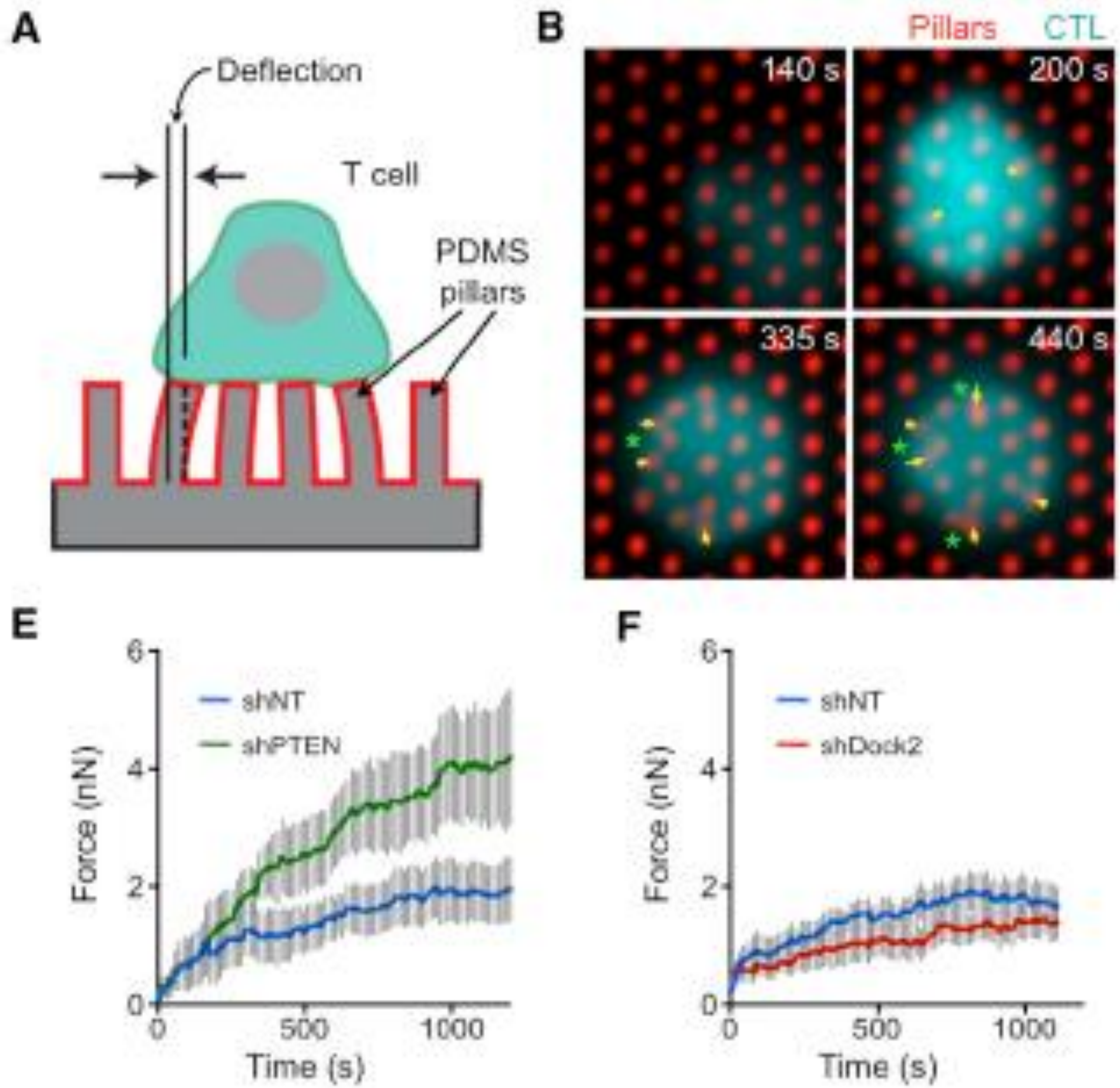
Adapted from StudyBlue, Iowa State University



Ritter et al., 2015

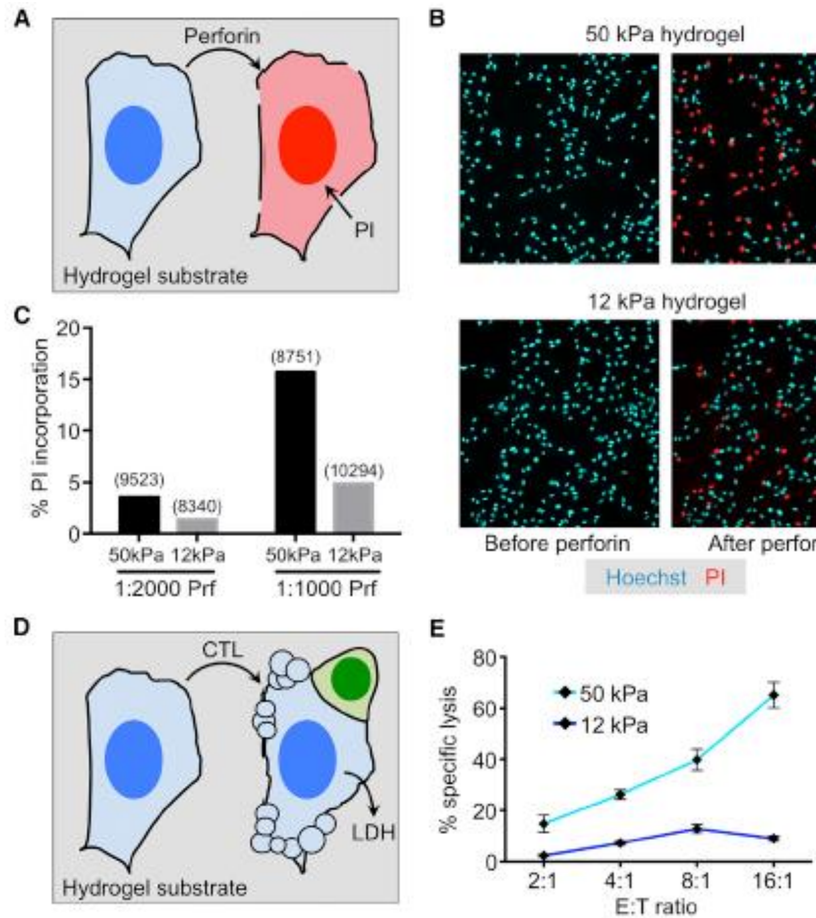
Synaptic force correlated with cytotoxicity

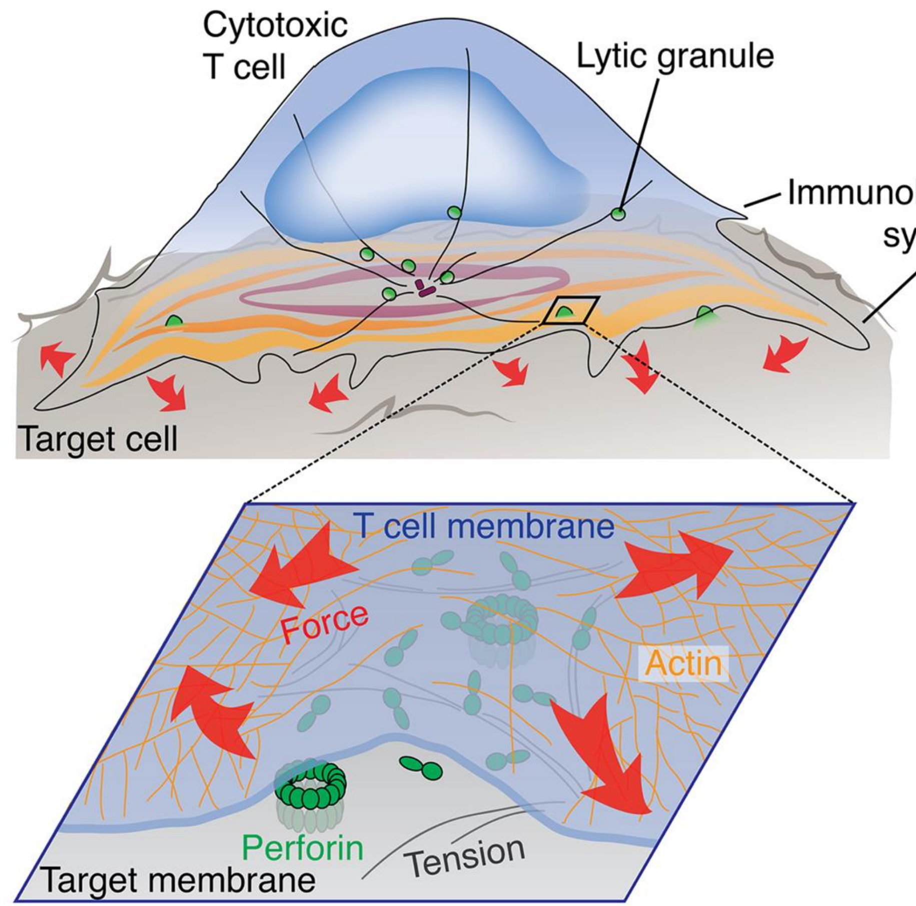
75X timelapse



Basu et al., 2016

Tension potentiates perforin-mediated lysis

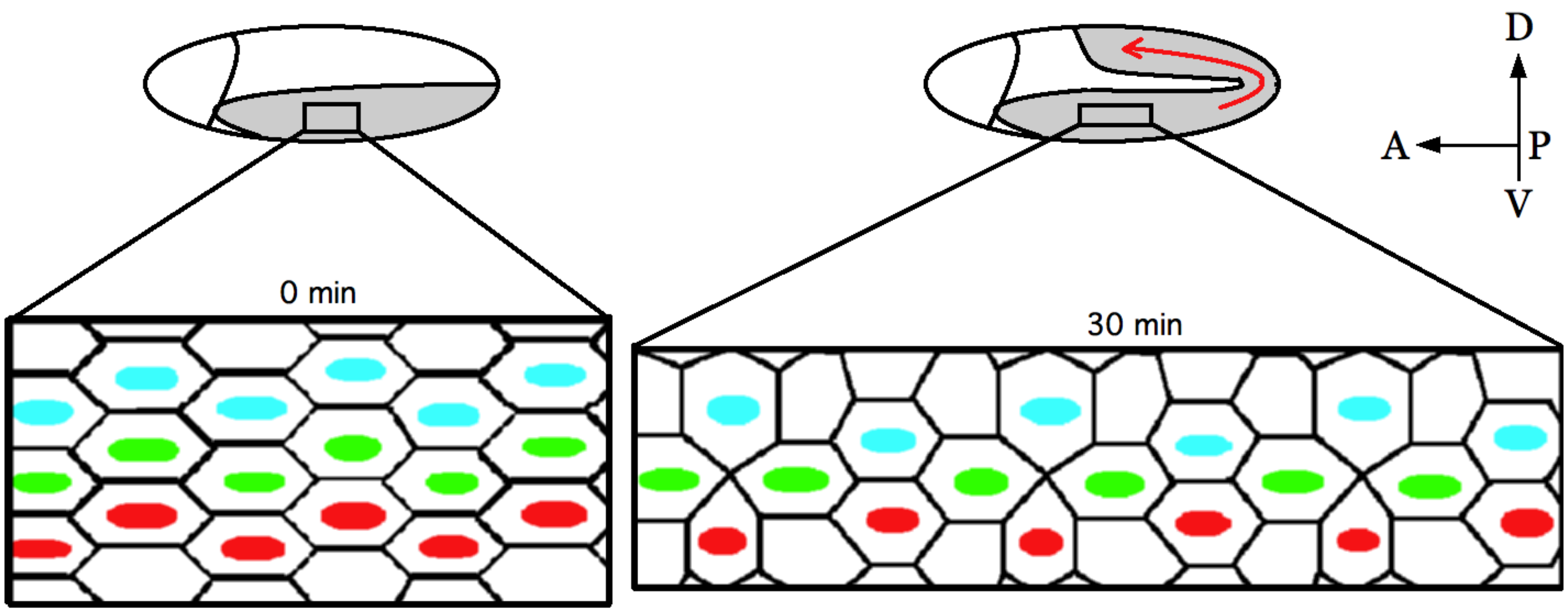




Basu et al., 2016

Embryonic development – convergent extension

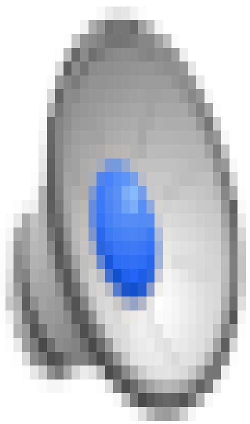
Enables development of a body axis from a homogeneous layer of cells.



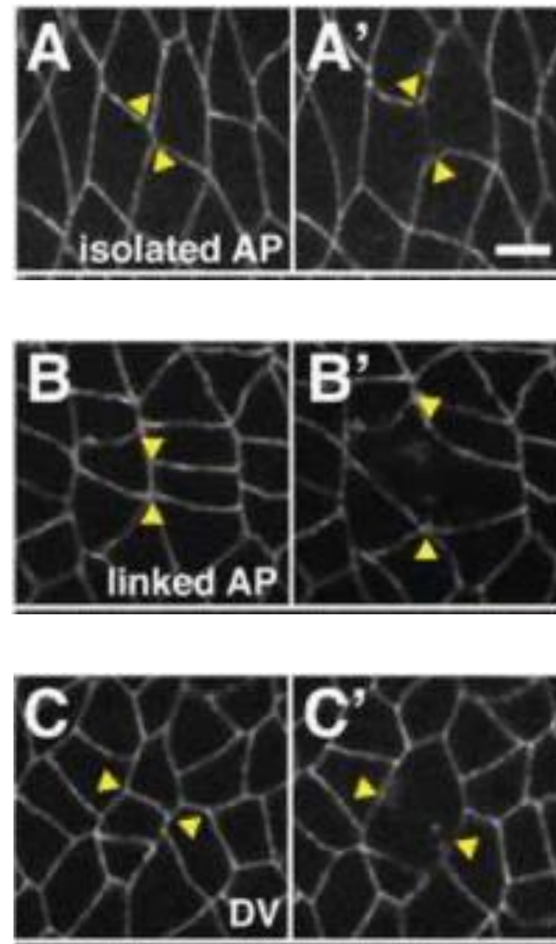
Wikipedia

Myosin contractility is crucial for convergent extension

Myosin label

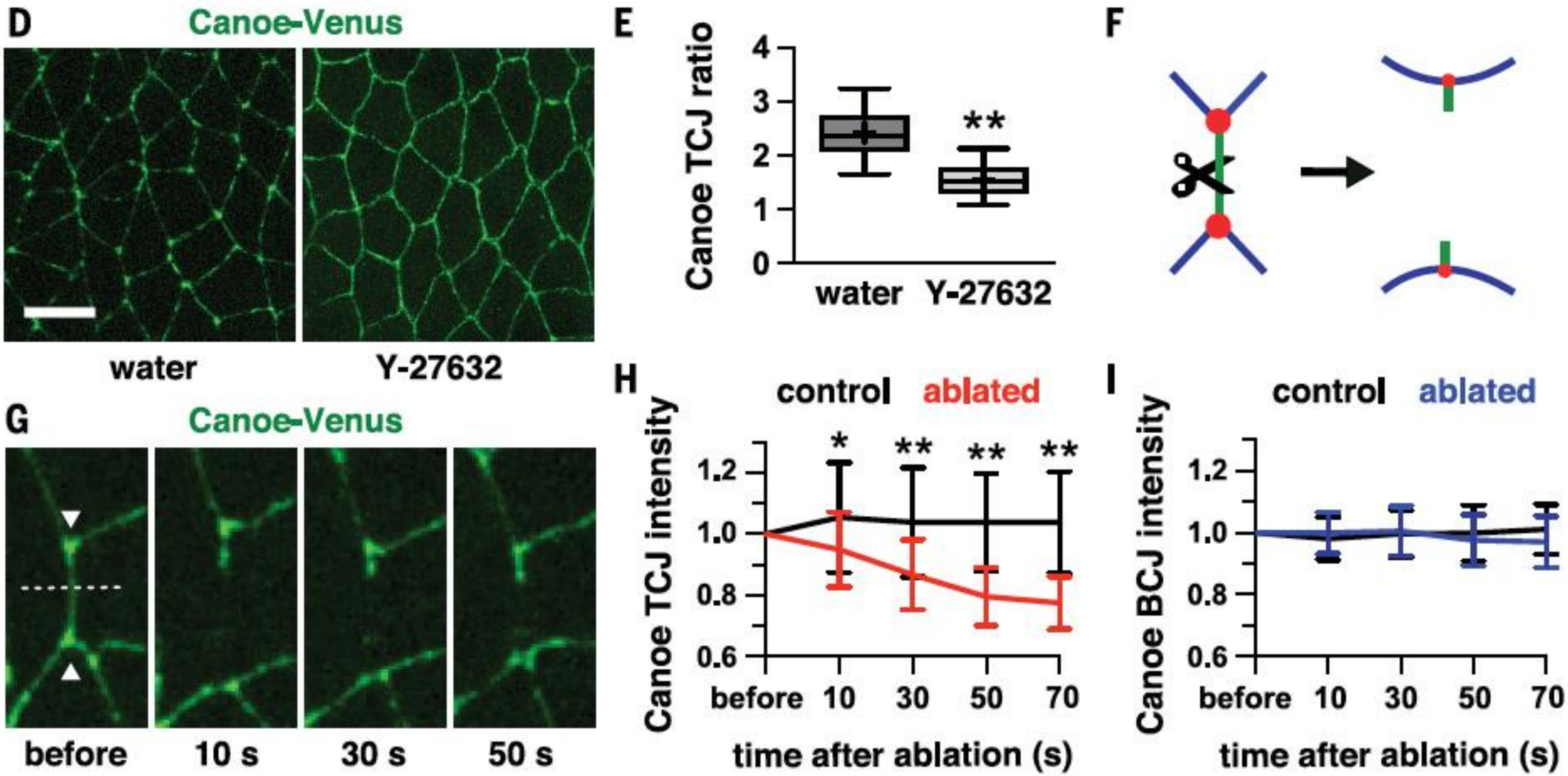


Laser ablation of cell-cell junctions.



Fernandez-Gonzalez et al, 2009

Tension stimulates mechanosensitive junction formation



Yu and Zallen, 2020