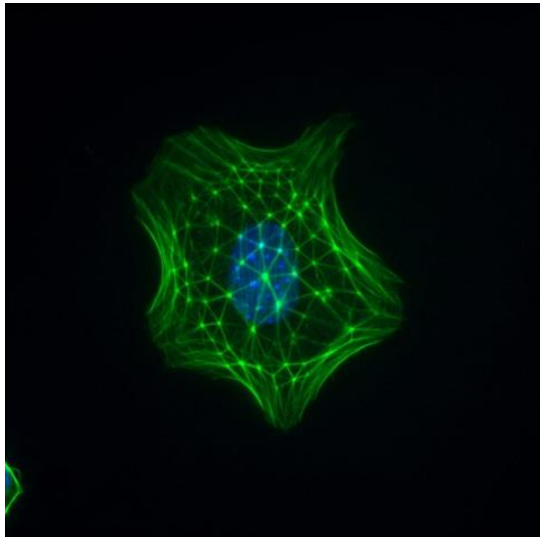
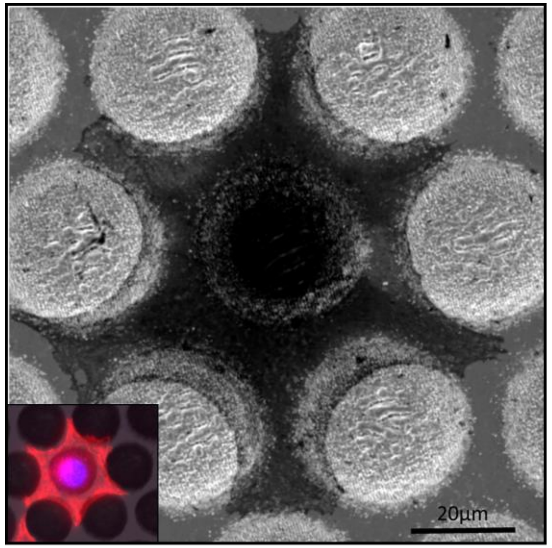
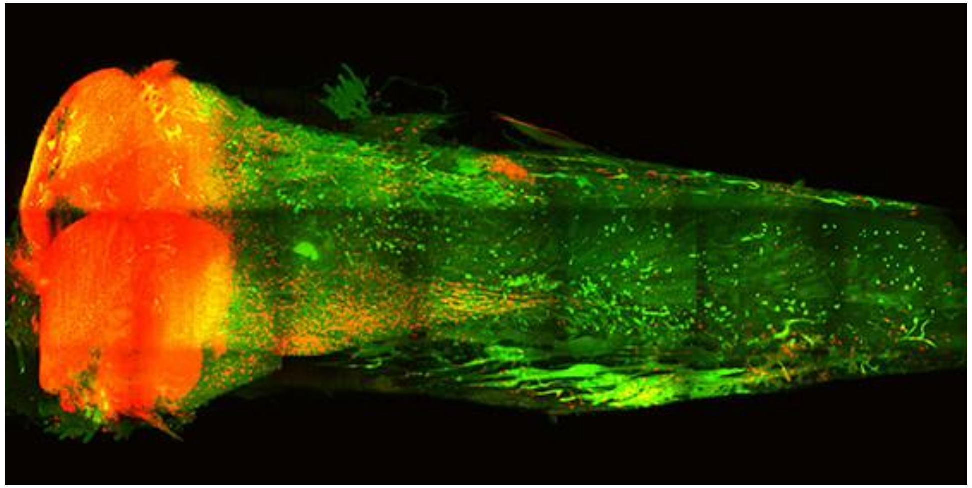
Alain GUIGNANDON
Stéphane Avril
SAINBIOSE - INSERM U1059

MECHANOTRANSDUCTION

Highlight on cell mechanics / Stem cells differentiation



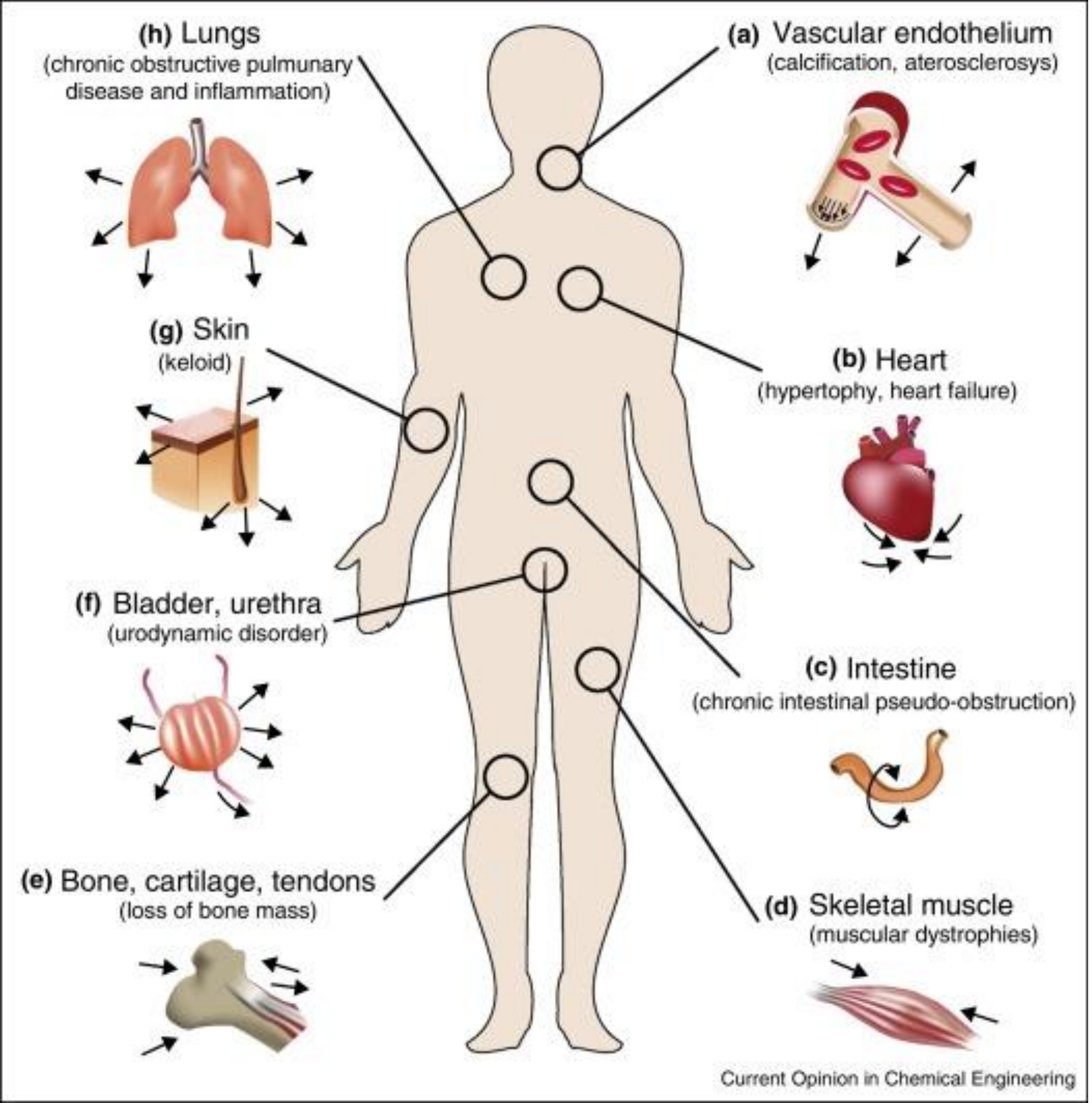

20µm



Mechanotransduction: use the force(s)

Abstract

Mechanotransduction - how cells sense physical forces and translate them into biochemical and biological responses - is a vibrant and rapidly-progressing field, and is important for a broad range of biological phenomena. This forum explores the role of mechanotransduction in a variety of cellular activities and highlights intriguing questions that deserve further attention.



Pathologies of defective mechanotransduction

Tissue type	Tissue or organ	E (kPa)	$t_{1/2}$ (s)	Refs
Interstitial and connective	Fat	0.02	100	47,147
	Tendon	310,000	1	147,148
	Skin	4.5–8	–	149
Vascular	Carotid artery	90	–	147
Nervous	Spinal cord	27–89	–	147
	Brain	0.2–1.0	100	47,147,150
Visceral	Lung	5	–	147
	Kidney	2.5	–	147
	Liver	0.64	100	47,147
	Lymph node	0.12	–	147
	Mammary gland	0.16	–	147
Musculoskeletal	Cardiac muscle	20–150	–	147
	Skeletal muscle	10–100	–	147,150
	Pre-calcified bone	30	–	150
	Bone marrow	0.3–24.7	10	47,151
	Cartilage	20	–	150
	Articular cartilage	950	–	147
	Bone, cancellous	350,000	–	152
	Bone, compact	11,500,000	–	152
	Tooth dentin	>10,000,000	–	153
	Tooth enamel	~100,000,000	–	153

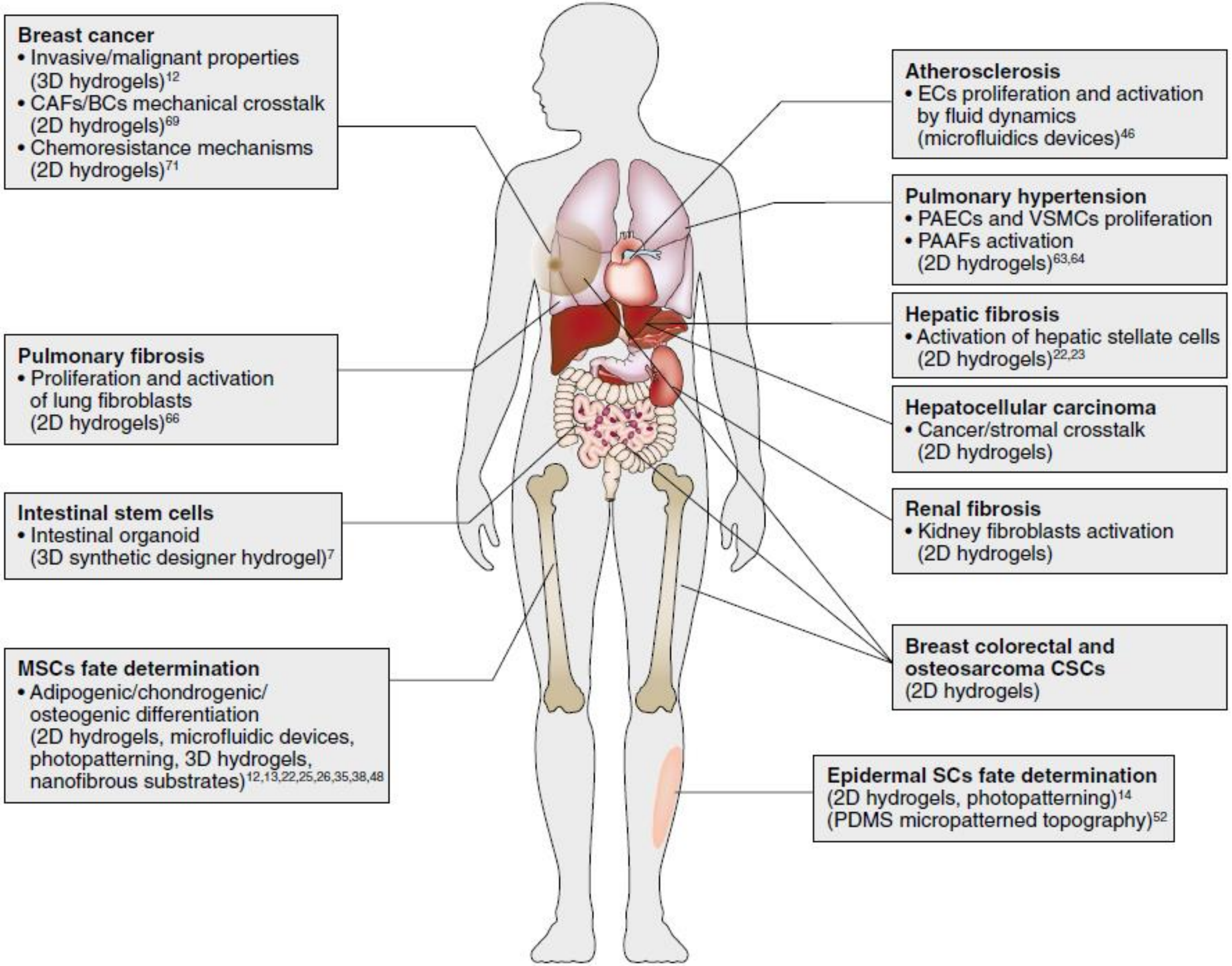
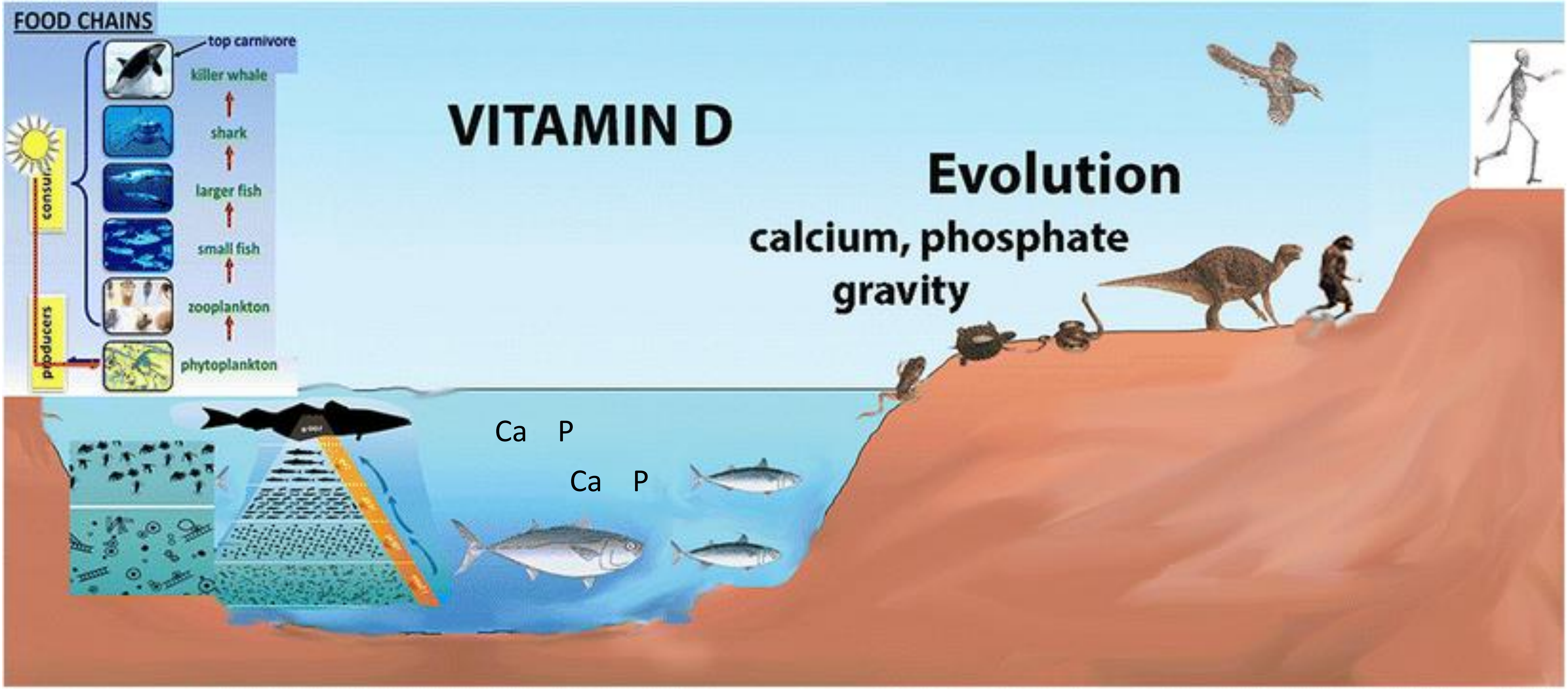


Fig. 3 | Biomaterials mimicking altered microenvironments in human diseases. Each arrow indicates a specific human disease or stem cell behaviour, the biomaterial-based system used to investigate it and the biological read-outs.

Bone: an organ designed to adapt to gravity

Ca/P: Hydroxyapatite



GRAVITY: mass tells space how to bend, and space tells mass how to move

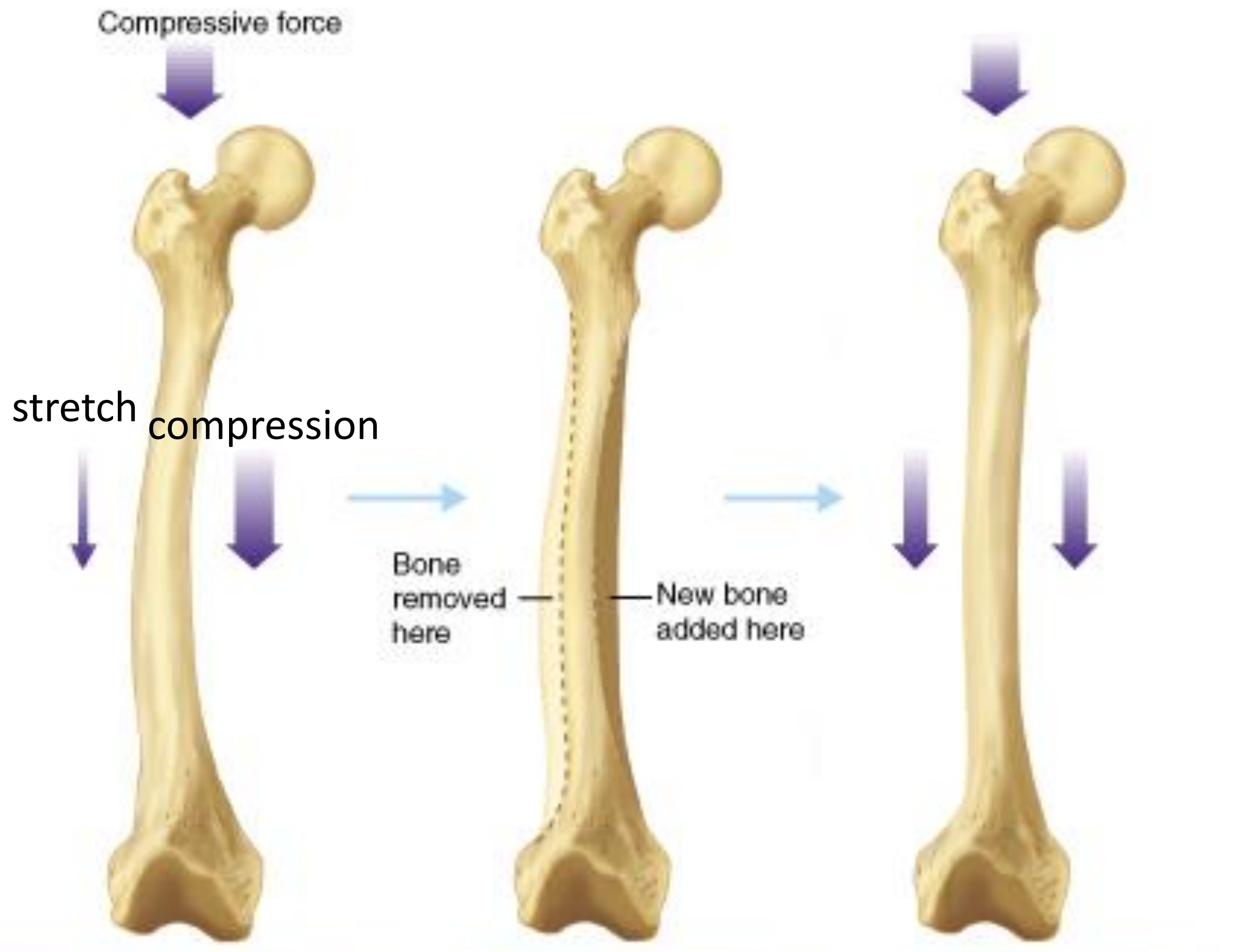
WOLF'S LAW

- **Wolff's Law** [Julius Wolff, German anatomist, 1836-1902]
- "For a uniform or constant fact or principle, more specifically, that a bone, either normal or abnormal, will develop the structure most suited to resist those forces acting on it."

"Bone is laid down in areas of high stress and reabsorbed in areas of low stress."

Frost's law : bone is a mechanostat

Bone is a smart material able to repair itself



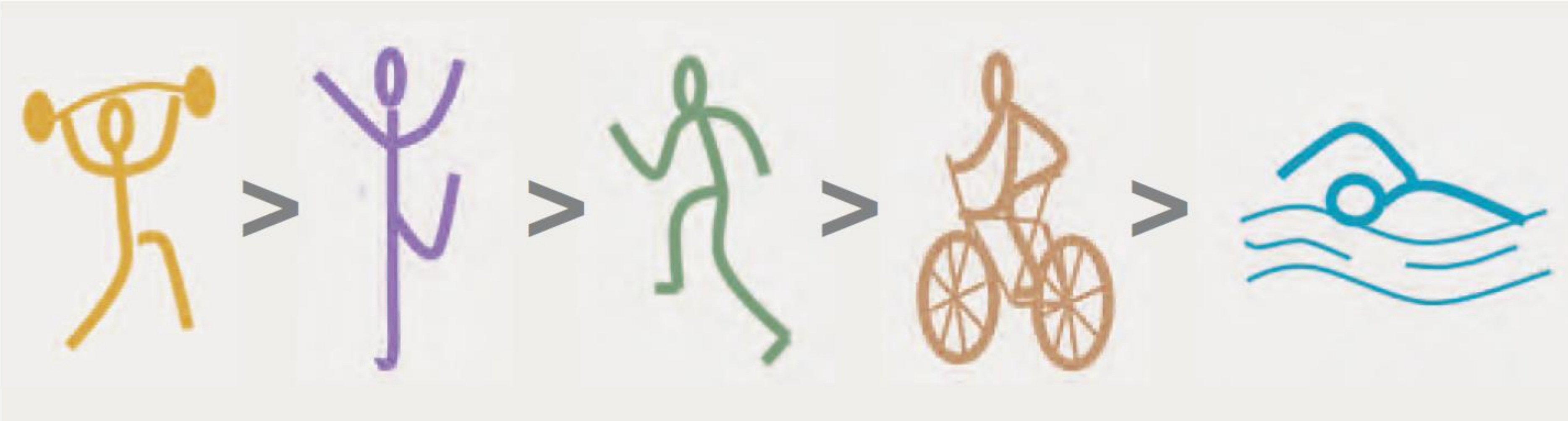
(a) The application of force to a slightly bent bone produces a greater compressive force on the inside curvature. Compressive force produces weak electrical currents which stimulate osteoblasts.

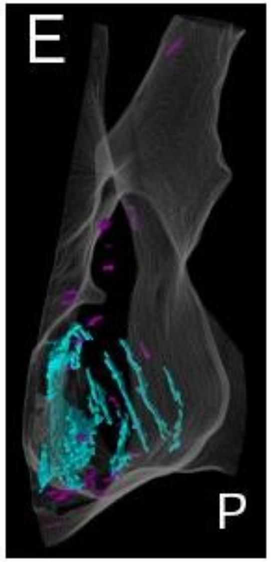
(b) Over time, bone is deposited on the inside curvature and removed from the outside curvature.

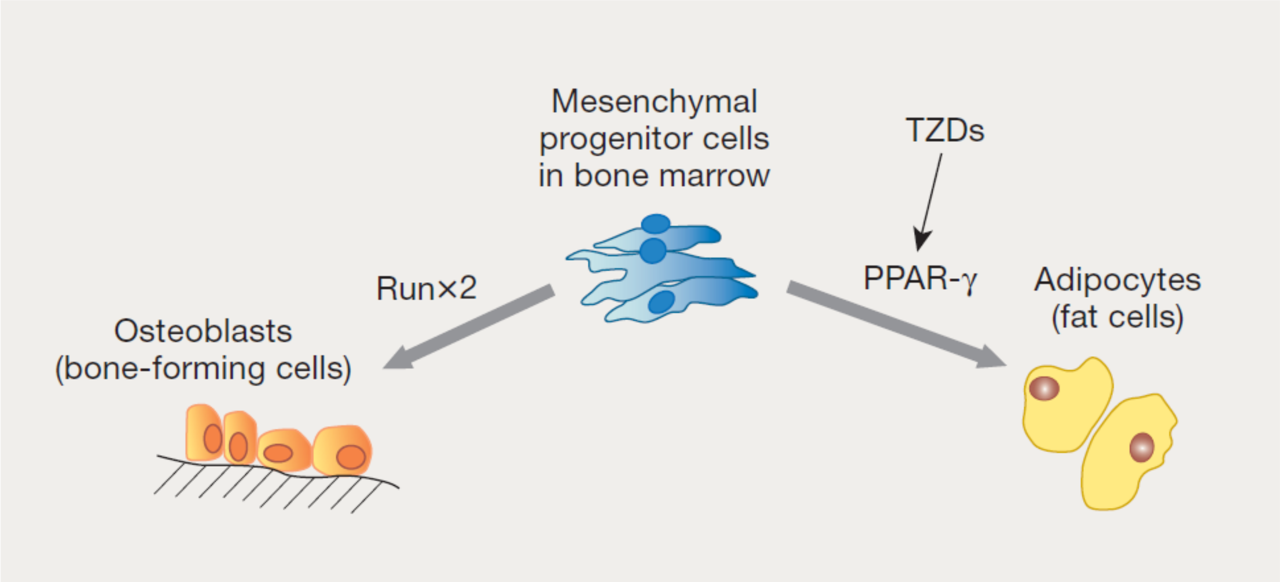
(c) The final result is a bone matched to the compressive force to which it is exposed.

Bone is the only tissue in the body that contains a cell type, the osteoclast, which has the function to actively destroy (resorb) the host tissue

Exercice is able to delay bone loss or to increase bone gain / Sedentarity is accelerating bone loss







Loss of Mechanical Stress

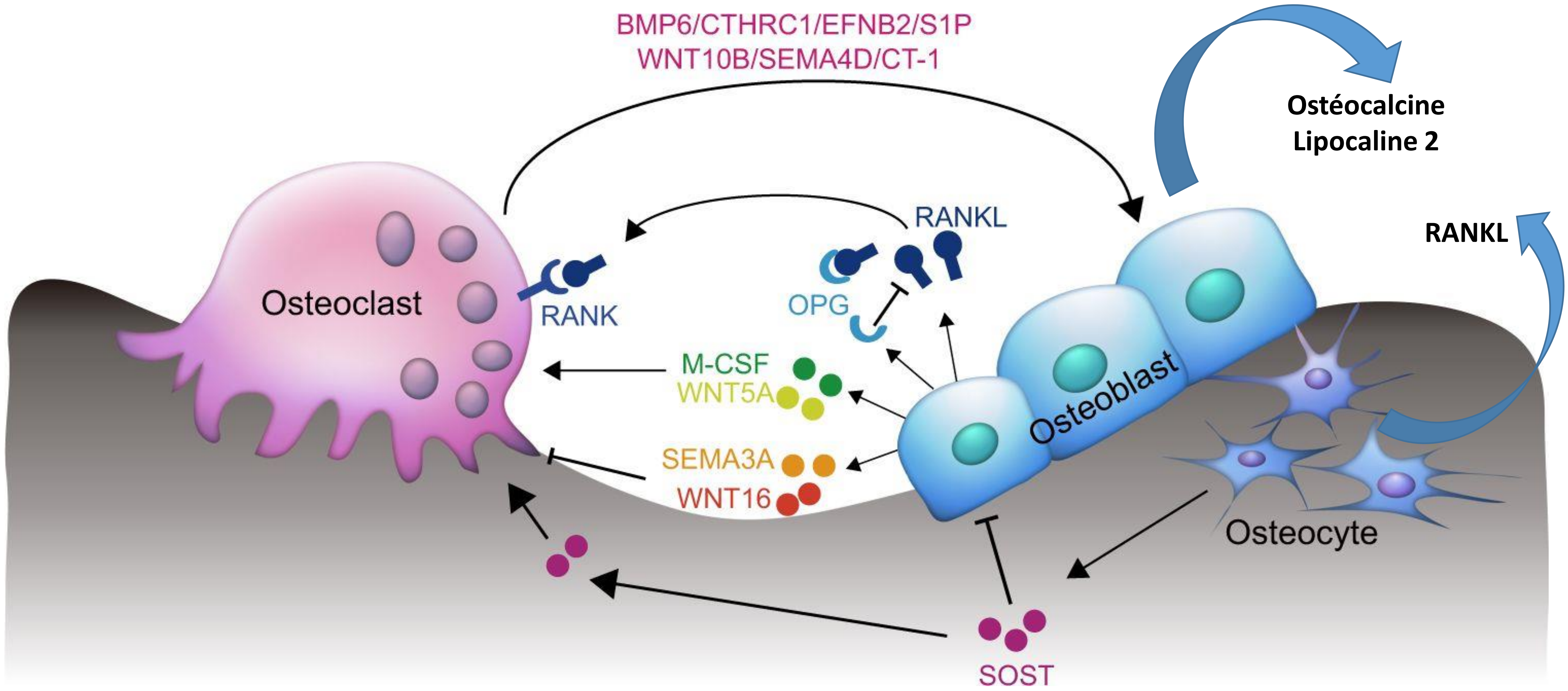
In fact, a loss of mechanical stress will lead to demineralization.

The two significant ways to lose mechanical stress are 1) loss of mobility or 2) zero gravity environments.

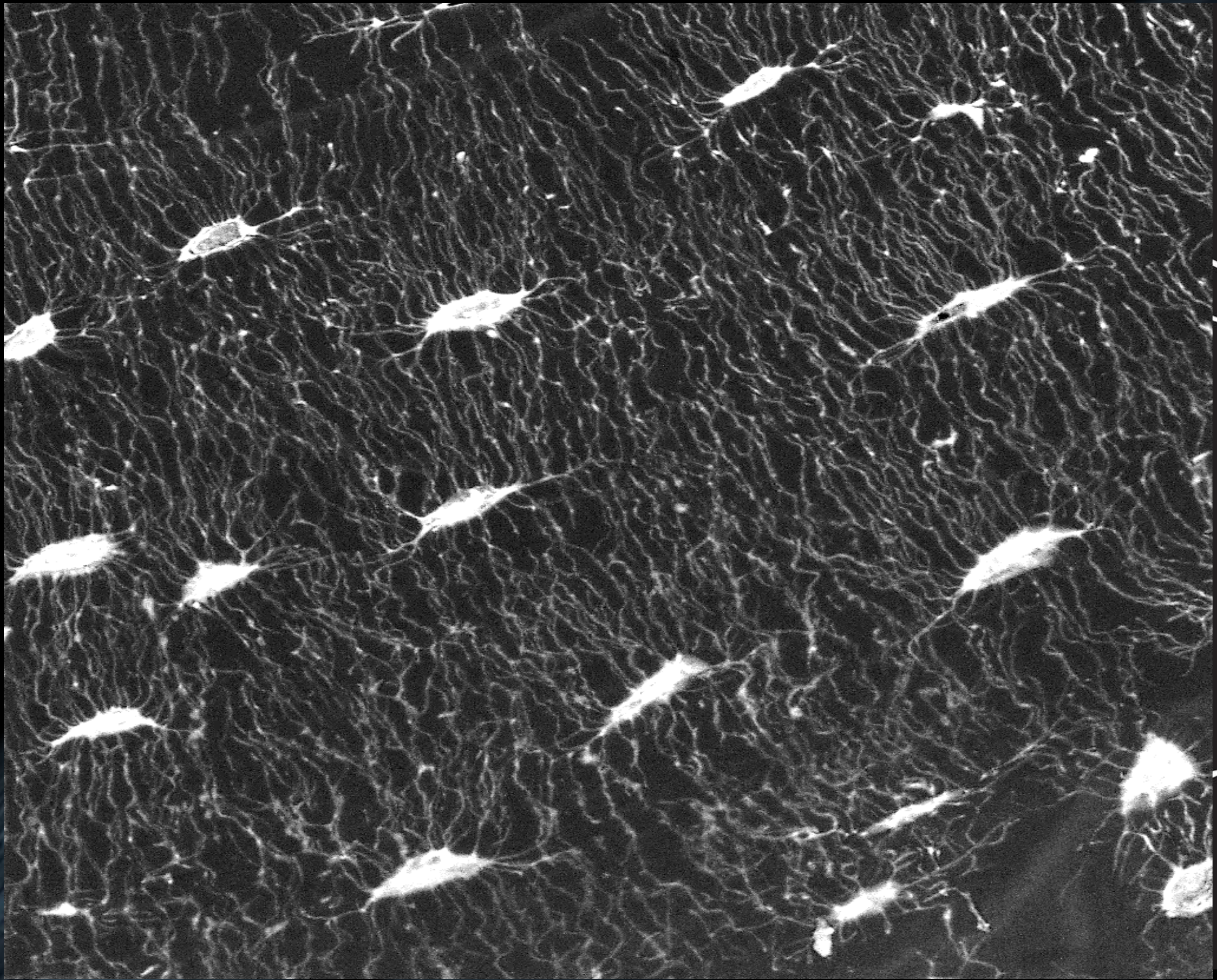
Studies done by scientists have shown that astronauts can lose about 1% bone mass/week.
They come back to earth with dramatically increased risk of breaking a bone.

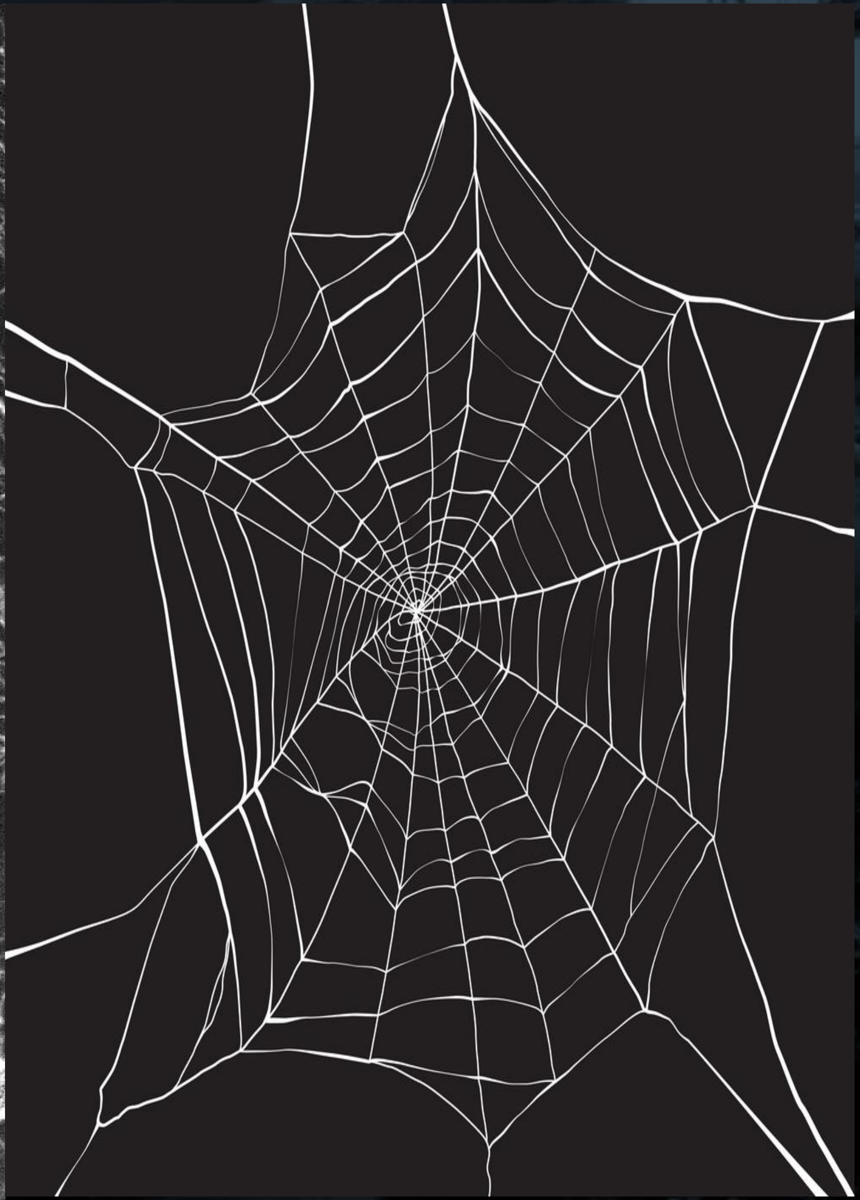
This problem can also happen to sick people who are bedridden or those in casts for very long time.

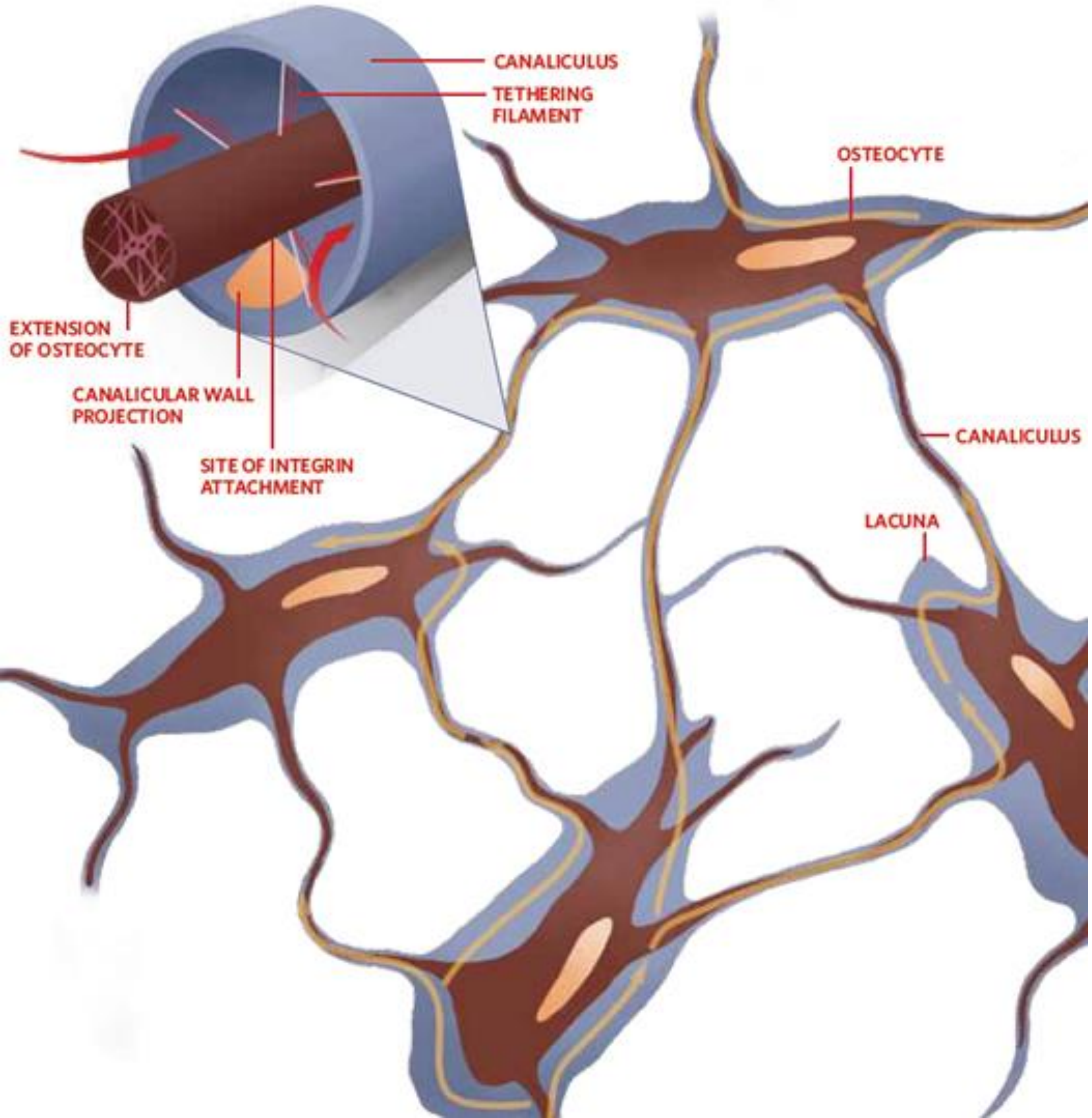
Molecular coupling of FORMATION and RESORPTION



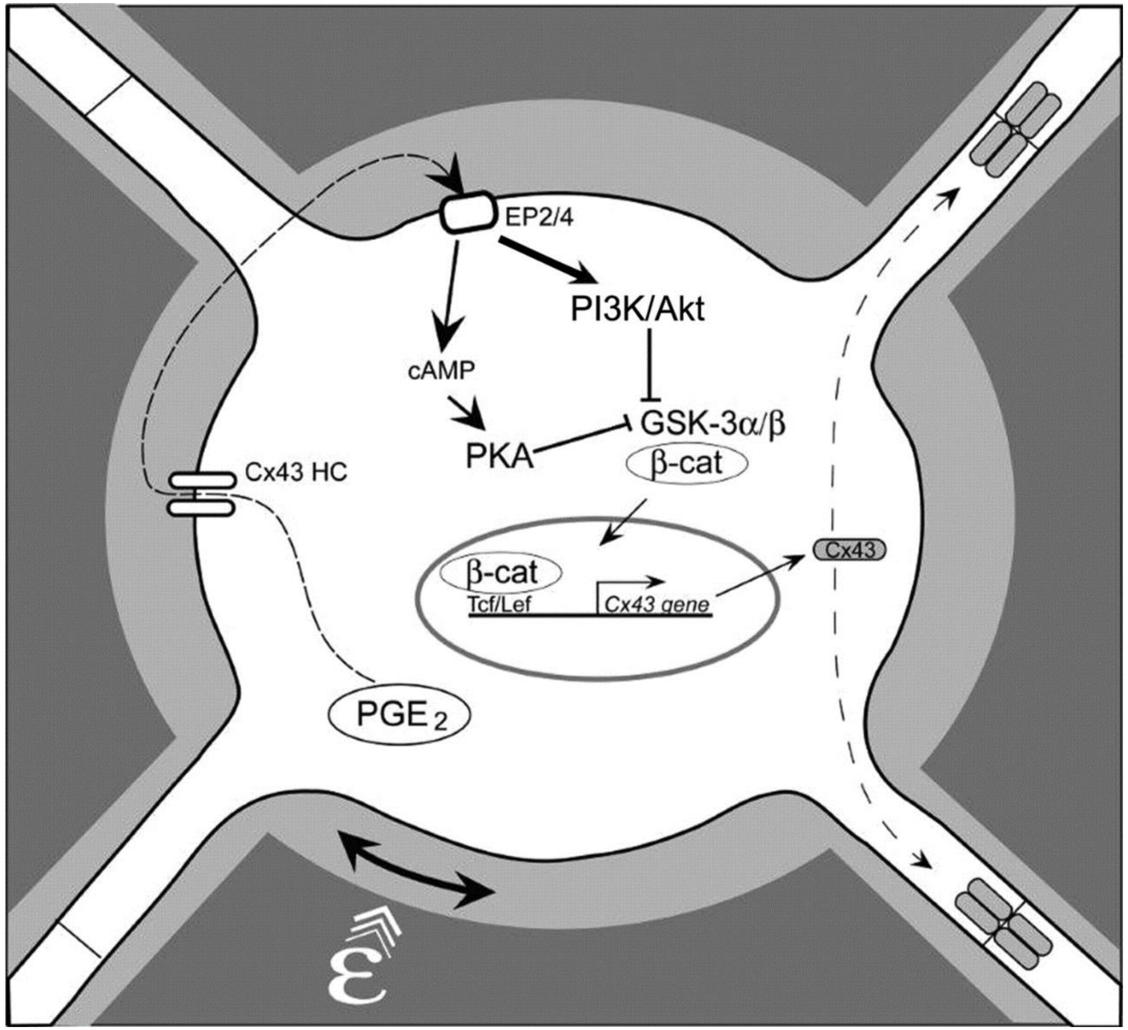
The osteocyte, the seismograph







mechanotransduction



Strain, flow, pressure, piezoelectricity, chemistry, oxygen tension

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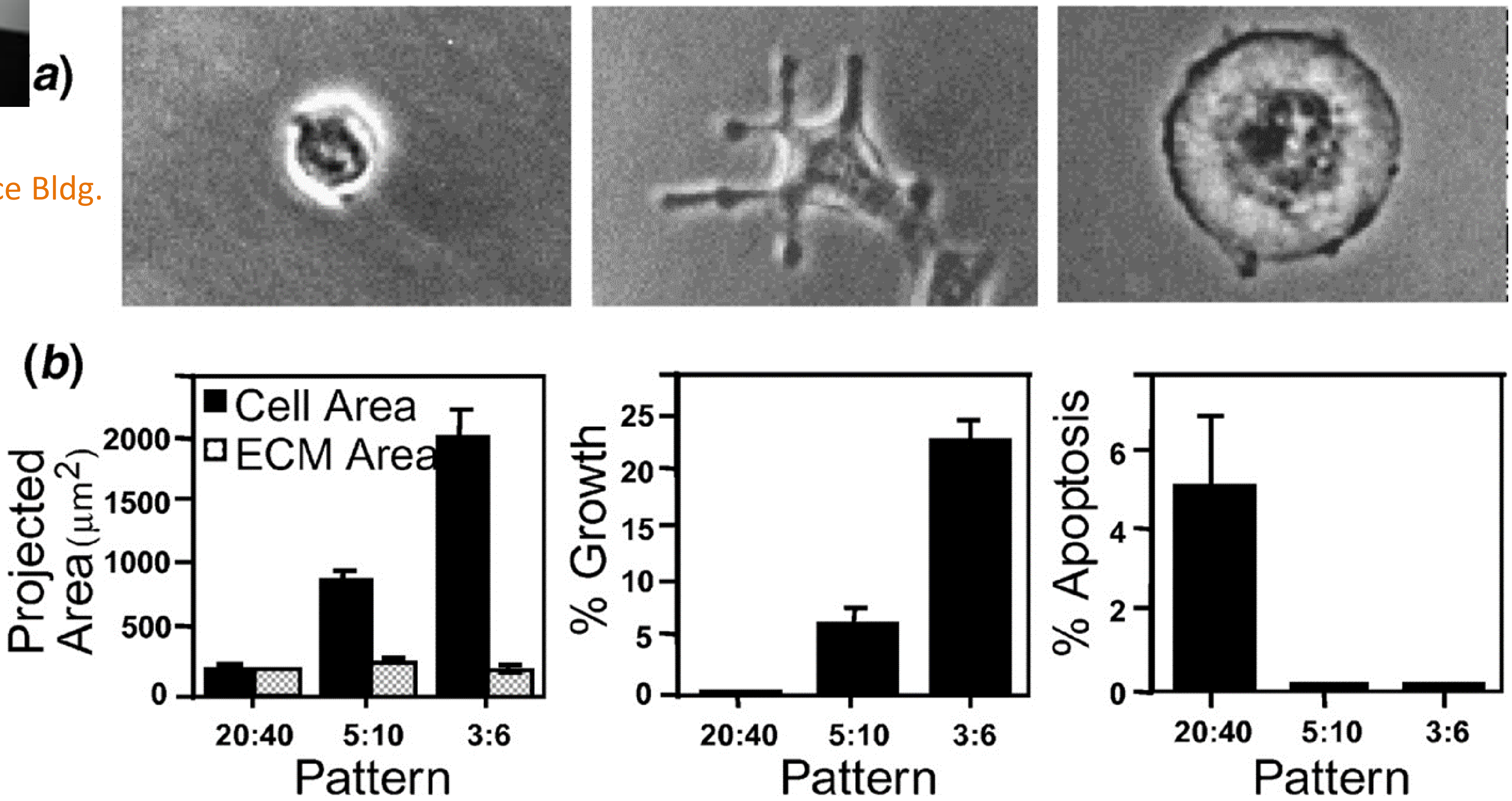
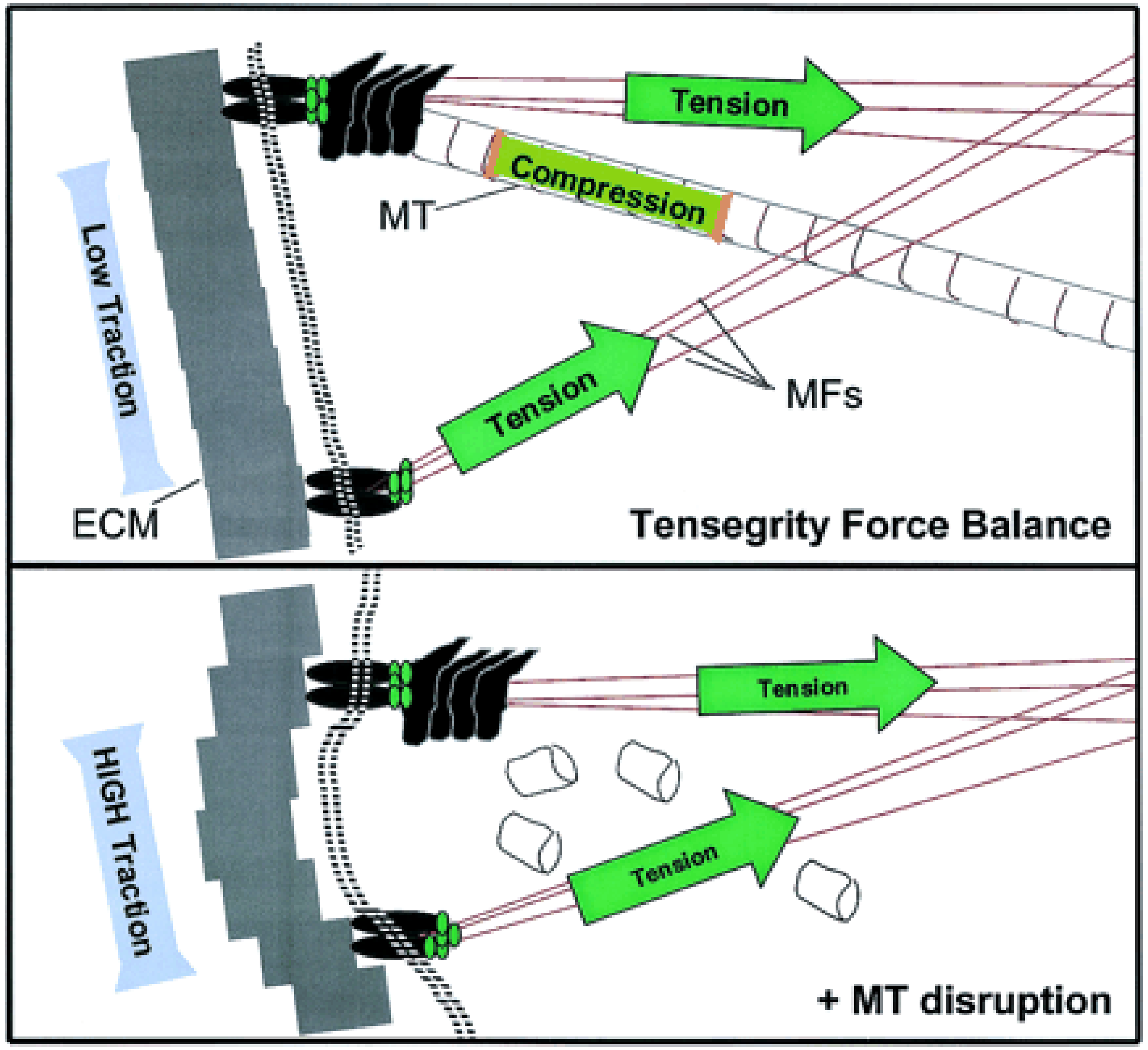
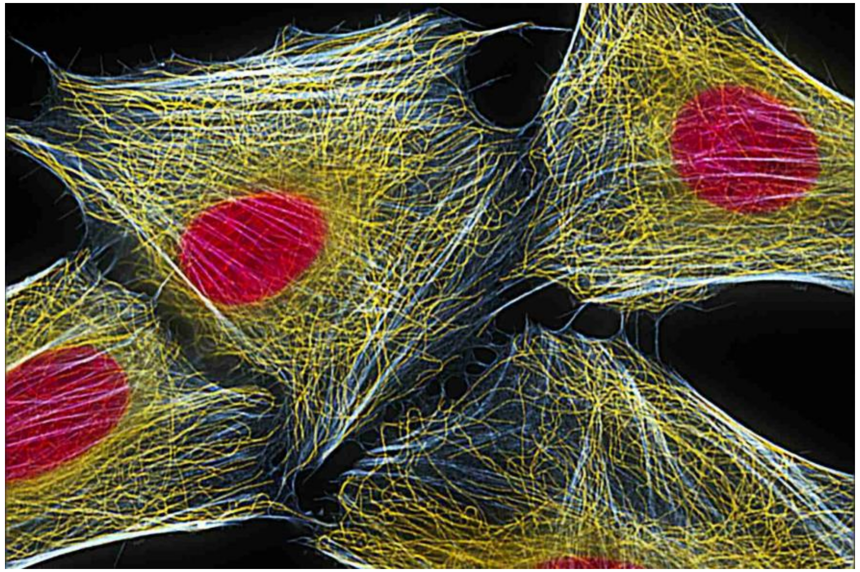


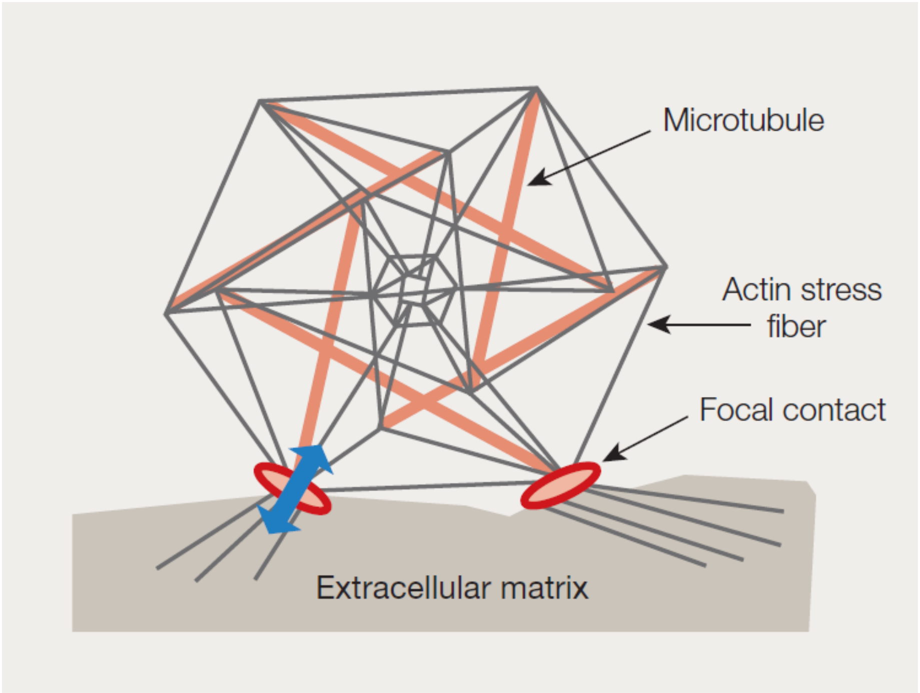
From Skeleton to Cytoskeleton and ….



Tensegrity model from Donald INGBER, Wyss Institute

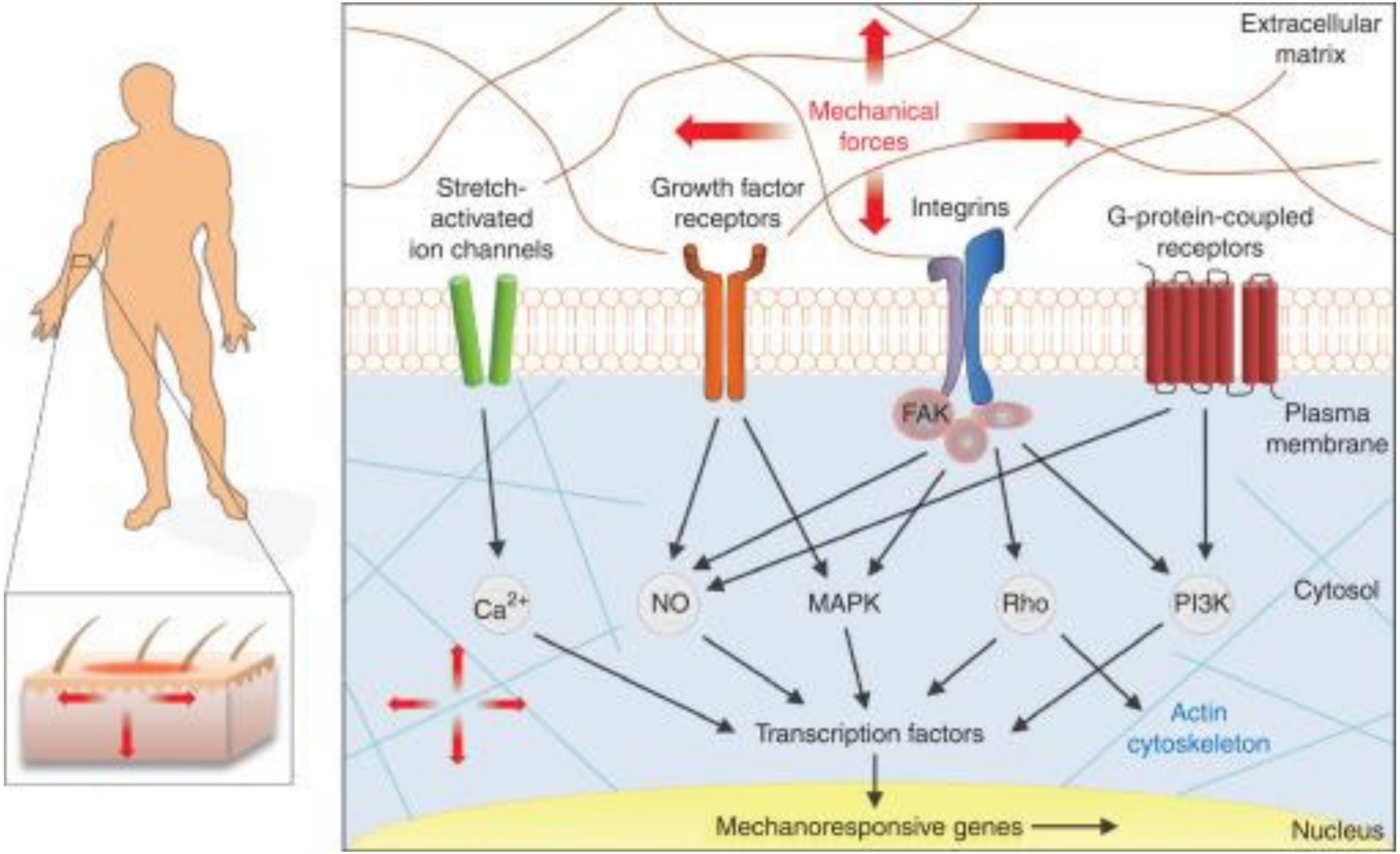


Microtubules : resist tension
Microfilaments generate tension



Tensegrity Kenneth Snelson

Actors....transductors



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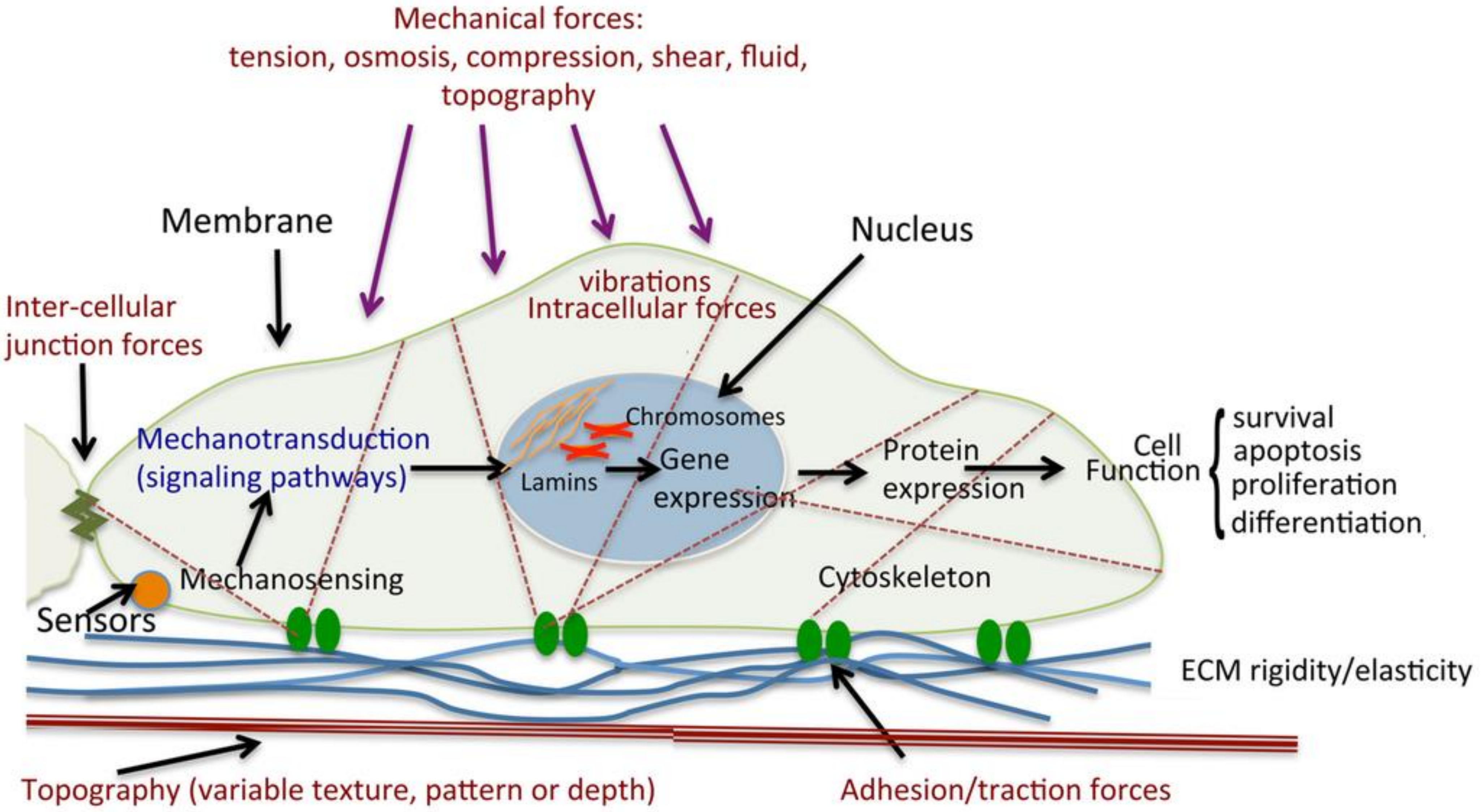

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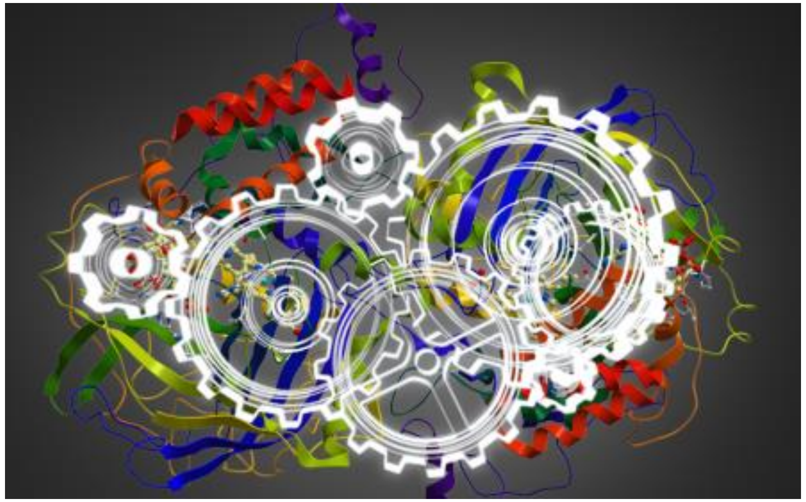
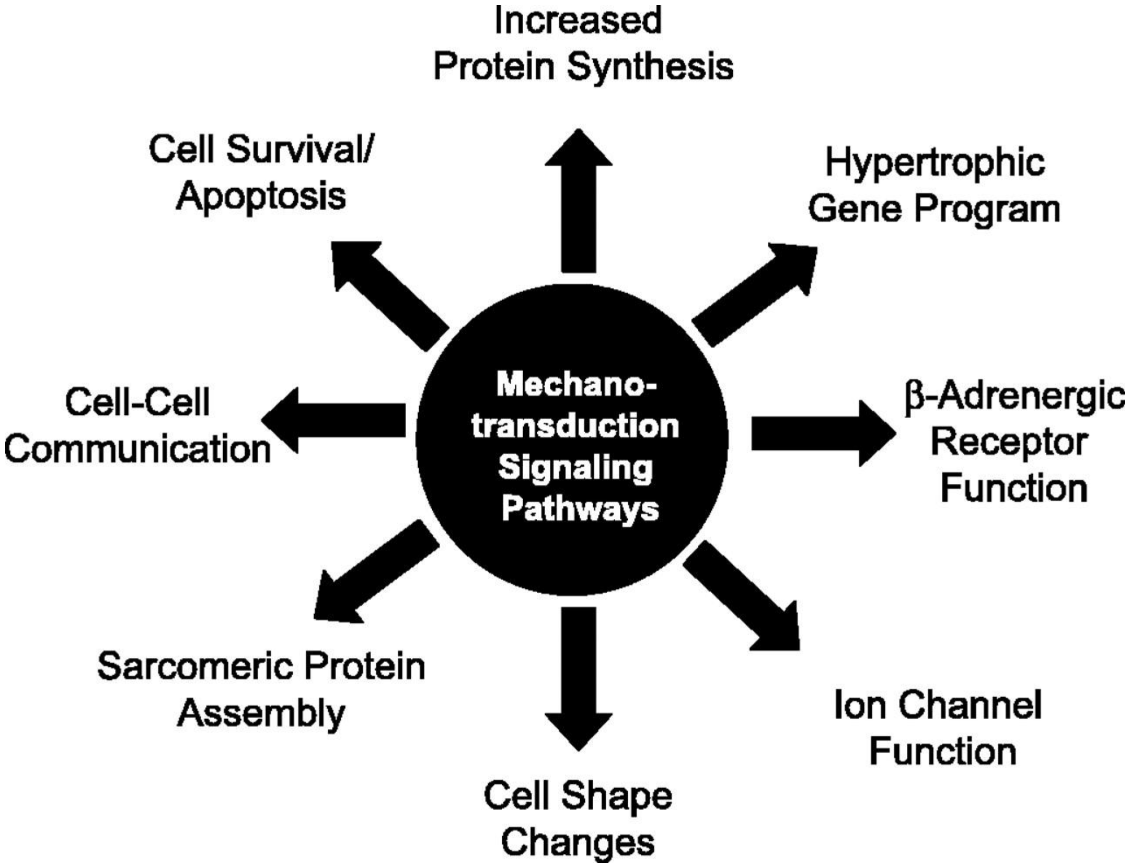




Cell biomechanics & signal transduction

Mechanotransduction

Mechanotherapeutics

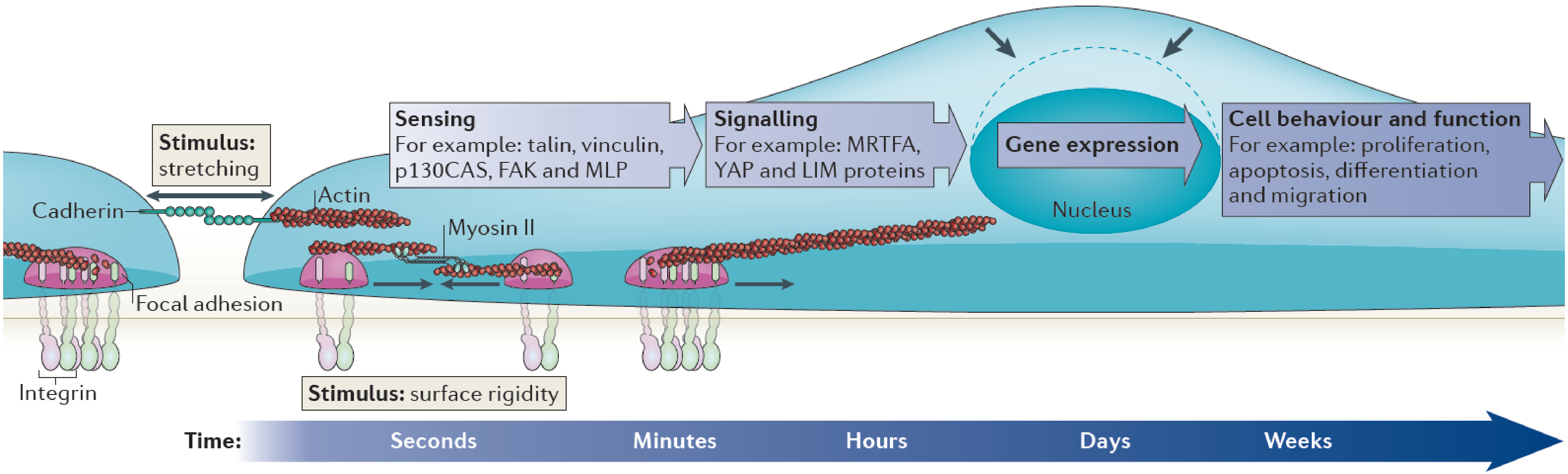
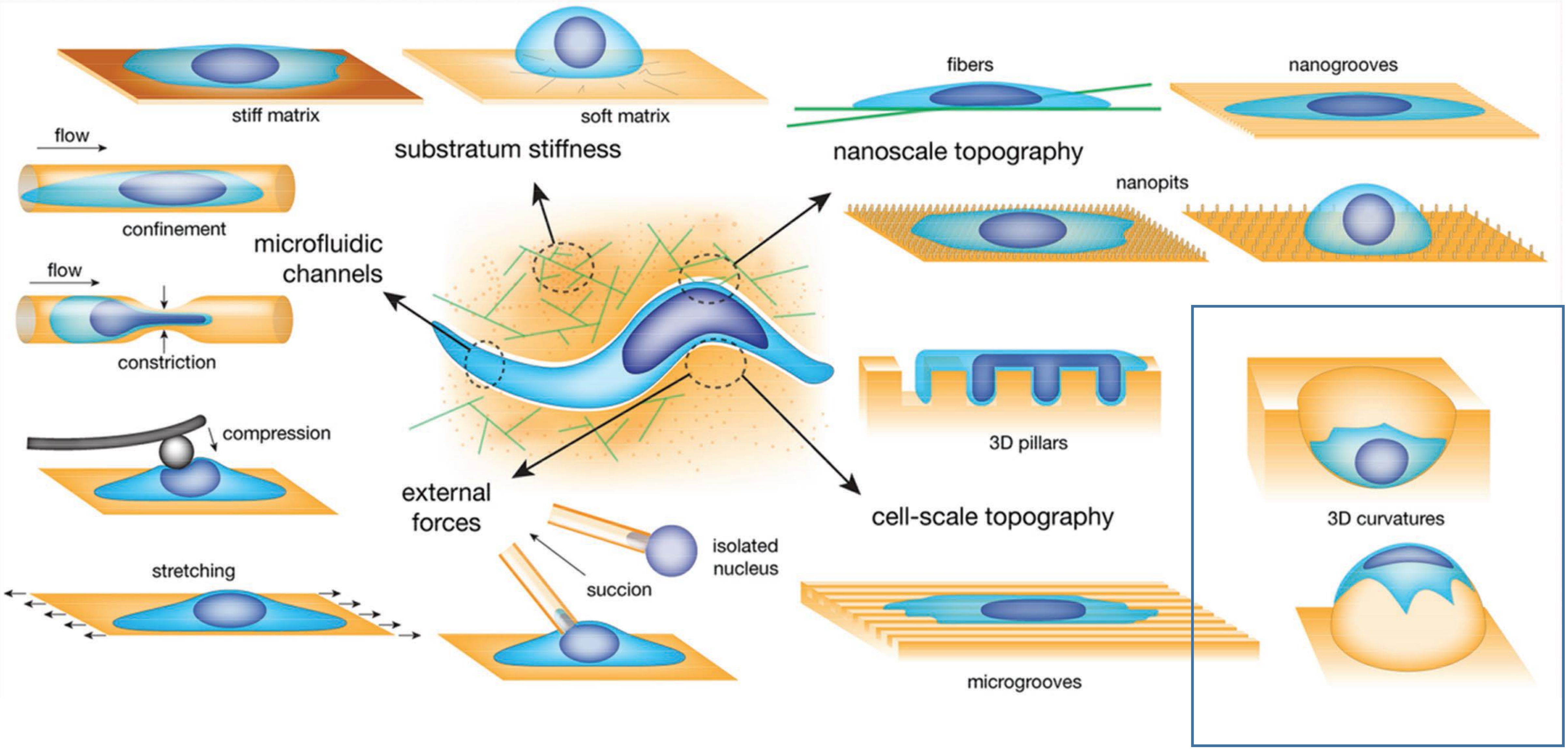


Figure 1 | **Mechanotransduction.** Mechanotransduction converts mechanical stimuli — such as substrate rigidity (through contractile units or mature integrin adhesions), stretching (through cell–cell contacts or integrin adhesions) or shear stress (not shown) — into chemical signals to regulate cell behaviour and function. Typically, the pathway involves receptors at focal adhesions or cell–cell contacts (for example, integrins and cadherins), mechanosensors (for example, stretchable proteins such as talin and p130CAS) and nuclear signalling factors to change gene and protein expression profiles. Nuclear deformation (the shape of the nucleus before force is applied is indicated by the dashed line) can also lead to changes in gene expression patterns. The timescale of these events ranges from milliseconds to seconds for the stretching of mechanosensors, hours for altered gene expression, days for changes in cell behaviour and function, and weeks for tissue development. FAK, focal adhesion kinase; MLP, muscle LIM protein; MRTFA, myocardin-related transcription factor A; YAP, Yes-associated protein.

All the surfaces are mechano-active for cells!



K Anselme, et al., Adv. Mat., 2018