Session 23

WHOLE CELL STUDIES

Cardiovascular Forces

- Stretch
  - Systolic and diastolic pressures cause up 10% cyclic strain
  - Endothelials, smooth muscle, and ECM are stretched
  - Stretch also relevant in lungs, tendons, and ligaments
- Shear
  - Flow in arteries has shear stress τ = 2-4 and τ_{max} = 10 Pa
  - Laminar vs. disturbed flow
  - Topology of endothelium induces quasi-steady flow

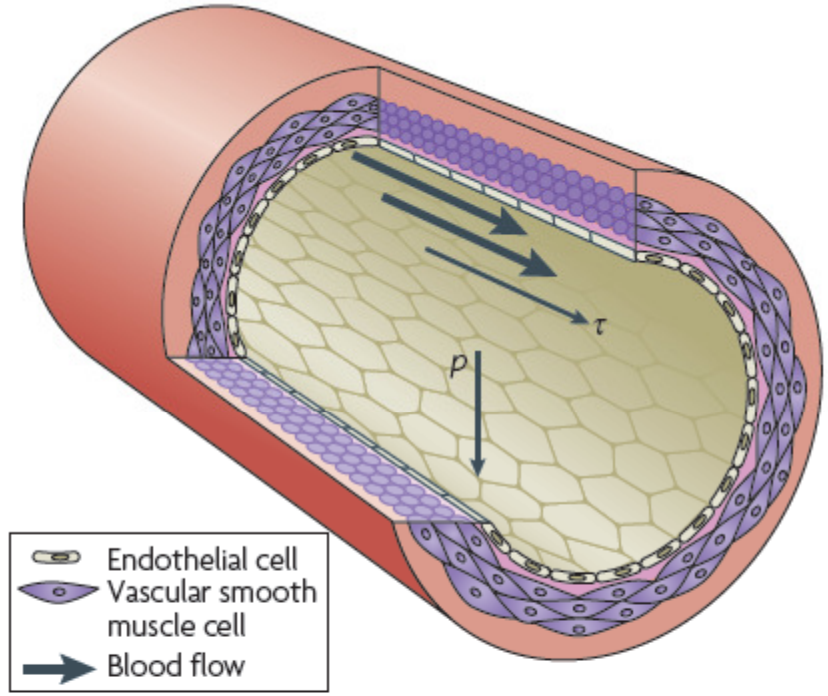
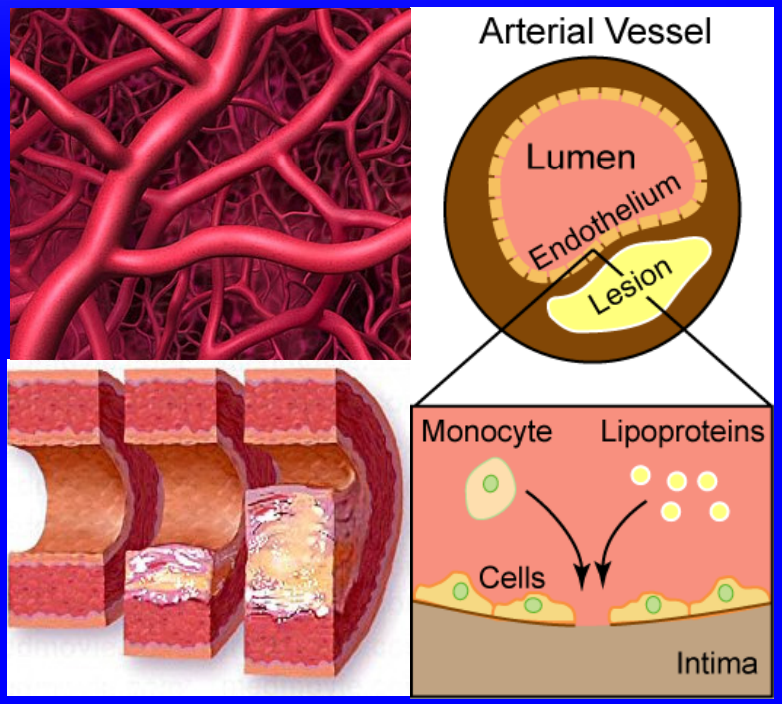
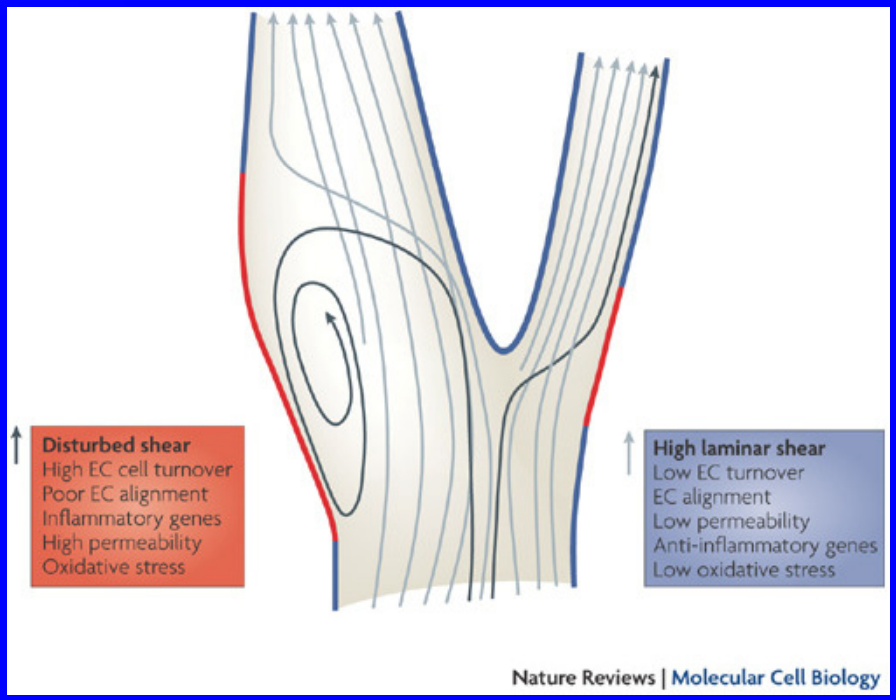


Figure 1 | **Mechanical forces on the vessel wall.** A section of an artery wall shows the endothelial cells that form the inner lining and align longitudinally, and vascular smooth muscle cells that form the outer layers and align circumferentially. Pressure (*p*) is normal to the vessel wall, which results in circumferential stretching of the vessel wall. Shear stress (τ) is parallel to the vessel wall and is exerted longitudinally in the direction of blood flow.

Shear and Atherosclerosis

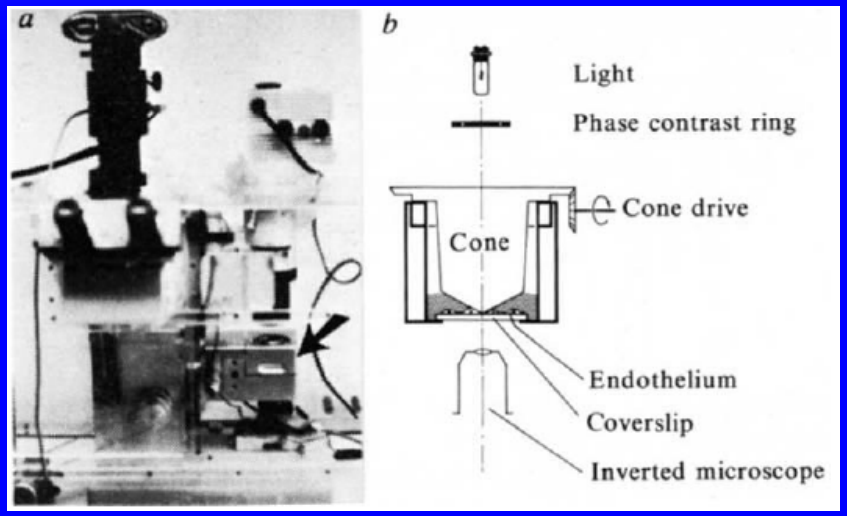
- Focal inflammation and high permeability lead to atherosclerotic lesions



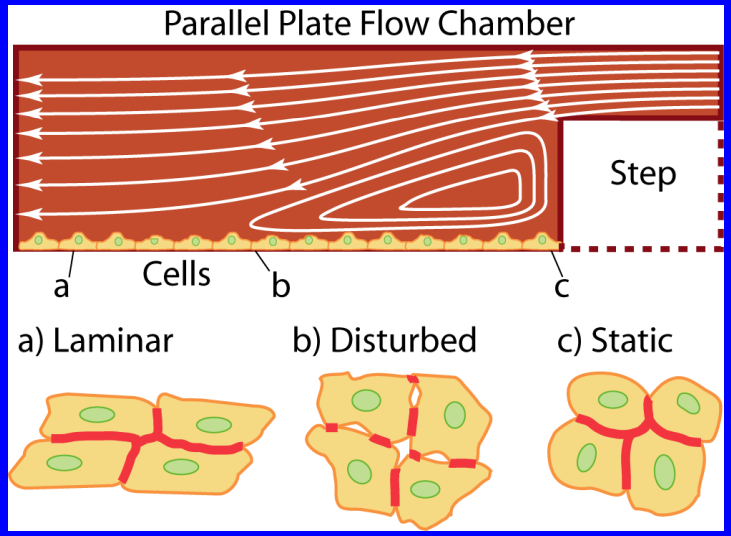


Shear Flow Systems

- Cup-and-cone

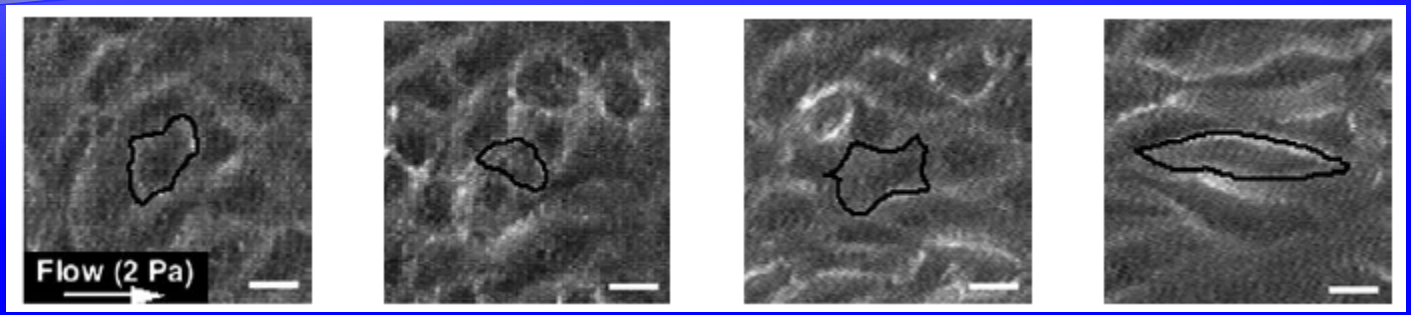


- Parallel Plate

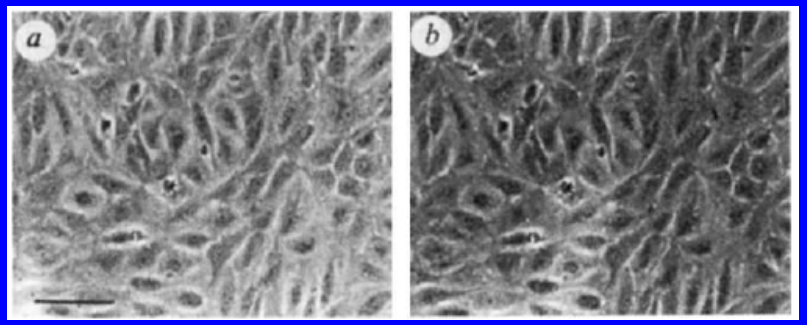


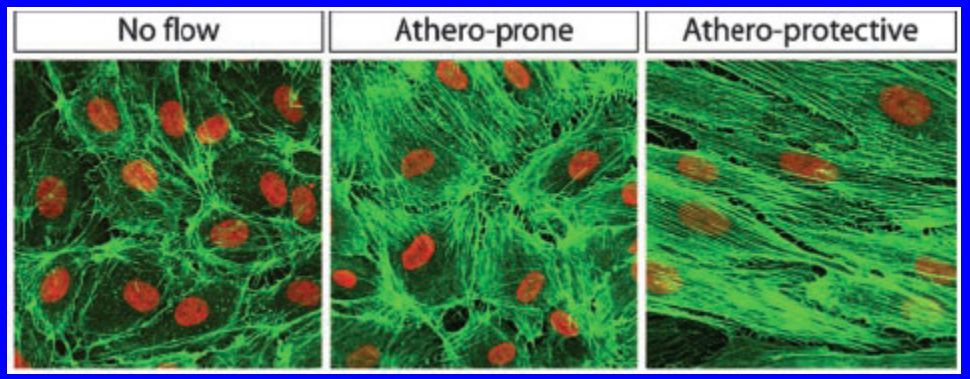
Cell Alignment

- Parallel Plate



- Cup-and-Cone

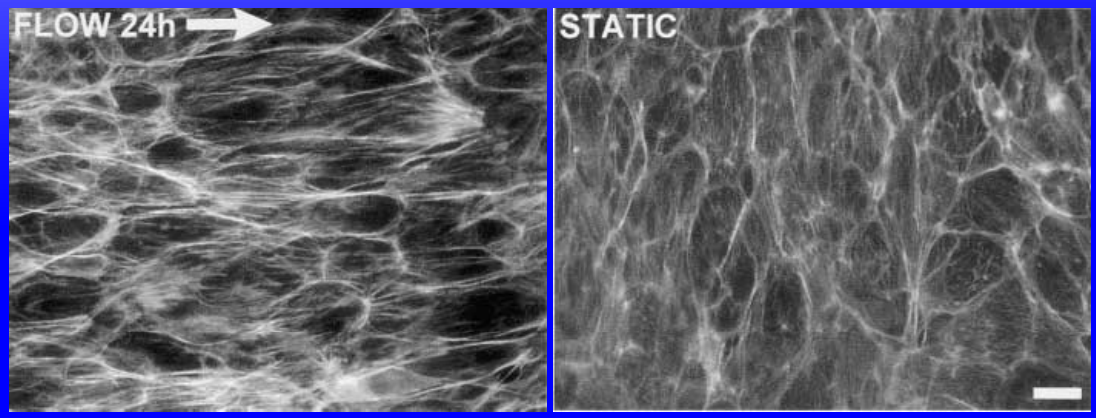




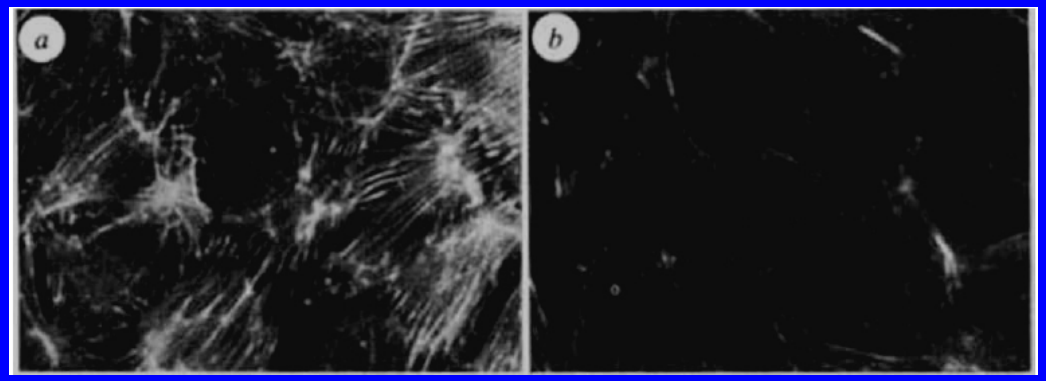
Dia, Gimbrone (2004) *PNAS*, 101 (41):14871

Stress Fibers

- Parallel Plate

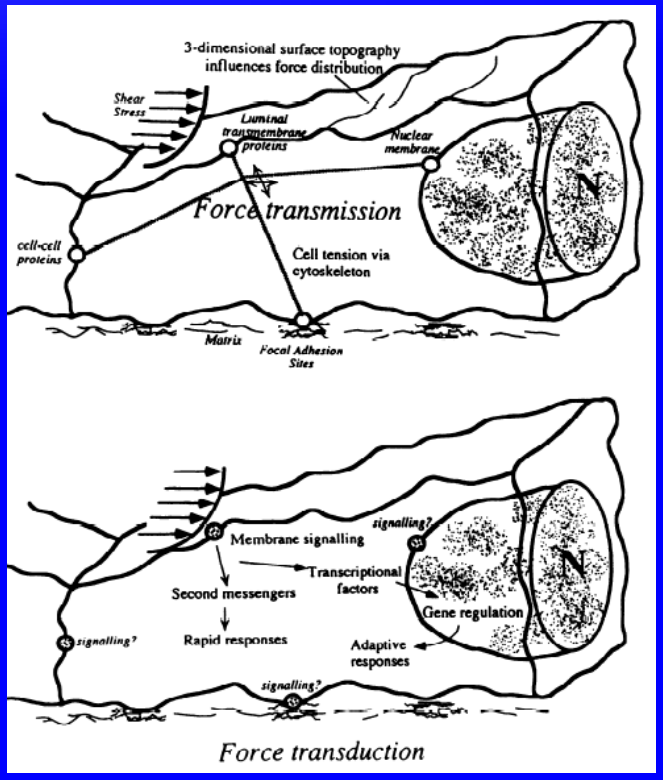


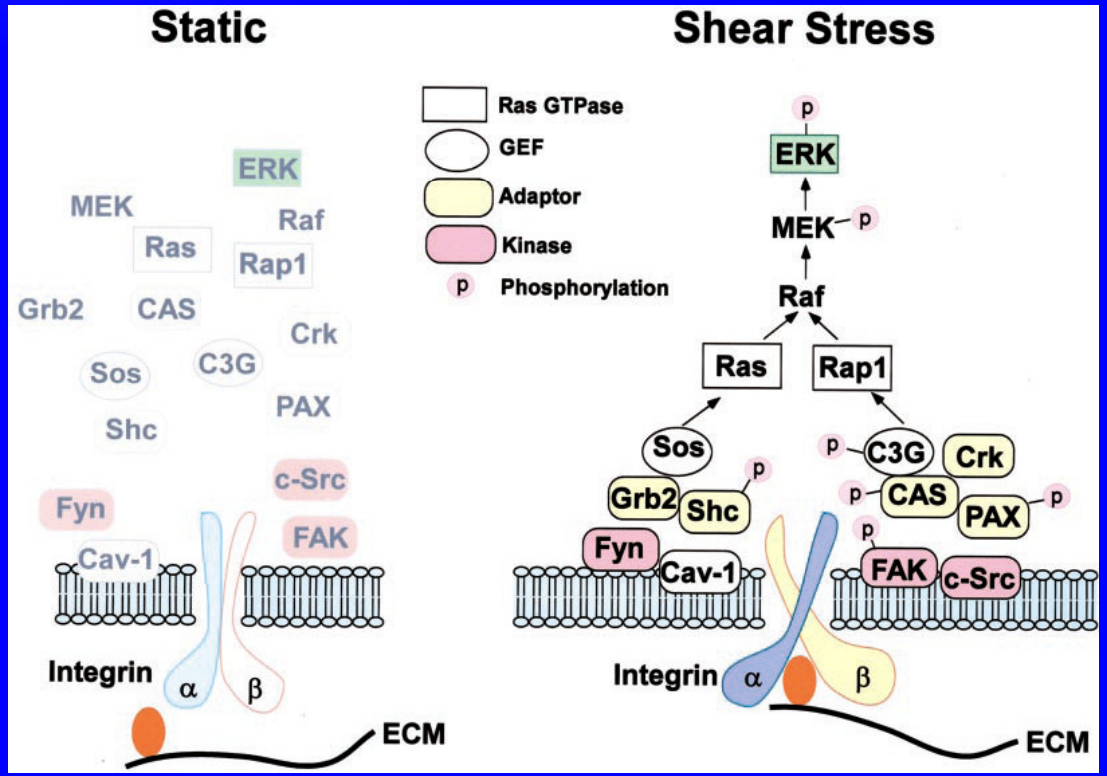
- Cup and Cone



Force Transmission & Transduction

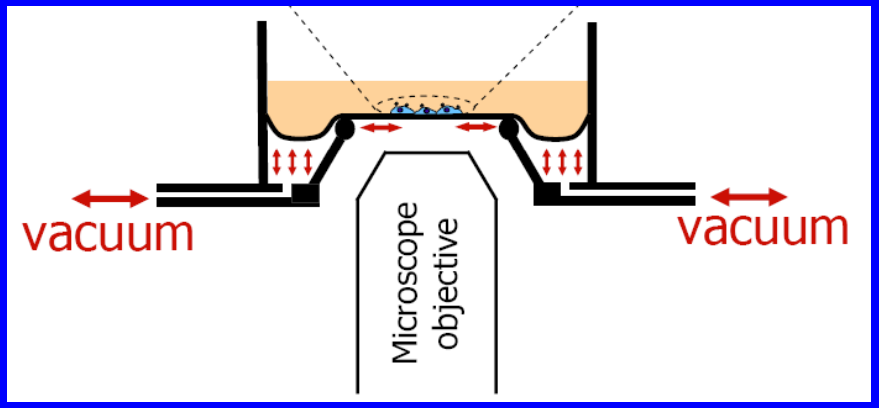
- Shear on the luminal surface can have local or transmitted transduction

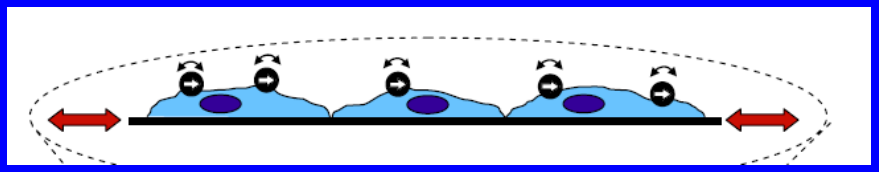




Stretching Systems

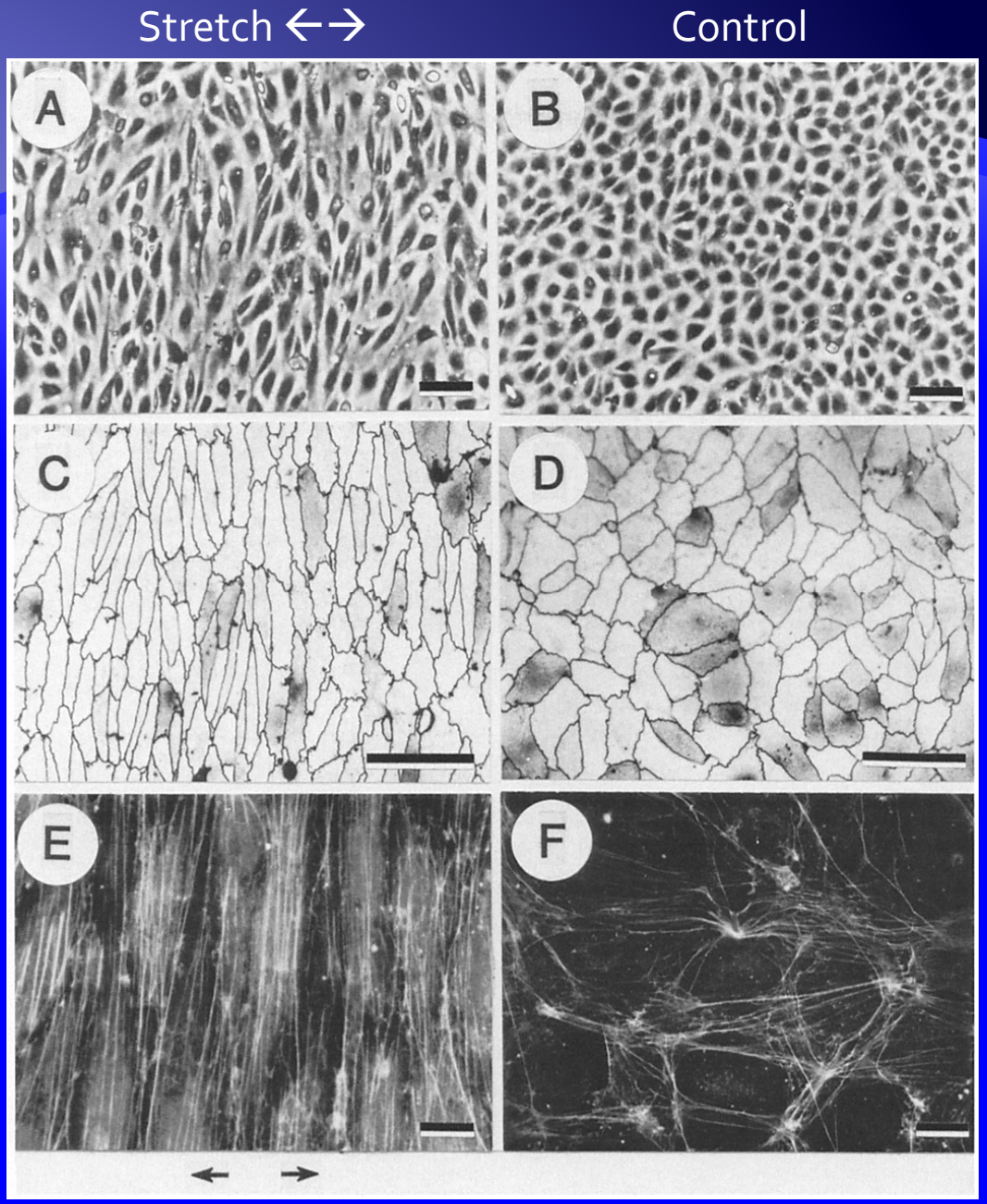
- Flexcell System
- Custom stretching system





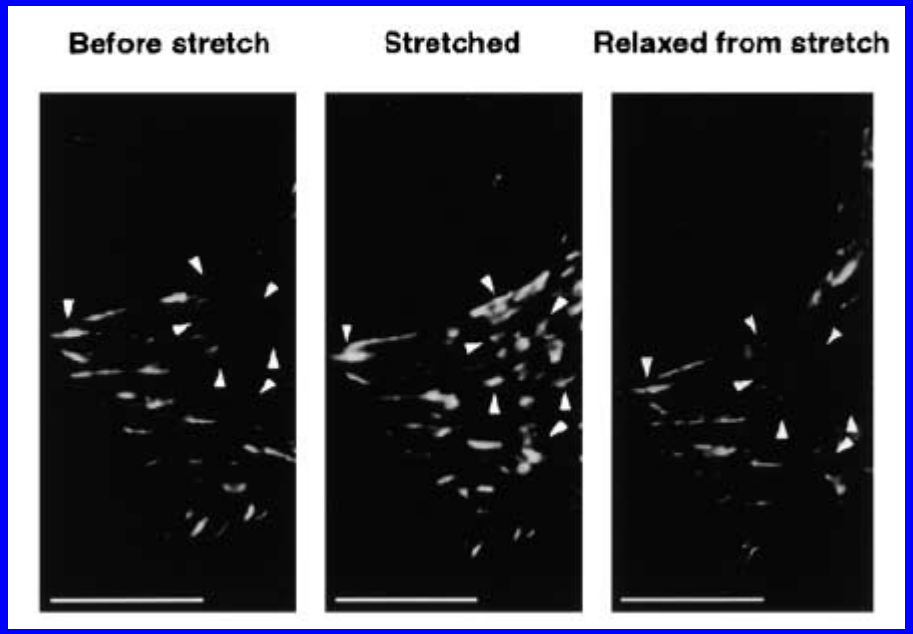
Perpendicular Alignment

- Cell shape
- Stress fibers

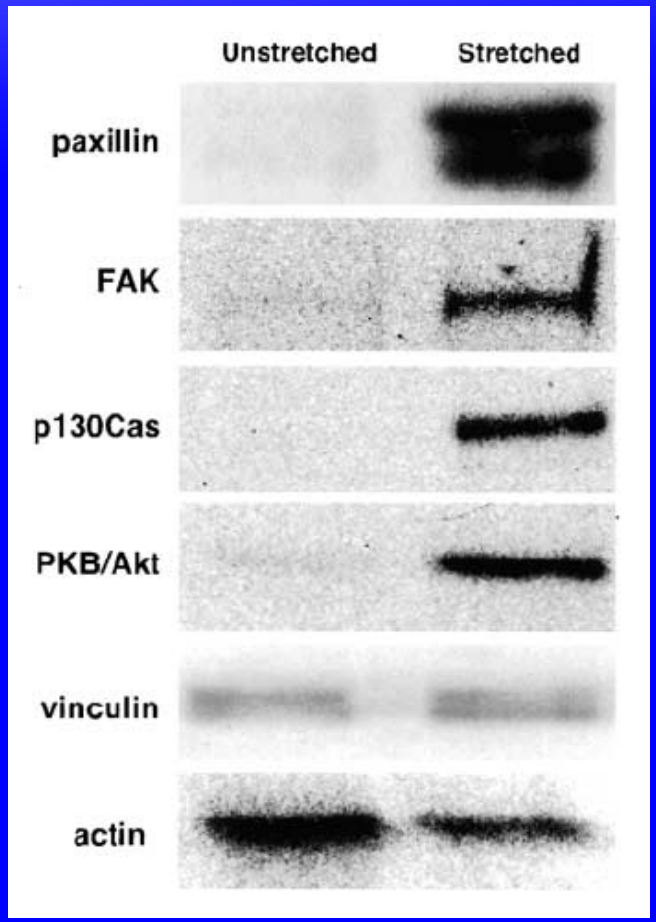


Focal Adhesion Reinforcement

- FAs increase with stretch and disappear with unstretch



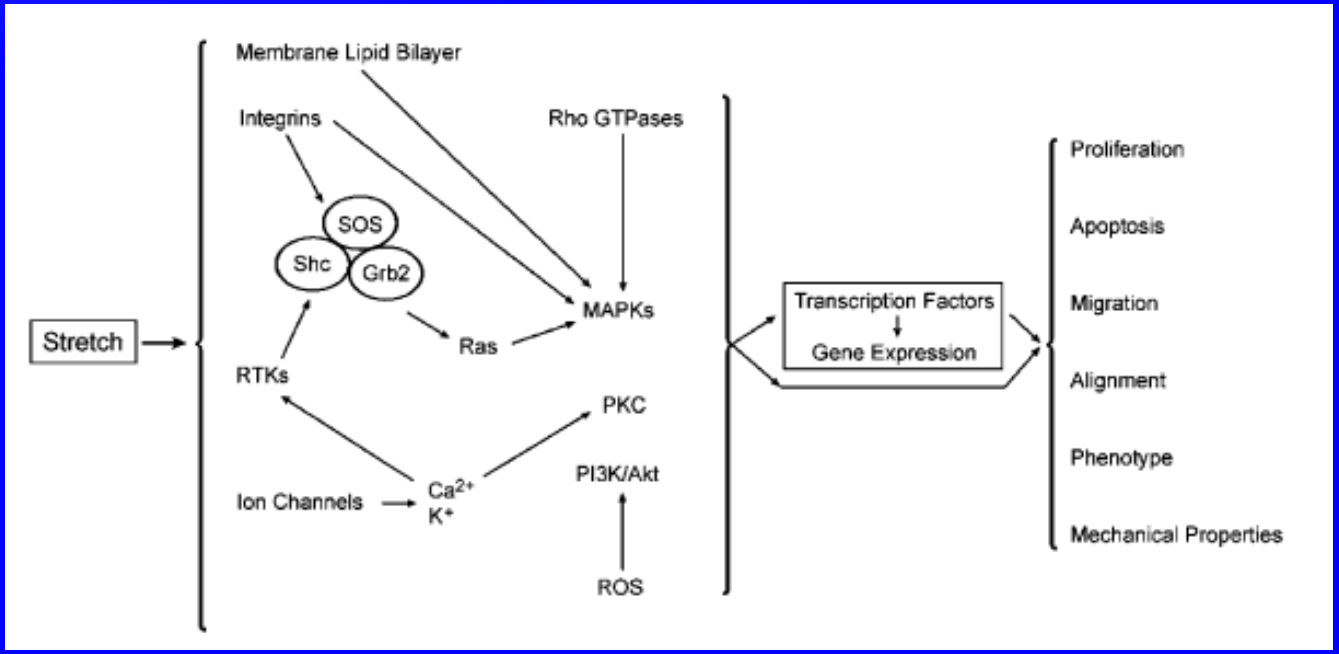
GFP-vinculin



Sawada & Sheetz, J Cell Biol 2002

Stretch Mechanotransduction

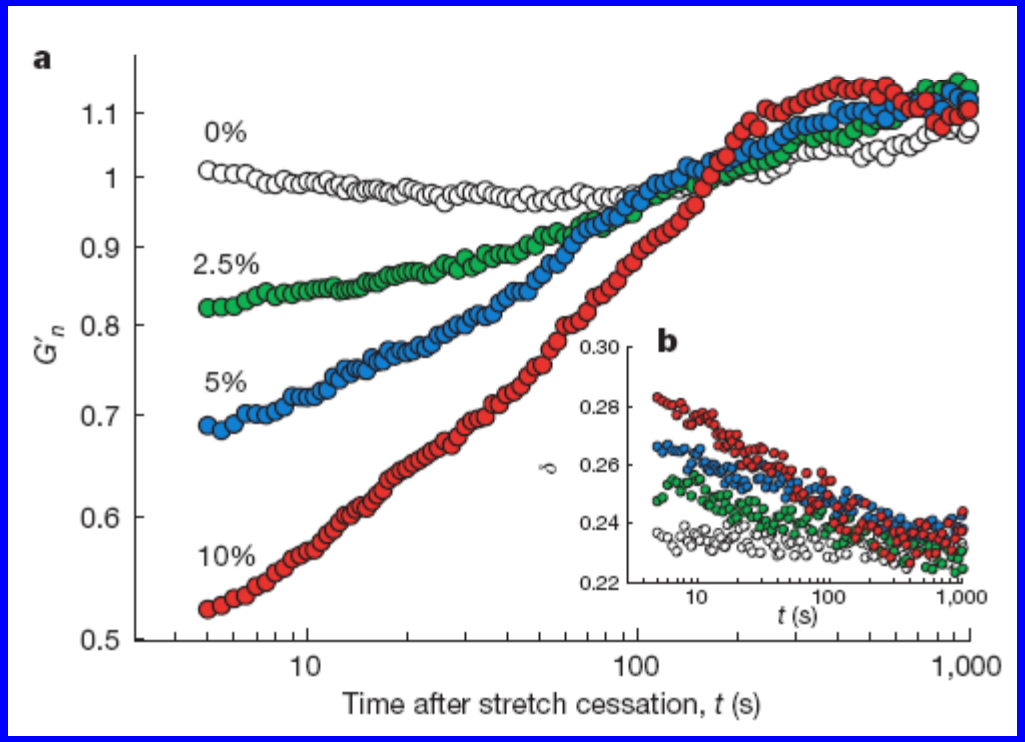
- Multiple mechanotransduction triggers
- Variety of cell function responses



Haga & Chien S (2007) *J Biomechanics*, 40:947

Trepat et al.

- "Physical forces seem to be more than a trigger"
- Stretch causes transient fluidization ($\delta = \pi/2$) and slow solidification ($\delta = 0$).



Elastic (storage) modulus:

G' = Re(G*)

Loss modulus:

G'' = Im(G*)

Phase angle

$\delta = \tan^{-1} G''/G'$

Loss tangent:

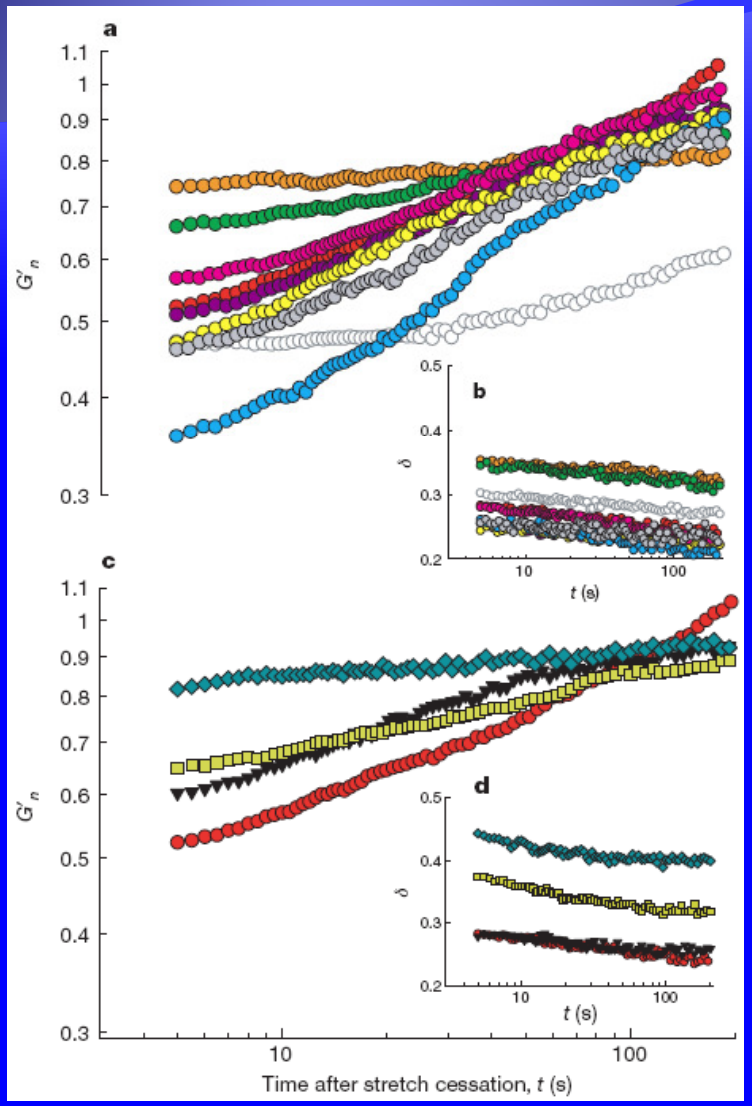
$\eta = G''/G'$

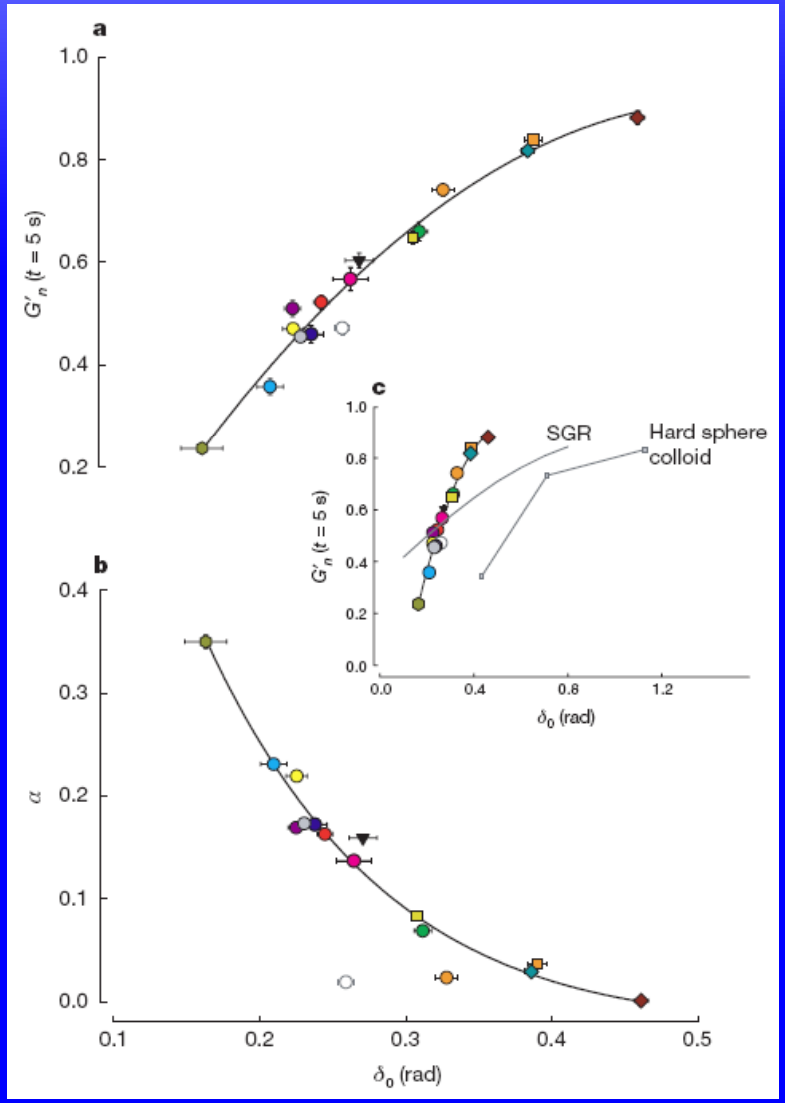
$= \tan \pi/2(x-1)$

(a-b) Groups are latrunculin A (orange), DBcAMP (green), ML7 (10 min incubation, bright pink; 45 min incubation, dark pink), histamine (yellow), EGTA (grey), jasplakinolide (bright blue), ATP depletion (open symbols), and untreated cells (red).

(c-d) MDCK (blue diamonds), HBE (yellow squares), HLF (black triangles) and HASM (red circles).

Universality





Mechanotransduction vs. Mechanics

- Conventional wisdom
  - Force stiffness the CSK network through passive strain-stiffening
  - Force-activated signaling causes structural reinforcement
- Unifying wisdom
  - Changes not limited to molecular transducers
  - Fluidization of cell depends on degree of cell in solid-like state before stretch
  - Master parameter is x (δ)