Mechanical control and stem cell fate decision

Presented in the Embryo Physics Course http://www.embryophysics.org
September 29, 2010

By
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Principle investigator: Cao Tong

- Differentiation of human embryonic stem cell and mouse bone marrow stem cell
- Using tissue engineering approach for regeneration
- Non-therapeutic applications of stem cells

Mechanical control

Stem cell fate decision

Mechanics and embryology

- Mechanics during physiological embryogenesis – in situ, the way of mother nature

- Mechanics during embryonic stem cell (ESC) differentiation – in vitro, with intervention

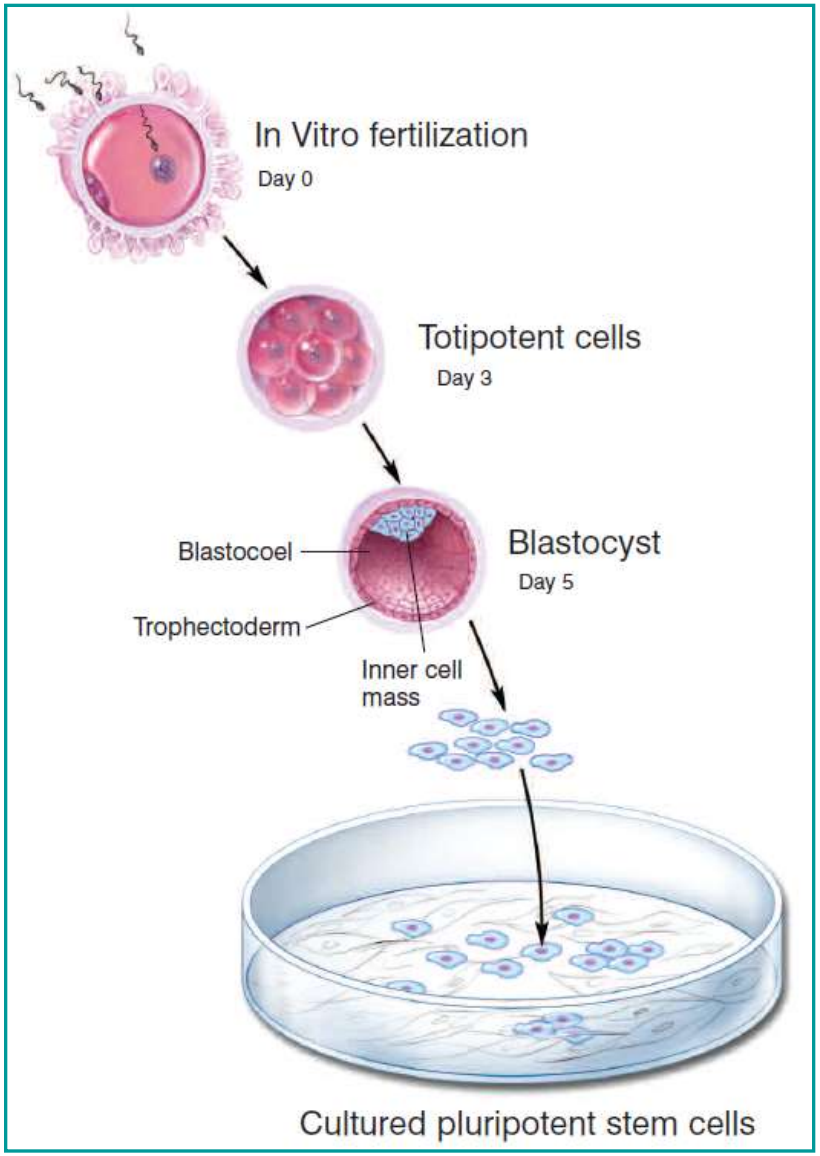
Classification of stem cells

- Adult stem cells: *bone marrow stromal stem cell, hematopoietic stem cell, etc.*

- Embryonic stem cells (ESCs)

More information of stem cell on ***http://stemcells.nih.gov/info***

Introduction to embryonic stem cell



Adopted from *NIH Stem Cell Reports*

Characteristics

- **Self-renewal:** Dividing to make copies of themselves for a prolonged period of time without differentiating
- **Pluripotency:** Giving rise to cells from all three embryonic germ layers

Methods to induce stem cell differentiation

- Soluble factors: chemicals and growth factors

- Modify cell's surrounding physical environment: change matrices stiffness and apply mechanical force

Recent reports on mechanical signalling to induce cell differentiation

Full Speed Ahead Volume 23 | Issue 12 | Page 26 The Scientist

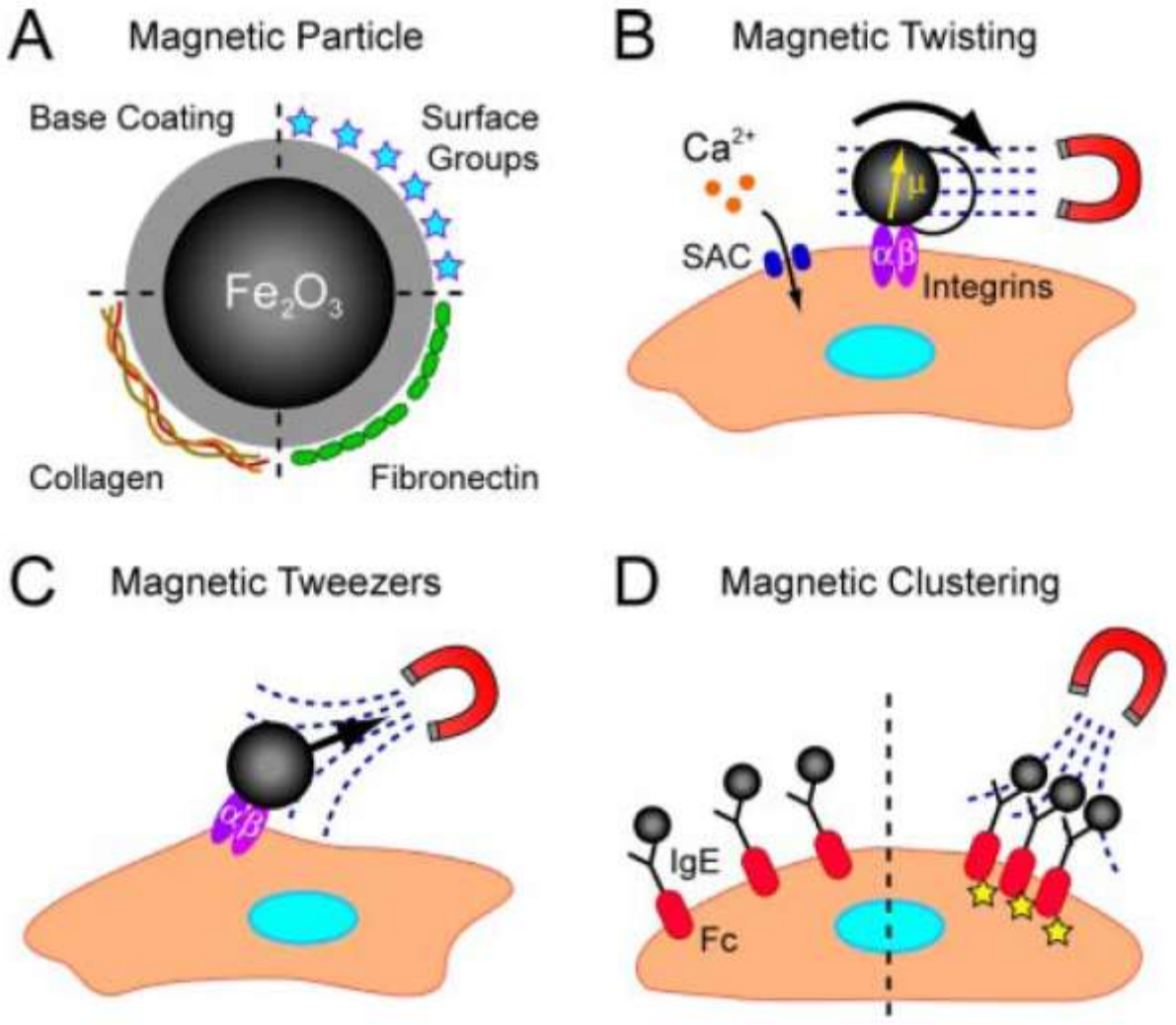
By Jef Akst

Physical forces acting in and around cells are fast

—and making waves in the world of molecular biology.

Circulated earlier by Susan Crawford-Young

Magnetic micro-/nano-particles for mechanical activation of cell receptors



Adopted from *Endocrinology. 2010.151(2): 451-457*

Nat Mater. 2010 Jan;9(1):82-8. Epub 2009 Oct 18.

Material properties of the cell dictate stress-induced spreading and differentiation in embryonic stem cells.

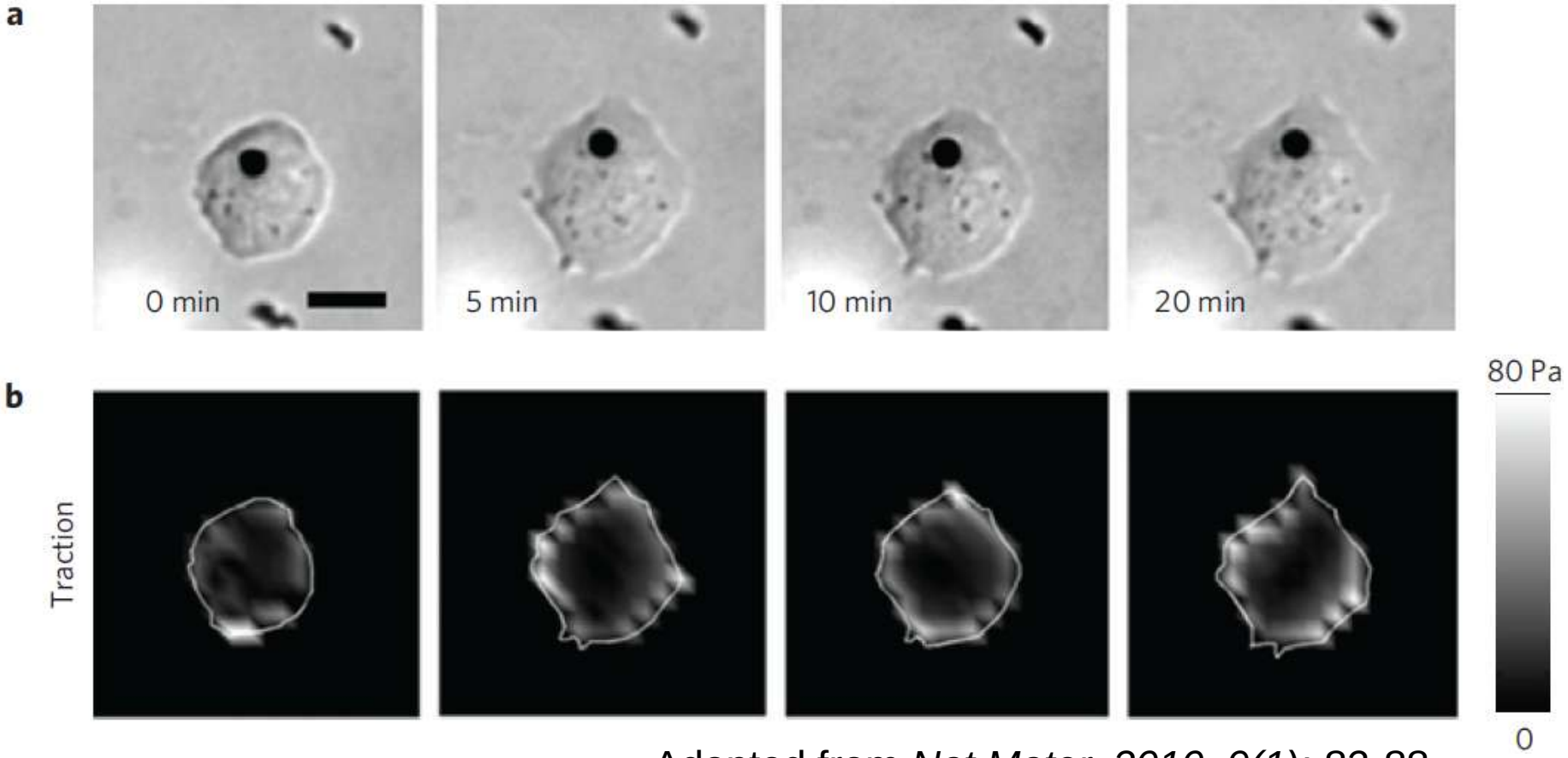
Chowdhury F, Na S, Li D, Poh YC, Tanaka TS, Wang F, Wang N.

Department of Mechanical Science and Engineering, University of Illinois at Urbana-Champaign, Illinois 61801, USA.

Methods

- Grow ESCs on substrates with 0.6 kPa stiffness
- Bind a 4 um magnetic bead to integrins on the apical surface of the cell
- Apply a small, oscillatory stress (17.5 Pa at 0.3 Hz) continuously

Stress induces spreading of ESC but not differentiated cells

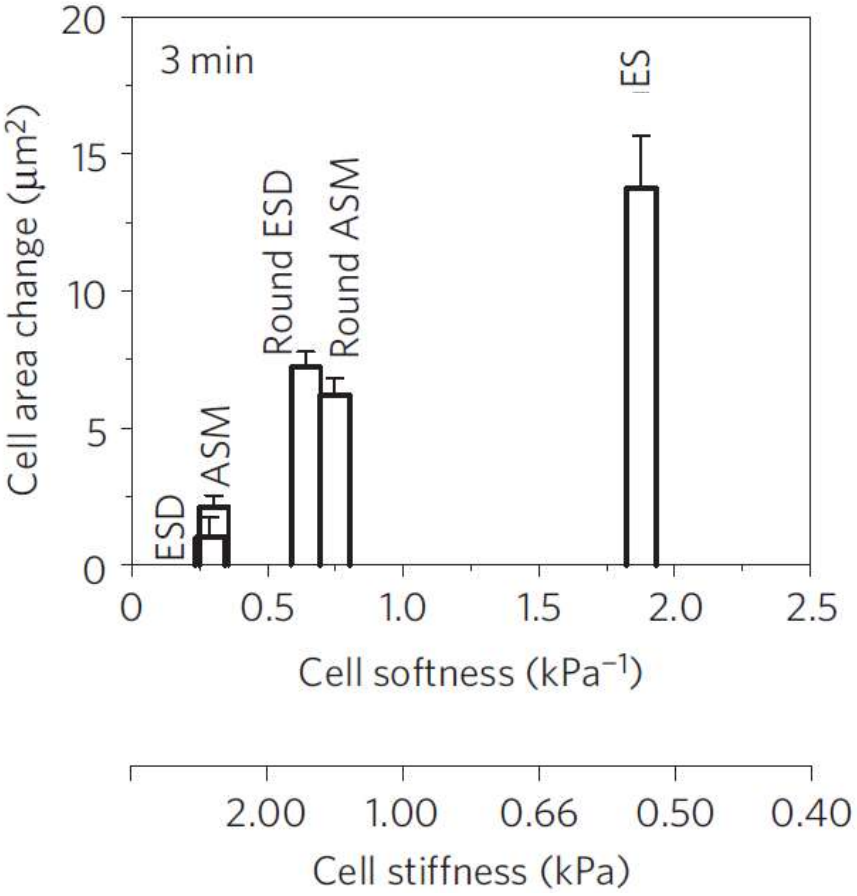


Adopted from *Nat Mater. 2010. 9(1): 82-88*

Cell softness dictates response to stress

- Unfertilized egg: ~10 Pa
- **Embryonic stem cell (ESC)**: ~500 Pa
- Brain neural cell: ~100-500 Pa
- **Typical differentiated tissue**: ~1-5 kPa
- Skeletal-muscle cell: ~12 kPa

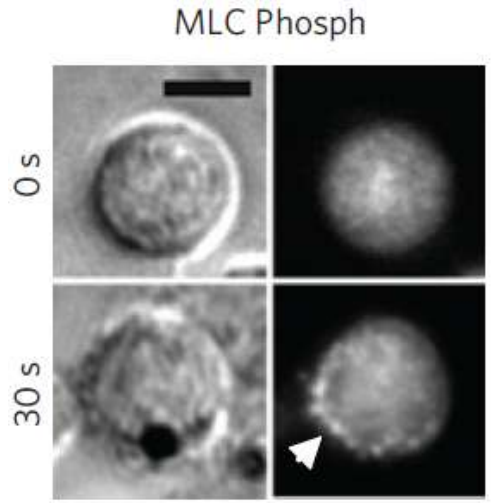
Cell softness dictates response to stress

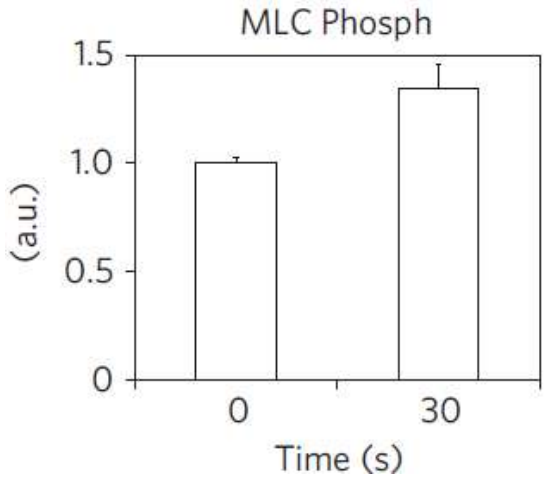


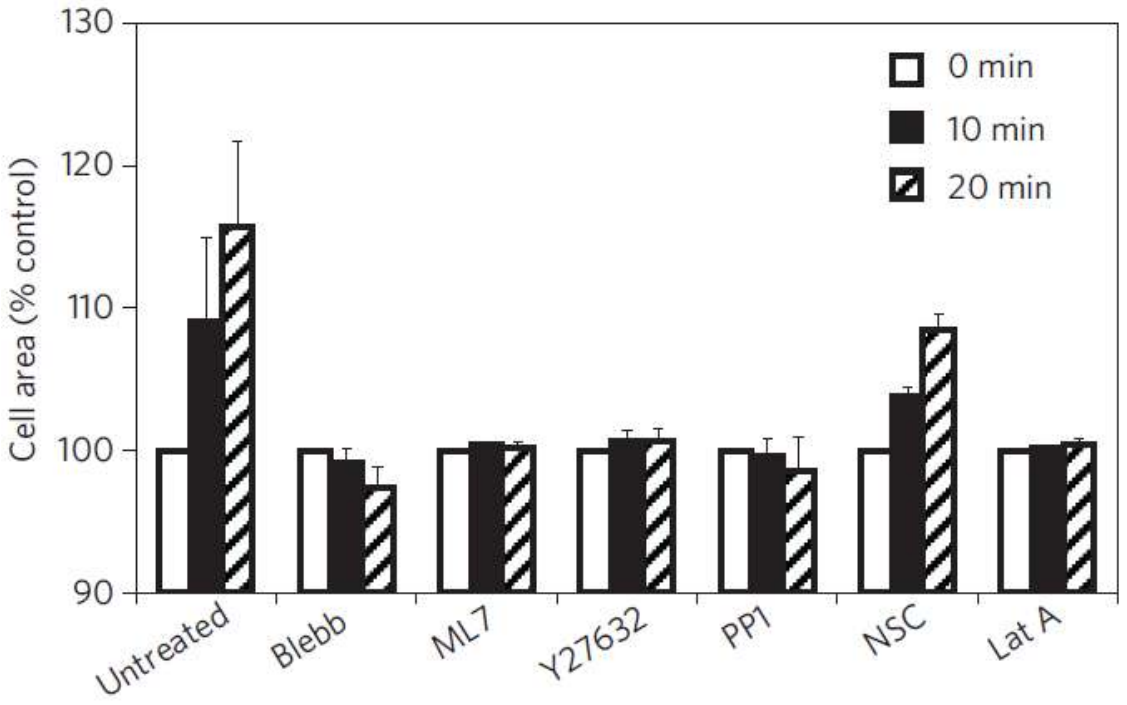
ES: embryonic stem cell
ESD: differentiated ESC
ASM: airway smooth muscle

Adopted from *Nat Mater. 2010. 9(1): 82-88*

Interplay of stress and molecular pathways during cell spreading



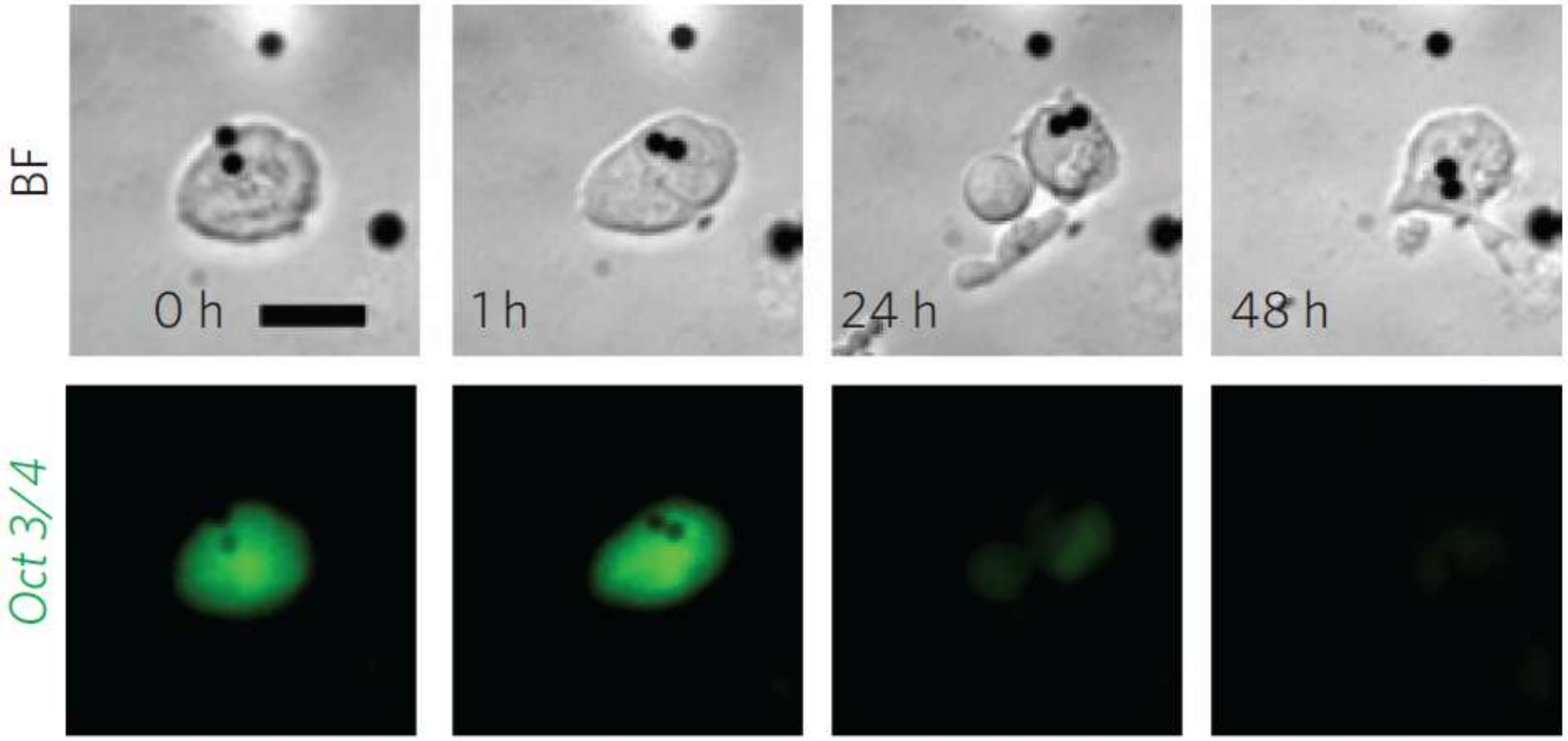




Blebbistatin: myosin II ATPase inhibitor
ML-7: myosin light chain kinase inhibitor
Y27632: Rho-associated kinase (ROCK) inhibitor
PP1: Src activity inhibitor
NSC23766: Rac inhibitor
Latrunculin A: F-action disruptor

Adopted from *Nat Mater. 2010. 9(1): 82-88*

Stress causes ESC to differentiate despite the presence of soluble factors that maintain pluripotency



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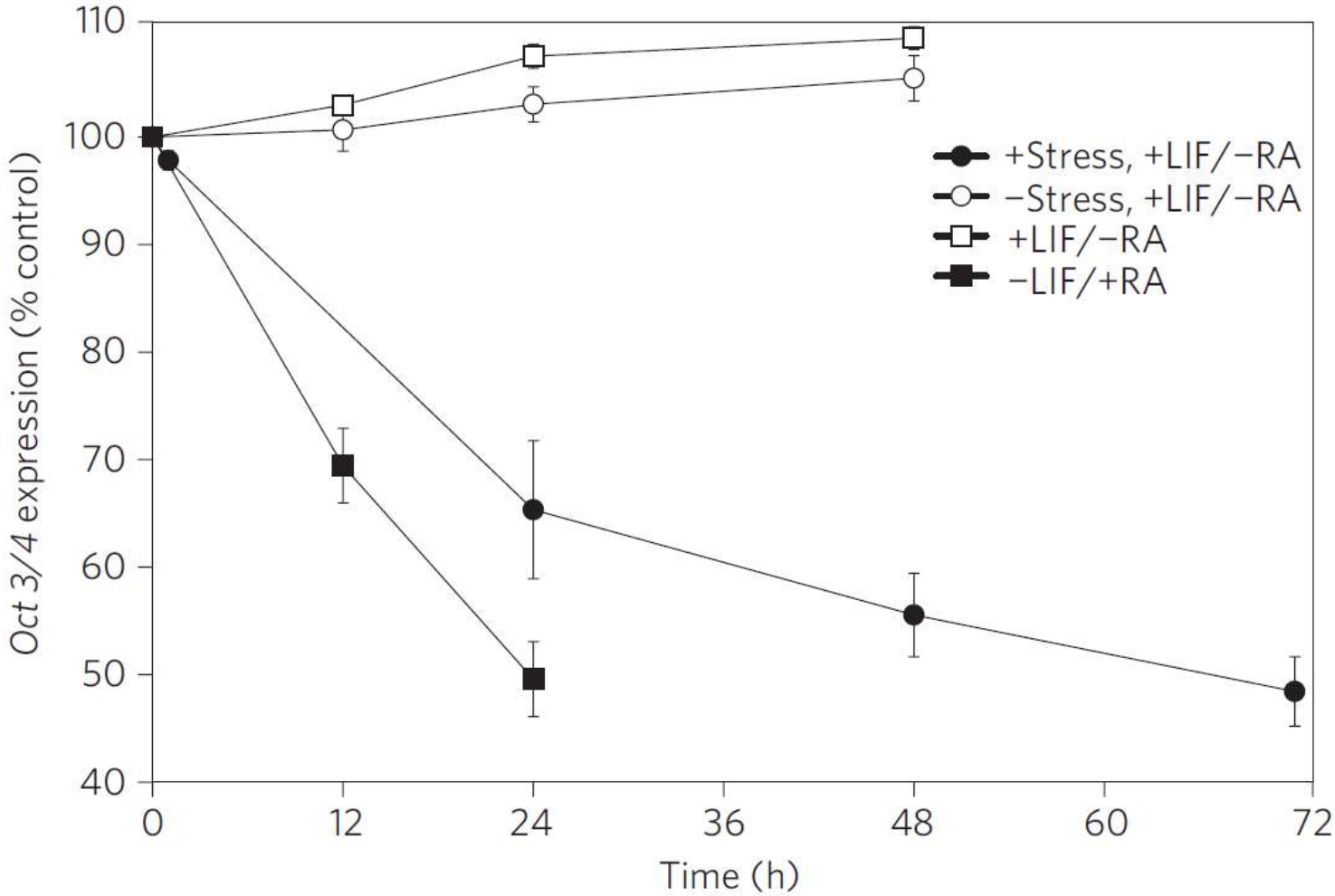

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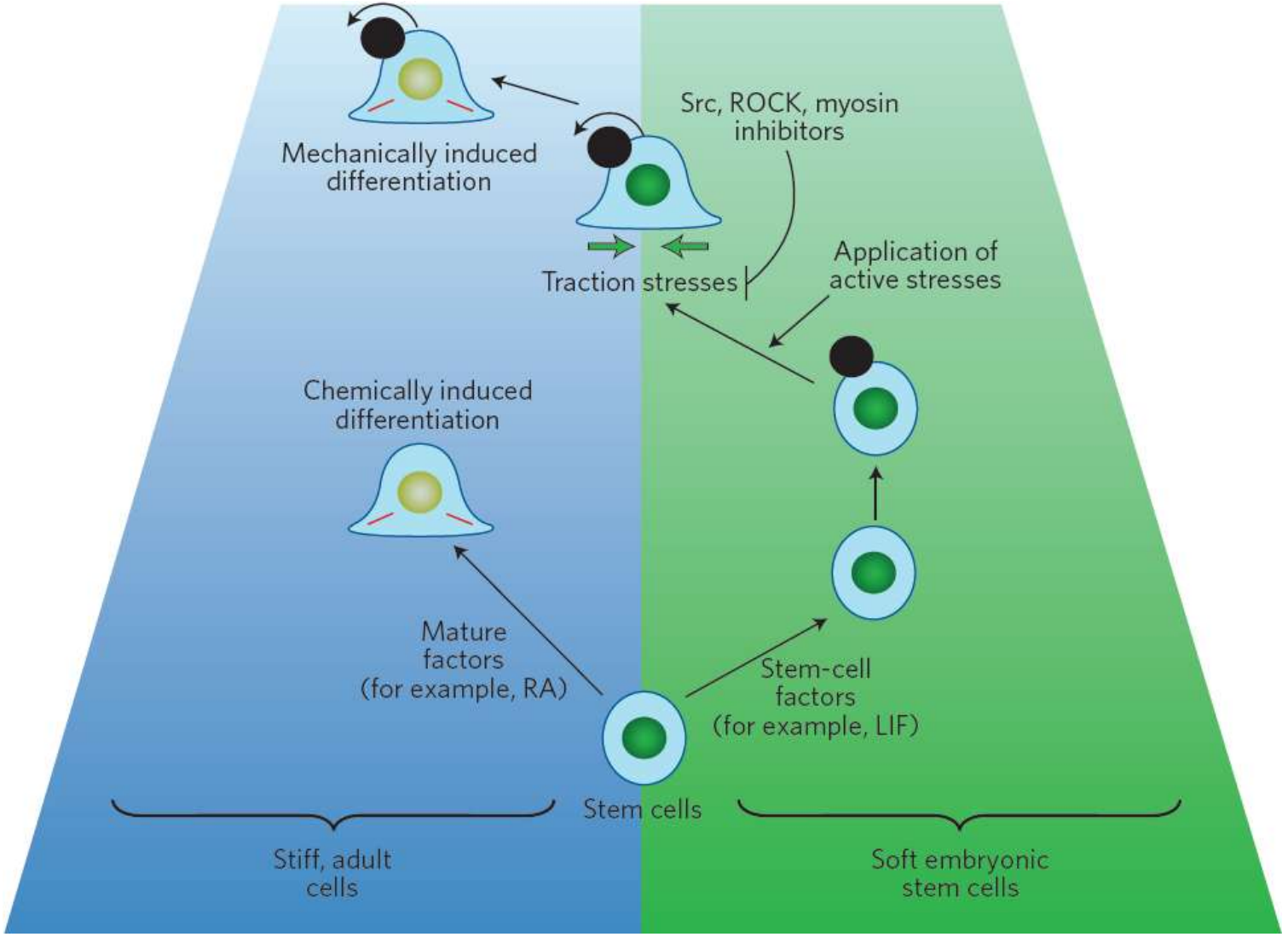
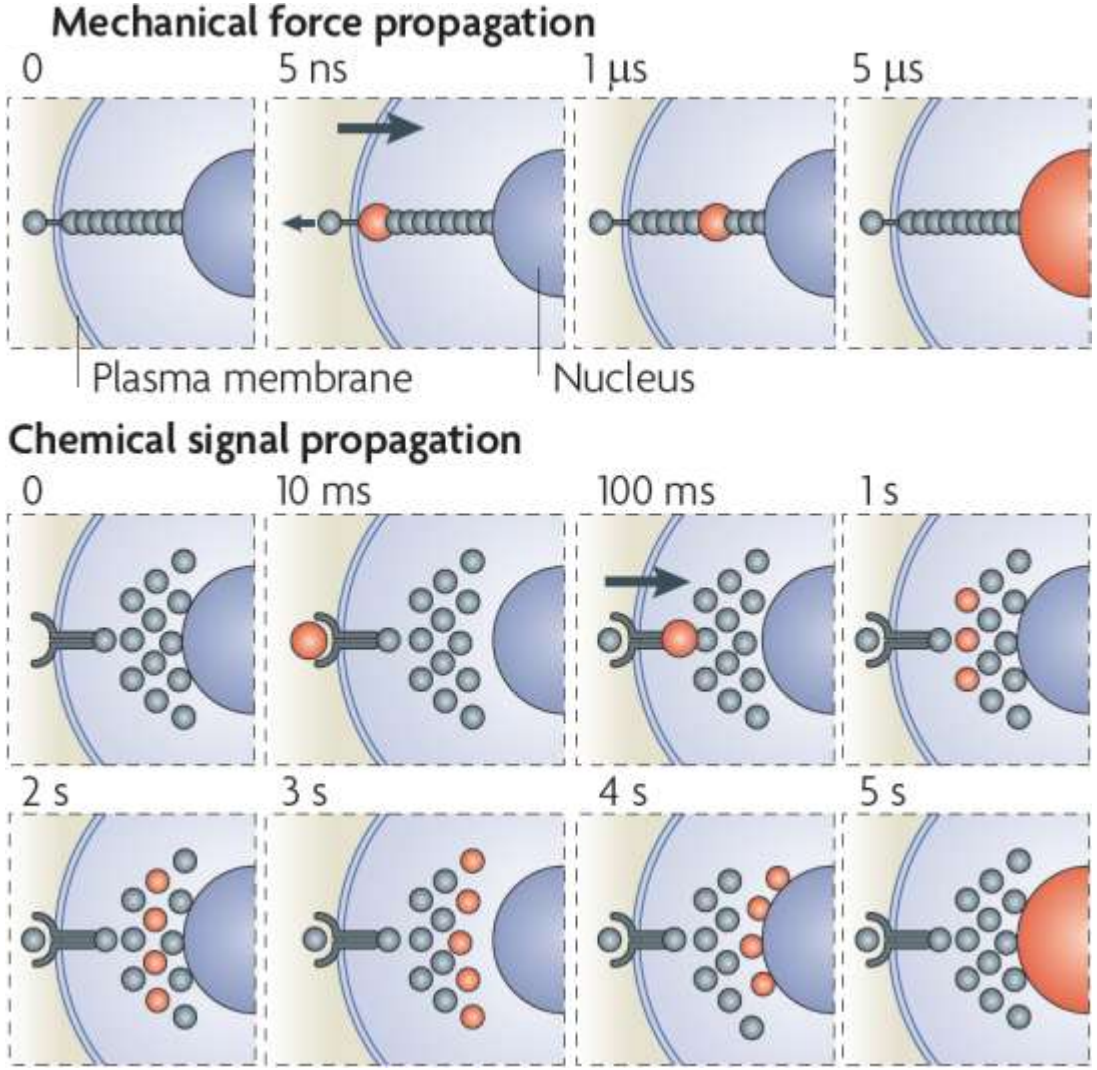
Conclusion



Adopted from *Nat Mater. 2010. 9(1): 4-6.*

Comparison of mechanical and chemical signal propagation in cells



Adopted from *Nat Rev Mol Cell Biol. 2009. 10(1): 75-82.*

Current status of research on mechanotransduction

- Study of mechanotransduction focuses mainly on the cell surface

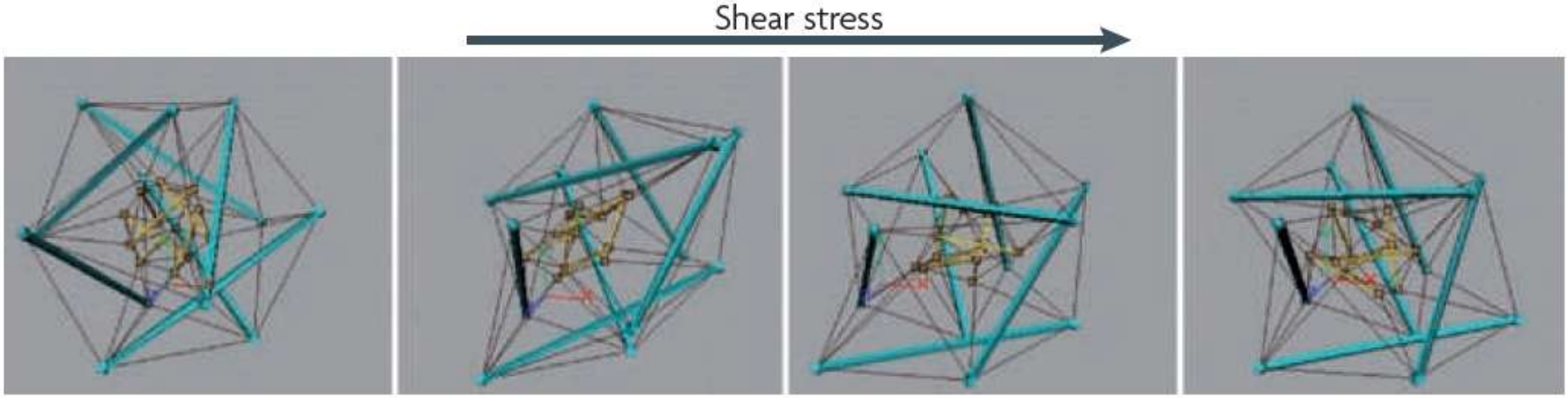
- Only surface-adhesion receptors and focal adhesion proteins are considered important to mechanical signalling in cells

Traditional homogeneous model of cell structure

- Cell as an elastic membrane that surrounds a viscous cytoplasm that is filled with cytoskeletal filaments that continuously depolymerize and repolymerize

- Mechanical stresses will dissipate quickly (within 10 um) after passing through the plasma membrane

Prestressed inhomogeneous (tensegrity) model of cell structure: the hard-wired cell



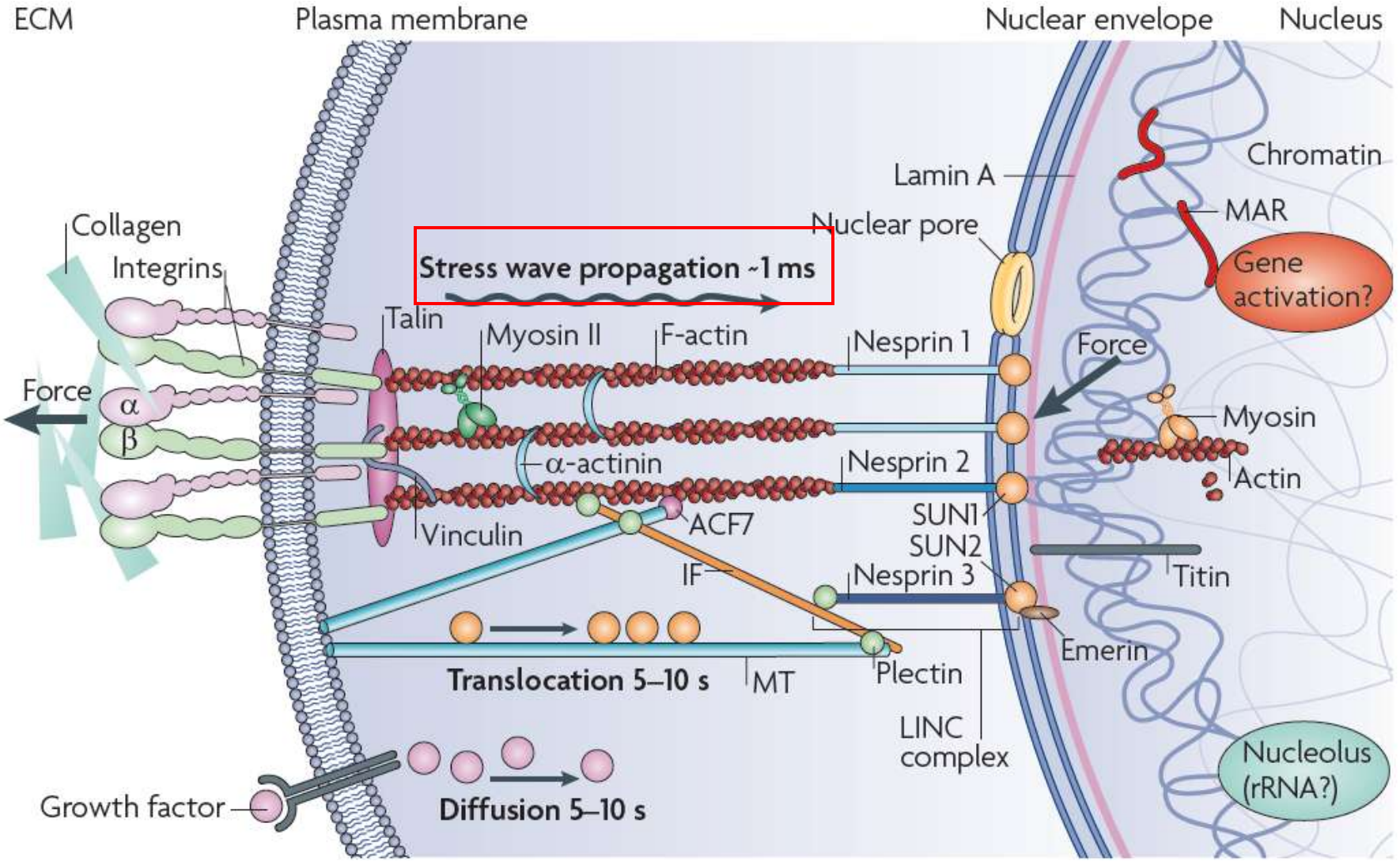
Adopted from *Nat Rev Mol Cell Biol. 2009. 10(1): 75-82.*

Prestressed inhomogeneous (tensegrity) model of cell structure

- Surface-adhesion receptors are physically coupled to cytoskeletal filament networks that link to nuclear scaffolds, nucleoli, chromatin and DNA inside the nucleus

- Mechanical forces at cell surface promote structural rearrangements deep in the cytoplasm and nucleus (~100 um away)

Molecular connectivity from extra cellular matrix (ECM) to nucleus



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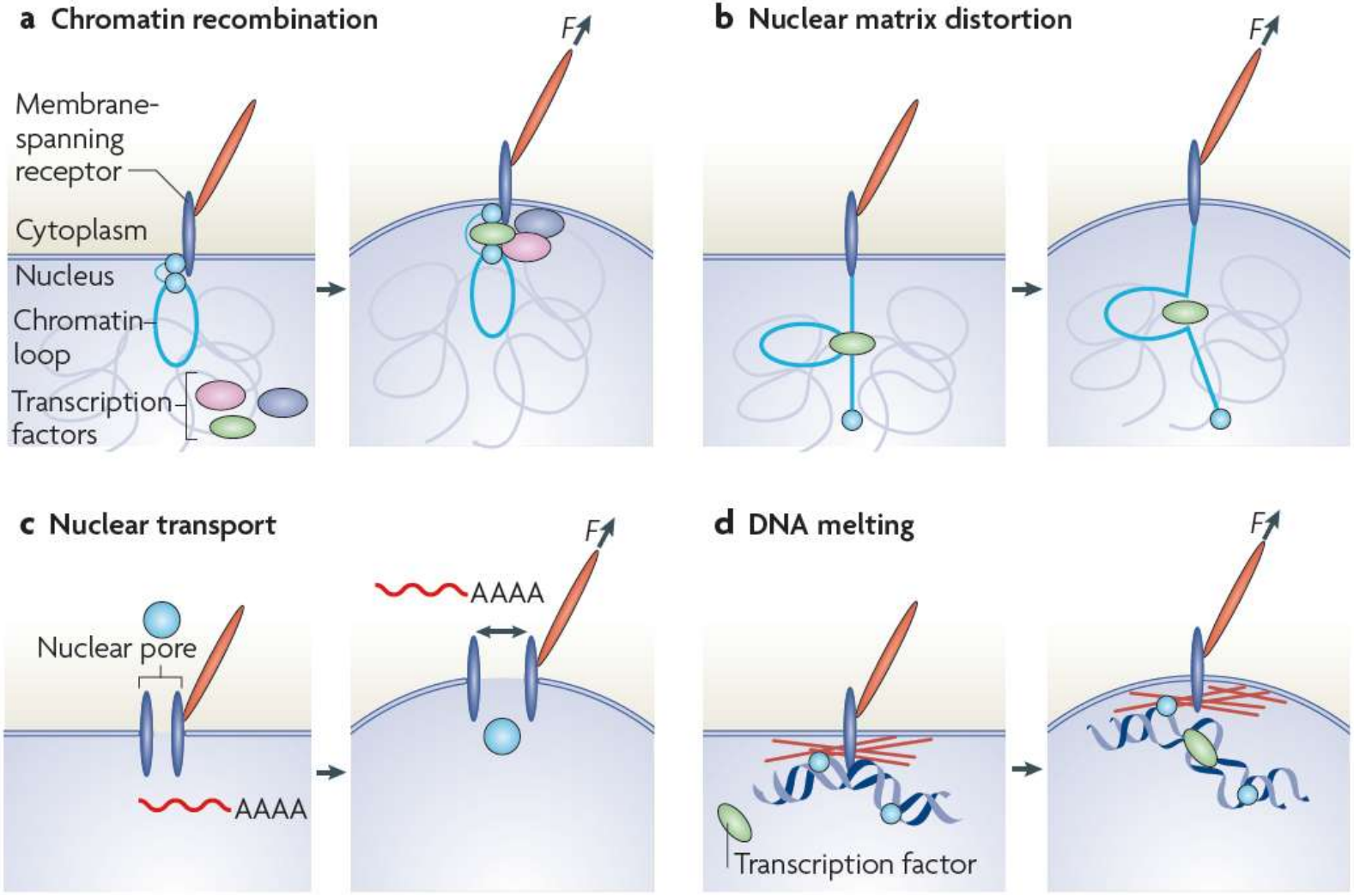
Hypothesized nuclear mechano-chemical conversion mechanisms



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Future directions?