First Congress

International Society of Diamagnetic Therapy

Mechanotransduction and Neuromodulation

13th – 14th September 2024
Magna Graecia University - Catanzaro

Dr. Prof. Felipe Torres MD.

PERISO ACADEMY

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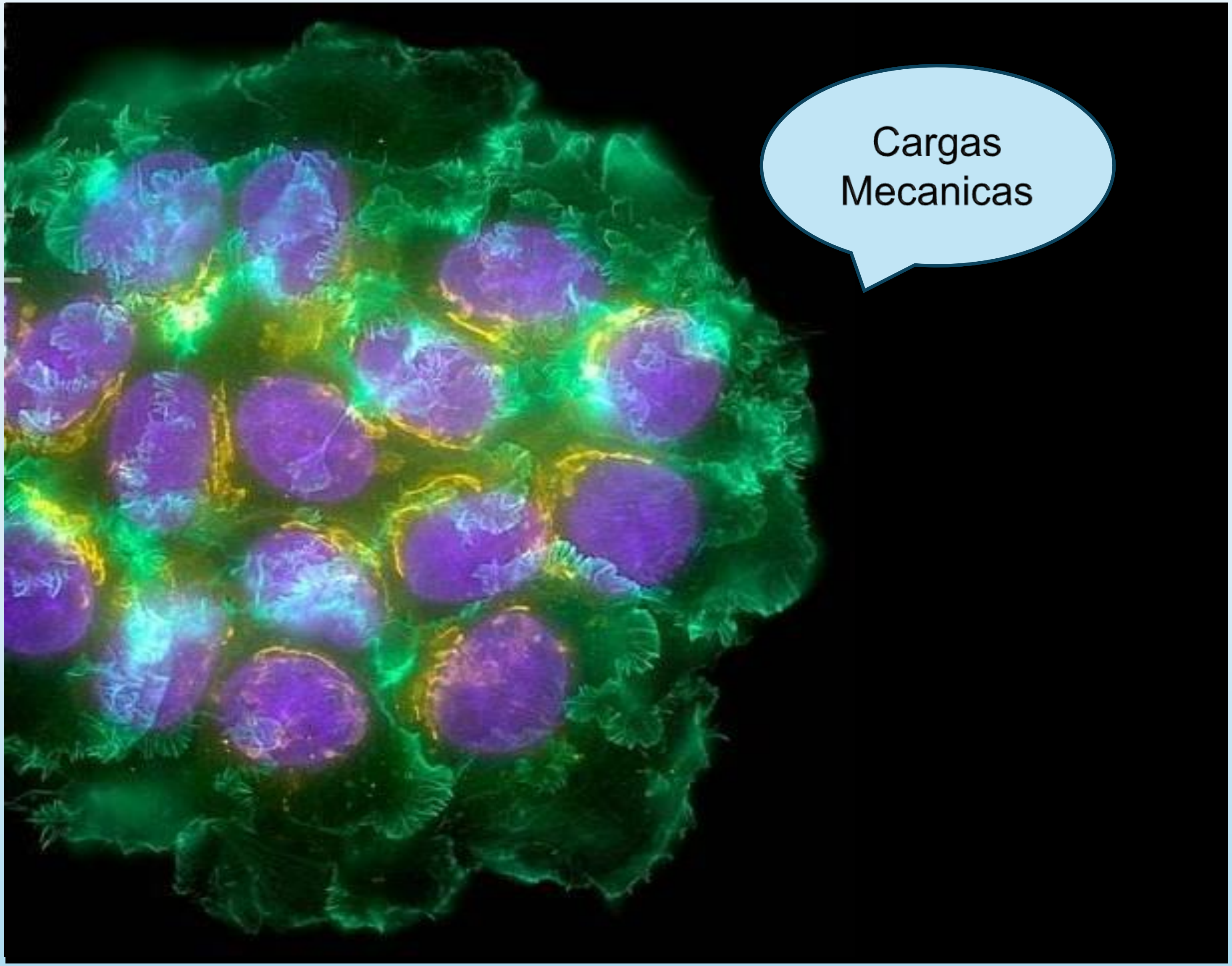
Cargas
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NUCLEUS
2024, VOL. 15, NO. 1, 2374854
https://doi.org/10.1080/19491034.2024.2374854

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REVIEW

OPEN ACCESS Check for updates

Sensing the squeeze: nuclear mechanotransduction in health and disease

Luv Kishore Srivastava [a] and Allen J. Ehrlicher [a,b,c,d,e,f]

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ABSTRACT

The nucleus not only is a repository for DNA but also a center of cellular and nuclear mechanotransduction. From nuclear deformation to the interplay between mechanosensing components and genetic control, the nucleus is poised at the nexus of mechanical forces and cellular function. Understanding the stresses acting on the nucleus, its mechanical properties, and their effects on gene expression is therefore crucial to appreciate its mechanosensitive function. In this review, we examine many elements of nuclear mechanotransduction, and discuss the repercussions on the health of cells and states of illness. By describing the processes that underlie nuclear mechanosensation and analyzing its effects on gene regulation, the review endeavors to open new avenues for studying nuclear mechanics in physiology and diseases.

ARTICLE HISTORY
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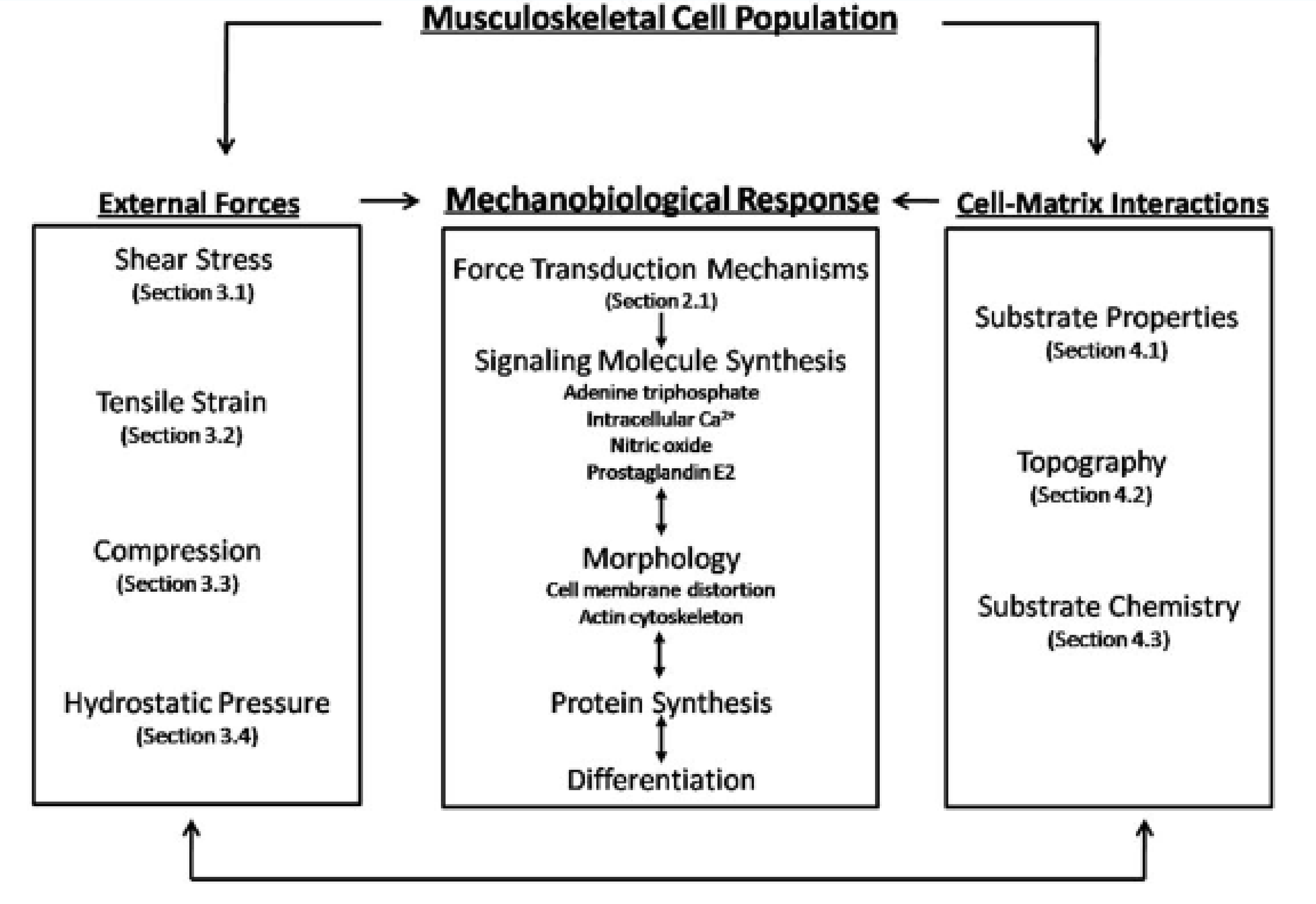
KEYWORDS
Chromatin; lamin A/C; LINC complex; mechanotransduction; nuclear deformation


Musculoskeletal Cell Population
External Forces
Mechanobiological Response
Cell-Matrix Interactions
Shear Stress
(Section 3.1)
Tensile Strain
(Section 3.2)
Compression
(Section 3.3)
Hydrostatic Pressure
(Section 3.4)
Force Transduction Mechanisms
(Section 2.1)
Signaling Molecule Synthesis
Adenine triphosphate
Intracellular Ca2+
Nitric oxide
Prostaglandin E2
Morphology
Cell membrane distortion
Actin cytoskeleton
Protein Synthesis
Differentiation
Substrate Properties
(Section 4.1)
Topography
(Section 4.2)
Substrate Chemistry
(Section 4.3)

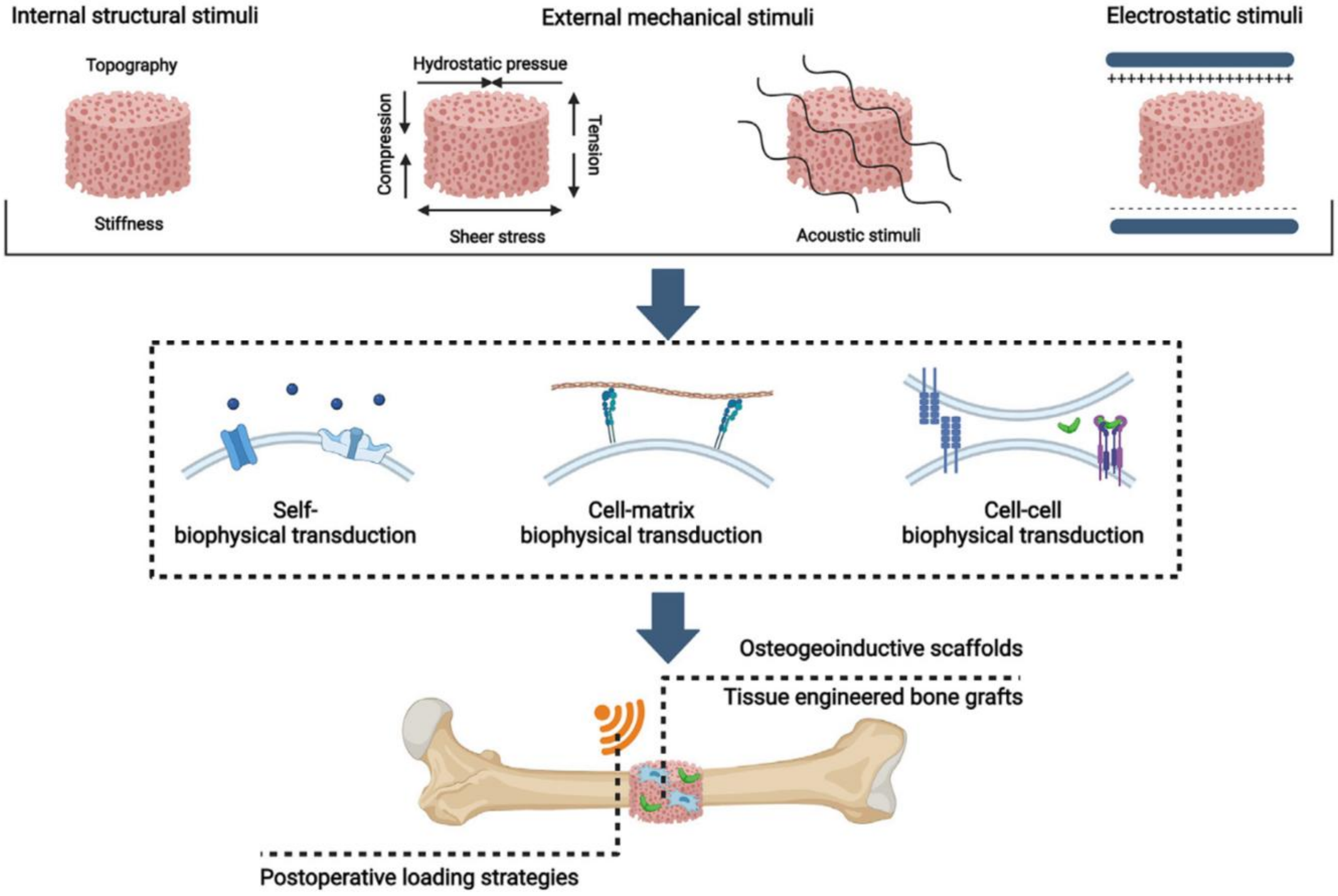


FIGURE 1 | Overview of biophysical stimuli for bone tissue engineering: distinctive patterns, osteoinductive mechanisms, and bone tissue engineering applications. Created with BioRender.com.

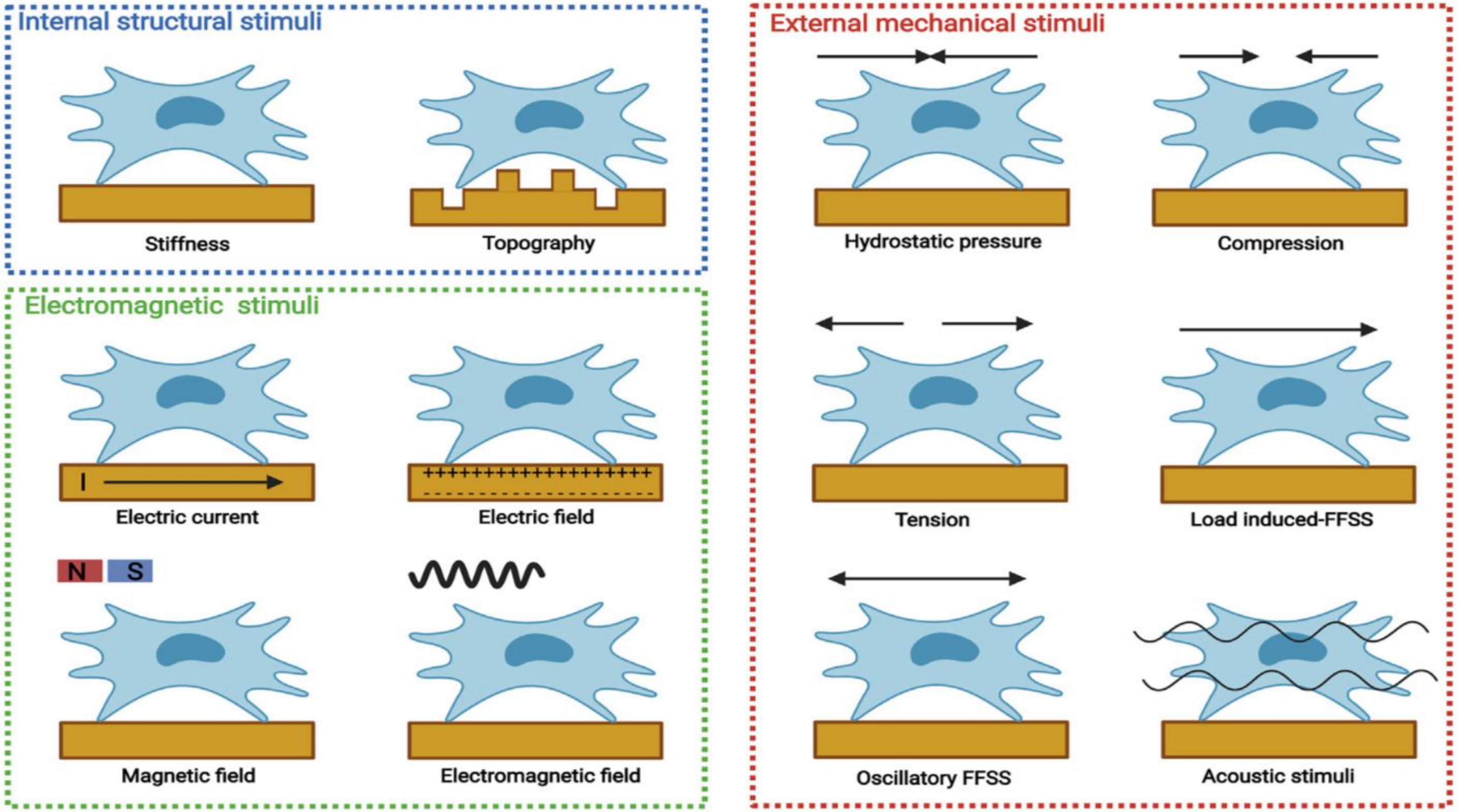
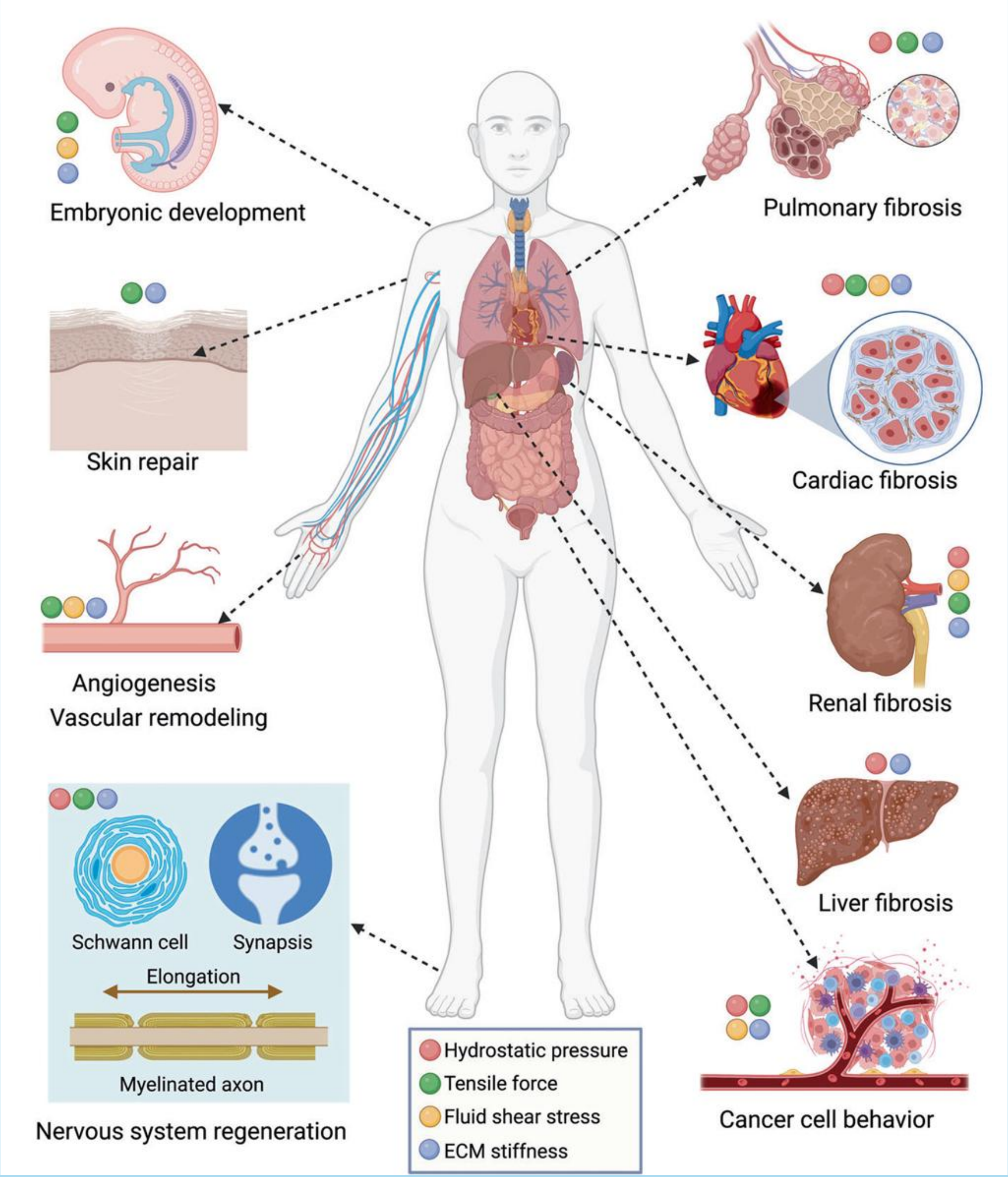


FIGURE 2 | Distinctive biophysical stimuli for bone tissue engineering, including internal structural stimuli (stiffness and topography), external mechanical stimuli [hydrostatic pressure, compression, tension, load induced-fluid flow shear stress (FFSS), oscillatory FFSS without load, and acoustic stimuli], and electromagnetic stimuli (electric current, electric field, magnetic field, and electromagnetic field). Created with BioRender.com.



13th – 14th September 2024

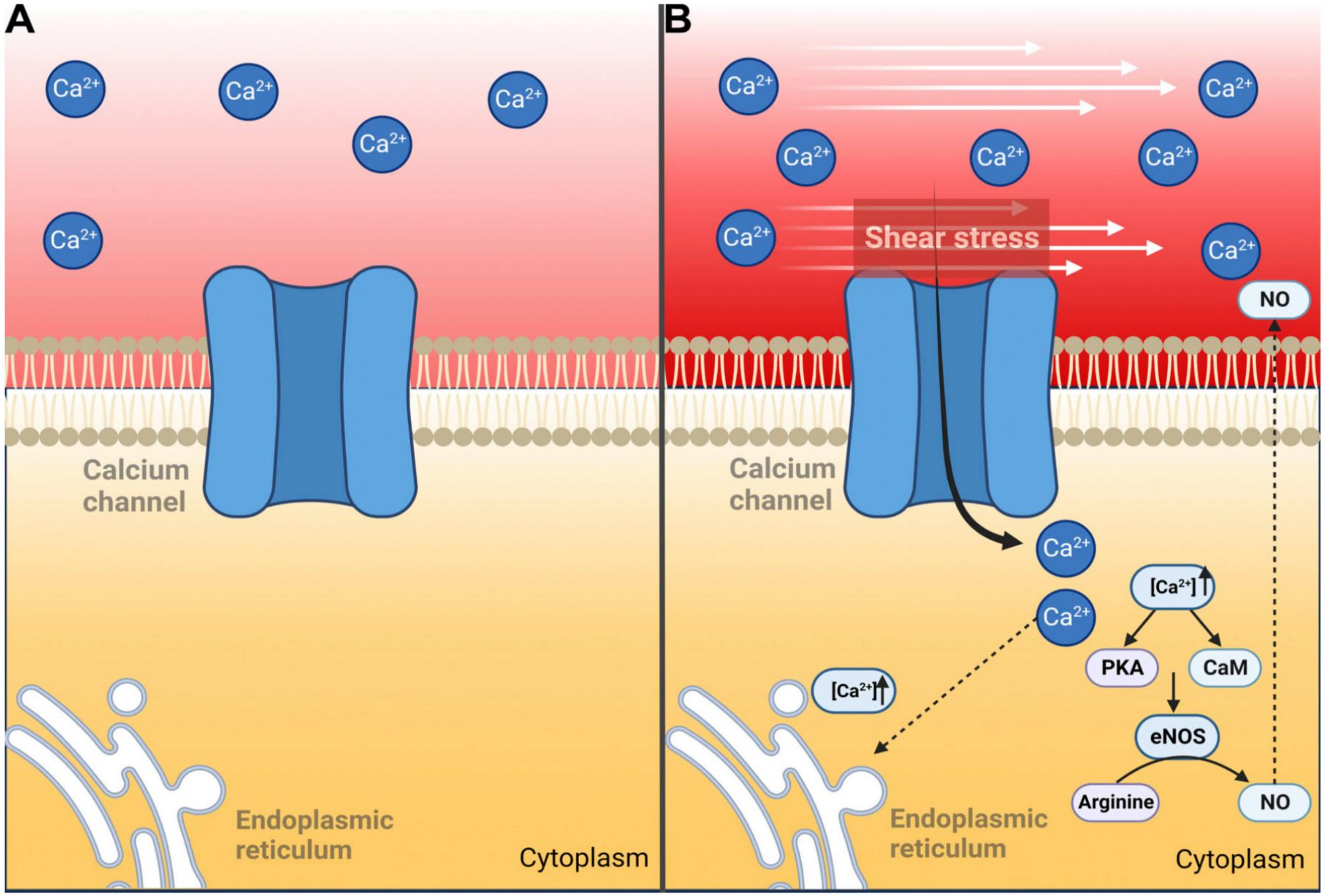
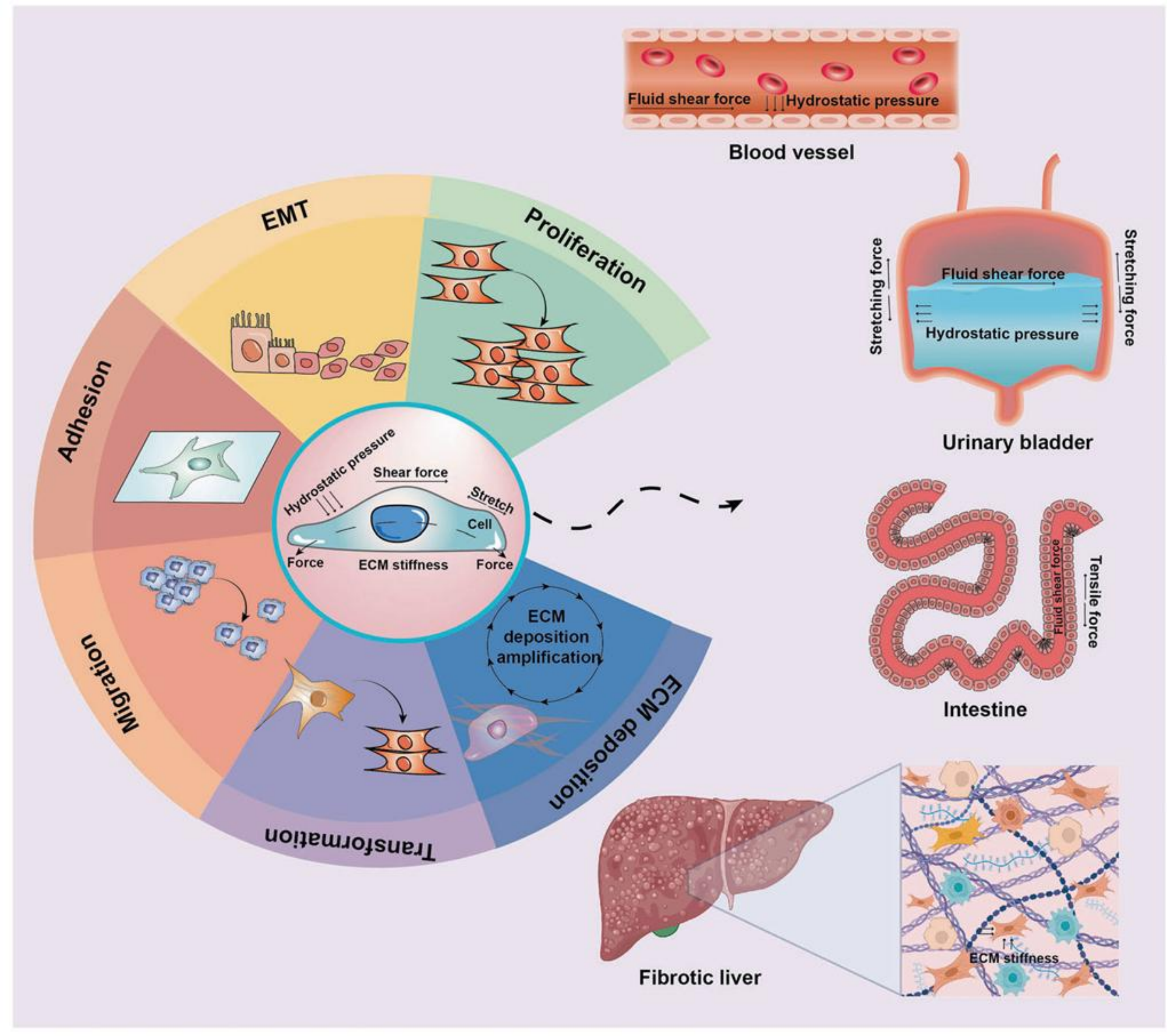
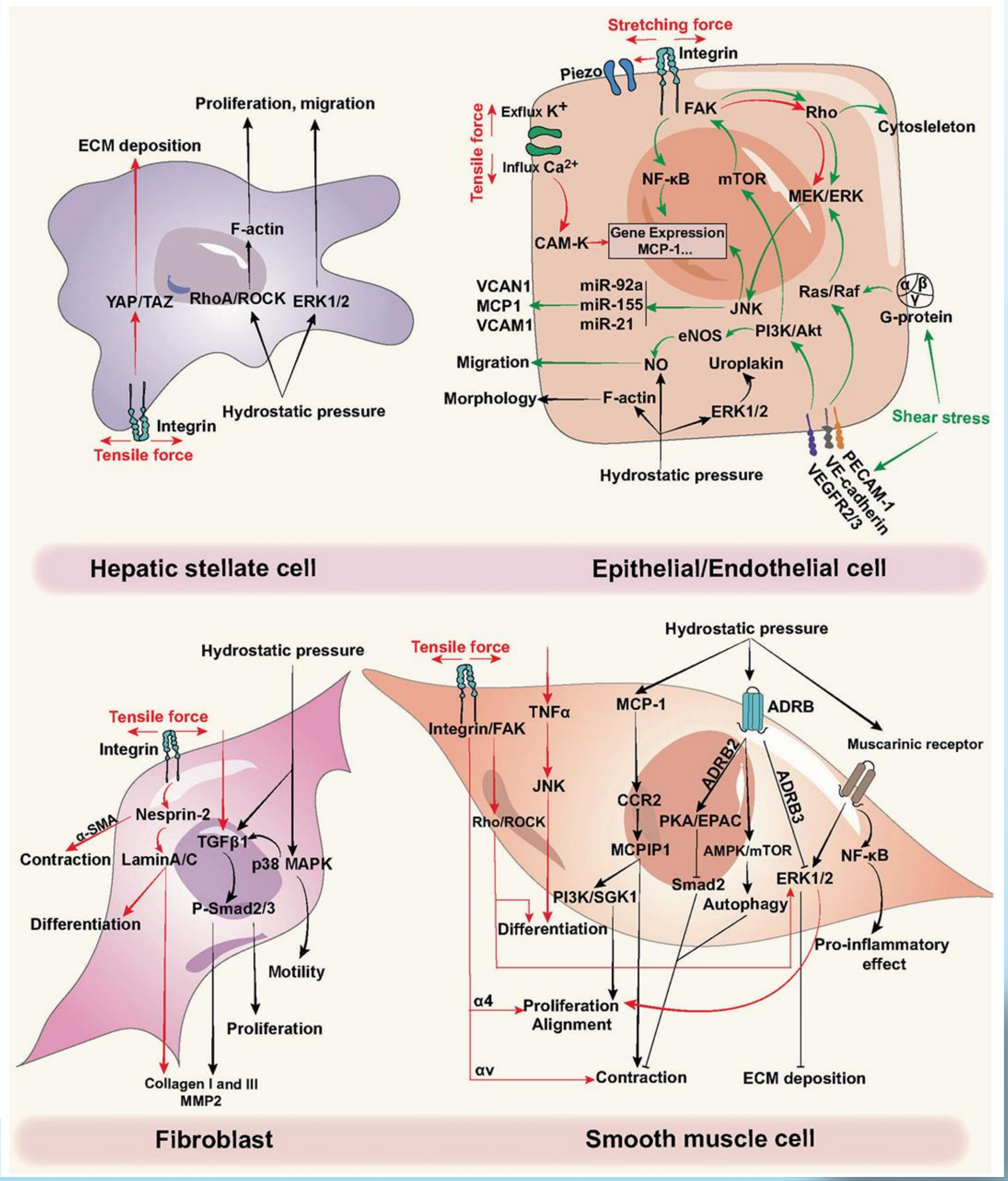


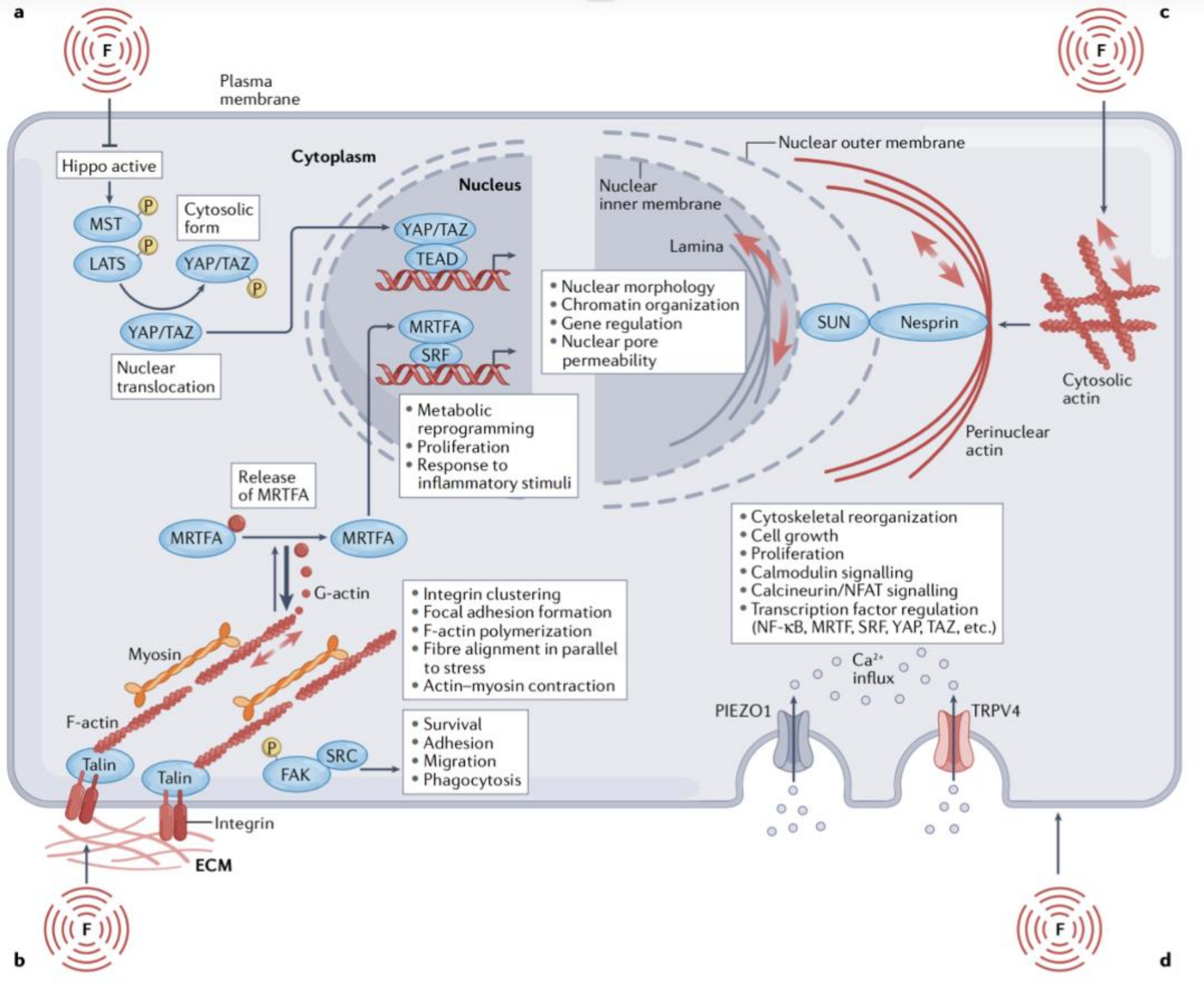
Figure 3. **Mechanosensitive calcium channels. (A)** Inactive mechanosensitive channels, without mechanical stimuli. **(B)** The active mechanosensitive channels that respond to membrane tension by altering their conformation between an open state and a closed state. eNOS increases NO expression following calcium increase through the CaM and PKA pathway. NO can freely diffuse. Furthermore, the increase in intracellular calcium concentration enhances endoplasmic reticulum calcium signaling. Abbreviations: CaM, calmodulin; PKA, protein kinase A; eNOS, endothelial nitric oxide synthase; NO, nitric oxide.



Fluid shear force
Hydrostatic pressure
Blood vessel
Urinary bladder
Stretching force
Fluid shear force
Hydrostatic pressure
Stretching force
Intestine
Fluid shear force
Tensile force
Fibrotic liver
ECM stiffness
EMT
Proliferation
Adhesion
Migration
Transformation
ECM deposition
ECM deposition amplification
Hydrostatic pressure
Shear force
Stretch
Cell
Force
ECM stiffness
Force



Proliferation, migration
ECM deposition
F-actin
YAP/TAZ
RhoA/ROCK
ERK1/2
Hydrostatic pressure
Integrin
Tensile force
Hepatic stellate cell
Stretching force
Integrin
Piezo
Exflux K+
Tensile force
Influx Ca2+
FAK
Rho
Cytosleleton
NF-κB
mTOR
MEK/ERK
CAM-K
Gene Expression MCP-1...
VCAN1
MCP1
VCAM1
miR-92a
miR-155
miR-21
JNK
Ras/Raf
G-protein
eNOS
PI3K/Akt
Migration
NO
Uroplakin
Morphology
F-actin
ERK1/2
Shear stress
Hydrostatic pressure
PECAM-1
VE-cadherin
VEGFR2/3
Epithelial/Endothelial cell
Hydrostatic pressure
Tensile force
Integrin
α-SMA
Nesprin-2
Contraction
LaminA/C
TGFβ1
p38 MAPK
P-Smad2/3
Differentiation
Motility
Proliferation
Collagen I and III
MMP2
Fibroblast
Tensile force
Hydrostatic pressure
Integrin/FAK
TNFα
MCP-1
ADRB
Muscarinic receptor
JNK
CCR2
ADRB2
ADRB3
Rho/ROCK
PKA/EPAC
MCPIP1
AMPK/mTOR
NF-κB
Smad2
ERK1/2
PI3K/SGK1
Autophagy
Differentiation
Pro-inflammatory effect
α4
Proliferation
Alignment
αv
Contraction
ECM deposition
Smooth muscle cell



a
Plasma membrane
Hippo active
Cytoplasm
Nucleus
MST
LATS
Cytosolic form
YAP/TAZ
YAP/TAZ
Nuclear translocation
YAP/TAZ
TEAD
MRTFA
SRF
• Metabolic reprogramming
• Proliferation
• Response to inflammatory stimuli
Release of MRTFA
MRTFA
MRTFA
G-actin
Myosin
F-actin
Talin
Talin
Integrin
ECM
FAK
SRC
• Integrin clustering
• Focal adhesion formation
• F-actin polymerization
• Fibre alignment in parallel to stress
• Actin–myosin contraction
• Survival
• Adhesion
• Migration
• Phagocytosis
b
c
Nuclear outer membrane
Nuclear inner membrane
Lamina
• Nuclear morphology
• Chromatin organization
• Gene regulation
• Nuclear pore permeability
SUN
Nesprin
Cytosolic actin
Perinuclear actin
• Cytoskeletal reorganization
• Cell growth
• Proliferation
• Calmodulin signalling
• Calcineurin/NFAT signalling
• Transcription factor regulation (NF-κB, MRTF, SRF, YAP, TAZ, etc.)
Ca2+ influx
PIEZO1
TRPV4
d

Journal article

Cytoskeleton. 2024 sep. 6;

Characterization of open chromatin sensitive to actin polymerization and identification of core-binding factor subunit beta as mechanosensitive nucleocytoplasmic shuttling protein.

Yaxin Li, Kangjing Li, Fumihiko Nakamura

PMID: 39239837

Hide Details

Mechanotransduction leads to a variety of biological responses including gene expression, changes in cell shape, migration, tissue development, and immune responses. Dysregulation of mechanotransduction is implicated in the progression of various diseases such as cardiovascular diseases and cancer. The actin cytoskeleton plays a crucial role in transmitting mechanical stimuli. Actin filaments, essential for cell motility and shape changes, respond to mechanical cues by remodeling, influencing gene expression via the linker of nucleoskeleton and cytoskeleton complex and mechanosensitive transcription factors. This study employs the dithiobis(succinimidyl propionate) (DSP)-micrococcal nuclease (MNase) proteogenomics method to explore the relationship between cellular mechanosensing, chromatin architecture, and the identification of proteins involved in mechanosensitive nucleocytoplasmic shuttling, revealing how

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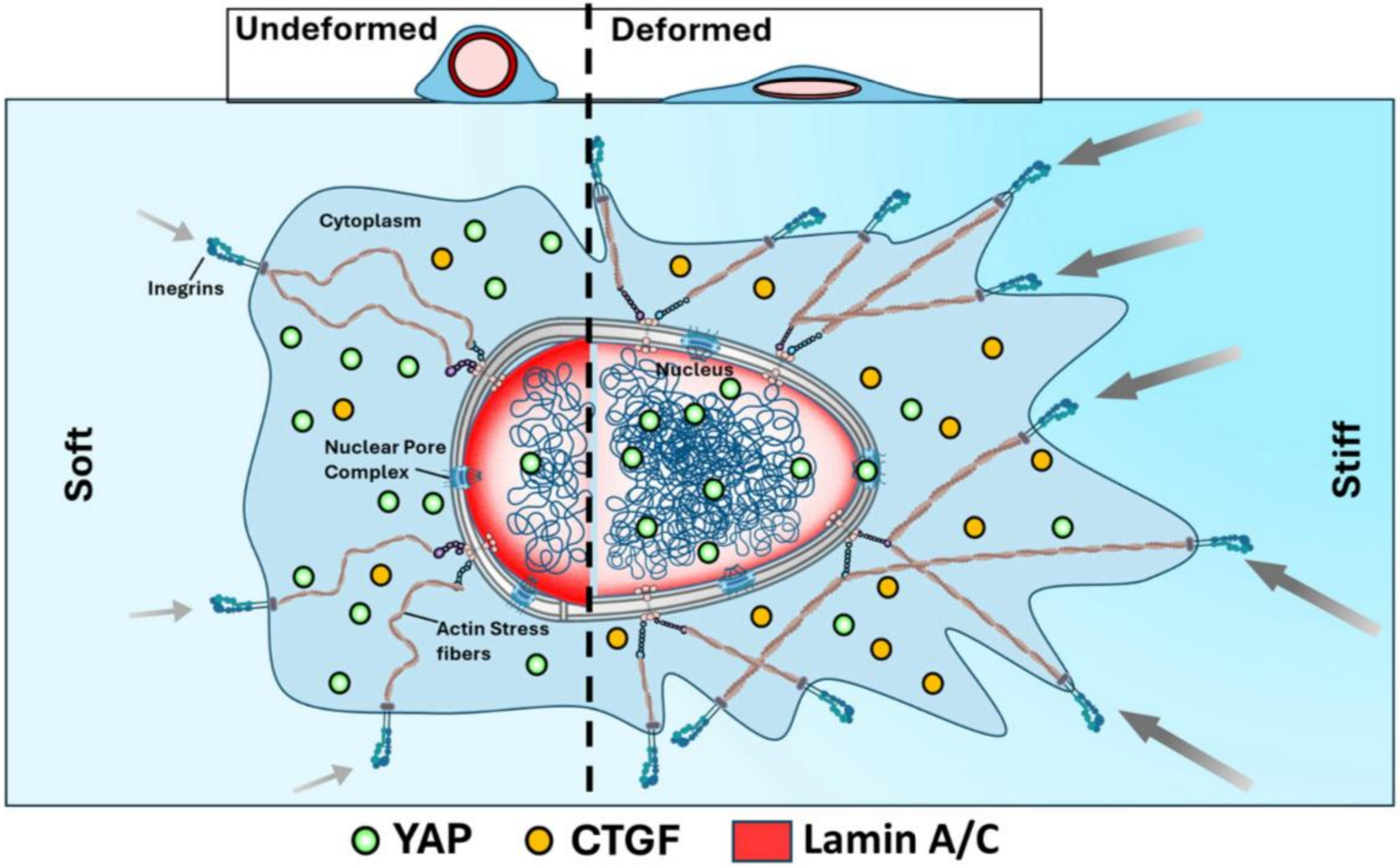

Figure 2. A schematic illustration that irrespective of the mechanism of nuclear deformation, leads to elevated YAP nuclear translocation and enhanced expression of downstream proteins such as connective tissue growth factor (CTGF).

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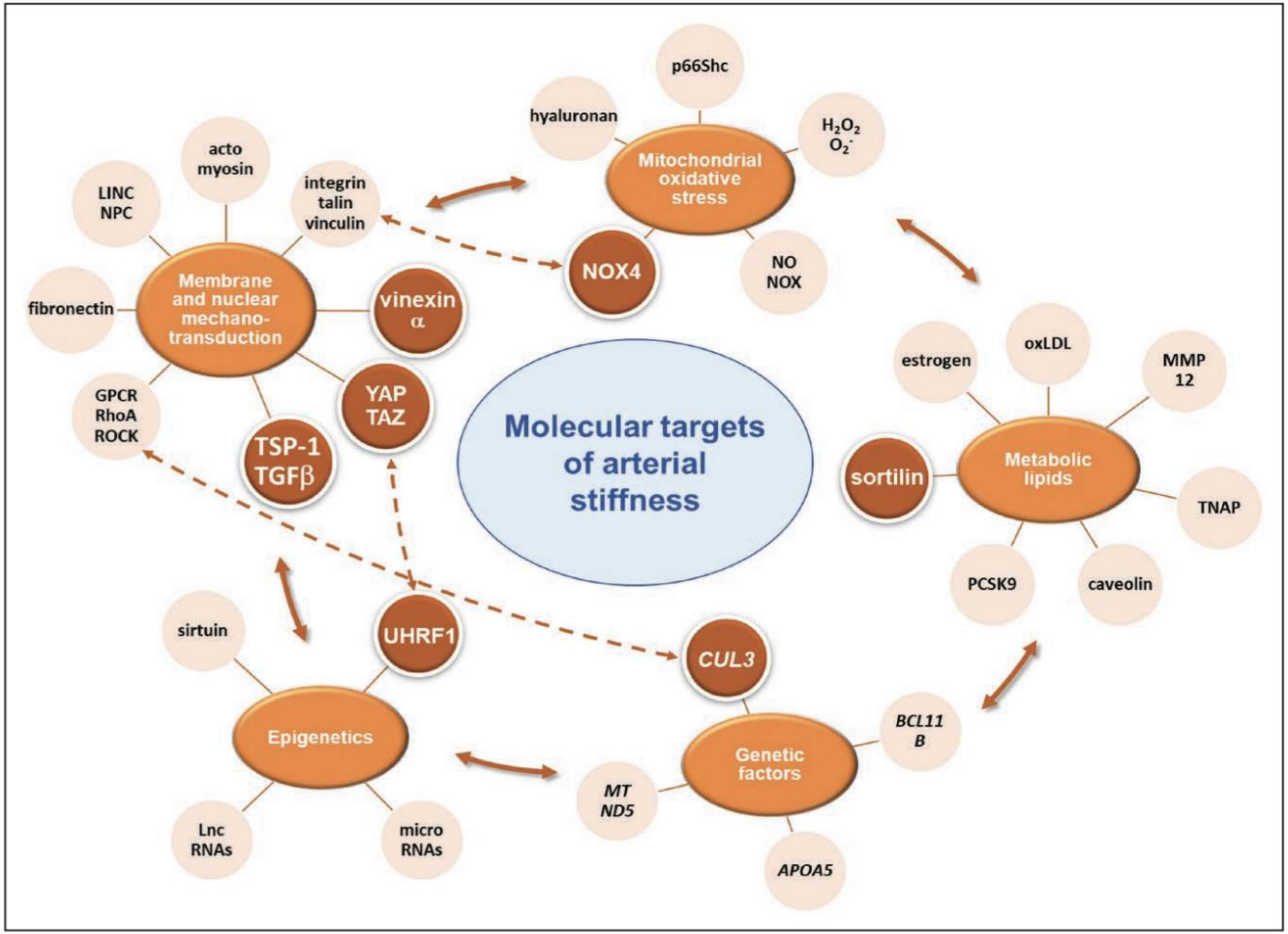

Figure 2. Integrative view of overlapping determinants of arterial stiffness.
The orange nodes are well-established key pathways, whereas the molecules/genes highlighted in brown are emerging modulators of arterial stiffness. Dashed arrows indicate links between new and well-known players. LINC indicates linker of nucleoskeleton and cytoskeleton; MMP, matrix metalloproteinase; NPC, nuclear pore complex; oxLDL, oxidized LDL; PCSK9, proprotein convertase subtilisin/kexin type 9; TAZ, transcriptional coactivator with a PDZ-binding motif; TGFβ, transforming growth factor β; TNAP, tissue nonspecific alkaline phosphatase; and YAP, yes-associated protein.

Journal article

Biophysical Journal. 2024 sep. 3;

YAP phosphorylation within integrin adhesions: insights from a computational model.

Hamidreza Jafarinia, Lidan Shi, Haguy Wolfenson, Aurélie Carlier

PMID: 39233443

Hide Details

Mechanical and biochemical cues intricately activate YAP, which is pivotal for the cellular responses to these stimuli. Recent findings reveal an unexplored role of YAP in influencing the apoptotic process. It has been shown that on soft matrices YAP is recruited to small adhesions, phosphorylated at Y357, and translocated into the nucleus triggering apoptosis. Interestingly, YAP Y357 phosphorylation is significantly reduced in larger mature focal adhesions on stiff matrices. Building upon these novel insights, we have developed a stochastic model to delve deeper into the complex dynamics of YAP phosphorylation within integrin adhesions. Our findings emphasize several key points: firstly, increasing the cytosolic diffusion rate of YAP correlates with higher levels of phosphorylated YAP (pYAP), secondly, increasing the number of binding sites and distributing them across the membrane surface, mimicking smaller adhesions, leads to higher pYAP levels, particularly at lower diffusion rates. Moreover, we show that the binding and release rate of YAP to adhesions as well as adhesion lifetimes significantly influence the size-effect of adhesion-induced YAP phosphorylation. The results highlight the complex and dynamic interplay between adhesion lifetime, the rate of pYAP unbinding from adhesions, and dephosphorylation rates, collectively shaping overall pYAP levels. In summary, our work advances the understanding of YAP mechanotransduction and opens avenues for experimental validation.

Journal article

Journal of Cell Biology. 2024 nov. 4; 223 (11).

Purinergic signaling through the P2Y2 receptor regulates osteocytes' mechanosensitivity.

View Details

Osteocytes' response to dynamic loading plays a crucial role in regulating the bone mass but quickly becomes saturated such that downstream induction of bone formation plateaus. The underlying mechanisms that downregulate osteocytes' sensitivity and overall response to loading remain unknown. In other cell types, purinergic signaling through the P2Y2 receptor has the potential to downregulate the sensitivity to loading by modifying cell stiffness through actin polymerization and cytoskeleton organization. Herein, we examined the role of P2Y2 activation in regulating osteocytes' mechanotransduction using a P2Y2 knockout cell line alongside conditional knockout mice. Our findings demonstrate that the absence of P2Y2 expression in MLO-Y4 cells prevents actin polymerization while increasing the sensitivity to fluid flow-induced shear stress. Deleting osteocytes' P2Y2 expression in conditional-knockout mice enabled bone formation to increase when increasing the duration of exercise. Overall, P2Y2 activation under loading produces a negative feedback loop, limiting osteocytes' response to continuous loading by shifting the sensitivity to mechanical strain through actin stress fiber formation.

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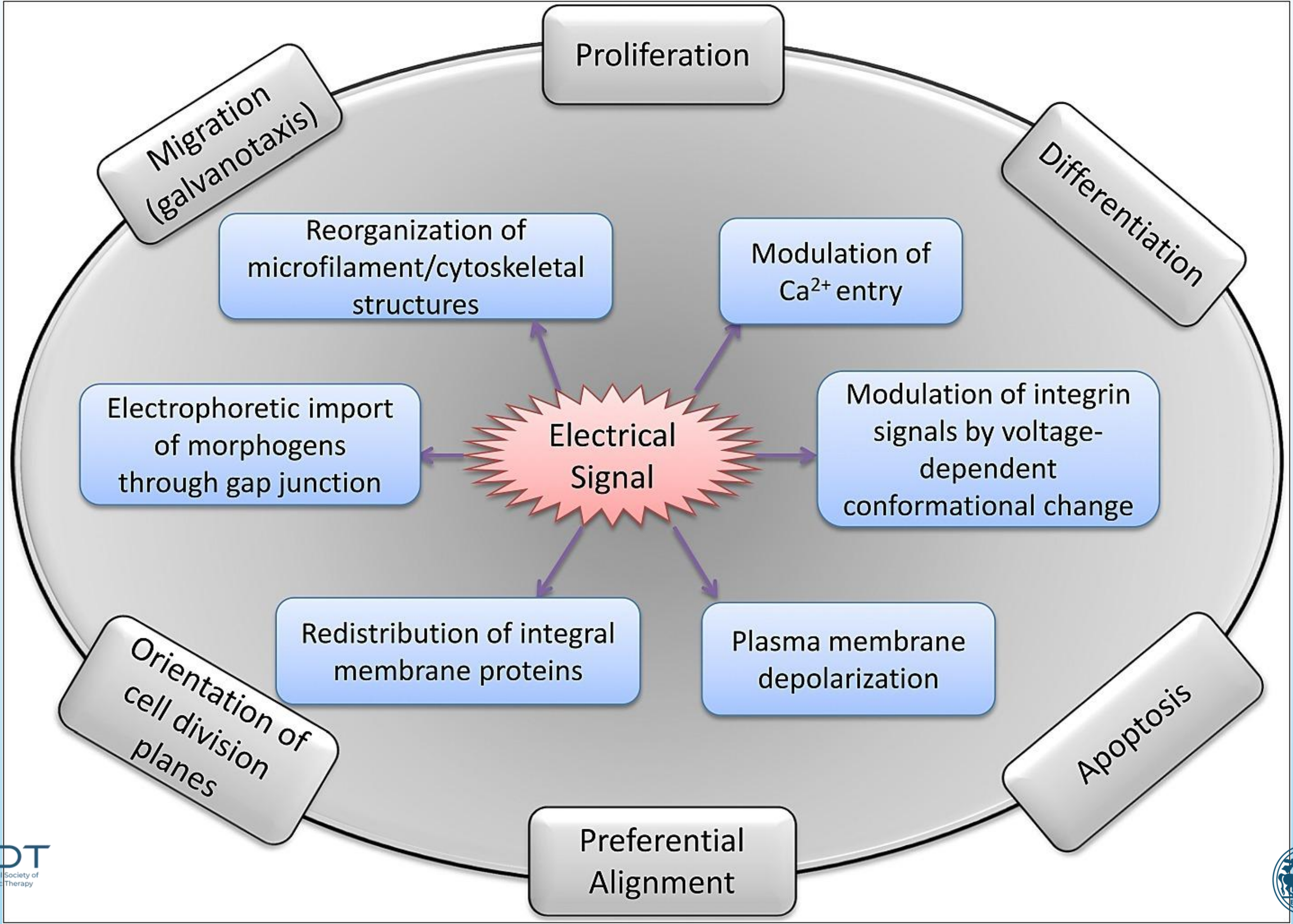

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Conceptually, it would be possible to improve the mechanical effect of SW in ECM by the means of the combined action with **other forms of biochemical transduction**, including that one related to the Pulsed Electromagnetic Fields along with the magnetic properties of the matter, in particular the **Diamagnetic effect** .

Journal article

Methods in Enzymology. 2024; 694 : 321-354.

Magnetic tweezers in cell mechanics.

Claudia Tanja Mierke

PMID: 38492957

Hide Details

The chapter provides an overview of the applications of magnetic tweezers in living cells. It discusses the advantages and disadvantages of magnetic tweezers technology with a focus on individual magnetic tweezers configurations, such as electromagnetic tweezers. Solutions to the disadvantages identified are also outlined. The specific role of magnetic tweezers in the field of mechanobiology, such as mechanosensitivity, mechano-allostery and mechanotransduction are also emphasized. The specific usage of magnetic tweezers in mechanically probing cells via specific cell surface receptors, such as mechanosensitive channels is discussed and why mechanical probing has revealed the opening and closing of the channels. Finally, the future direction of magnetic tweezers is presented.

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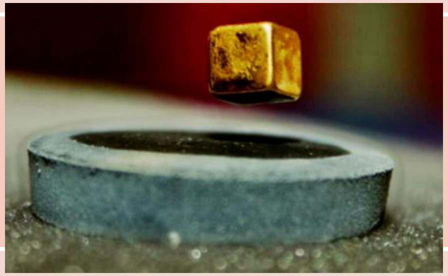

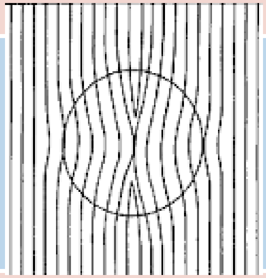

Diamagnetismo	Ferromagnéticos	Paramagnéticos
Agua	Hierro	Aluminio
Iones	Cobalto	Titanio
Plata, oro, cobre	Niquel	Magnesio
TEJIDOS BIOLOGICOS		

Types of magnetism

	Diamagnetic	Paramagnetic
Electron pairing	↑↓ ↑↓ ↑↓ No unpaired electrons	↑↓ ↑↓ ↑ At least one unpaired electron
Spin alignment with magnetic field **B**	B Anti-parallel	B Parallel
Reaction to magnets	N S Very weakly repelled	N S Attracted
Effect on magnetic field lines	Field bends slightly away from the material	Field bends toward the material

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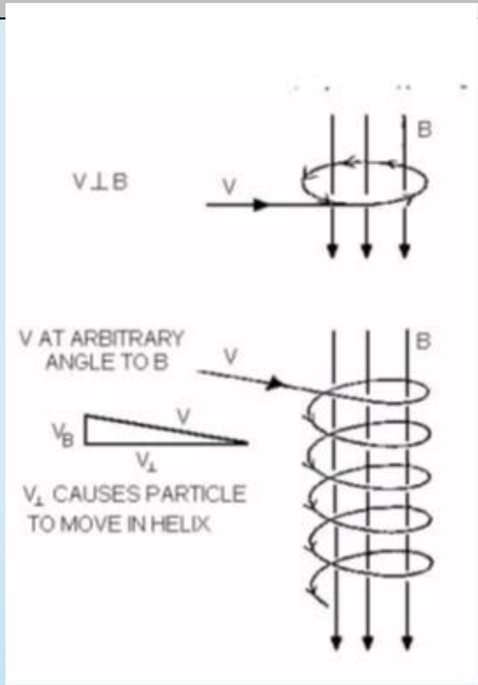
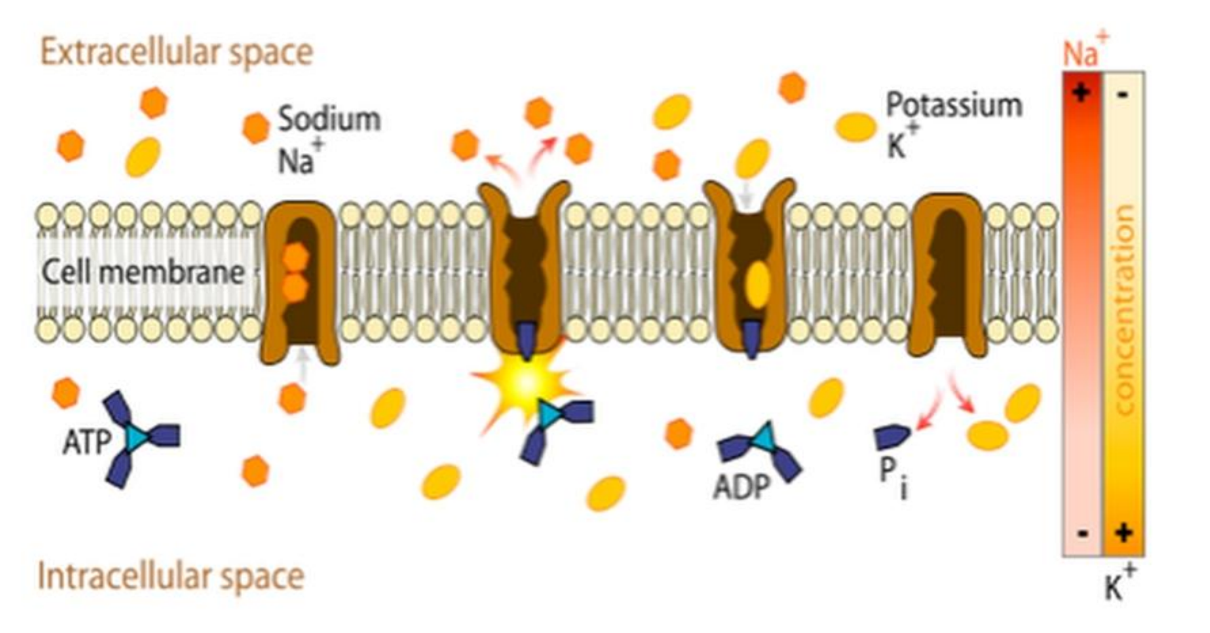
For the Magnetic Field

Induced Electric Field (Lorentz Force)





The **pulsed and variable** MF induces the vibration of transmembrane ions and their passage through the cell membrane **thanks to the activation of mechano-sensitive and electro- sensitive channels .**

Discovery Medicine. 2016 nov.; 22 (122) : 257-273.

The dielectrophoretic disassociation of chloride ions and the influence on diamagnetic anisotropy in cell membranes.

Chloride channels represent ubiquitously expressed proteins that regulate fundamental cellular processes including membrane potential, maintenance of intracellular pH, and regulation of cell volume. However, mechanisms to modulate this large family of ion channels have remained elusive to date. This large chloride channel family does not appear to operate with selectivity similar to the sodium and potassium channels. These unique channels appear to be bi-directional cotransporters of two or more different molecules or ions across a bilayer phospholipid membrane. Here we show how 3 amperes of direct current from a device that generates an electromagnetic field in a 3 mM hypotonic saline solution leads to a dielectrophoretic disassociation of the chloride ion from its chloro-metabolites transforming it into a polymorphic diamagnetically disassociated bio-chloride (bCl-). This field treated aqueous solution appears to continue to induce a magnetic moment change in solution for some hours when no longer under the influence of the direct current; for when this field influenced solution is used to reconstitute growth media of human breast carcinoma (MDA-MB-231) and human breast epithelial (MCF-10A) cells in vitro, significant changes in chloride ion channel expression, membrane potential, cell volume, and a massive transcriptional reprogramming of 2,468 genes expressions by Human Genome U133 Plus 2.0 Gene Chip Array (Affymetrix) analyses occur. We will highlight how the strong changes in chloride ion channel expression and cell physiology could be intricately linked to enhanced diamagnetic anisotropy in cell membranes that occur under the influence of this disassociated polymorphic bCl-.

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ANALYTICAL SCIENCES JANUARY 2013, VOL. 29

Faraday Rotation Dispersion Measurements of Diamagnetic Organic Liquids and Simultaneous Determination of Natural Optical Rotatory Dispersion Using a Pulsed Magnetic Field

Masayori SUWA,*† Kayoko MIYAMOTO,* and Hitoshi WATARAI**

**Department of Chemistry, Graduate School of Science, Osaka University, 1-1 Machikaneyama, Toyonaka, Osaka 560-0043, Japan*

***Institute for Nanoscience Design, Osaka University, 1-3 Machikaneyama, Toyonaka, Osaka 560-8531, Japan*

We constructed an apparatus to measure the wavelength dispersion of the Faraday rotation in the visible region, and determined the Verdet constants of diamagnetic organic liquids, including aliphatic compounds, benzene derivatives, and naphthalene derivatives. These three groups were easily distinguished by the magnitudes of their Verdet constants. Based on the theory developed by Serber, we determined the enhancing effect of $\pi^*\leftarrow\pi$ transitions on the visible-light Faraday rotation angles observed for aromatic compounds. Furthermore, we propose a novel approach for simultaneously observing Faraday rotation dispersion and natural optical rotatory dispersion.

(Received September 10, 2012; Accepted November 12, 2012; Published January 10, 2013)

ECM general structure

Glycosaminoglycans (GAGs)

Glycosaminoglycans (GAGs) are linear polysaccharides composed of two basic saccharides.

- **Hyaluronan is the simplest GAG**

The other GAGs are

- **Chondroitin Sulfate (CS)**
- **Dermatan Sulfate (DS)**
- **Keratan Sulfate (KS)**
- **Heparan Sulfate (HS) (fundamental for the modulation of the ECM electrostatic properties)**

Proteoglycans

A proteoglycan is composed of a core protein with one or more covalently attached GAGs. They are stored in secretory granules, inserted into the plasma membrane or secreted into the ECM.

Glycoproteins

Laminin
Fibronectin

Fibrous proteins

Collagen Twenty-eight types of collagens (I–XXVIII) have been identified so far in vertebrates.

Water

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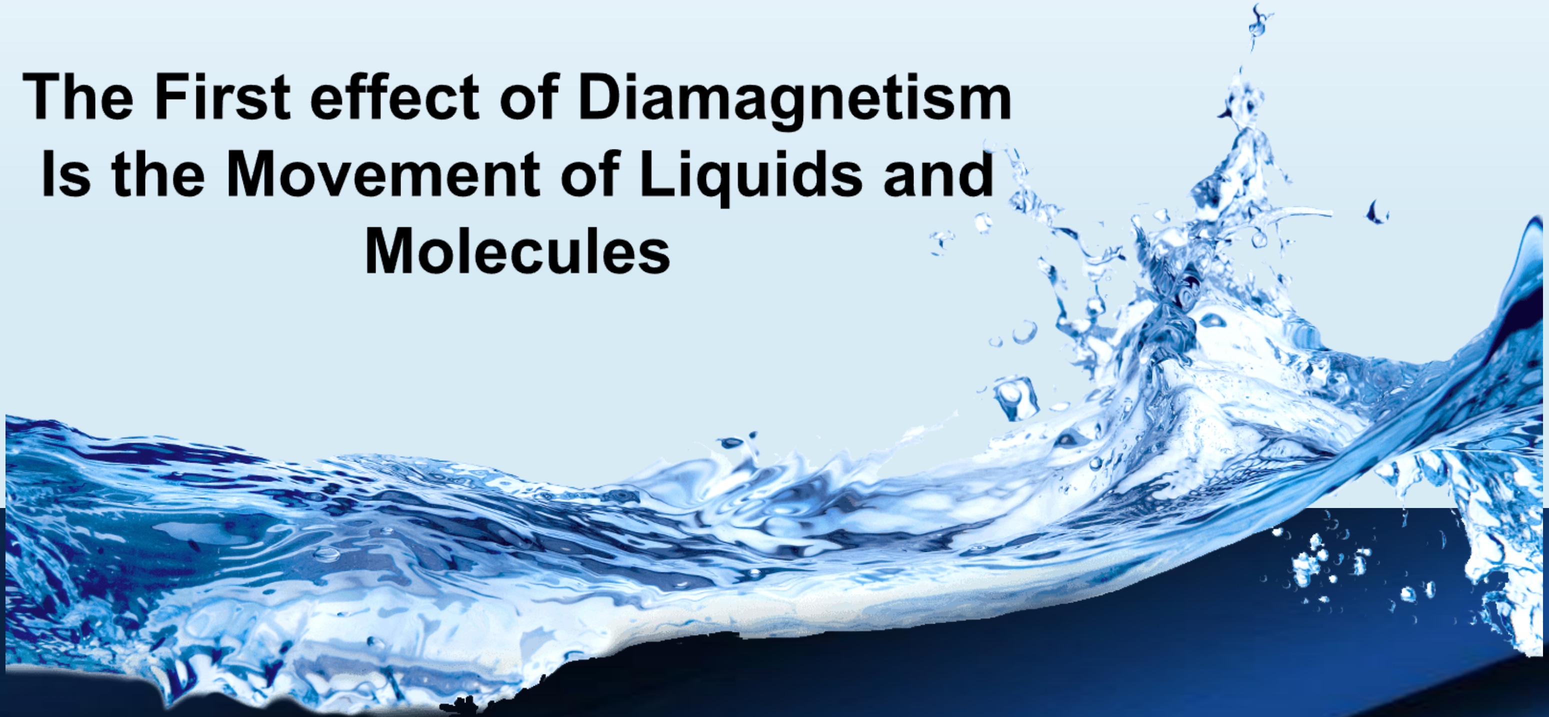
https://www.sigmaaldrich.com/life-science/stem-cell-biology/hystem-cell-culture/extracellular-

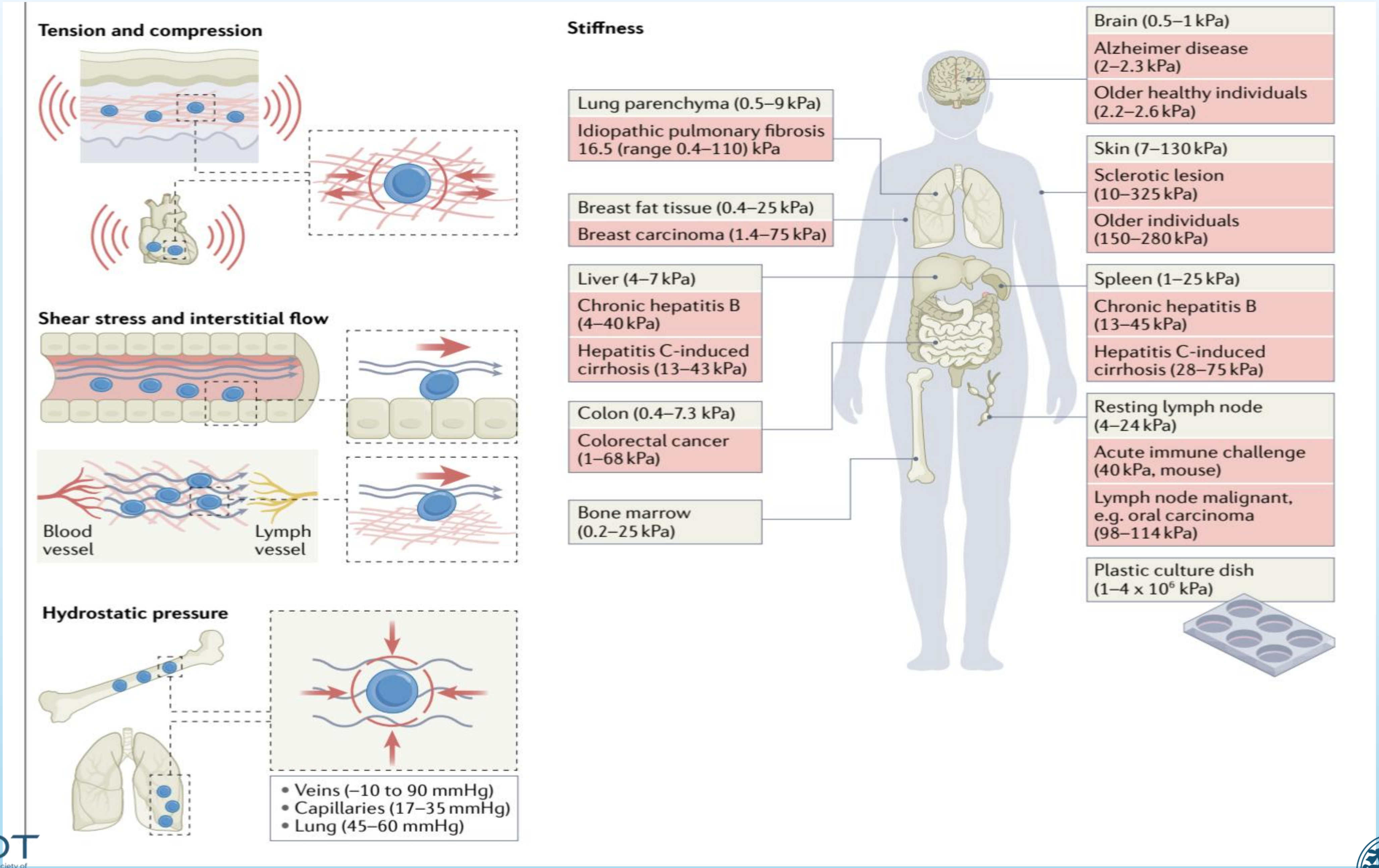
The First effect of Diamagnetism Is the Movement of Liquids and Molecules



Molecular Migration from a High Magnetic Field area to a Low Magnetic Field area.

National Research Council, Committee on Opportunities in High Magnetic Field Science. Solid State Sciences Committee.2005.Washington:National Academies Press . http:/books.nap.edu/catalog/11211.html/.

Tissue	Water (%)
Lung	83.74
Striated Muscle	79.52
Kidney	79.47
Digestive tract	79,07
Spleen	78,69
Brain, spinal cord, nerve trunks	73.69
Hearth	73,69
Pancreas	73,08
Liver	71,46
Skin	64,86
Adipose tissue	50.09
Skeleton	31.81
Teeth	5
Liquid Tissues	93,33
Remaining Solid Tissues	70,40


Tension and compression
Shear stress and interstitial flow
Blood vessel
Lymph vessel
Hydrostatic pressure
• Veins (–10 to 90 mmHg)
• Capillaries (17–35 mmHg)
• Lung (45–60 mmHg)
Stiffness
Lung parenchyma (0.5–9 kPa)
Idiopathic pulmonary fibrosis 16.5 (range 0.4–110) kPa
Breast fat tissue (0.4–25 kPa)
Breast carcinoma (1.4–75 kPa)
Liver (4–7 kPa)
Chronic hepatitis B (4–40 kPa)
Hepatitis C-induced cirrhosis (13–43 kPa)
Colon (0.4–7.3 kPa)
Colorectal cancer (1–68 kPa)
Bone marrow (0.2–25 kPa)
Brain (0.5–1 kPa)
Alzheimer disease (2–2.3 kPa)
Older healthy individuals (2.2–2.6 kPa)
Skin (7–130 kPa)
Sclerotic lesion (10–325 kPa)
Older individuals (150–280 kPa)
Spleen (1–25 kPa)
Chronic hepatitis B (13–45 kPa)
Hepatitis C-induced cirrhosis (28–75 kPa)
Resting lymph node (4–24 kPa)
Acute immune challenge (40 kPa, mouse)
Lymph node malignant, e.g. oral carcinoma (98–114 kPa)
Plastic culture dish (1–4 x 10^6 kPa)

Tissue Eng Regen Med
https://doi.org/10.1007/s13770-024-00666-w

Online ISSN 2212-5469

ORIGINAL ARTICLE

Determining Which Hydrostatic Pressure Regimes Promote Osteogenesis in Human Mesenchymal Stem Cells

James R. Henstock[1] · **Joshua C. F. A. Price**[2] · **Alicia J. El Haj**[3]

Received: 9 April 2024 / Revised: 19 July 2024 / Accepted: 26 July 2024

Abstract

BACKGROUND: Compressive loading of bone causes hydrostatic pressure changes which have been proposed as an osteogenic differentiation stimulus for mesenchymal stem cells (hMSCs). We hypothesised that hMSCs are adapted to differentiate only in response to cyclic hydrostatic pressures above critical thresholds of magnitude and frequency which correspond to physiological levels of anabolic bone loading.

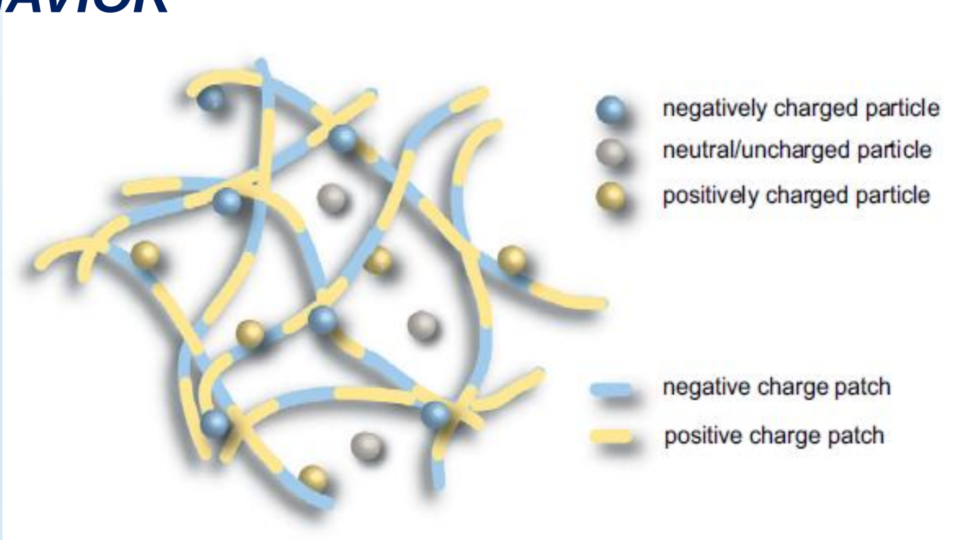
METHODS: Using a pneumatic-hydrostatic bioreactor, we applied hydrostatic pressure regimes to human hMSCs in 3D collagen hydrogel cultures for 1 h/day over 28 days to determine which levels of pressure and frequency stimulated osteogenesis *in vitro*.

RESULTS: Stimulation of the 3D cultures with 0–280 kPa cyclic hydrostatic pressure at 1 Hz resulted in up to 75% mineralisation in the hydrogel (without exogenous growth factors), whilst static culture or variations of the regime with either constant high pressure (280 kPa, 0 Hz), low-frequency (0.05 Hz, 280 kPa) or low-magnitude (70 kPa, 1 Hz)

13th – 14th September

HEPARAN SULFATE CHAINS CONTROLS ECM ELECTROSTATIC BEHAVIOR

In order to detach and flow charged molecules, it is essential to intervene on the electrostatic conditions of the ECM



heparan sulfate chains [the anionic polysaccharide side chain of HS proteoglycans (HSPGs)]

are important key factor for the electric barrier function.

HEPARAN SULFATE CHAINS POLYMERIZATION *is controlled by*

pH

ROS

Lieleg O, Baumgärtel RM, Bausch AR. Selective filtering of particles by the extracellular matrix: an electrostatic bandpass. Biophys J. 2009 Sep 16;97(6):1569-77.

Collagen turnover is controlled by specific enzymes and their respective inhibiting molecules

MMPs

Matrix metalloproteinases

22 human proteolytic enzymes

degradation

TIMPs

Tissues inhibitors of metalloproteinases

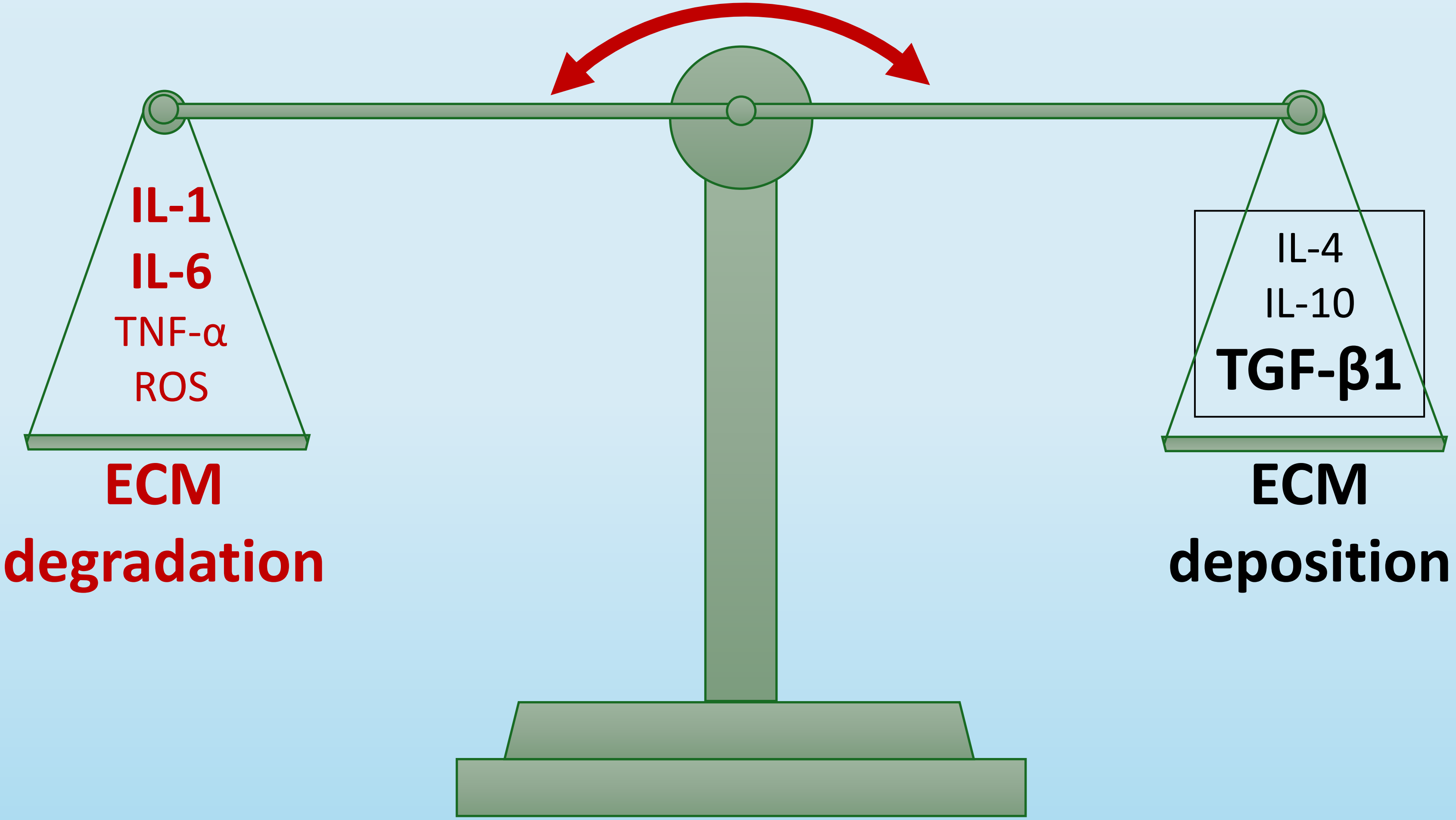
4 MMP inhibitory proteins

synthesis

TIMPs inhibit MMPs with 1 : 1 stoichiometry

WHO LEADS EXTRA -CELLULAR MATRIX HOMEOSTASIS?

In the structural scafold of **ECM** is important the **cytokines controlled balance between fibrolysis and fibrogenesis**. **Interleukin-1, interferon-gamma and TNF** stimulate **proteolytic enzyme as TGF-beta supported by interleukin-4 and interleukin-10** always stimulates **inhibitors** of proteolytic enzymes.



Siwik DA, Colucci WS. Regulation of matrix metalloproteinases by cytokines and reactive oxygen/nitrogen species in the myocardium. Heart Fail Rev. 2004;9(1):43-51.

SCIENCE ADVANCES | RESEARCH ARTICLE

CELL BIOLOGY

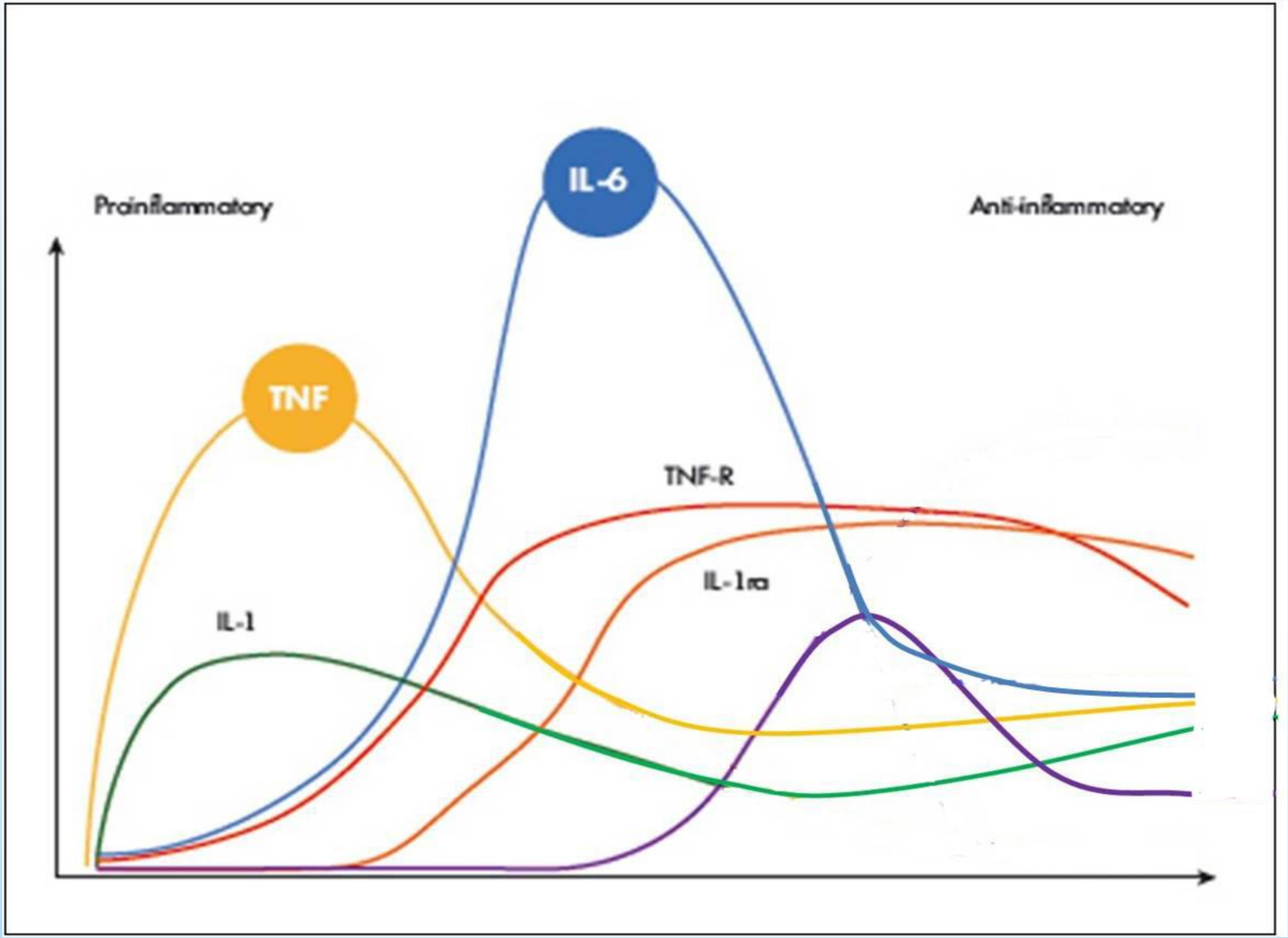
Cellular stiffness sensing through talin 1 in tissue mechanical homeostasis

Manasa Chanduri[1]†, Abhishek Kumar[1]†, Dar Weiss[2], Nir Emuna[2], Igor Barsukov[3], Miusi Shi[1]‡, Keiichiro Tanaka[1], Xinzhe Wang[4], Amit Datye[4], Jean Kanyo[5], Florine Collin[5], TuKiet Lam[5,6], Udo D. Schwarz[4,7], Suxia Bai[8], Timothy Nottoli[8], Benjamin T Goult[3,9], Jay D. Humphrey[2], Martin A. Schwartz[1,2,10]*

Tissue mechanical properties are determined mainly by the extracellular matrix (ECM) and actively maintained by resident cells. Despite its broad importance to biology and medicine, tissue mechanical homeostasis remains poorly understood. To explore cell-mediated control of tissue stiffness, we developed mutations in the mechanosensitive protein talin 1 to alter cellular sensing of ECM. Mutation of a mechanosensitive site between talin 1 rod-domain helix bundles R1 and R2 increased cell spreading and tension exertion on compliant substrates. These mutations promote binding of the ARP2/3 complex subunit ARPC5L, which mediates the change in substrate stiffness sensing. Ascending aortas from mice bearing these mutations showed less fibrillar collagen, reduced axial stiffness, and lower rupture pressure. Together, these results demonstrate that cellular stiffness sensing contributes to ECM mechanics, directly supporting the mechanical homeostasis hypothesis and identifying a mechanosensitive interaction within talin that contributes to this mechanism.

A new concept

Induction of the **inflammation pro-resolution phase** and **tissue repair.**



Petersen AM[1], Pedersen BK. The anti-Inflammatory effect of exercise. J Appl Physiol (1985). 2005 Apr;98(4):1154-62
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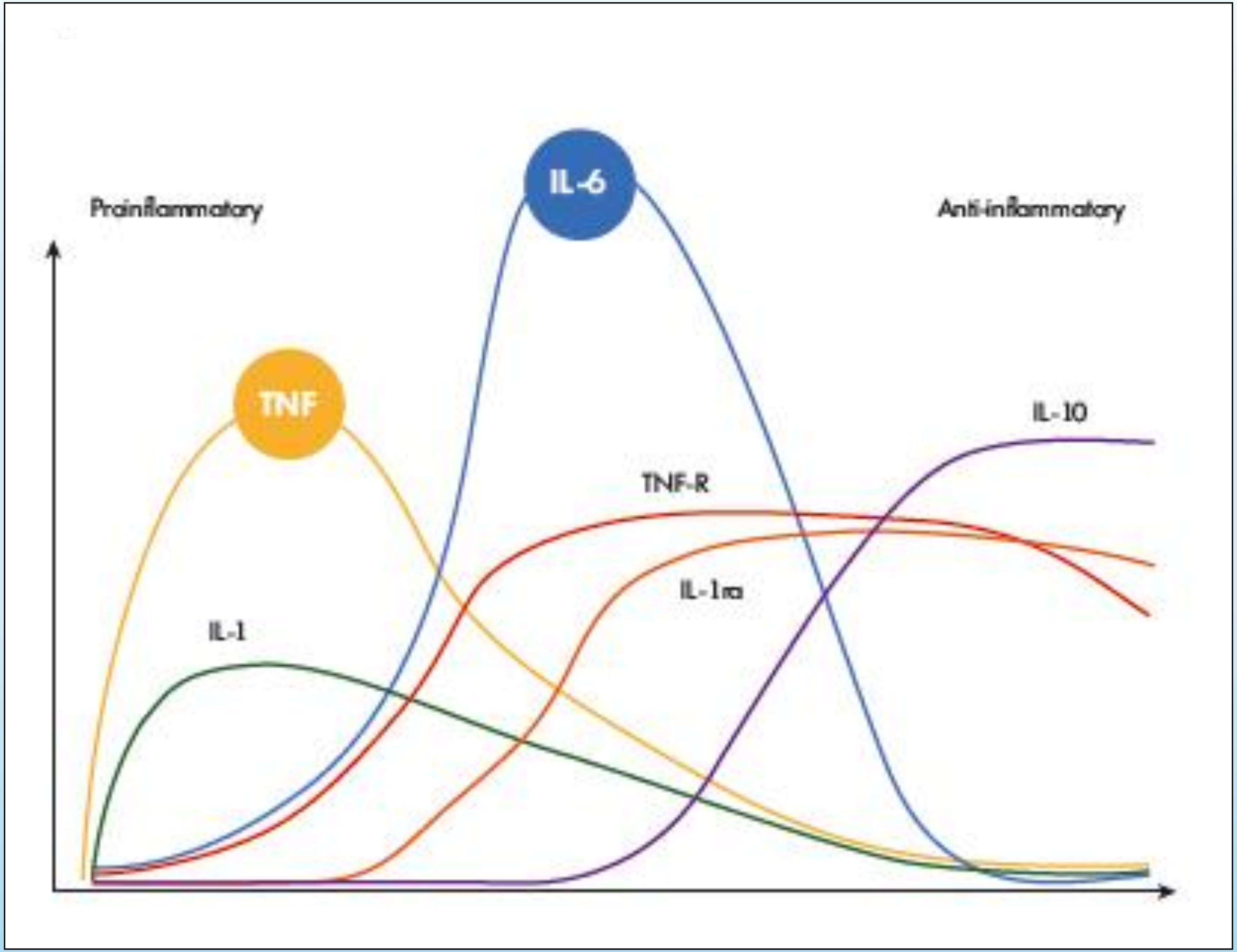

Petersen AM[1], Pedersen BK. The anti-Inflammatory effect of exercise. J Appl Physiol (1985). 2005 Apr;98(4):1154-62

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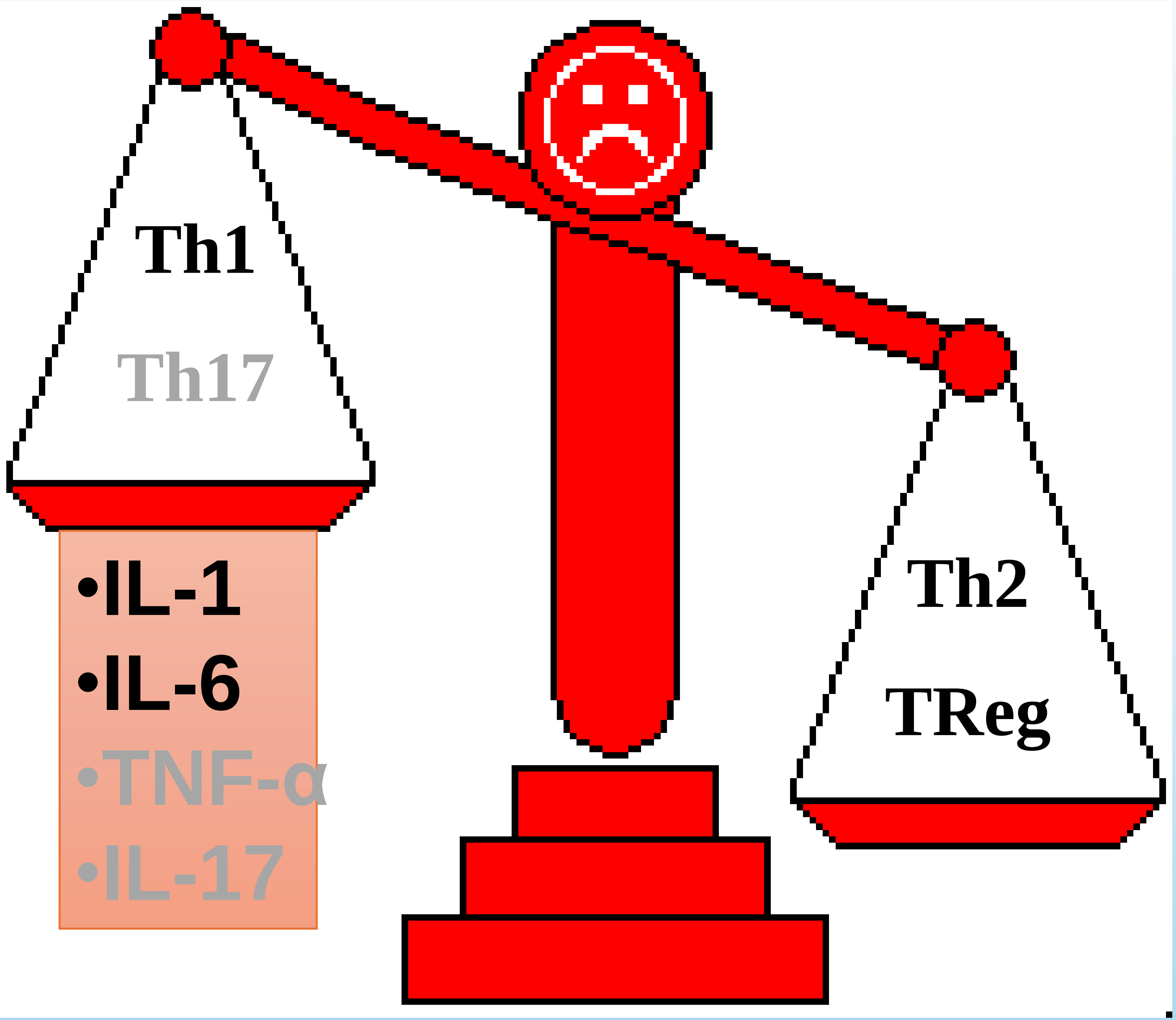
Th1
Th17
•IL-1
•IL-6
•TNF-α
•IL-17
Th2
TReg

CHANNELS
2024, VOL. 18, NO. 1, 2393088
https://doi.org/10.1080/19336950.2024.2393088

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REVIEW ARTICLE

OPEN ACCESS Check for updates

The role of mechanosensitive ion channel Piezo1 in knee osteoarthritis inflammation

Dingchang He[a], Xin Liu[a], Wenhao Yang[a], Taiyuan Guan[a], and Guoyou Wang[a,b]

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ABSTRACT

Mechanosensitive ion channel Piezo1 is known to mediate a variety of inflammatory pathways and is also involved in the occurrence and development of many orthopedic diseases. Although its role in the inflammatory mechanism of knee osteoarthritis (KOA) has been reported, a systematic explanation is yet to be seen. This article aims to summarize the role of inflammatory responses in the pathogenesis of KOA and elucidate the mechanism by which the Piezo1-mediated inflammatory response contributes to the pathogenesis of KOA, providing a theoretical basis for the prevention and treatment of knee osteoarthritis. The results indicate that in the mechanism leading to knee osteoarthritis, Piezo1 can mediate the inflammatory response through chondrocytes and synovial cells, participating in the pathological progression of KOA. Piezo1 has the potential to become a new target for the prevention and treatment of this disease. Additionally, as pain is one of the most severe manifestations in KOA patients, the inflammatory response mediated by Piezo1, which causes the release of inflammatory mediators and pro-inflammatory factors leading to pain, can be further explored.

ARTICLE HISTORY
Received 1 June 2024
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KEYWORDS
Osteoarthritis; Piezo1; inflammatory response; chondrocytes; synovial cells; pain

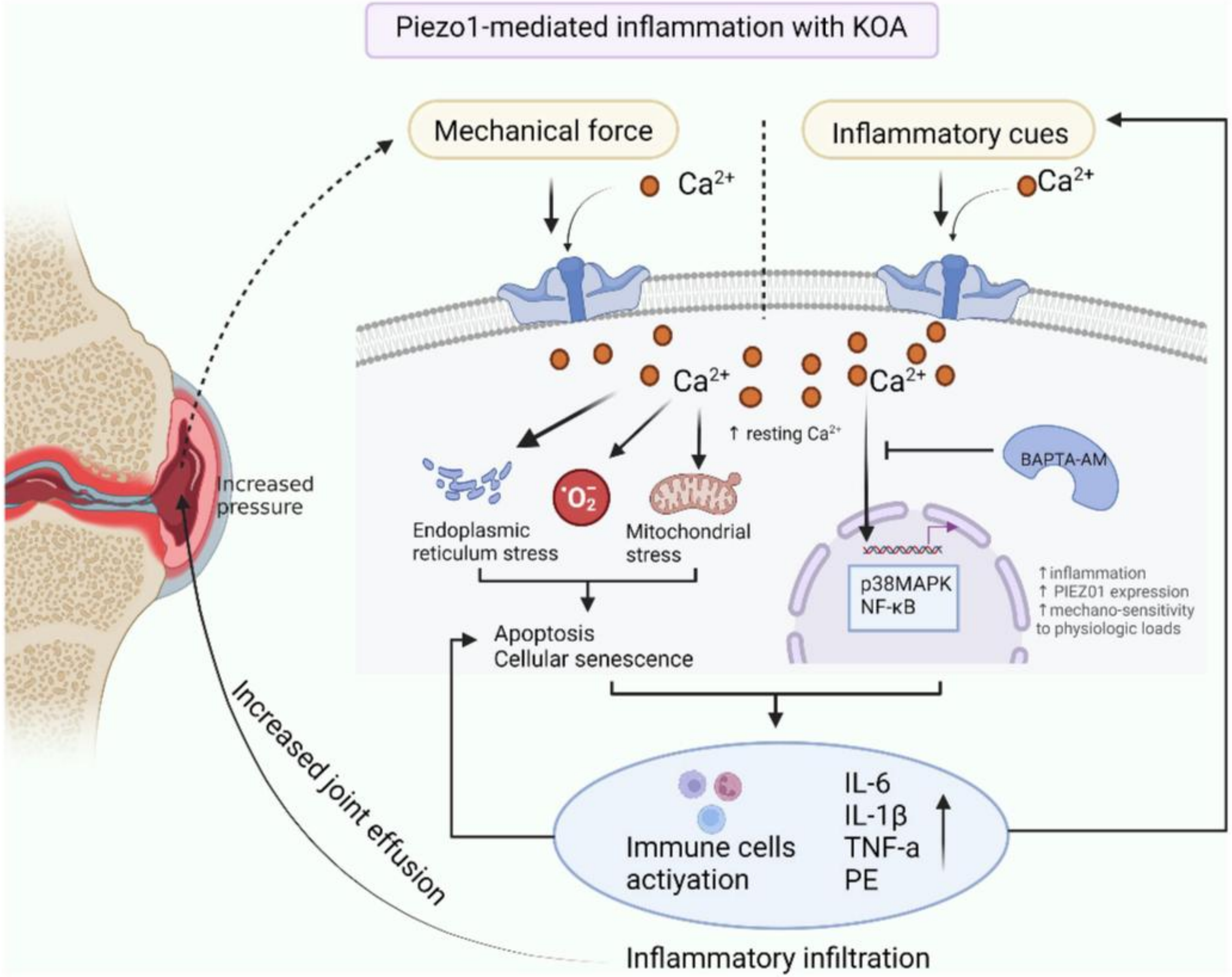
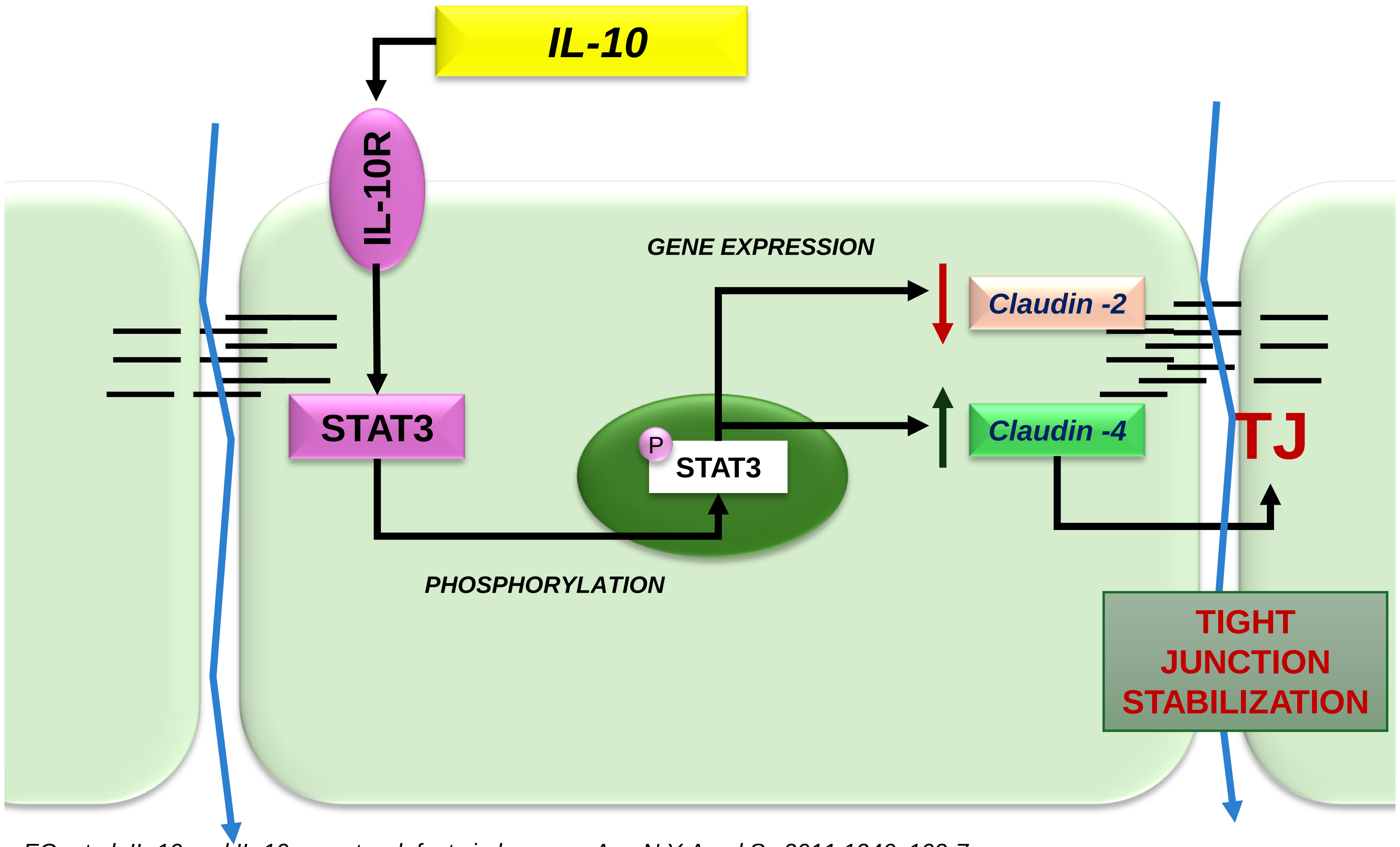


Figure 2. Schematic diagram of Piezo1-mediated inflammatory response KOA.

IL-10 PROTECTS EPITHELIAL CELLS AND TIGHT JUNCTIONS ENHANCING CLAUDIN-4 EXPRESSION (AND REDUCING CLAUDIN-2 SYNTHESIS)



•Glocker EO, et al. IL-10 and IL-10 receptor defects in humans. Ann N Y Acad Sc 2011;1246: 102-7.

•Zhang W, et al. Protective effect of bone marrow mesenchymal stem cells in intestinal barrier permeability after heterotopic intestinal transplantation.World J Gastroenterol. 2014;20(23):7442-51.

•García-Hernández V, et al. EGF regulates claudin-2 and -4 expression through Src and STAT3 in MDCK cells. J Cell Physiol. 2015;230(1):105-15.

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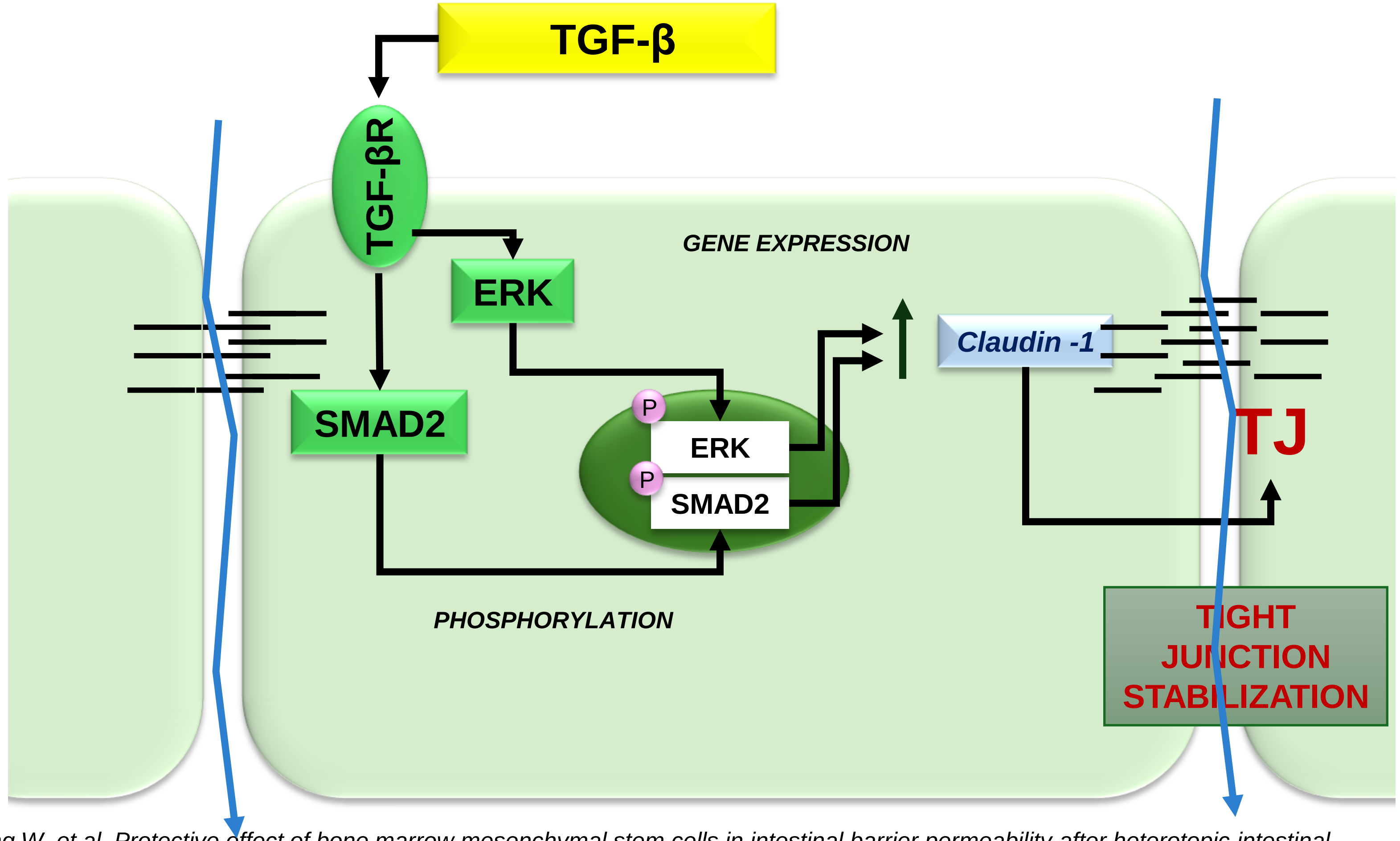
TGF-B STABILIZES TIGHT JUNCTIONS ENHANCING CLAUDIN 1 EXPRESSION



•Zhang W, et al. Protective effect of bone marrow mesenchymal stem cells in intestinal barrier permeability after heterotopic intestinal transplantation.World J Gastroenterol. 2014;20(23):7442-51.

•Howe KL, et al. Transforming growth factor-beta regulation of epithelial tight junction proteins enhances barrier function and blocks enterohemorrhagic Escherichia coli O157:H7-induced increased permeability. Am J Pathol. 2005;167(6):1587-97

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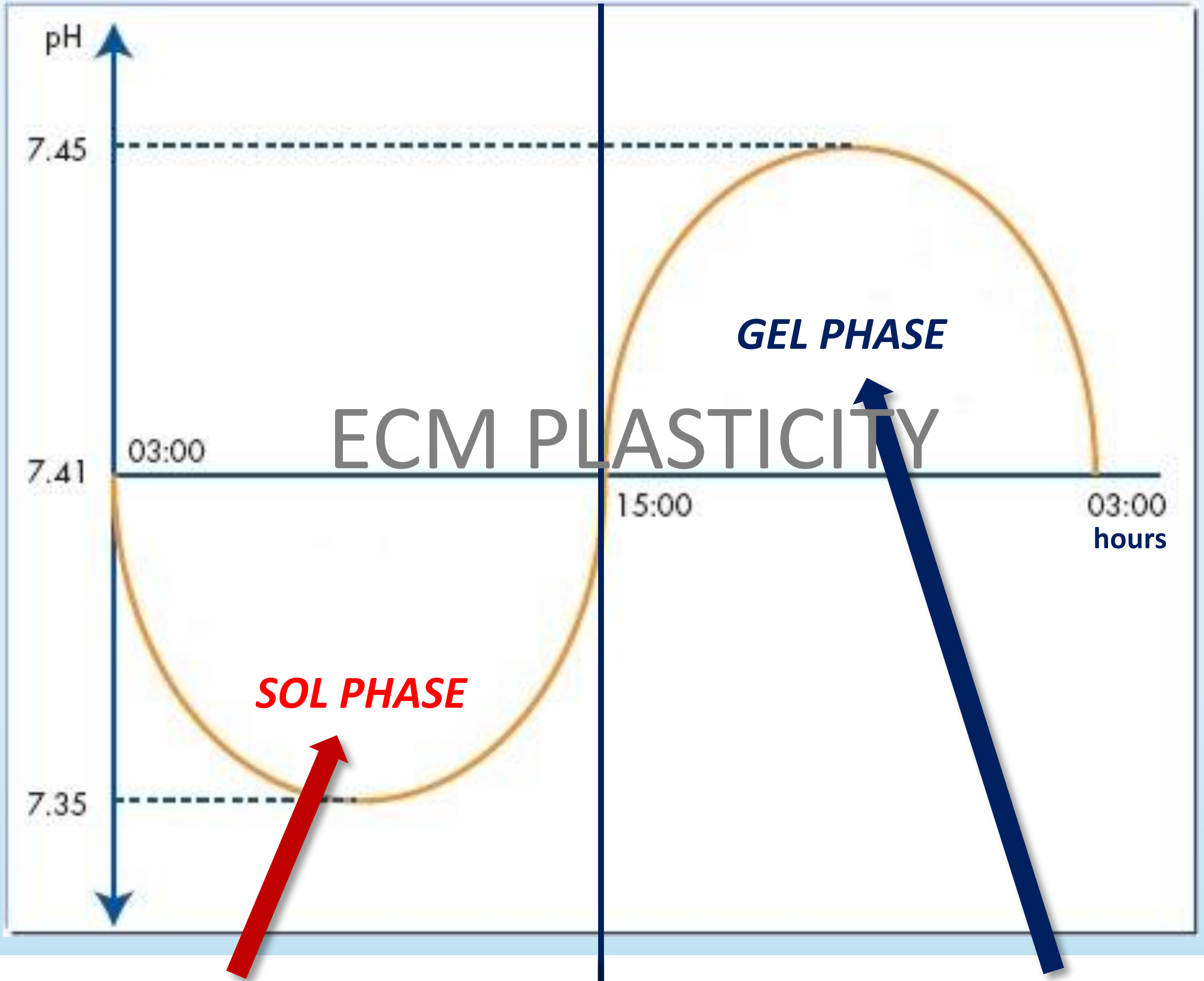
Journal of Cell Science. 2023 ago 1; 136 (15).

Mechanotransduction through hemidesmosomes during aging and longevity.

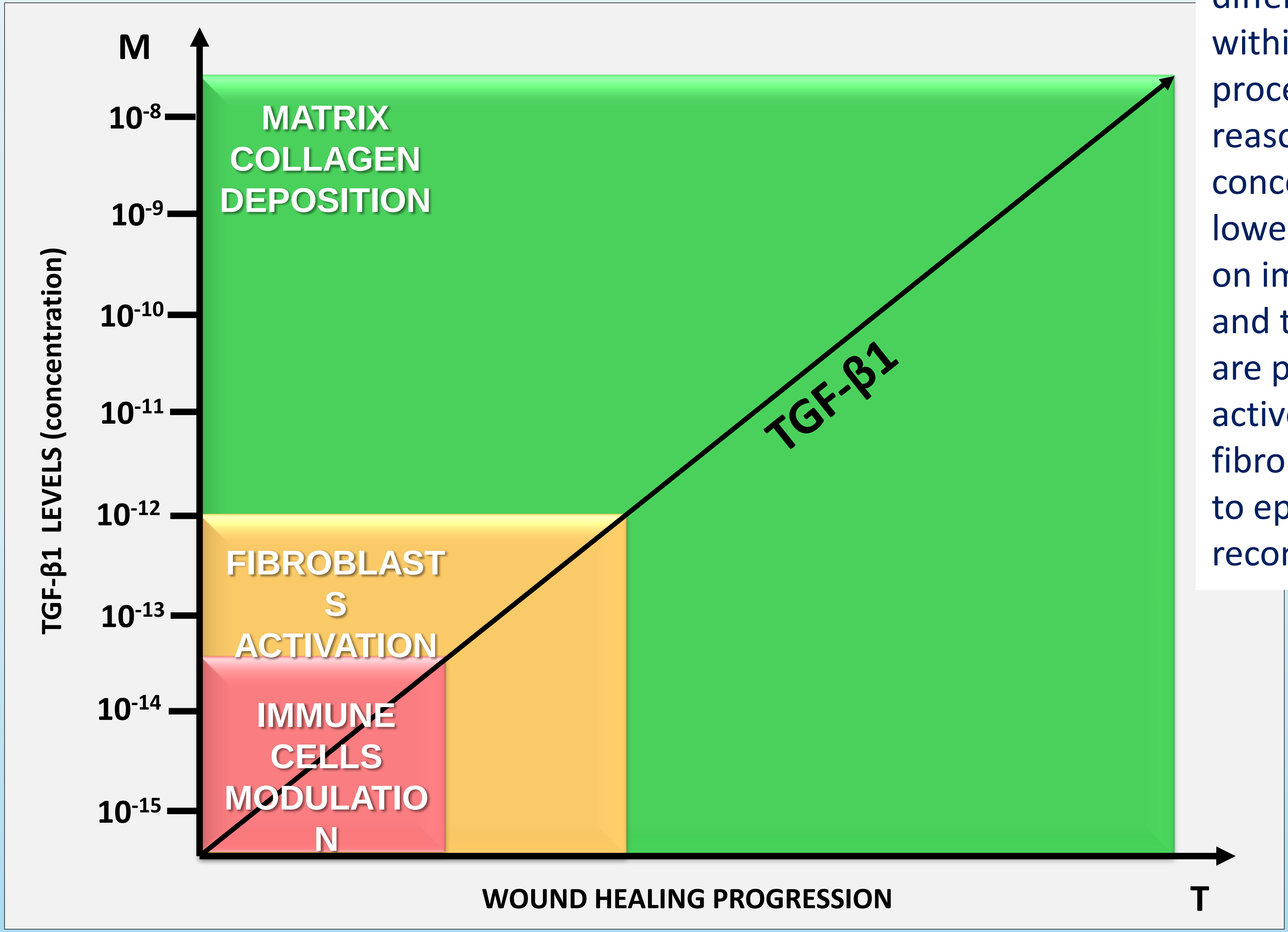
Hemidesmosomes are structural protein complexes localized at the interface of tissues with high mechanical demand and shear forces. Beyond tissue anchoring, hemidesmosomes have emerged as force-modulating structures important for translating mechanical cues into biochemical and transcriptional adaptation (i.e. mechanotransduction) across tissues. Here, we discuss the recent insights into the roles of hemidesmosomes in age-related tissue regeneration and aging in C. elegans, mice and humans. We highlight the emerging concept of preserved dynamic mechanoregulation of hemidesmosomes in tissue maintenance and healthy aging.

ECM PHYSIOLOGIC TURNOVER -CHRONOBIOLOGY-



- ***PROTEASE ACTIVITY***
- ***HYDROLYSIS OF MATRIX PROTEINS***
- ***MATRIX REMODELLING***
- ***SOL PHASE***
- ***INCREASE OF TEMP°***
- ***HISTAMINE ACTIVITY***
- ***MYELOID TENDENCY***
- ***SYMPATHETICOTONY***
- ***ACIDOSIS***

- ***ANTI-PROTEASE ACTIVITY***
- **RE-SYNTHESIS OF MATRIX PROTEINS**
- **REBUILDING OF MATRIX**
- **GEL PHASE**
- **DECREASING OF TEMP°**
- **LYMPHOID TENDENCY**
- **VAGOTONY**
- **ALKALOSIS**



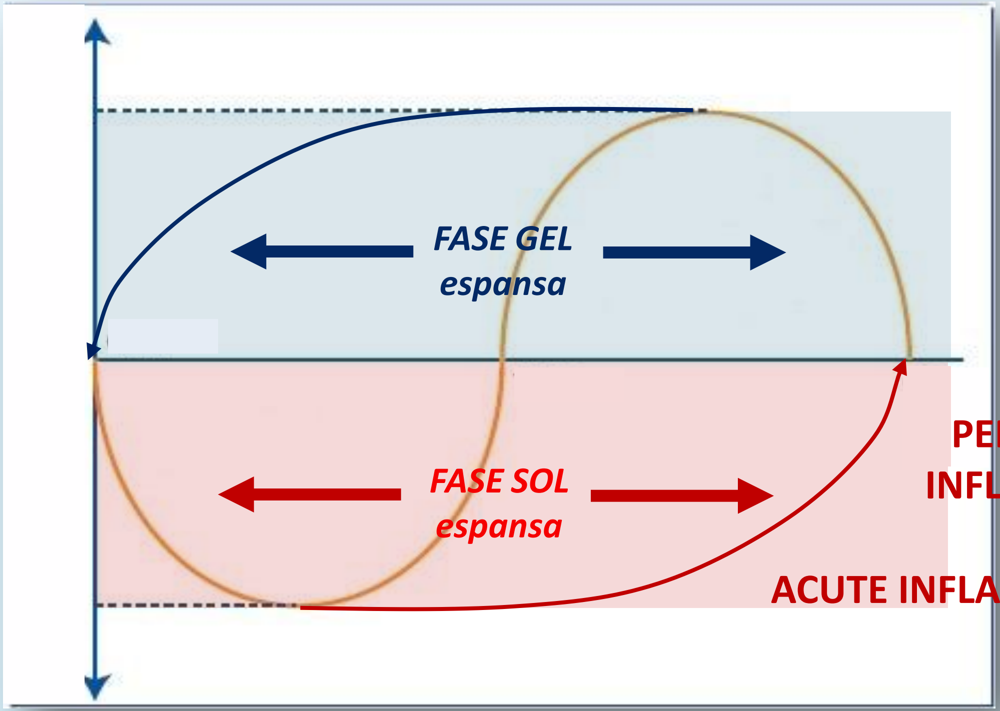
TGF- β1 exerts different function within healing processes in reason of its concentration: the lowest are active on immune cell and the highest are progressively active on fibroblasts leading to epithelial reconstruction.

Cytokines, ROS, pH and ECM modifications

FIBROSIS (TGF-β1)

ECM RIGIDITY
(deposition of type III collagen)

LOW GRADE CHRONIC INFLAMMATION (IL-6)



PERSISTENT ACUTE INFLAMMATION (IL-1)

ACUTE INFLAMMATION (IL-1)

- **OVEREXPRESSION OF PRO-INFLAMMATORY CYTOKINES**
- **OVEREXPRESSION OF ROS**
- **REDUCTION OF pH**

Review > J Mater Chem B. 2022 May 19. doi: 10.1039/d2tb00428c. Online ahead of print.

Magnetomechanical force: an emerging paradigm for therapeutic applications

Junlie Yao [1], Chenyang Yao [1, 2], Aoran Zhang [1], Xiawei Xu [1], Aiguo Wu [1, 3], Fang Yang [1, 3]

Affiliations + expand

PMID: 35587231 DOI: 10.1039/d2tb00428c

Abstract

Mechanical forces, which play a profound role in cell fate regulation, have prompted the rapid development and popularization of mechanobiology. More recently, magnetic fields in combination with intelligent materials featuring magnetic responsiveness have been identified as a spatially and time-controlled transducing paradigm to generate magnetomechanical forces and induce a therapeutic effect. Herein, recent magnetic materials and magnetic regulation systems are summarized, which offer opportunities for magnetomechanical force manipulation in a precise manner. Additionally, promising applications based on magnetomechanical force including drug controlled release, cancer therapy, and regenerative medicine are highlighted, with respect to both *in vitro* and *in vivo*. Furthermore, perspectives on the further development of magnetomechanical force are commented on, mainly emphasizing scientific restrictions and exploitation directions.

nature COMMUNICATIONS

ARTICLE

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https://doi.org/10.1038/s41467-022-30809-3 OPEN

Mechanically active integrins target lytic secretion at the immune synapse to facilitate cellular cytotoxicity

Mitchell S. Wang[1,2], Yuesong Hu[3], Elisa E. Sanchez[1,4], Xihe Xie[5], Nathan H. Roy[6], Miguel de Jesus[1], Benjamin Y. Winer[1], Elizabeth A. Zale[1], Weiyang Jin[7], Chirag Sachar[7], Joanne H. Lee[7], Yeonsun Hong[8], Minsoo Kim[8], Lance C. Kam[7], Khalid Salaita[3] & Morgan Huse[1✉]

Cytotoxic lymphocytes fight pathogens and cancer by forming immune synapses with infected or transformed target cells and then secreting cytotoxic perforin and granzyme into the synaptic space, with potent and specific killing achieved by this focused delivery. The mechanisms that establish the precise location of secretory events, however, remain poorly understood. Here we use single cell biophysical measurements, micropatterning, and functional assays to demonstrate that localized mechanotransduction helps define the position of secretory events within the synapse. Ligand-bound integrins, predominantly the $\alpha_L\beta_2$ isoform LFA-1, function as spatial cues to attract lytic granules containing perforin and granzyme and induce their fusion with the plasma membrane for content release. LFA-1 is subjected to pulling forces within secretory domains, and disruption of these forces via depletion of the adaptor molecule talin abrogates cytotoxicity. We thus conclude that lymphocytes employ an integrin-dependent mechanical checkpoint to enhance their cytotoxic power and fidelity.

ISDT International Society of Diamagnetic Therapy

13th – 14th September 2024

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frontiers in Cell and Developmental Biology

REVIEW
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doi: 10.3389/fcell.2022.852878

Check for updates

Integrin Regulated Autoimmune Disorders: Understanding the Role of Mechanical Force in Autoimmunity

Souradeep Banerjee[*†], *Ritika Nara*[†], *Soham Chakraborty, Debojyoti Chowdhury and Shubhasis Haldar*[*]

Department of Biological Sciences, Ashoka University, Sonepat, India

The pathophysiology of autoimmune disorders is multifactorial, where immune cell migration, adhesion, and lymphocyte activation play crucial roles in its progression. These immune processes are majorly regulated by adhesion molecules at cell–extracellular matrix (ECM) and cell–cell junctions. Integrin, a transmembrane focal adhesion protein, plays an indispensable role in these immune cell mechanisms. Notably, integrin is regulated by mechanical force and exhibit bidirectional force transmission from both the ECM and cytosol, regulating the immune processes. Recently, integrin mechanosensitivity has been reported in different immune cell processes; however, the underlying mechanics of these integrin-mediated mechanical processes in autoimmunity still remains elusive. In this review, we have discussed how integrin-mediated mechanotransduction could be a linchpin factor in the causation and progression of autoimmune disorders. We have provided an insight into how tissue stiffness exhibits a positive correlation with the autoimmune diseases' prevalence. This provides a plausible connection between mechanical load and autoimmunity. Overall, gaining insight into the role of mechanical force in diverse immune cell processes and their dysregulation during autoimmune disorders will open a new horizon to understand this physiological anomaly.

Keywords: integrin, autoimmune diseases, mechanical force, focal adhesion, tissue stiffness

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2024

The *plasticity* of ECM is fundamental for the maintenance of all its biological functions.

The plasticity of ECM is ensured by its physiological SOL-GEL TURNOVER.

Progress in Biophysics and Molecular Biology 141 (2019) 25–36

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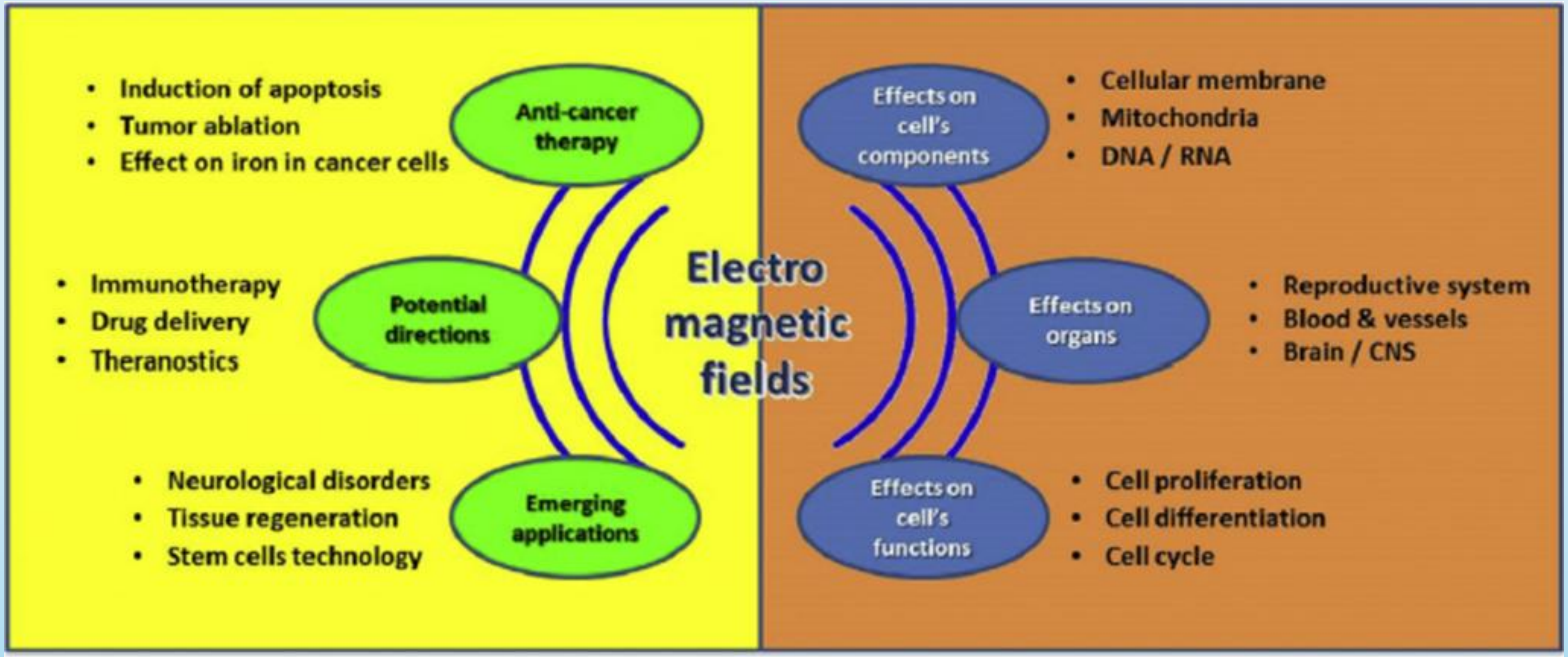
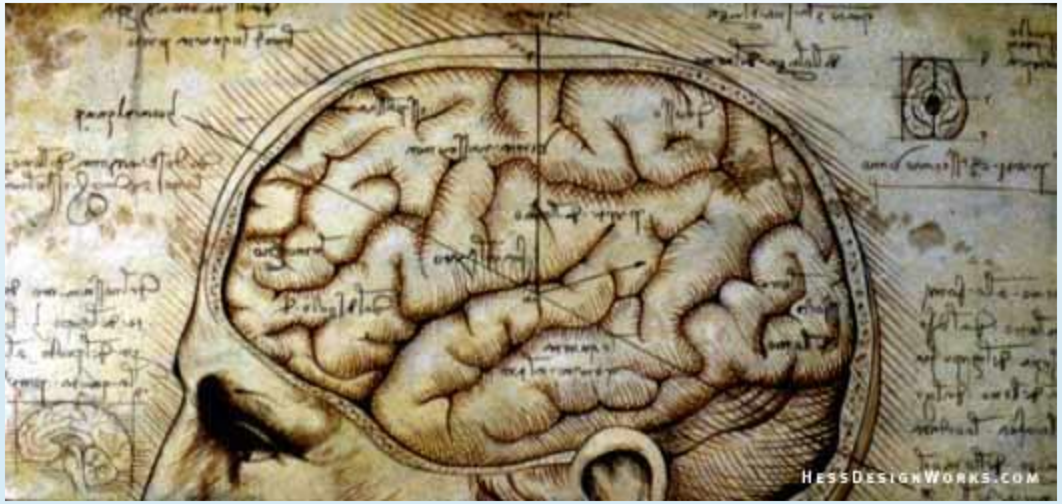
Biological effects of non-ionizing electromagnetic fields: Two sides of a coin

Timur Saliev [a, b, *], Dinara Begimbetova [b], Abdul-Razak Masoud [b], Bakhyt Matkarimov [b]





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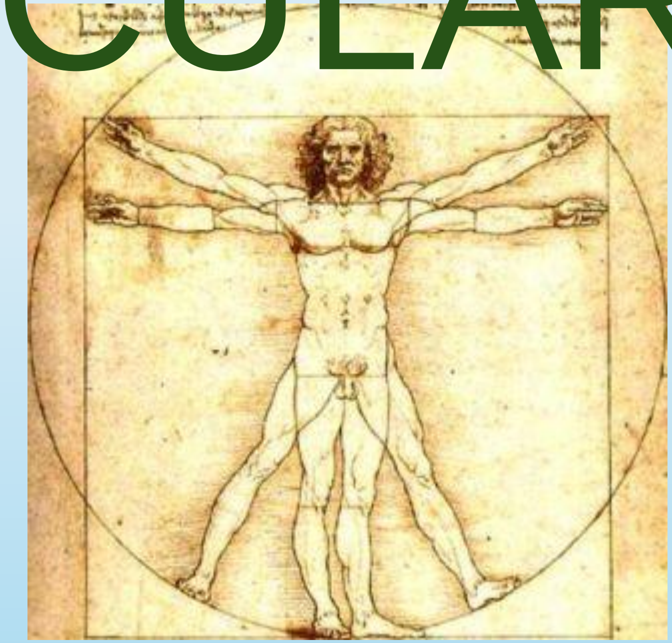

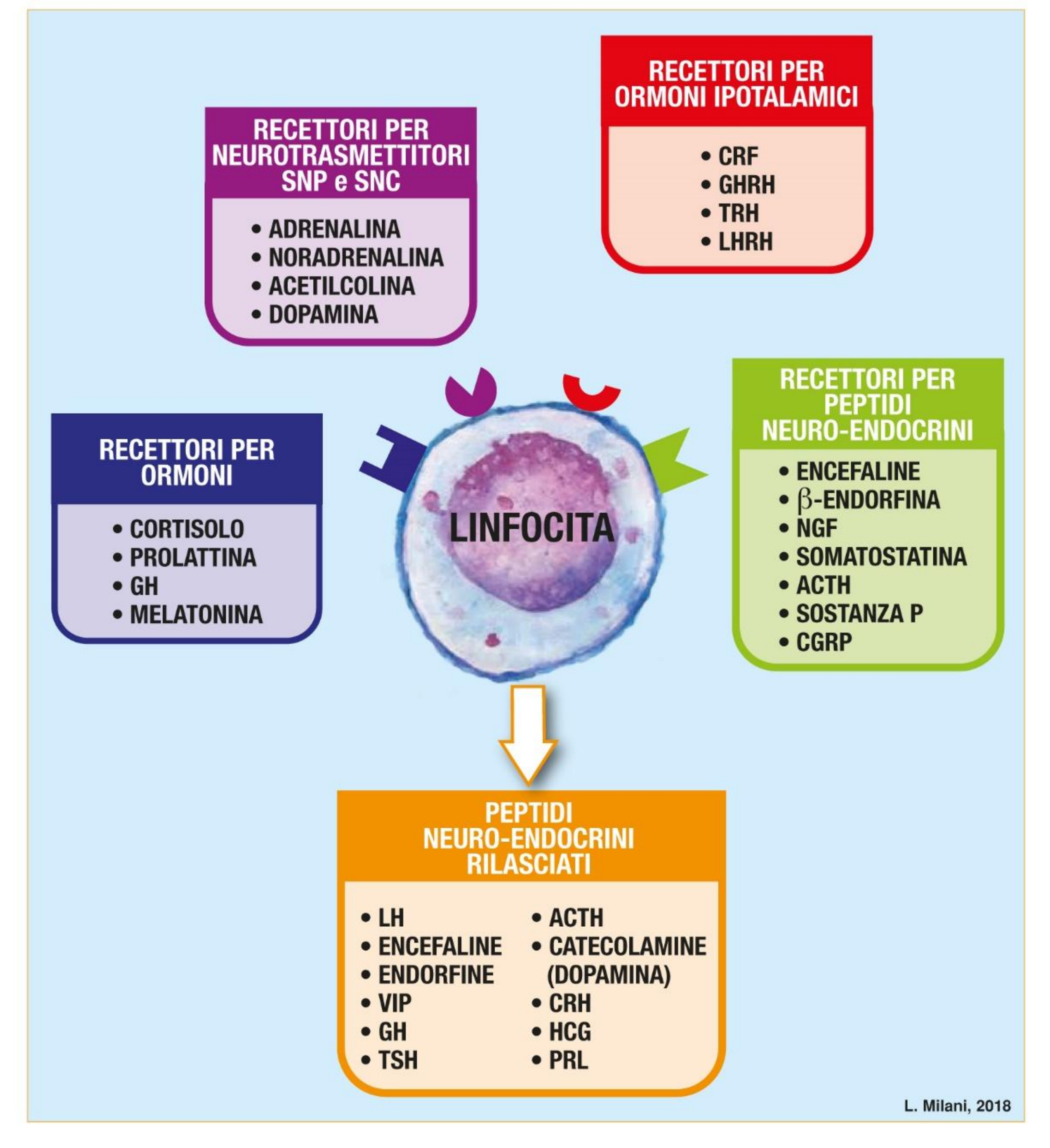
RECETTORI PER NEUROTRASMETTITORI SNP e SNC
• ADRENALINA
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• DOPAMINA
RECETTORI PER ORMONI IPOTALAMICI
• CRF
• GHRH
• TRH
• LHRH
RECETTORI PER ORMONI
• CORTISOLO
• PROLATTINA
• GH
• MELATONINA
LINFOCITA
RECETTORI PER PEPTIDI NEURO-ENDOCRINI
• ENCEFALINE
• β-ENDORFINA
• NGF
• SOMATOSTATINA
• ACTH
• SOSTANZA P
• CGRP
PEPTIDI NEURO-ENDOCRINI RILASCIATI
• LH
• ENCEFALINE
• ENDORFINE
• VIP
• GH
• TSH
• ACTH
• CATECOLAMINE (DOPAMINA)
• CRH
• HCG
• PRL
L. Milani, 2018

STRESS AND IMMUNE SYSTEM

IL-2 and IL-6 trend in presence of psychologic stress

NeuroImmunoModulation

Original Paper

Neuroimmunomodulation 2007;14:248–254
DOI: 10.1159/000112050

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Published online: December 10, 2007

Disturbance of Serum Interleukin-2 and Interleukin-8 Levels in Posttraumatic and Non-Posttraumatic Stress Disorder Earthquake Survivors in Northern China

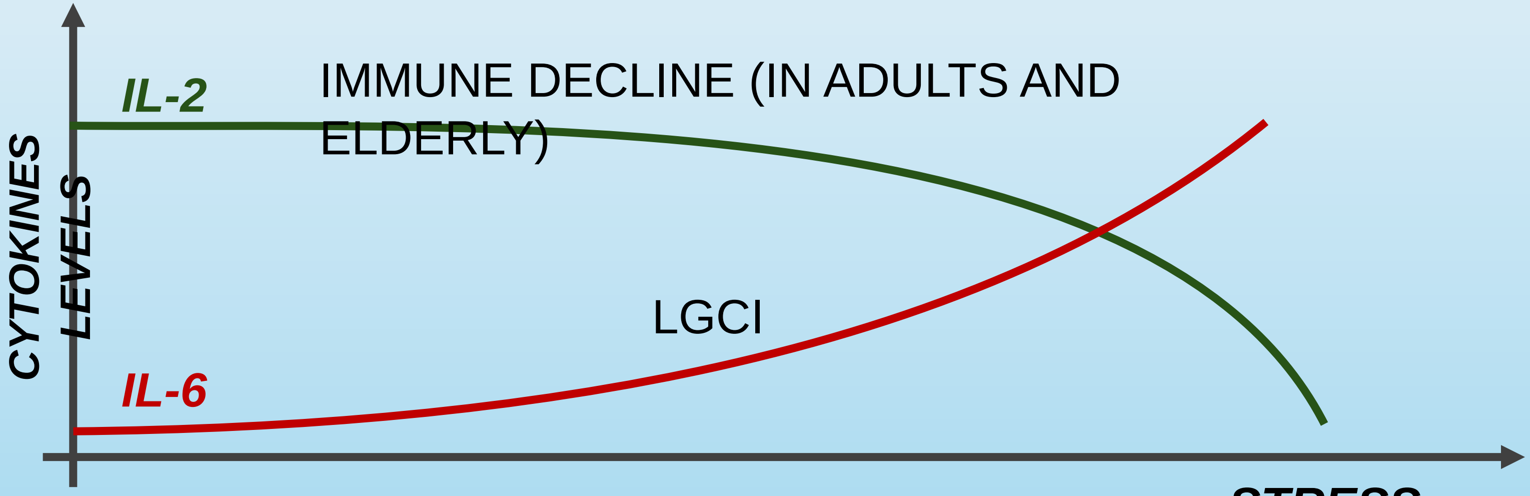
Yuqing Song[a, b] Dongfeng Zhou[a] Zhenquan Guan[a] Xiangdong Wang[a]

frontiers in Neuroscience

MINI REVIEW
published: 24 April 2019
doi: 10.3389/fnins.2019.00384

The Interplay Between Stress, Inflammation, and Emotional Attention: Relevance for Depression

*Viktoriya Maydych**



13th – 14th September 2024

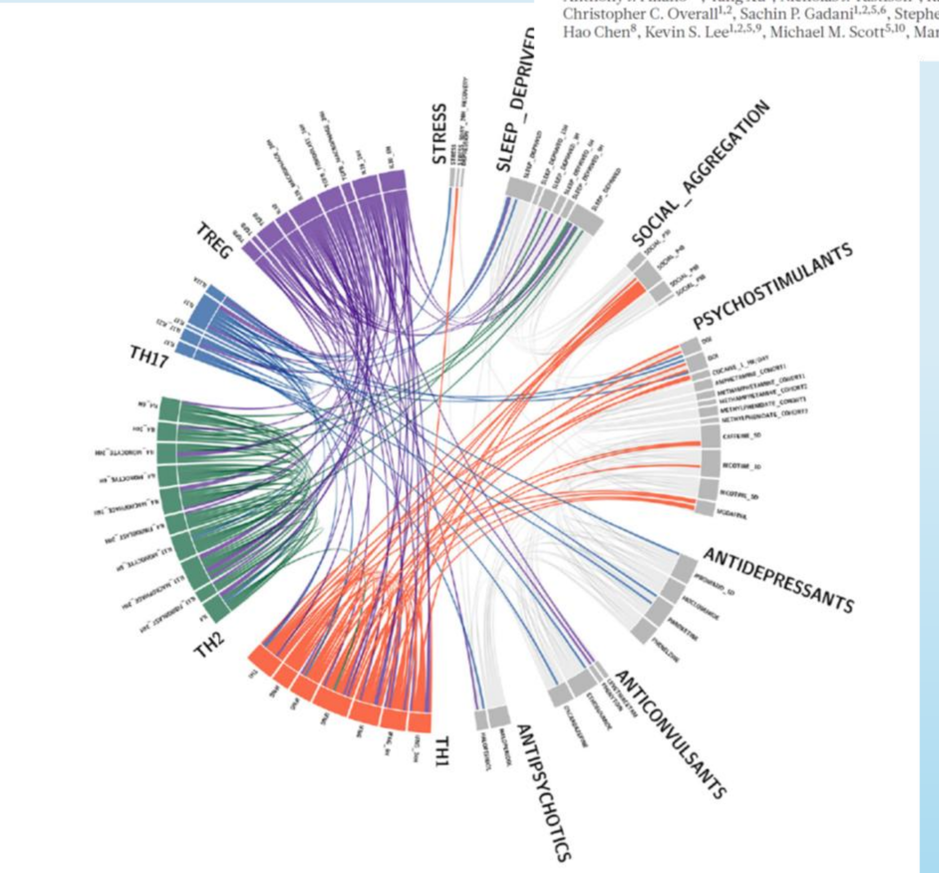
The role of IFN-γ in presence of psychological stress

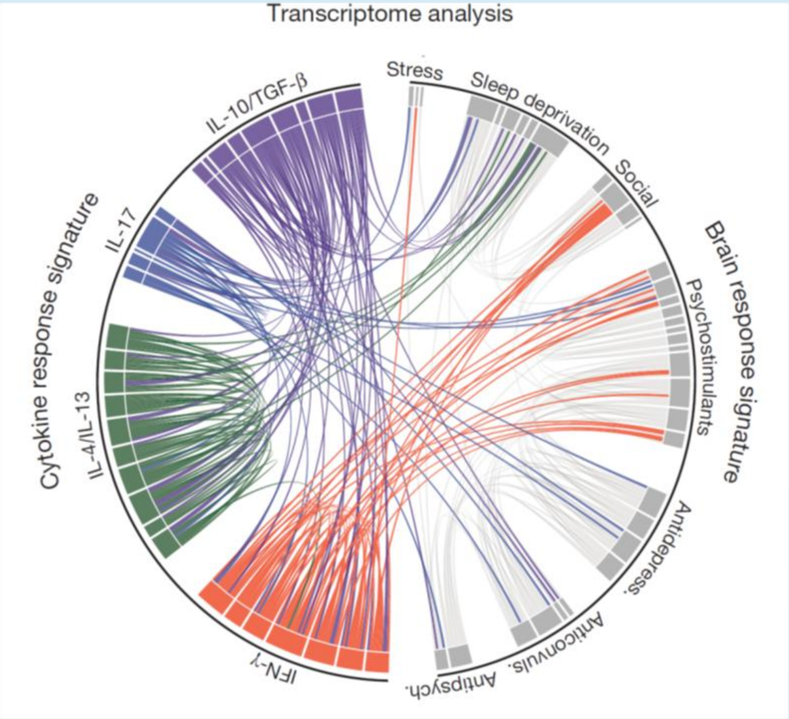
LETTER

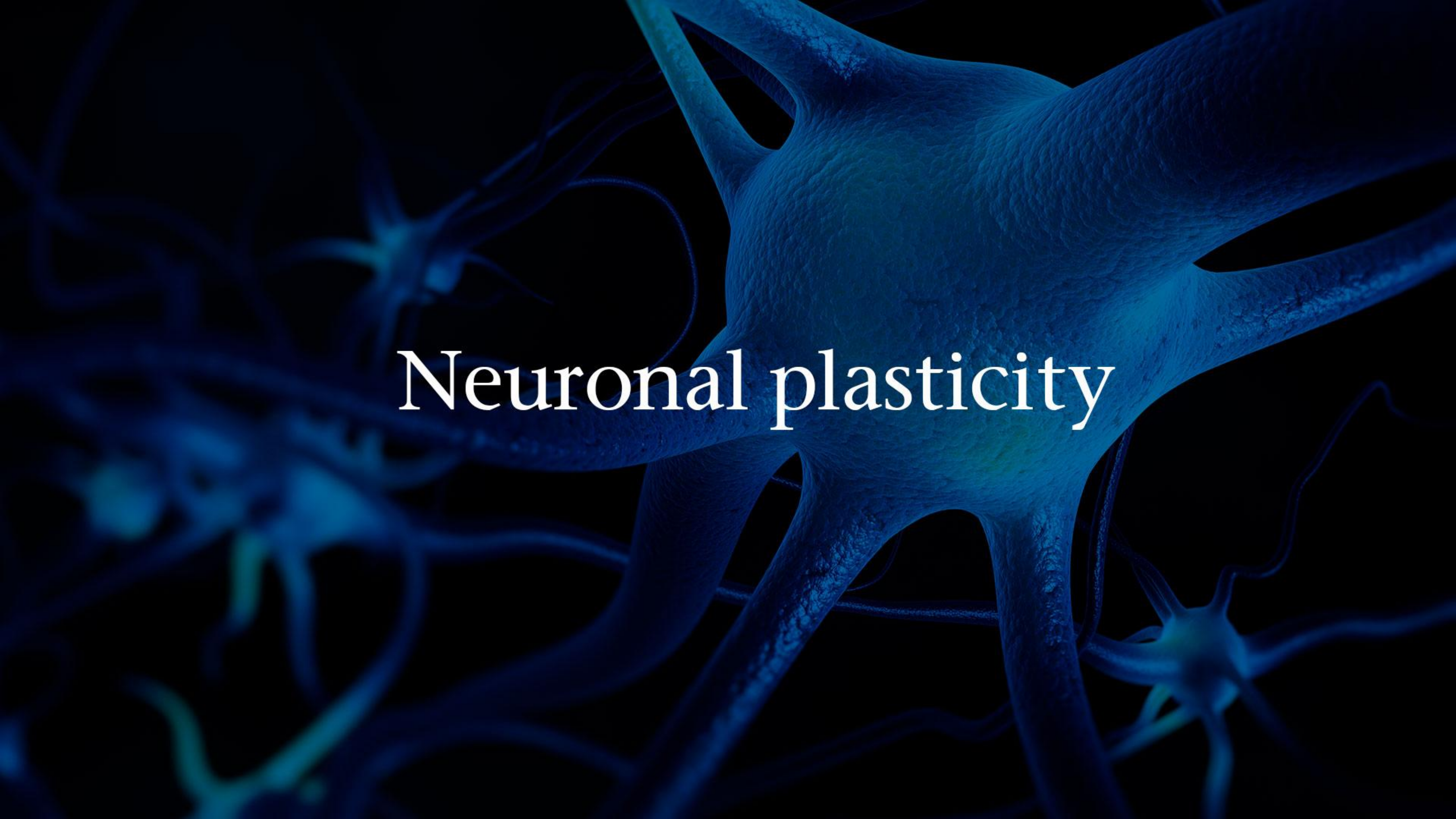
doi:10.1038/nature18626

Unexpected role of interferon-γ in regulating neuronal connectivity and social behaviour

Anthony J. Filiano[1,2], Yang Xu[3], Nicholas J. Tustison[4], Rachel L. Marsh[1,2], Wendy Baker[1,2], Igor Smirnov[1,2], Christopher C. Overall[1,2], Sachin P. Gadani[1,2,5,6], Stephen D. Turner[7], Zhiping Weng[8], Sayeda Najamussahar Peerzade[3], Hao Chen[8], Kevin S. Lee[1,2,5,9], Michael M. Scott[5,10], Mark P. Beenhakker[5,10], Vladimir Litvak[3]* & Jonathan Kipnis[1,2,5,6]*



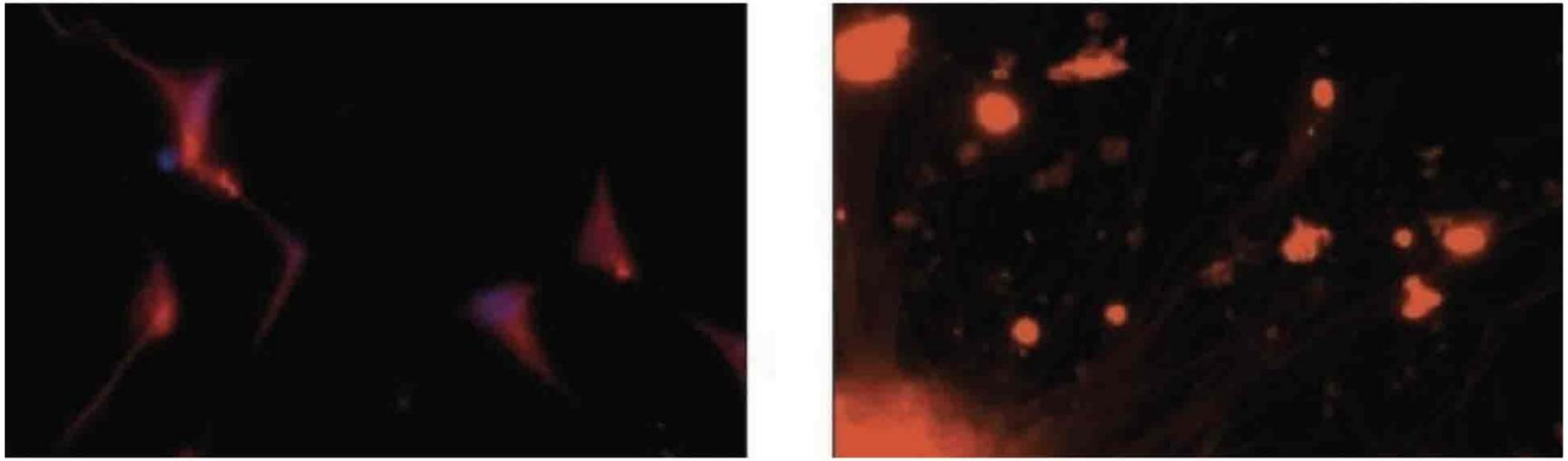



Neuronal plasticity

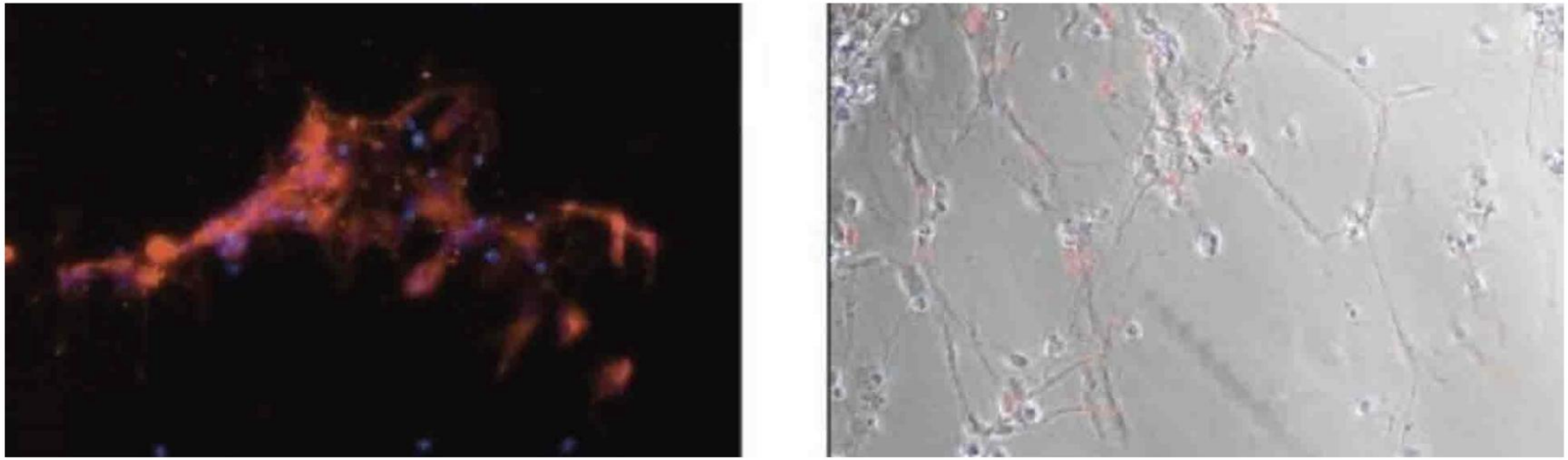
General concepts

Neuroplasticity is a process that represents the ability of the nervous system to change its reactivity as a result of successive activations. Such reactivity allows nerve tissue to undergo adaptive or reorganization changes in a physiological state with or without alteration. It is also considered as any brain response that originates against internal or external changes and is due to reorganization changes in perception and cognition. This group of definitions approximates neuroplasticity, as one of the substrates that supports highly complex processes, such as higher cognitive functions, understood from a connectionist and non-locationist perspective.

Neurogenesis has been reported to persist in adults in certain brain regions, such as the hippocampus, the olfactory mucosa and the periventricular area. One way to materialize the neuroplastic process is through the cerebral cortex. This is how we talk about cortical plasticity and several authors divide it into two threads: physiological cortical plasticity (substrate of learning and human memory, and subprocess that is carried out in neurodevelopment), and pathological cortical plasticity (which is subdivided into adaptive and poorly adaptive). Neuroplasticity is the basis and foundation of experimental and clinical neurorehabilitation processes. For this reason, in 2006, neuroplasticity was defined as a continuous, short, medium and long-term process of remodeling of neurosynaptic maps, which optimizes the functioning of brain networks during phylogeny, ontogeny and after system damage nervous. The neuroplasticity that occurs during ontogeny for the development of new circuits induced by the learning and maintenance of neural networks, both in adults and in the elderly, is called natural plasticity. After peripheral or central lesions of the nervous system there is remodeling or changes that underlie partial or complete clinical recovery, and is referred to as post-lesion plasticity. Bruce Dobkin, one of the leading experts in neuronal plasticity in the clinical field, divides plastic mechanisms into two groups: plasticity of neural networks and plasticity at synapses.



Astrocytes and astrogenesis



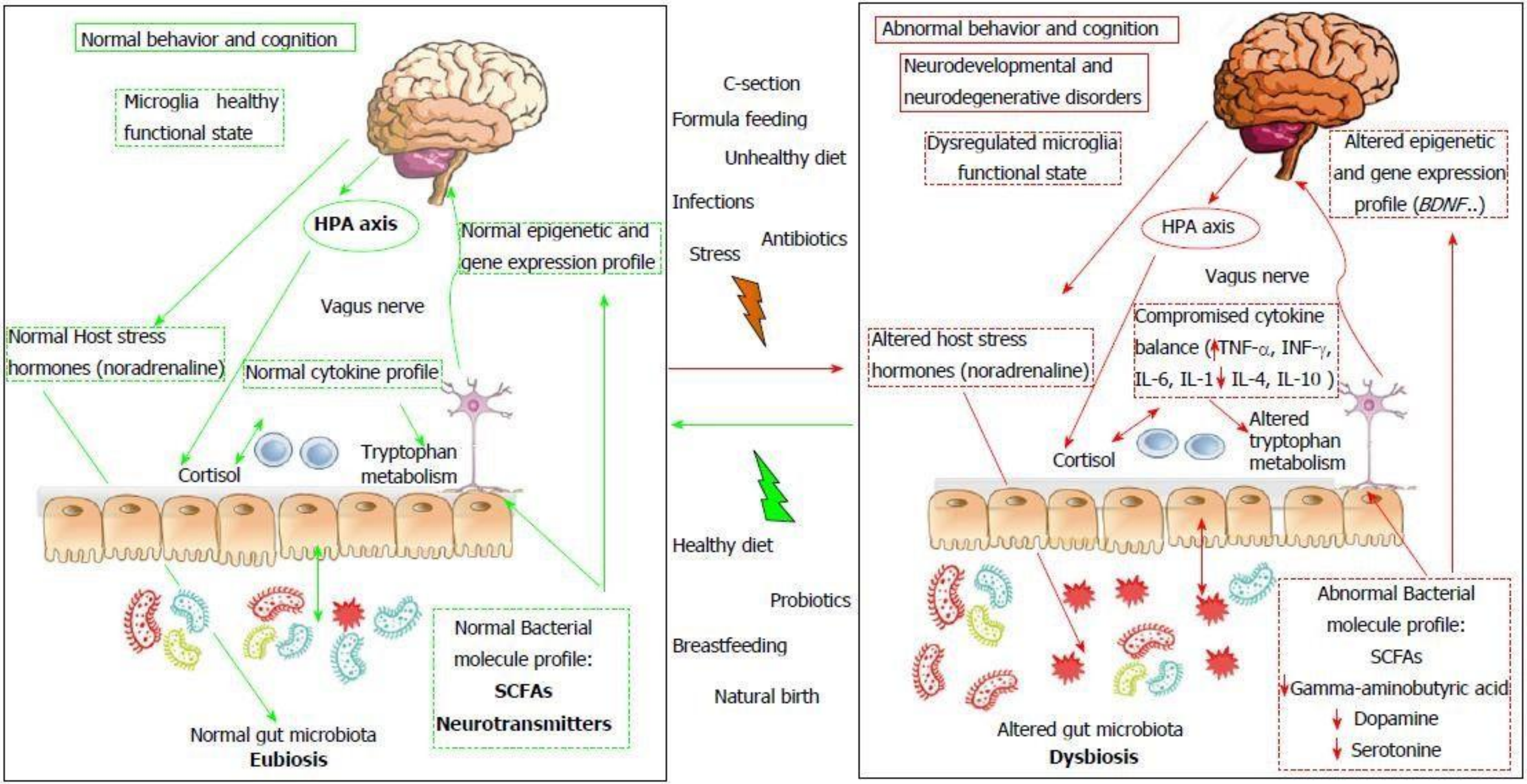
Oligodendrocytes and oligodendrogenesis

Biomolecular processes of neurobiochemical, neurogenomic and neuroproteomic type, allow that the neuronal response to inputs or signaling is not always programmed in a constitutive way. These processes are mentioned below.

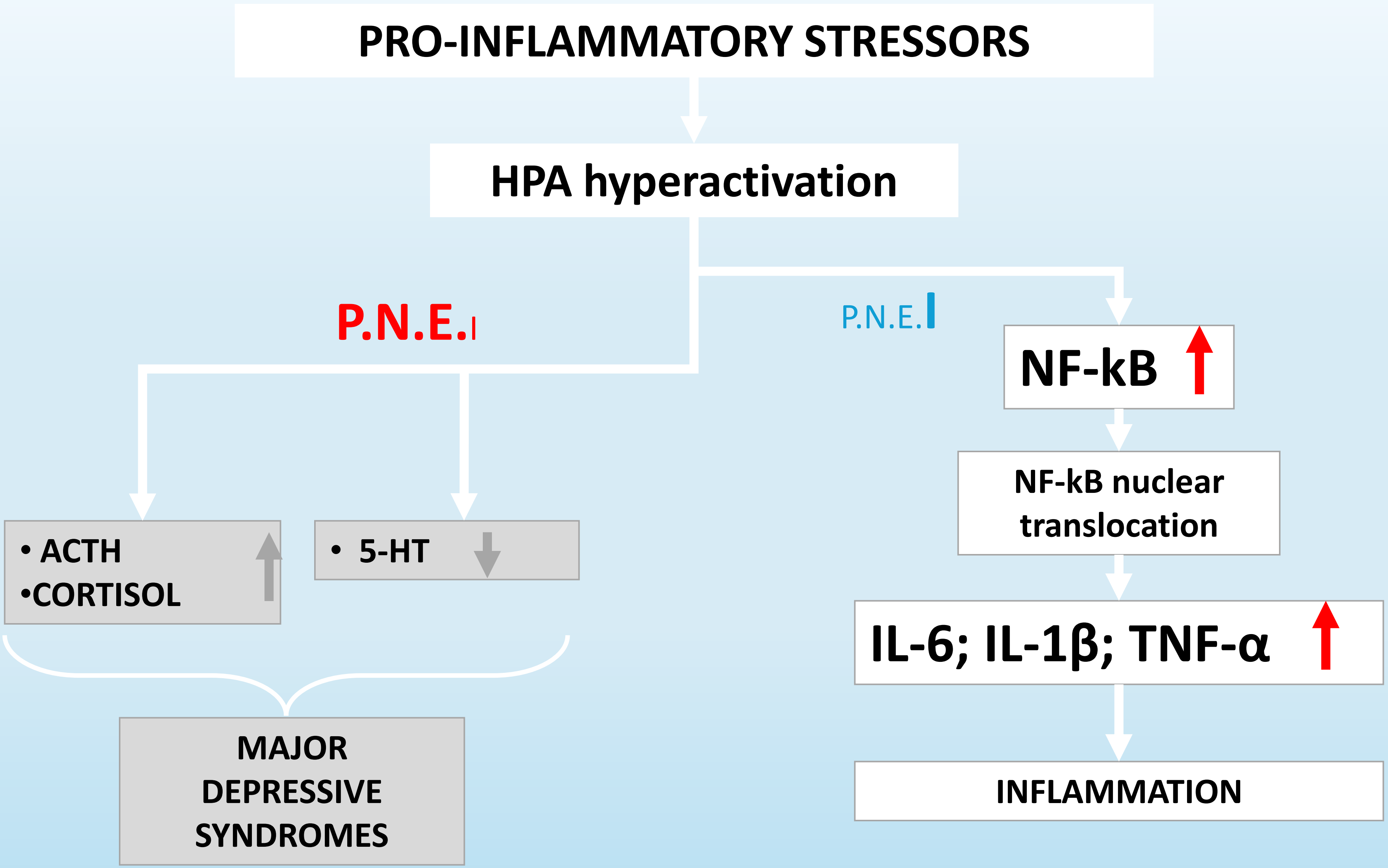
Genetics and protein expression in brain plasticity, from the postgenomic era, with works of genetics and protein expression - necessary for the acquisition and development of human language -, began a large series of discoveries that revealed products of immediate genes in synaptic plasticity (FOX, Homer1a and NACC-1 gene type), protein signaling of neuroplastic changes in frontal and prefrontal cortex, growth factors such as cerebral neurotrophic factor (BDNF), the Vascular endothelial growth (VEGF), insulin-derived growth factor (IGF) and apoproteins. Neuroplastic homeostasis, largely mediated by IGF and the molecular mechanisms of synaptic plasticity, play an important role in the regulation of neurogenic processes (cell birth, promotion, maturation and neuronal maintenance. FOXP2 gene is one of the genes of neuroplasti-city more studied so far, since language as an innate and acquired process, requires processes of physiological and natural plasticity.

This gene is expressed in motor circuits related to language and speech (basal ganglia, thalamus, inferior olives and cerebellum). It belongs to a member of the large FOX family, transcription factors. FOXP2 mutations are associated with difficulties in learning and language acquisition and in their normal expression are involved in the production of sequences of coordinated facial gold movements. There are other genes such as the ε2 and ε3 alleles of the apo E proteins, which appear to be related to a greater capacity for synaptic repair, so they are capable of inducing improvements in neuroplasticity. Neuro biochemistry and physiology of some brain plasticity processes. Neuroplasticity has several mechanisms of electrical, genetic, structural, biochemical and functional order that represent more one of the most complete definitions was described by Mary L. Dombovy in 2011, who says that plasticity are changes in neural networks in response to training , injury, rehabilitation, pharmacotherapy, electrical or magnetic stimulation and gene and stem cell therapies.

The plasticity of the central nervous system includes neurogenesis, apoptosis, dendritic and axonic outbreaks, long-term potentiation of synaptic transmission, long-term depression of synaptic transmission, recruitment of the adjacent cortex and recruitment of the contralateral hemisphere. From the above, it is known that the nervous system has more than one mechanism of neuroplasticity. Among them are the synaptic plasticity and the plasticity of intrinsic neuronal excitability and those mentioned above. The level of complexity is so high that the understanding of this biological phenomenon requires the focus of a systems biology, computational models of synaptic and neuroinformatic plasticity.



Normal behavior and cognition
Microglia healthy functional state
HPA axis
Normal epigenetic and gene expression profile
Vagus nerve
Normal Host stress hormones (noradrenaline)
Normal cytokine profile
Cortisol
Tryptophan metabolism
Normal Bacterial molecule profile:
SCFAs
Neurotransmitters
Normal gut microbiota
Eubiosis
C-section
Formula feeding
Unhealthy diet
Infections
Stress
Antibiotics
Healthy diet
Probiotics
Breastfeeding
Natural birth
Abnormal behavior and cognition
Neurodevelopmental and neurodegenerative disorders
Dysregulated microglia functional state
Altered epigenetic and gene expression profile (BDNF..)
HPA axis
Vagus nerve
Compromised cytokine balance (↑TNF-α, INF-γ, IL-6, IL-1 ↓ IL-4, IL-10)
Altered host stress hormones (noradrenaline)
Cortisol
Altered tryptophan metabolism
Abnormal Bacterial molecule profile:
SCFAs
↓Gamma-aminobutyric acid
↓ Dopamine
↓ Serotonine
Altered gut microbiota
Dysbiosis



Leonard BE. Impact of inflammation on neurotransmitter changes in major depression: An insight into the action of antidepressants. Progress in Neuro-Psychopharmacology & Biological Psychiatry 2014. Benson S.
Effects of obesity on neuroendocrine, cardiovascular, and immune cell responses to acute psychosocial stress in premenopausal women. Psychoneuroendocrinology. 2009

Possible links between chronic depression and dementia

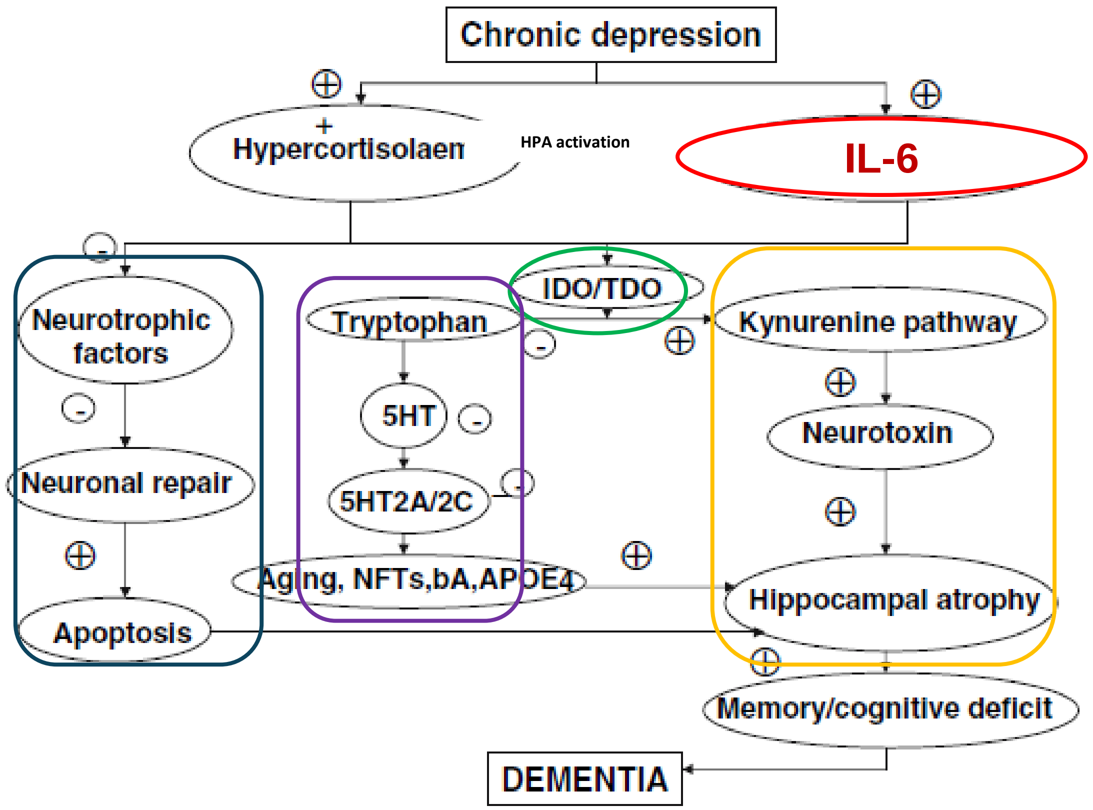


Fig. 1 Possible links between chronic depression and dementia.NFT's = neurofibrillary tangles, bA = beta amyloid, APOE 4 = apolipoprotein E4 (+) = increase; (–) = decrease

Leonard BE. Inflammation, Depression and Dementia: Are they Connected? Neurohem Res 2007

Tryptophan dioxygenase (*TDO*) and indoleamine 2,3-dioxygenase (*IDO*)

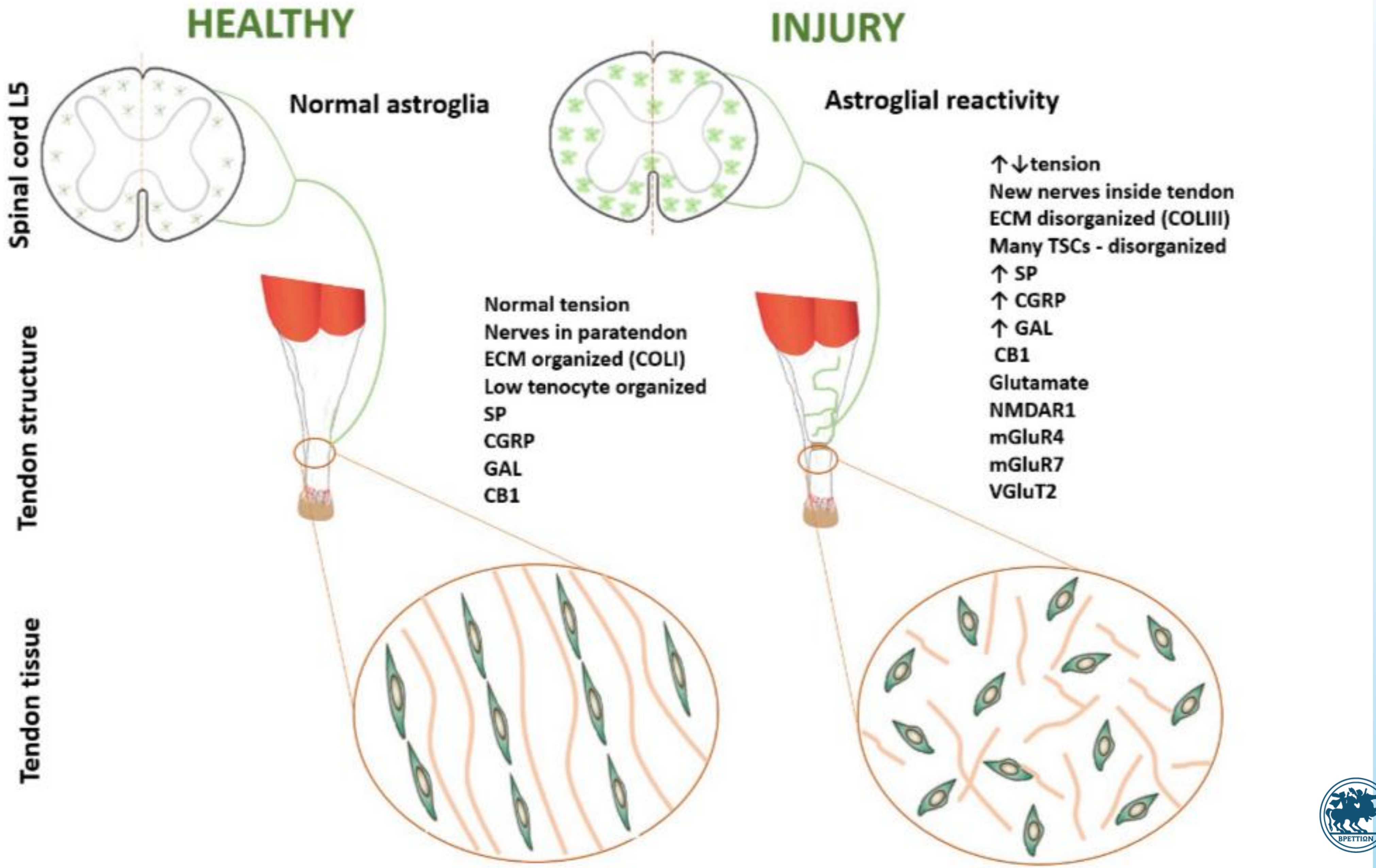
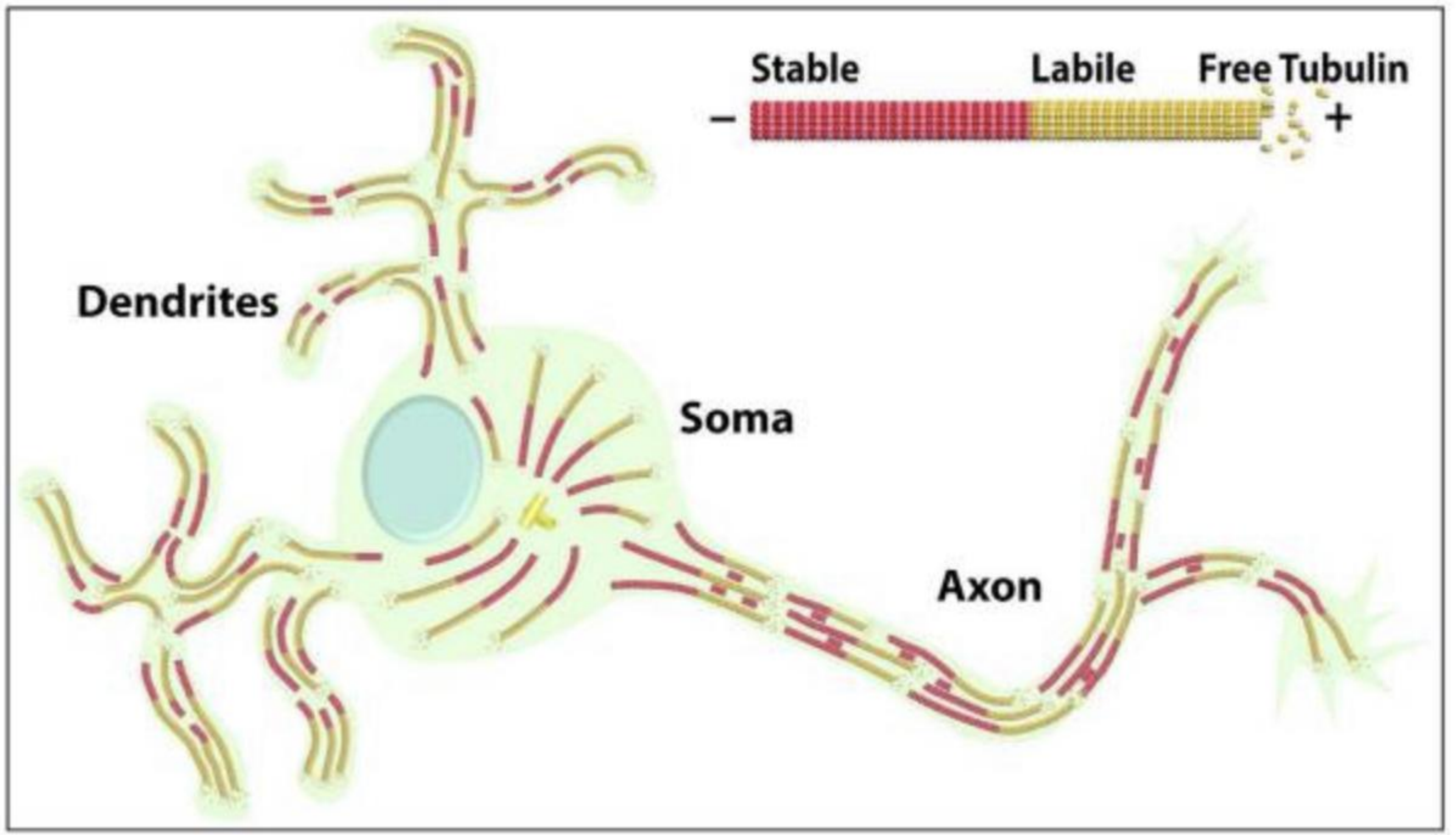
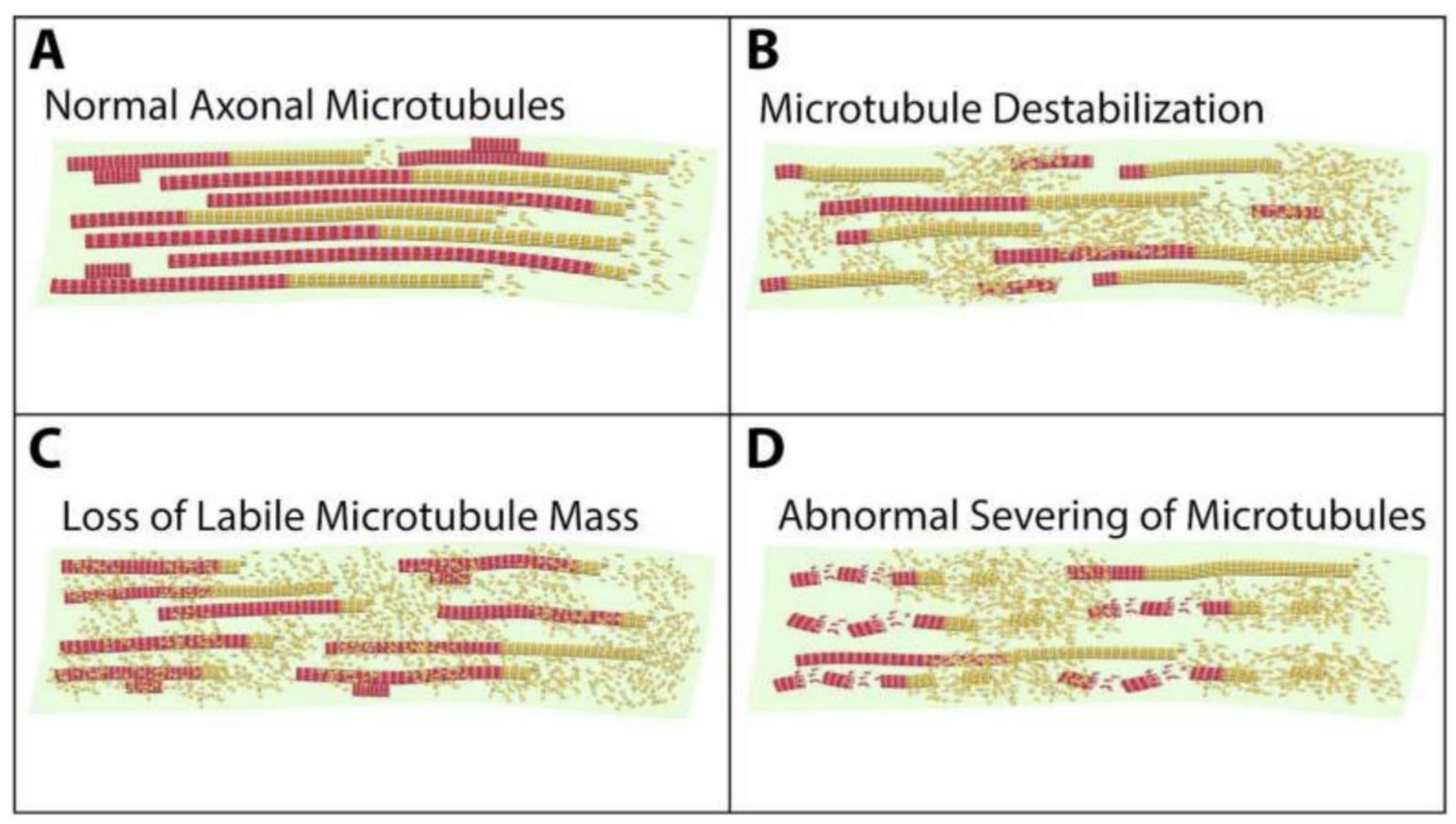


Figure 1 | An overview of the involvement of glial reactivity, mechanotransduction, and substances related to pain in the pathogenesis of tendon injury.


Stable
Labile
Free Tubulin
–
+
Dendrites
Soma
Axon



A
Normal Axonal Microtubules
B
Microtubule Destabilization
C
Loss of Labile Microtubule Mass
D
Abnormal Severing of Microtubules

frontiers | Frontiers in Neuroscience

REVIEW
published: 28 April 2022
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Mechanotransduction: Exploring New Therapeutic Avenues in Central Nervous System Pathology

Daniela Nogueira Rocha[1,2], *Eva Daniela Carvalho*[1,2,3], *João Bettencourt Relvas*[2,4,5], *Maria José Oliveira*[1,2,6] *and Ana Paula Pêgo*[1,2,6]*

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Cells are continuously exposed to physical forces and the central nervous system (CNS) is no exception. Cells dynamically adapt their behavior and remodel the surrounding environment in response to forces. The importance of mechanotransduction in the CNS is illustrated by exploring its role in CNS pathology development and progression. The crosstalk between the biochemical and biophysical components of the extracellular matrix (ECM) are here described, considering the recent explosion of literature demonstrating the powerful influence of biophysical stimuli like density, rigidity and geometry of the ECM on cell behavior. This review aims at integrating mechanical properties into our understanding of the molecular basis of CNS disease. The mechanisms that mediate mechanotransduction events, like integrin, Rho/ROCK and matrix metalloproteinases signaling pathways are revised. Analysis of CNS pathologies in this context has revealed that a wide range of neurological diseases share as hallmarks alterations of the tissue mechanical properties. Therefore, it is our belief that the understanding of CNS mechanotransduction pathways may lead to the development of improved medical devices and diagnostic methods as well as new therapeutic targets and strategies for CNS repair.

Keywords: mechanobiology, extracellular matrix, mechanotransduction, central nervous system, neurodegenerative disorders

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Journal article

Neuron. 2022 sept 21; 110 (18) : 2984-2999.e8.

Astrocytic Piezo1-mediated mechanotransduction determines adult neurogenesis and cognitive functions.

Adult brain activities are generally believed to be dominated by chemical and electrical transduction mechanisms. However, the importance of mechanotransduction mediated by mechano-gated ion channels in brain functions is less appreciated. Here, we show that the mechano-gated Piezo1 channel is expressed in the exploratory processes of astrocytes and utilizes its mechanosensitivity to mediate mechanically evoked Ca^{2+} responses and ATP release, establishing Piezo1-mediated mechano-chemo transduction in astrocytes. Piezo1 deletion in astrocytes causes a striking reduction of hippocampal volume and brain weight and severely impaired (but ATP-rescuable) adult neurogenesis in vivo, and it abolishes ATP-dependent potentiation of neural stem cell (NSC) proliferation in vitro. Piezo1-deficient mice show impaired hippocampal long-term potentiation (LTP) and learning and memory behaviors. By contrast, overexpression of Piezo1 in astrocytes sufficiently enhances mechanotransduction, LTP, and learning and memory performance. Thus, astrocytes utilize Piezo1-mediated mechanotransduction mechanisms to robustly regulate adult neurogenesis and cognitive functions, conceptually highlighting the importance of mechanotransduction in brain structure and function.

RESEARCH ARTICLE

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Remote and Selective Control of Astrocytes by Magnetomechanical Stimulation

*Yichao Yu, Christopher Payne, Nephtali Marina, Alla Korsak, Paul Southern, Ana García-Prieto, Isabel N. Christie, Rebecca R. Baker, Elizabeth M. C. Fisher, Jack A. Wells, Tammy L. Kalber, Quentin A. Pankhurst, Alexander V. Gourine, and Mark F. Lythgoe**

Astrocytes play crucial and diverse roles in brain health and disease. The ability to selectively control astrocytes provides a valuable tool for understanding their function and has the therapeutic potential to correct dysfunction. Existing technologies such as optogenetics and chemogenetics require the introduction of foreign proteins, which adds a layer of complication and hinders their clinical translation. A novel technique, magnetomechanical stimulation (MMS), that enables remote and selective control of astrocytes without genetic modification is described here. MMS exploits the mechanosensitivity of astrocytes and triggers mechanogated Ca^{2+} and adenosine triphosphate (ATP) signaling by applying a magnetic field to antibody-functionalized magnetic particles that are targeted to astrocytes. Using purpose-built magnetic devices, the mechanosensory threshold of astrocytes is determined, a sub-micrometer particle for effective MMS is identified, the in vivo fate of the particles is established, and cardiovascular responses are induced in rats after particles are delivered to specific brainstem astrocytes. By eliminating the need for device implantation and genetic modification, MMS is a method for controlling astroglial activity with an improved prospect for clinical application than existing technologies.

1. Introduction

Astrocytes are a major type of glial cells in the central nervous system (CNS). They constitute an integral part of neural circuitry,[1] regulate a wide range of homeostatic processes,[2] and play key roles in the brain's defense against disease and injury.[3] Due to their extensive involvement in CNS function, astrocytes are implicated in many neurological disorders including neurodegenerative diseases,[4] epilepsy[4] and stroke.[5] In recent years, it has become possible to modulate astroglial activity with spatial, temporal and cell type specificity thanks to the advent of cell control methods such as optogenetics and chemogenetics.[6] These technological advances have not only provided better tools to study these important cells in health and disease,[4,6] but also opened new avenues for therapy development.[7–9] For example, optogenetics has been used to introduce a light-gated ion channel such as channelrhodopsin-2 (ChR2) into astrocytes and enable photostimulation of intracellular Ca^{2+} signaling and adenosine triphosphate (ATP) release, thereby helping researchers to elucidate how astrocytes regulate respiration[10] and pain sensitivity.[11] Chemogenetics involves using a designer drug to specifically activate an exogenous designer G protein-coupled receptor and it has been employed to demonstrate astroglial regulation of feeding

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Neuron
Review

Traumatic Brain Injury and the Neuronal Microenvironment: A Potential Role for Neuropathological Mechanotransduction

Matthew A. Hemphill,[1] Stephanie Dauth,[1] Chung Jong Yu,[1] Borna E. Dabiri,[1] and Kevin Kit Parker[1,*]
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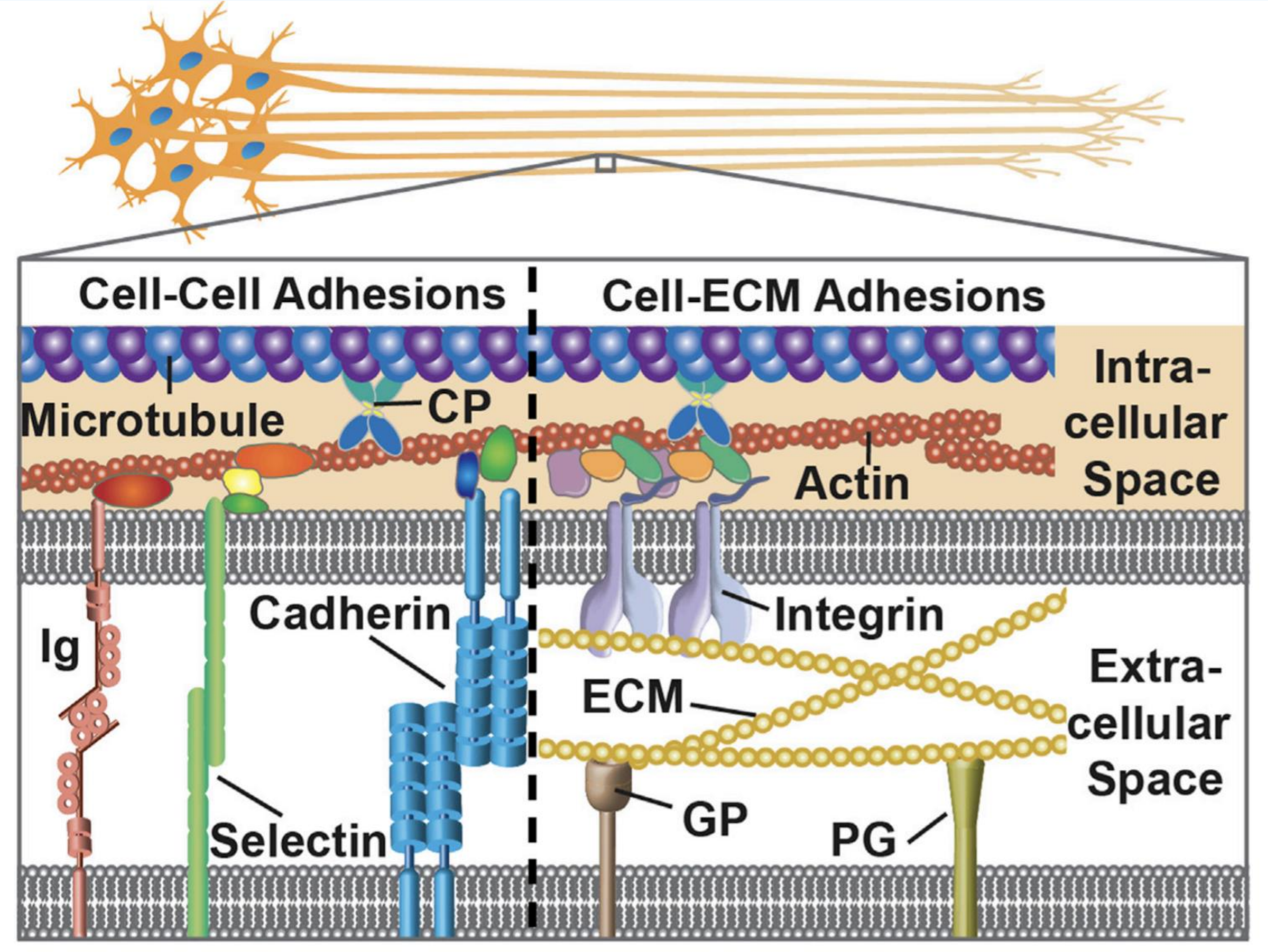
*Correspondence: kkparker@seas.harvard.edu
http://dx.doi.org/10.1016/j.neuron.2015.02.041

Traumatic brain injury (TBI) is linked to several pathologies for which there is a lack of understanding of disease mechanisms and therapeutic strategies. To elucidate injury mechanisms, it is important to consider how physical forces are transmitted and transduced across all spatial scales of the brain. Although the mechanical response of the brain is typically characterized by its material properties and biological structure, cellular mechanotransduction mechanisms also exist. Such mechanisms can affect physiological processes by responding to exogenous mechanical forces directed through sub-cellular components, such as extracellular matrix and cell adhesion molecules, to mechanosensitive intracellular structures that regulate mechanochemical signaling pathways. We suggest that cellular mechanotransduction may be an important mechanism underlying the initiation of cell and sub-cellular injuries ultimately responsible for the diffuse pathological damage and clinical symptoms observed in TBI, thereby providing potential therapeutic opportunities not previously explored in TBI.



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Neurosurgical Review (2023) 46:127
https://doi.org/10.1007/s10143-023-02032-1

REVIEW

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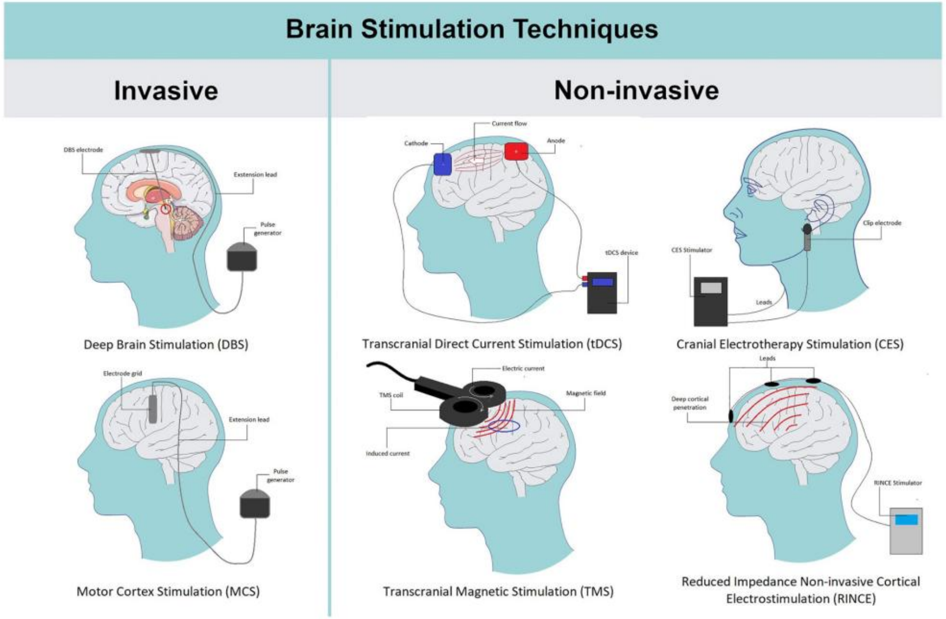
Brain stimulation for chronic pain management: a narrative review of analgesic mechanisms and clinical evidence

Michał Szymoniuk[1] · Jia-Hsuan Chin[1] · Łukasz Domagalski[1] · Mateusz Biszewski[1] · Katarzyna Jóźwik[1] · Piotr Kamieniak[2]

Received: 7 March 2023 / Revised: 1 May 2023 / Accepted: 10 May 2023

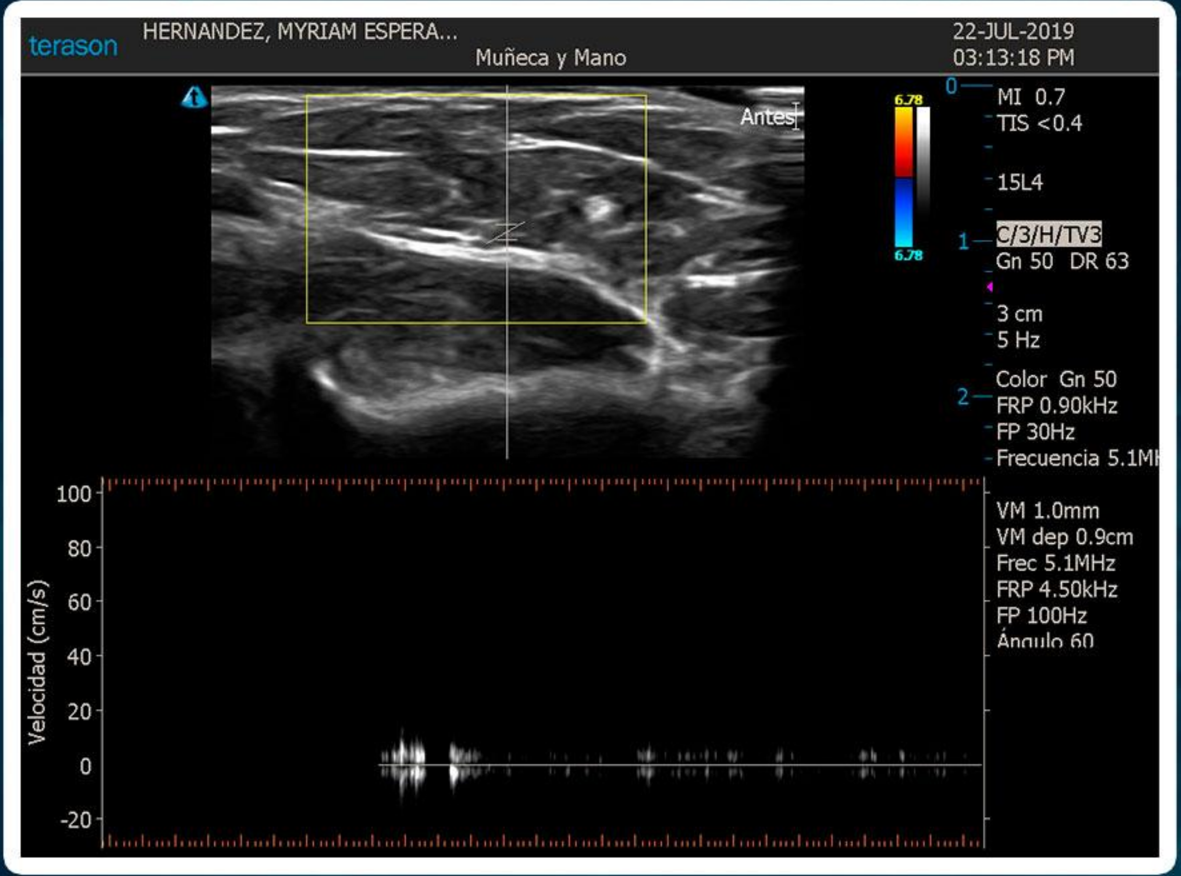
Abstract

Chronic pain constitutes one of the most common chronic complaints that people experience. According to the International Association for the Study of Pain, chronic pain is defined as pain that persists or recurs longer than 3 months. Chronic pain has a significant impact on individuals' well-being and psychosocial health and the economy of healthcare systems as well. Despite the availability of numerous therapeutic modalities, treatment of chronic pain can be challenging. Only about 30% of individuals with non-cancer chronic pain achieve improvement from standard pharmacological treatment. Therefore, numerous therapeutic approaches were proposed as a potential treatment for chronic pain including non-opioid pharmacological agents, nerve blocks, acupuncture, cannabidiol, stem cells, exosomes, and neurostimulation techniques. Although some neurostimulation methods such as spinal cord stimulation were successfully introduced into clinical practice as a therapy for chronic pain, the current evidence for brain stimulation efficacy in the treatment of chronic pain remains unclear. Hence, this narrative literature review aimed to give an up-to-date overview of brain stimulation methods, including deep brain stimulation, motor cortex stimulation, transcranial direct current stimulation, repetitive transcranial magnetic stimulation, cranial electrotherapy stimulation, and reduced impedance non-invasive cortical electrostimulation as a potential treatment for chronic pain.



Patient evaluation

Before



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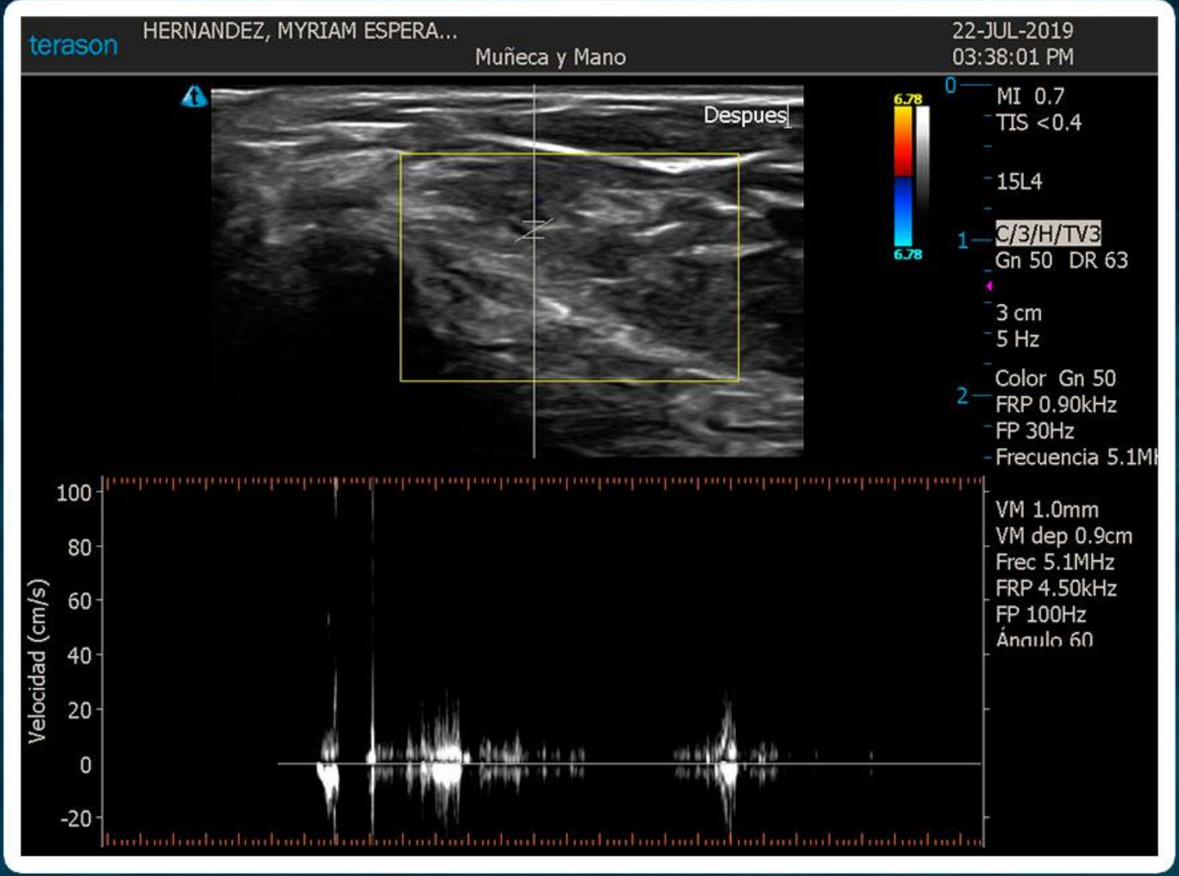
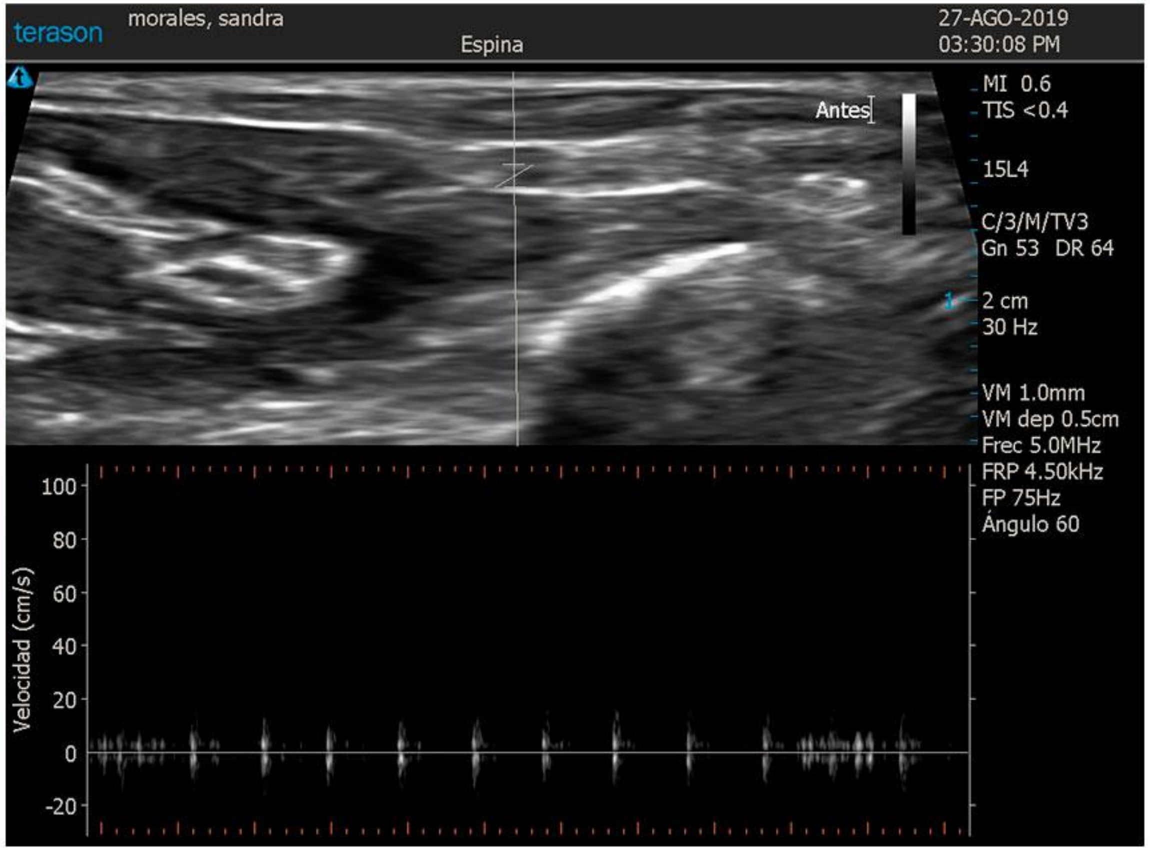


Patient evaluation

Before



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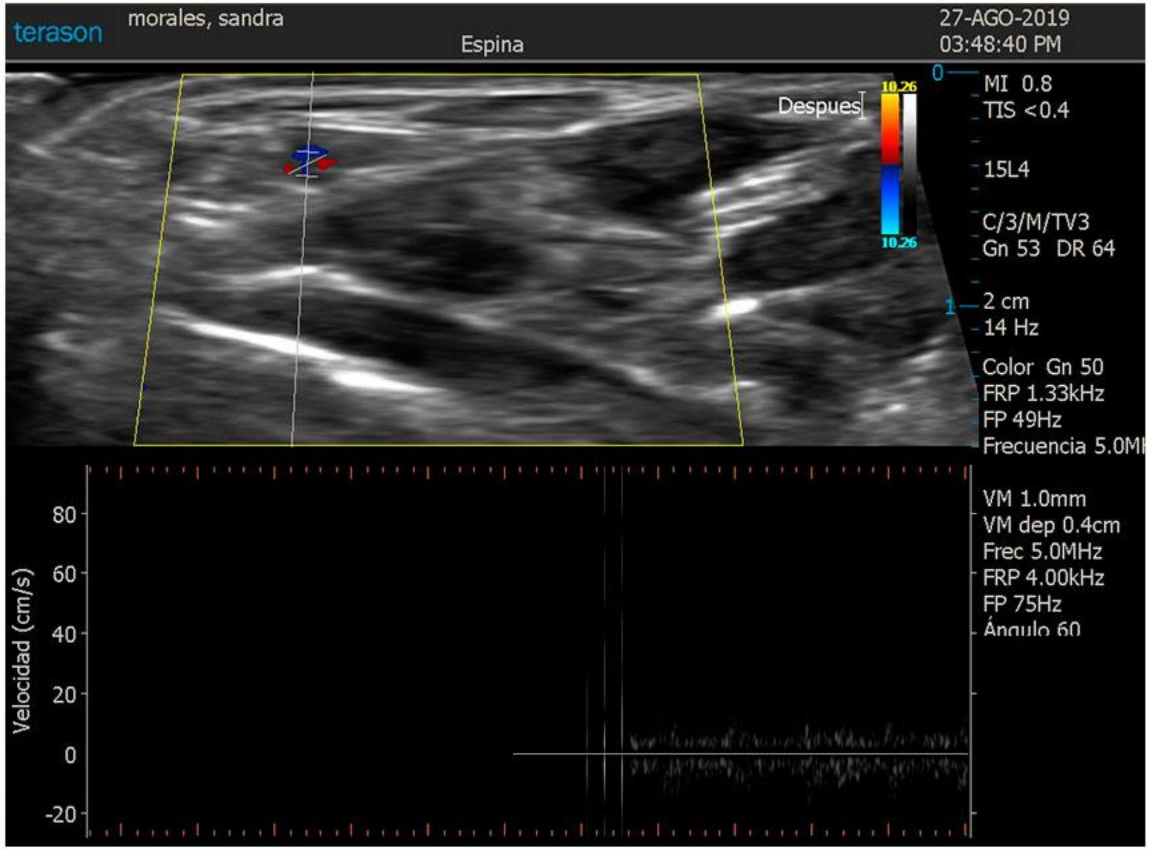
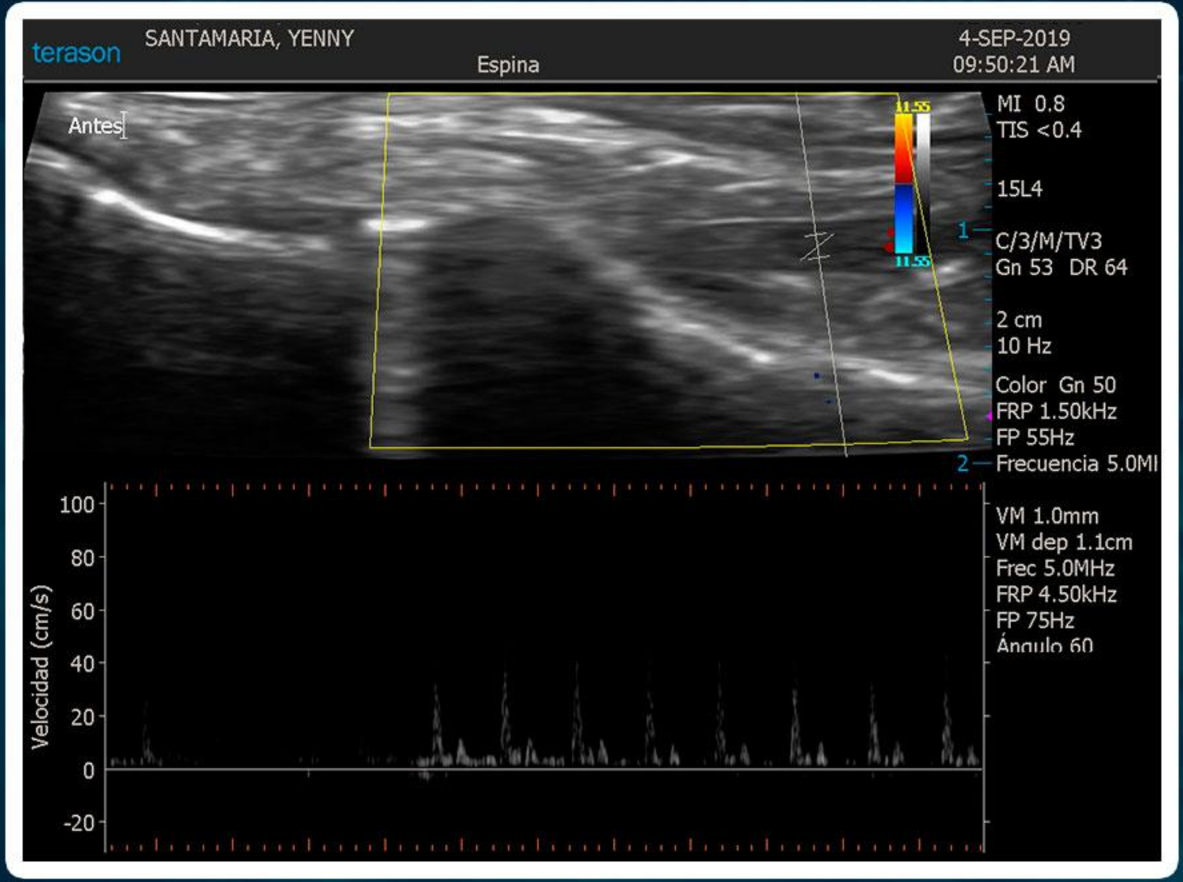


Patient evaluation

Before



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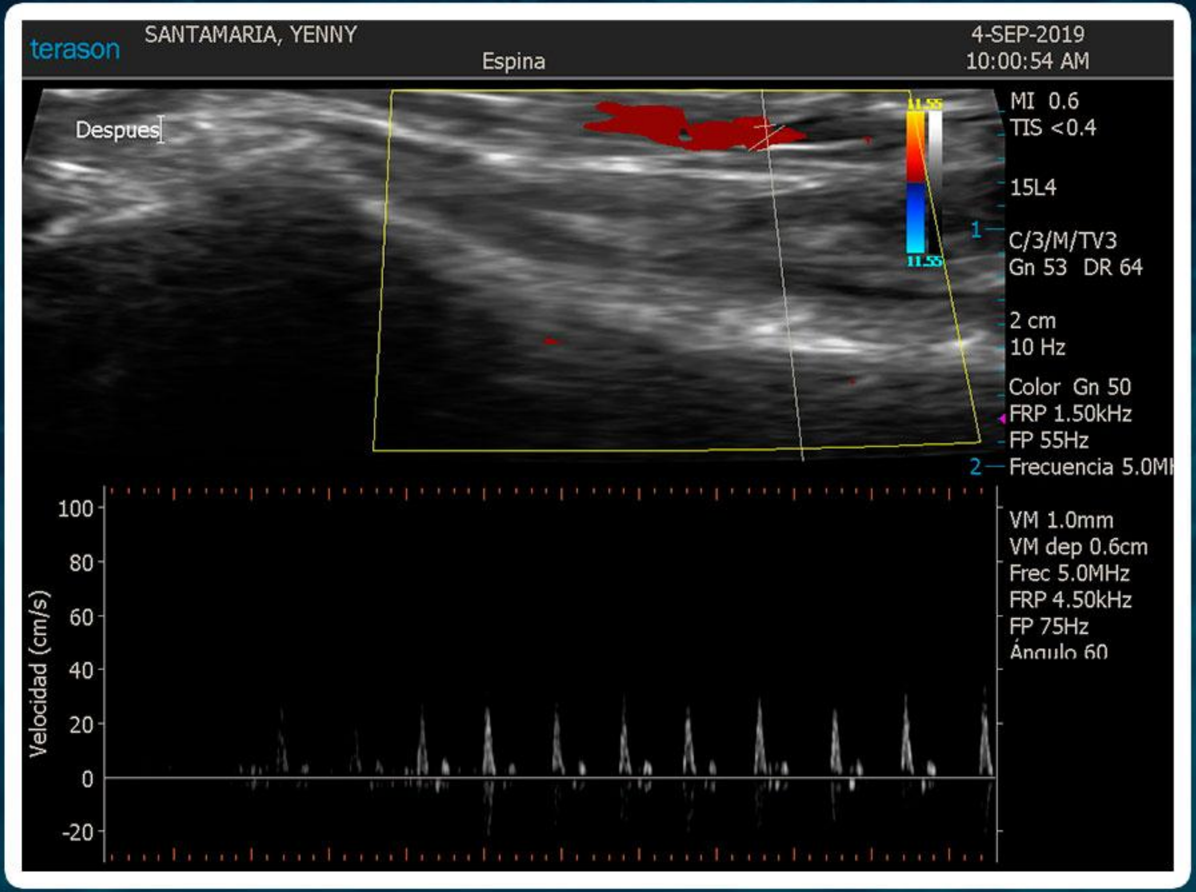
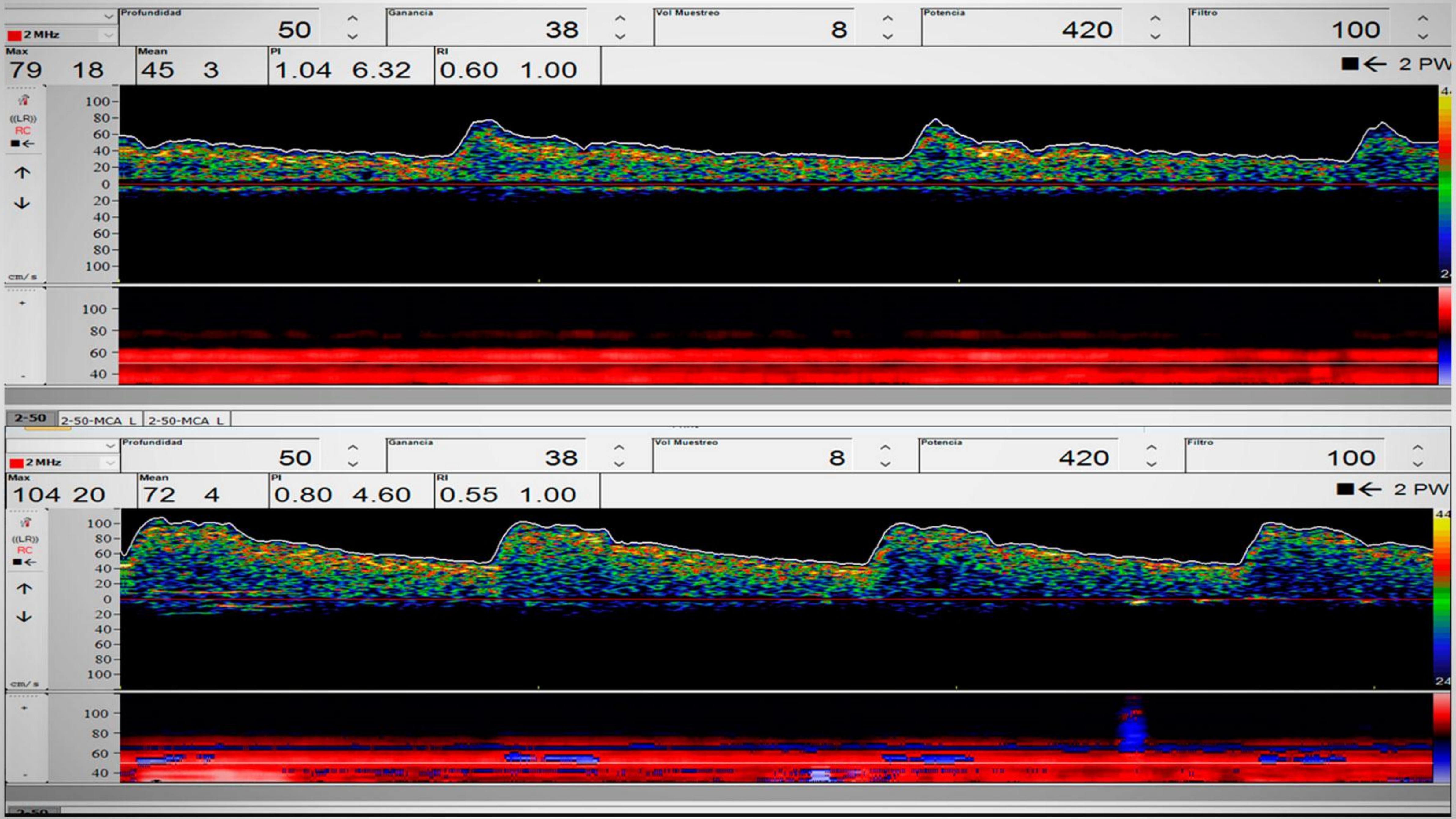


Transcranial Doppler

Brain blood flow speed (cm/s) in explored arteria

Arteria	Average	ED	Range
ACM-D	121,6	48,1	49 - 287
ACM-I	115,6	49,6	45 - 291
ACA-D	87,3	29,9	37 - 170
ACA-I	86,7	37,6	26 - 206
ACI-D	66,2	20,6	30 - 141
ACI-I	64,7	21,5	23 - 150


2 MHz
Profundidad 50
Ganancia 38
Vol Muestreo 8
Potencia 420
Filtro 100
Max 79 18
Mean 45 3
PI 1.04 6.32
RI 0.60 1.00
2 PW
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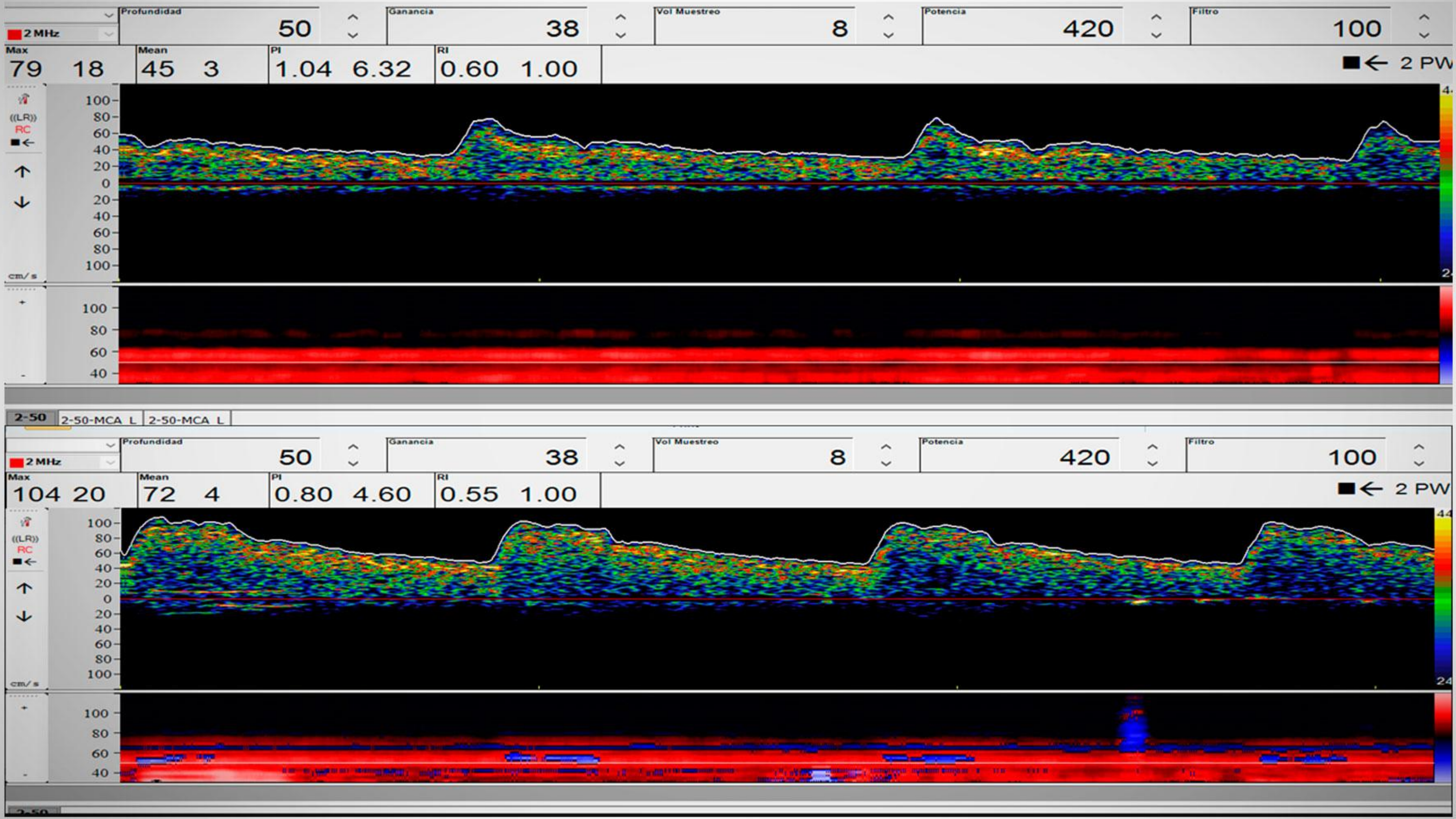
cm/s
2-50
2-50-MCA L
2-50-MCA L
2 MHz
Profundidad 50
Ganancia 38
Vol Muestreo 8
Potencia 420
Filtro 100
Max 104 20
Mean 72 4
PI 0.80 4.60
RI 0.55 1.00
2 PW
RC
cm/s



Profundidad 50
Ganancia 38
Vol Muestreo 8
Potencia 420
Filtro 100
2 MHz
Max 79 18
Mean 45 3
PI 1.04 6.32
RI 0.60 1.00
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cm/s
2-50
2-50-MCA L
2-50-MCA L
Profundidad 50
Ganancia 38
Vol Muestreo 8
Potencia 420
Filtro 100
2 MHz
Max 104 20
Mean 72 4
PI 0.80 4.60
RI 0.55 1.00
2 PW
cm/s

frontiers in Physiology

REVIEW
published: 22 December 2020
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Blood-Brain Barrier Damage in Ischemic Stroke and Its Regulation by Endothelial Mechanotransduction

Keqing Nian[1†], Ian C. Harding[1†], Ira M. Herman[2,3] and Eno E. Ebong[1,4,5]*

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Ischemic stroke, a major cause of mortality in the United States, often contributes to disruption of the blood-brain barrier (BBB). The BBB along with its supportive cells, collectively referred to as the "neurovascular unit," is the brain's multicellular microvasculature that bi-directionally regulates the transport of blood, ions, oxygen, and cells from the circulation into the brain. It is thus vital for the maintenance of central nervous system homeostasis. BBB disruption, which is associated with the altered expression of tight junction proteins and BBB transporters, is believed to exacerbate brain injury caused by ischemic stroke and limits the therapeutic potential of current clinical therapies, such as recombinant tissue plasminogen activator. Accumulating evidence suggests that endothelial mechanobiology, the conversion of mechanical forces into biochemical signals, helps regulate function of the peripheral vasculature and may similarly maintain BBB integrity. For example, the endothelial glycocalyx (GCX), a glycoprotein-proteoglycan layer extending into the lumen of bloods vessel, is abundantly expressed on endothelial cells of the BBB and has been shown to regulate BBB permeability. In this review, we will focus on our understanding of the mechanisms underlying BBB damage after ischemic stroke, highlighting current and potential future novel pharmacological strategies for BBB protection and recovery. Finally, we will address the current knowledge of endothelial mechanotransduction in BBB maintenance, specifically focusing on a potential role of the endothelial GCX.

Keywords: blood-brain barrier, ischemic stroke, endothelial cells, mechanotransduction, neuroprotection, neurovascular unit, endothelial glycocalyx

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13th – 14th September 2024

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Review

Physiological Reviews. 2023 abr. 1; 103 (2) : 1247-1421.

Vascular mechanotransduction.

This review aims to survey the current state of mechanotransduction in vascular smooth muscle cells (VSMCs) and endothelial cells (ECs), including their sensing of mechanical stimuli and transduction of mechanical signals that result in the acute functional modulation and longer-term transcriptomic and epigenetic regulation of blood vessels. The mechanosensors discussed include ion channels, plasma membrane-associated structures and receptors, and junction proteins. The mechanosignaling pathways presented include the cytoskeleton, integrins, extracellular matrix, and intracellular signaling molecules. These are followed by discussions on mechanical regulation of transcriptome and epigenetics, relevance of mechanotransduction to health and disease, and interactions between VSMCs and ECs. Throughout this review, we offer suggestions for specific topics that require further understanding. In the closing section on conclusions and perspectives, we summarize what is known and point out the need to treat the vasculature as a system, including not only VSMCs and ECs but also the extracellular matrix and other types of cells such as resident macrophages and pericytes, so that we can fully understand the physiology and pathophysiology of the blood vessel as a whole, thus enhancing the comprehension, diagnosis, treatment, and prevention of vascular diseases.

Arteriosclerosis, Thrombosis, and Vascular Biology

ATVB IN FOCUS:
Arterial Stiffness

Series Editors: Janet Powell and Gary Mitchell

Mechanisms of Arterial Stiffening

From Mechanotransduction to Epigenetics

Patrick Lacolley, Véronique Regnault, Stéphane Laurent

ABSTRACT: Arterial stiffness is a major independent risk factor for cardiovascular complications causing isolated systolic hypertension and increased pulse pressure in the microvasculature of target organs. Stiffening of the arterial wall is determined by common mechanisms including reduced elastin/collagen ratio, production of elastin cross-linking, reactive oxygen species–induced inflammation, calcification, vascular smooth muscle cell stiffness, and endothelial dysfunction. This brief review will discuss current biological mechanisms by which other cardiovascular risk factors (eg, aging, hypertension, diabetes mellitus, and chronic kidney disease) cause arterial stiffness, with a particular focus on recent advances regarding nuclear mechanotransduction, mitochondrial oxidative stress, metabolism and dyslipidemia, genome mutations, and epigenetics. Targeting these different molecular pathways at different time of cardiovascular risk factor exposure may be a novel approach for discovering drugs to reduce arterial stiffening without affecting artery strength and normal remodeling.

VISUAL OVERVIEW: An online visual overview is available for this article.

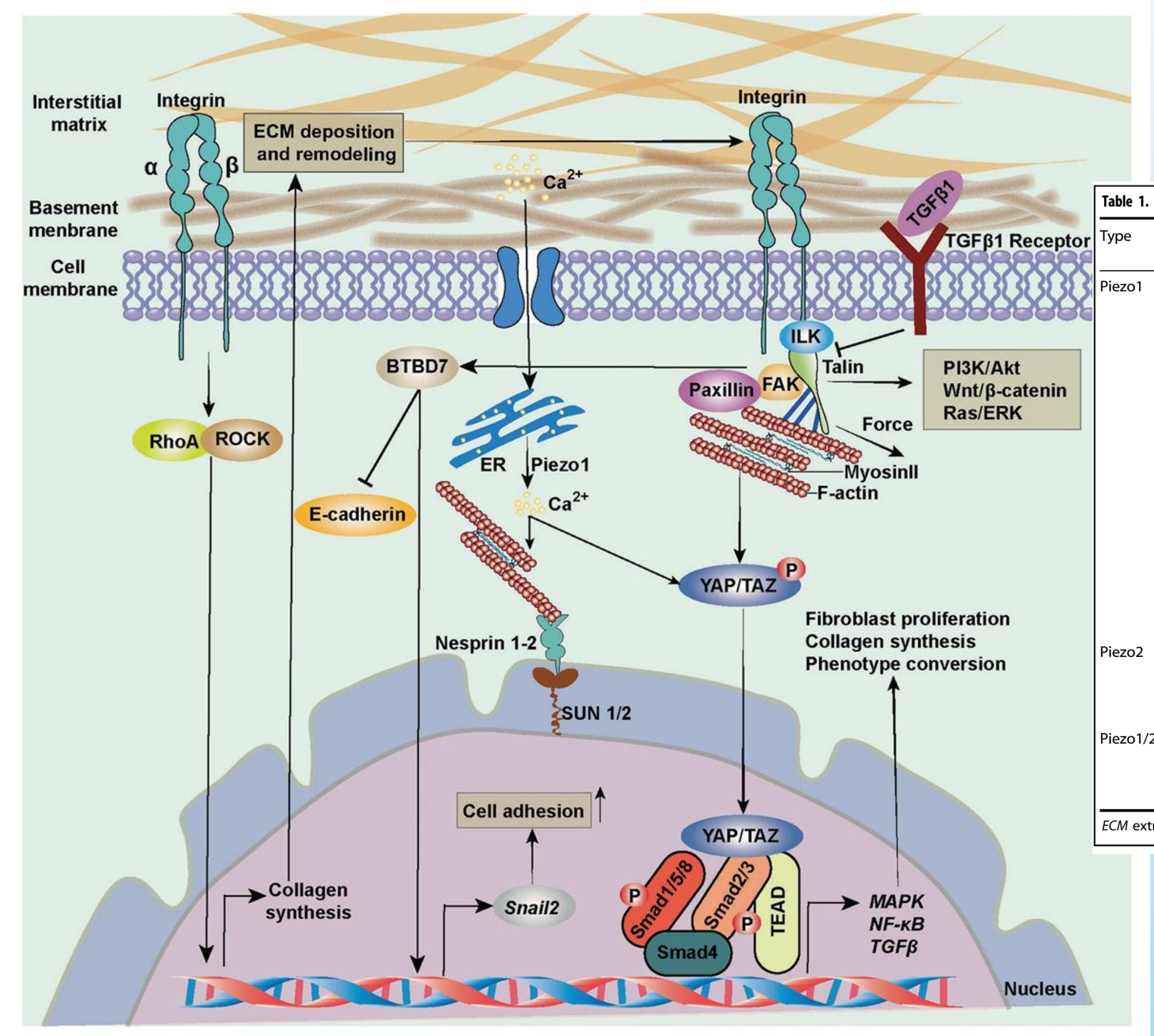

Table 1. Functions of Piezo channels in cellular mechanotransduction

Type	Target	Mechanical stimulation	Mechanism	Reference
Piezo1	Vascular endothelium development	Shear stress	Ca^{2+}influx→MTP-MMP signaling→focal adhesion and endothelial cell sprout formation;	232
	Vascular tone	Shear stress	Ca^{2+}influx→G-coupled endothelial adrenomedullin receptor→cAMP→eNOS→NO; Ca^{2+}influx→ATP→PI3K/AKT→eNOS→NO	198–200
	Vascular remodeling	Stretch	Ca^{2+}influx→transglutaminase →ECM remodeling	222
	Erythrocytes	Shear stress	Ca^{2+}influx→K^+ efflux→red blood cells dehydration	201
	Erythrocytes	Shear stress	Ca^{2+}influx→pannexin-1→ATP release	202
	Nervous system	Traction force	Ca^{2+}influx→neural differentiation →neuron-astrocyte interaction	203,204
	Gastric mucosa	Antrum distension	Activated G cells→gastrin secretion	205
	Lung endothelium	Shear stress	Ca^{2+}influx→calpain→Src cleavage→stabilization of adherens junctions	206
	Lung endothelium	Hydrostatic pressure	Ca^{2+}influx→calpain→disruption of adherens junctions	207
	Aoveoli	Stretch	Ca^{2+}influx→Bcl-2 pathway→type II epithelial cells apoptosis	208
	Urinary bladder	Stretch	Ca^{2+}influx→ATP→attenuate storage disorders	209
	Tumor	ECM stiffness	YAP-Piezo1→proliferation; Ca^{2+}influx→AKT/mTOR phosphorylation→proliferation; Piezo1–mitochondrial calcium uniporter–HIF-1α–VEGF axis→metastasis	210,211,213
Piezo2	Gastrointestinal epithelium	Mucosal force	5-HT pathway→mucosal secretion	212
	Airway	Stretch	Ablation of *Piezo2*→Airway-innervating sensory neurons→ respiratory distress and death in newborn mice	214,215
	Urinary bladder	Stretch	Sensory neuron→bladder filling sensation	221
Piezo1/2	Baroreceptor reflex	Shear stress	Elevated blood pressure→Piezo1/2 →nodose-petrosal-jugular-ganglion complex→ decreased blood pressure and heart rate	216–218
	Chondrocyte anabolic and biosynthesis	Mechanical stress	GsMTx4→Piezo1/2 inhibition→ alleviate chondrocyte injury	219,220

ECM extracellular matrix, *MMP* matrix metalloprotease, *5-HT* 5-hydroxytryptamine

Review

American Journal of Physiology. Heart and Circulatory Physiology. 2024 ago. 23;

Integrating molecular and cellular components of endothelial shear stress mechanotransduction .

Gavin Power, Larissa Ferreira-Santos, Luis A Martinez-Lemus, Jaume Padilla

PMID: 39178024

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The lining of blood vessels is constantly exposed to mechanical forces exerted by blood flow against the endothelium. Endothelial cells detect these tangential forces (i.e. , shear stress), initiating a host of intracellular signaling cascades that regulate vascular physiology. Thus, vascular health is tethered to the endothelial cells' capacity to transduce shear stress. Indeed, the mechanotransduction of shear stress underlies a variety of cardiovascular benefits, including some of those associated with increased physical activity. However, endothelial mechanotransduction is impaired in aging and disease states such as obesity and type 2 diabetes, precipitating the development of vascular disease. Understanding endothelial mechanotransduction of shear stress, as well as the molecular and cellular mechanisms by which this process becomes defective, is critical for the identification and development of novel therapeutic targets against cardiovascular disease. In this review, we detail the primary mechanosensitive structures that have been implicated in detecting shear stress, including junctional proteins such as PECAM-1, the extracellular glycocalyx and its components, and ion channels such as Piezo1. We delineate which molecules are truly mechanosenstive and which may simply be indispensable for the downstream transmission of force. Furthermore, we discuss how these mechanosensors interact with other cellular structures, such as the cytoskeleton and membrane lipid rafts, which are implicated in translating shear forces to biochemical signals. Based on findings to date, we also seek to integrate these cellular and molecular mechanisms with a view of deciphering endothelial mechanotransduction of shear stress, a tenet of vascular physiology.

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Stanford Medicine / News / Study: New depression treatment effective

Experimental depression treatment is nearly 80% effective in controlled study

In a double-blind controlled study, high doses of magnetic brain stimulation, given on an accelerated timeline and individually targeted, caused remission in 79% of trial participants with severe depression.

October 28, 2021 - By Mandy Erickson

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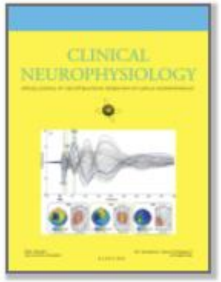
Clinical Neurophysiology

Volume 132, Issue 10, October 2021, Pages 2568-2607



Review

Diagnostic contribution and therapeutic perspectives of transcranial magnetic stimulation in dementia

Vincenzo Di Lazzaro [a], Rita Bella [b], Alberto Benussi [c], Matteo Bologna [d, e], Barbara Borroni [c], Fioravante Capone [a], Kai-Hsiang S. Chen [f], Robert Chen [g, h], Andrei V. Chistyakov [i], Joseph Classen [j], Matthew C. Kiernan [k], Giacomo Koch [l, m], Giuseppe Lanza [n, o], Jean-Pascal Lefaucheur [p, q], Hideyuki Matsumoto [r], Jean-Paul Nguyen [s], Michael Orth [t, u], Alvaro Pascual-Leone [v, w, x], Irena Rektorova [y, z], Patrik Simko [y, aa], John-Paul Taylor [ab], Sara Tremblay [ac, ad], Yoshikazu Ugawa [ae], Raffaele Dubbioso [af, 1], Federico Ranieri [ag, 1]

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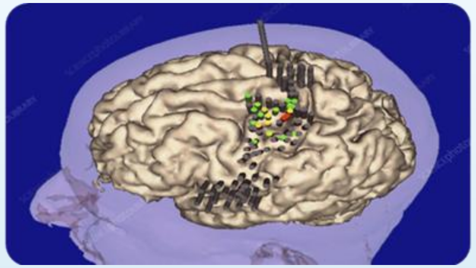
13th – 14th September

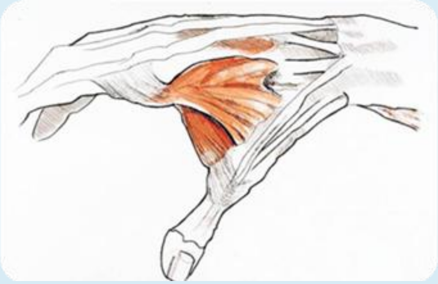
EFFETTI NEUROLOGICI DEL DIAMAGNETISMO

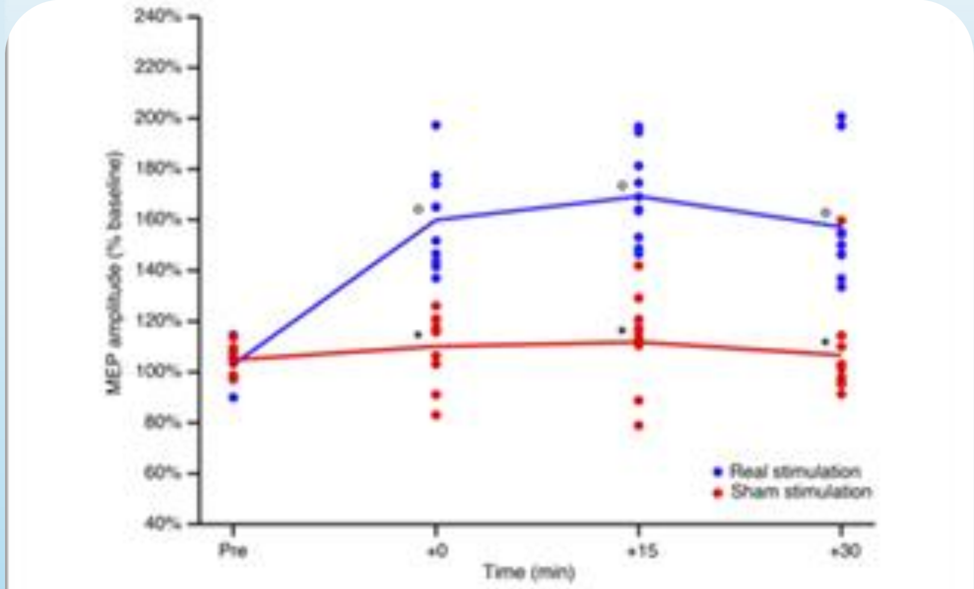
RESEARCH ARTICLE — Open Access

Modulation of long-term potentiation-like cortical plasticity in the healthy brain with low frequency-pulsed electromagnetic fields

Enrico Premi[1,2*], Alberto Benussi[2], Antonio La Gatta[3], Stefano Visconti[4], Angelo Costa[1], Nicola Gilberti[1], Valentina Cantoni[2], Alessandro Padovani[2], Barbara Borroni[2] and Mauro Magoni[1]







Single Diamagnetic stimulation of the Primary Motor Area (15') Induces motor evoked potentials (MEPs) at the level of the corresponding motor segment.

Journal of Neurology and Experimental Neural Science
Obando FT, et al. J Neurol Exp Neural Sci 4: 145.
www.doi.org/10.29011/2577-1442.100045
www.gavinpublishers.com

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Research Article

The Effects of Low-Frequency High-Intensity Pulsed Electromagnetic Fields (Diamagnetic Therapy) in the Treatment of Rare Diseases: A Case Series Preliminary Study

Felipe Torres Obando[1,3], Pietro Romeo[2,3*], Diego Vergara[1], Federica di Pardo[3], Adriana Soto[1]

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[2]Orthopedic Department, Istituto Ortopedico Galeazzi, Milano, Italy

[3]Periso Academy, Pazzallo, Switzerland

[*]**Corresponding author:** Pietro Romeo, Orthopedic Department, Istituto Ortopedico Galeazzi, Milano, Italy

Citation: Obando FT, Romeo P, Vergara D, di Pardo F, Soto A (2022) The Effects of Low-Frequency High-Intensity Pulsed Electromagnetic Fields (Diamagnetic Therapy) in the Treatment of Rare Diseases: A Case Series Preliminary Study. J Neurol Exp Neural Sci 4: 145. DOI: 10.29011/2577-1442.100045

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Abstract

Rare and orphan diseases are a group of multiorgan disabilities that limit the life quality in young and adult patients, affecting the socio-economic burden for the families and the community. Despite the continuous attempts in research, no standardized and effective therapies are nowadays available. Orthosis supports and rehabilitation remain the unique possibilities to alleviate these challenging conditions. Among the emerging therapeutic odds, Pulsed Electromagnetic Fields (PEMFs) express anti-inflammatory and regenerative effects on musculoskeletal and parenchymal tissues. They have also shown intriguing properties to stimulate the central and peripheral nervous system either as Transcranial Magnetic Stimulation (TMS) and Low Frequency - High-Intensity -Pulsed electromagnetic Field (LF-HI-PEMFs) or Diamagnetic Therapy (Diamagneto-therapy). This last modulates brain plasticity and is effective in pain, reducing muscles contractures and tissue oedema. Our experience refers to the use of Diamagnetic Therapy to rare and orphan diseases and reports promising functional and behavioural results, opening the possibility of therapeutic applications integrated with conventional rehabilitative methods.

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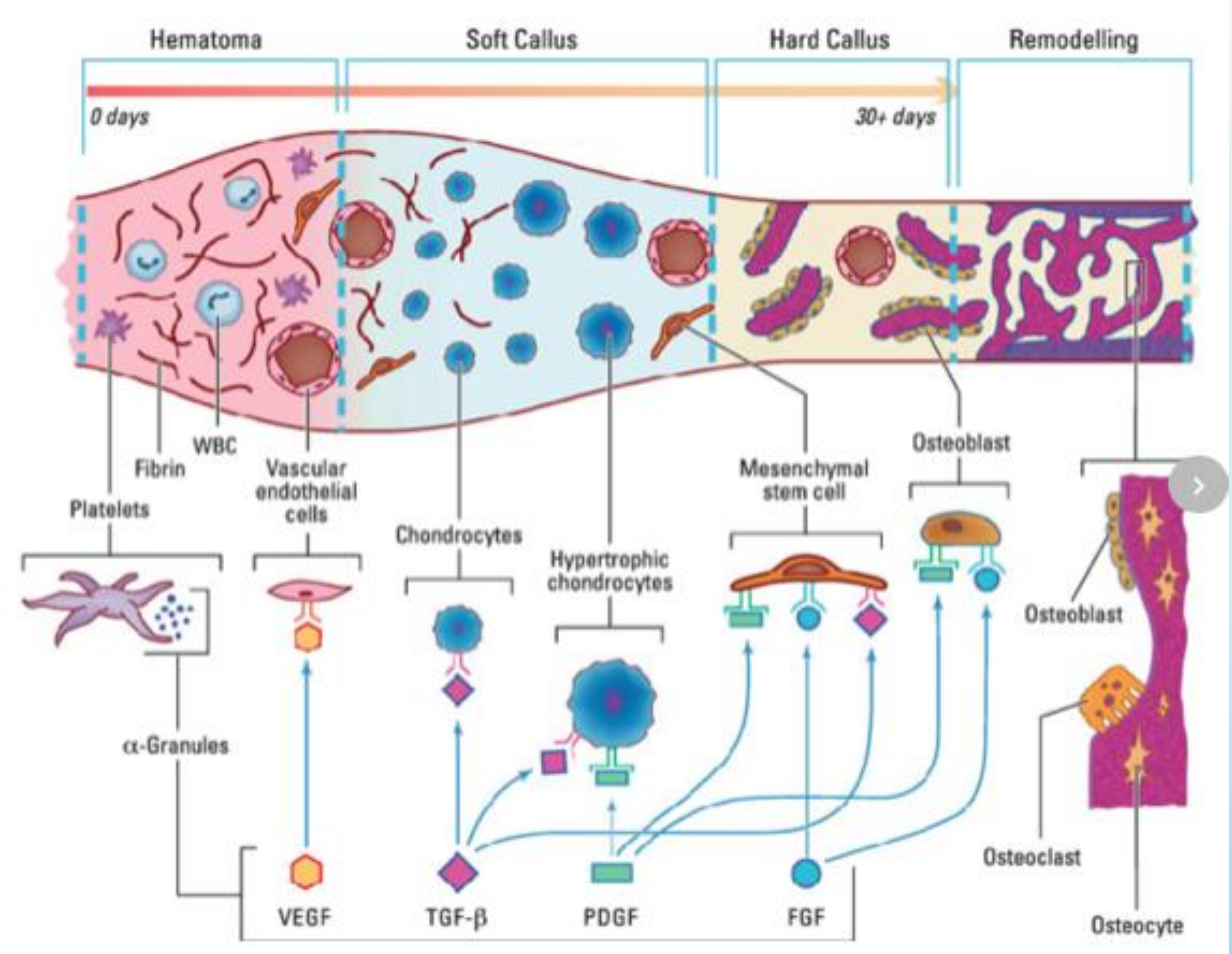

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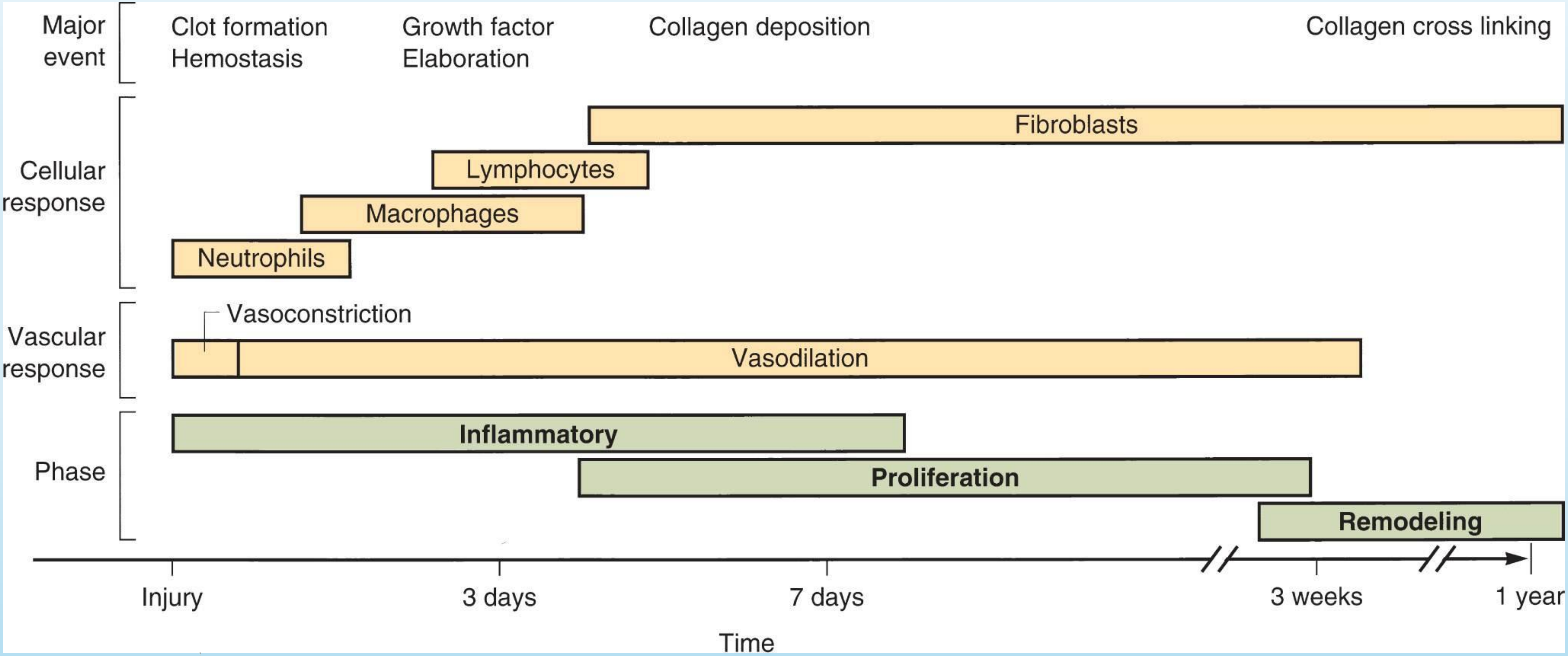
Major event
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Hemostasis
Growth factor
Elaboration
Collagen deposition
Collagen cross linking
Cellular response
Fibroblasts
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Macrophages
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Vascular response
Vasoconstriction
Vasodilation
Phase
Inflammatory
Proliferation
Remodeling
Injury
3 days
7 days
3 weeks
1 year
Time

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Current Opinion in Cell Biology

Mechanotransduction pathways in regulating epithelial-mesenchymal plasticity

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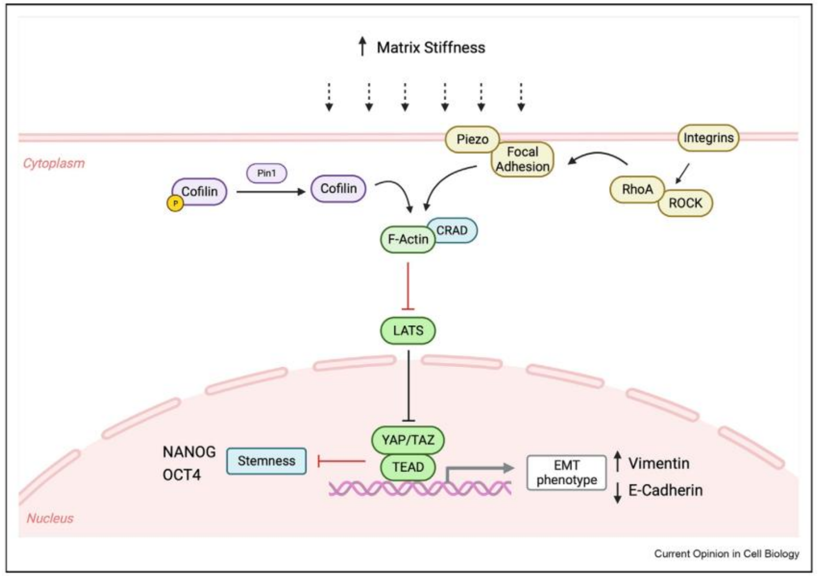
Abstract

The extracellular matrix (ECM) provides structural support for cells and mediates cell-stromal communications. In addition to ECM proteins, mechanical force exerted from the ECM serves as a critical regulator of many biological processes. Epithelial–mesenchymal transition (EMT) is a cellular process by which epithelial cells loosen their cellular junctions and migrate and invade in a more mesenchymal fashion. Recent studies show that increasing ECM stiffness can impinge on cellular signaling pathways through mechanotransduction to promote carcinoma cells to undergo EMT, suggesting that mechanical force exerted by the ECM plays a critical role in tumor invasion and metastasis. Here, we highlight recent work utilizing innovative approaches to study mechanotransduction and summarize newly discovered mechanisms by which mechanosensors and responders regulate EMT during tumor progression and metastasis.

While numerous biochemical signals have been extensively studied for their roles in regulating EMT, recent advances revealed critical roles of mechanical properties and composition of the extracellular matrix (ECM) in regulating EMT [2]. The mechanical properties of the tumor microenvironment (TME) include stiffness, topology, shear force, and, in the case of cancer, pressure from the surrounding tissue architecture due to increased cell proliferation. These physical properties can regulate cell morphology, proliferation, differentiation, and migration [3]. Recently, several studies have shown that high tumor ECM stiffness can induce tumor cells to undergo EMT and invade through mechanotransduction, the process of sensing and transmitting mechanical stimulus from the microenvironment to generate biochemical responses [4,5]. This review highlights important advances within the last couple of

Figure 2

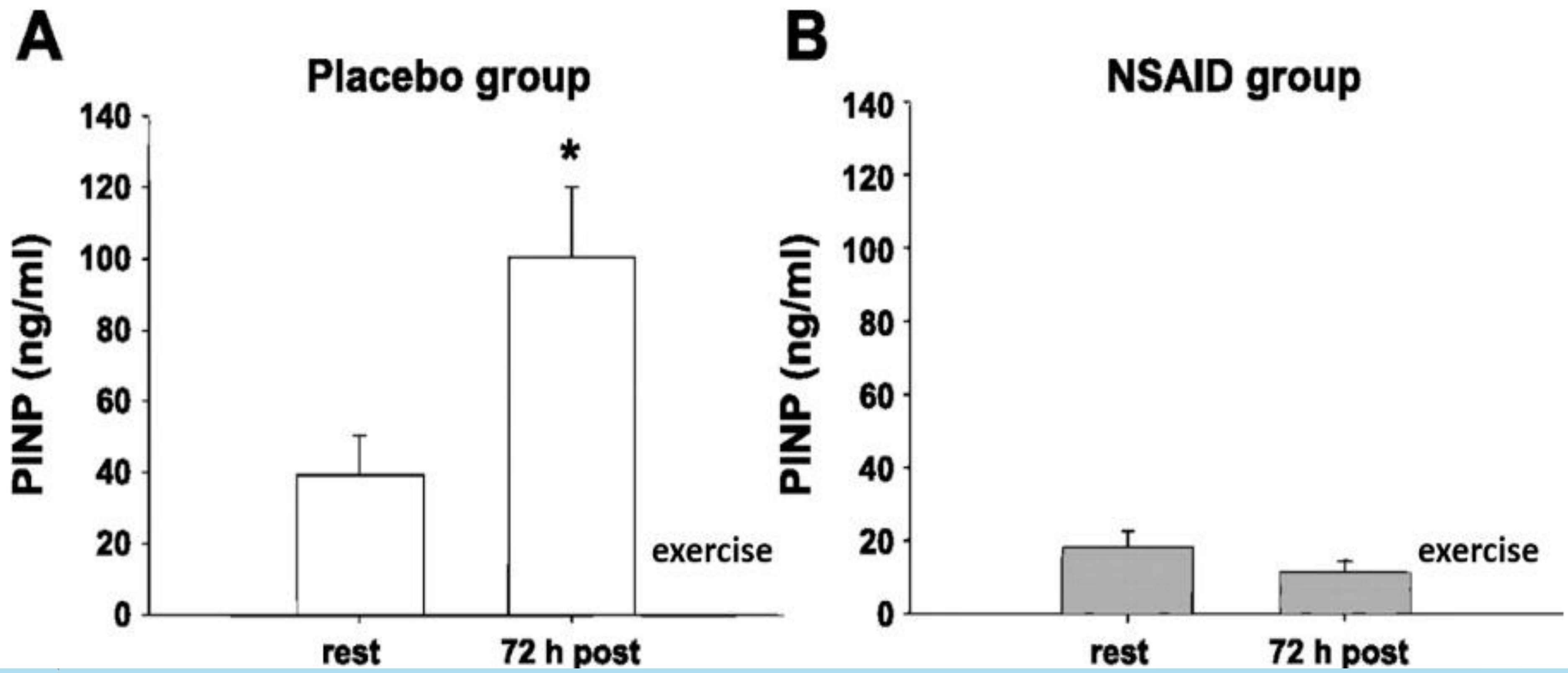


A schematic of the signaling pathways by which YAP/TAZ function as mechanoresponders to induce EMT at high matrix stiffness in various human cancers.

13th – 14th September 2024

Effects of PGE2 blockade on collagen synthesis in the patella tendon.

Journal of Applied Physiology



Journal article

Psychopathology. 2024 jul. 12;

The Glutamatergic Effects of Clinical Repetitive Transcranial Magnetic Stimulation in Depressed Populations: A Preliminary Meta-Analysis of Proton Magnetic Resonance Spectroscopy Studies.

View Details

INTRODUCTION: Repetitive transcranial magnetic stimulation (rTMS) alleviates symptoms of major depressive disorder, but its neurobiological mechanisms remain to be fully understood. Growing evidence from proton magnetic resonance spectroscopy (1HMRS) studies suggests that rTMS alters excitatory and inhibitory neurometabolites. This preliminary meta-analysis aims to quantify current trends in the literature and identify future directions for the field.

METHODS: Ten eligible studies that quantified Glutamate (Glu), Glu+Glutamine (Glx), or GABA before and after an rTMS intervention in depressed samples were sourced from PubMed, MEDLINE, PsychInfo, Google Scholar, and primary literature following PRISMA guidelines. Data were pooled using a random-effects model, Cohen's d effect sizes were calculated, and moderators, such as neurometabolite and 1HMRS sequence, were assessed. It was hypothesized that rTMS would increase cortical neurometabolites.

RESULTS: Within-subjects data from 224 cases encompassing 31 neurometabolite effects (k) were analyzed. Active rTMS in clinical responders ($n = 128$; $k = 22$) nominally increased glutamatergic neurometabolites ($d = 0.15$ [95% CI: -0.01, 0.30], $p = 0.06$). No change was found in clinical nonresponders ($p = 0.8$) or sham rTMS participants ($p = 0.4$). A significant increase was identified in Glx ($p = 0.01$), but not Glu ($p = 0.6$). Importantly, effect size across conditions were associated with the number of rTMS pulses patients received ($p = 0.05$), suggesting dose dependence.

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2024

Journal article

Cell Reports. 2024 ago. 22; 43 (9) : 114669.

Cells and circuits for amygdala neuroplasticity in the transition to chronic pain.

Takaki Kiritoshi, Vadim Yakhnitsa, Sudhuman Singh, Torri D Wilson, Sarah Chaudhry, Benjamin Neugebauer, Jeitzel M Torres-Rodriguez, Jenny L Lin, Yarimar Carrasquillo, Volker Neugebauer

PMID: 39178115

Hide Details

Maladaptive plasticity is linked to the chronification of diseases such as pain, but the transition from acute to chronic pain is not well understood mechanistically. Neuroplasticity in the central nucleus of the amygdala (CeA) has emerged as a mechanism for sensory and emotional-affective aspects of injury-induced pain, although evidence comes from studies conducted almost exclusively in acute pain conditions and agnostic to cell type specificity. Here, we report time-dependent changes in genetically distinct and projection-specific CeA neurons in neuropathic pain. Hyperexcitability of CRF projection neurons and synaptic plasticity of parabrachial (PB) input at the acute stage shifted to hyperexcitability without synaptic plasticity in non-CRF neurons at the chronic phase. Accordingly, chemogenetic inhibition of the PB→CeA pathway mitigated pain-related behaviors in acute, but not chronic, neuropathic pain. Cell-type-specific temporal changes in neuroplasticity provide neurobiological evidence for the clinical observation that chronic pain is not simply the prolonged persistence of acute pain.

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2024

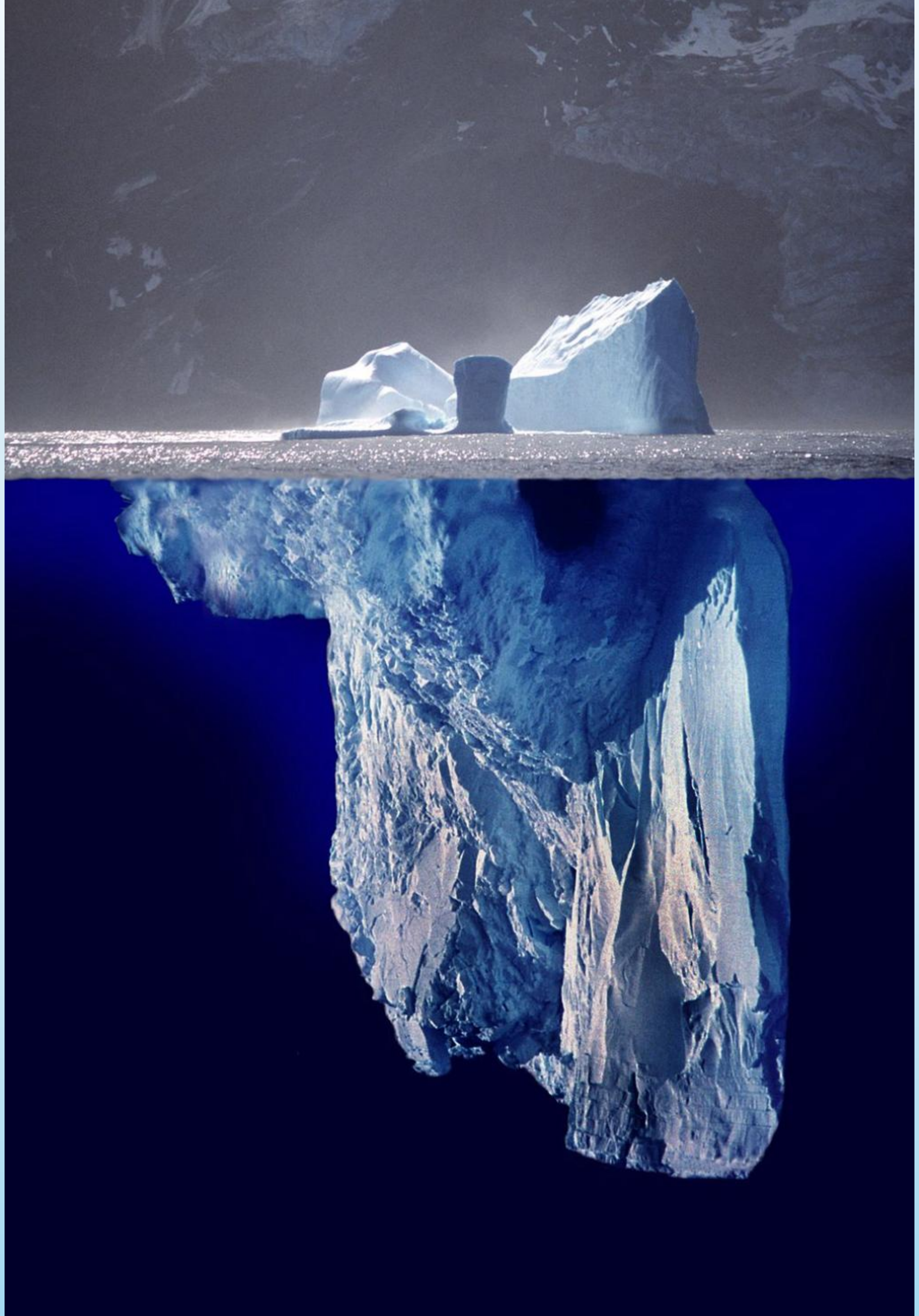
Review

Reproductive Sciences. 2024 mar. 12;

A Review: Biomechanical Aspects of the Fallopian Tube Relevant to its Function in Fertility.

View Details

The fallopian tube (FT) plays a crucial role in the reproductive process by providing an ideal biomechanical and biochemical environment for fertilization and early embryo development. Despite its importance, the biomechanical functions of the FT that originate from its morphological aspects, and ultrastructural aspects, as well as the mechanical properties of FT, have not been studied nor used sufficiently, which limits the understanding of fertilization, mechanotrasduction, and mechanobiology during embryo development, as well as the replication of the FT in laboratory settings for infertility treatments. This paper reviews and revives valuable information on human FT reported in medical literature in the past five decades relevant to the biomechanical aspects of FT. In this review, we summarized the current state of knowledge concerning the morphological, ultrastructural aspects, and mechanical properties of the human FT. We also investigate the potential arising from a thorough consideration of the biomechanical functions and exploring often neglected mechanical aspects. Our investigation encompasses both macroscopic measurements (such as length, diameter, and thickness) and microscopic measurements (including the height of epithelial cells, the percentage of ciliated cells, cilia structure, and ciliary beat frequency). Our primary focus has been on healthy women of reproductive age. We have examined various measurement techniques, encompassing conventional metrology, 2D histological data as well as new spatial measurement techniques such as micro-CT.



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