Course “Optics, Forces & Development”

Principles of Signalling in Mechanobiology

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Mechanical stresses regulate a diverse array of physiological functions and diseases

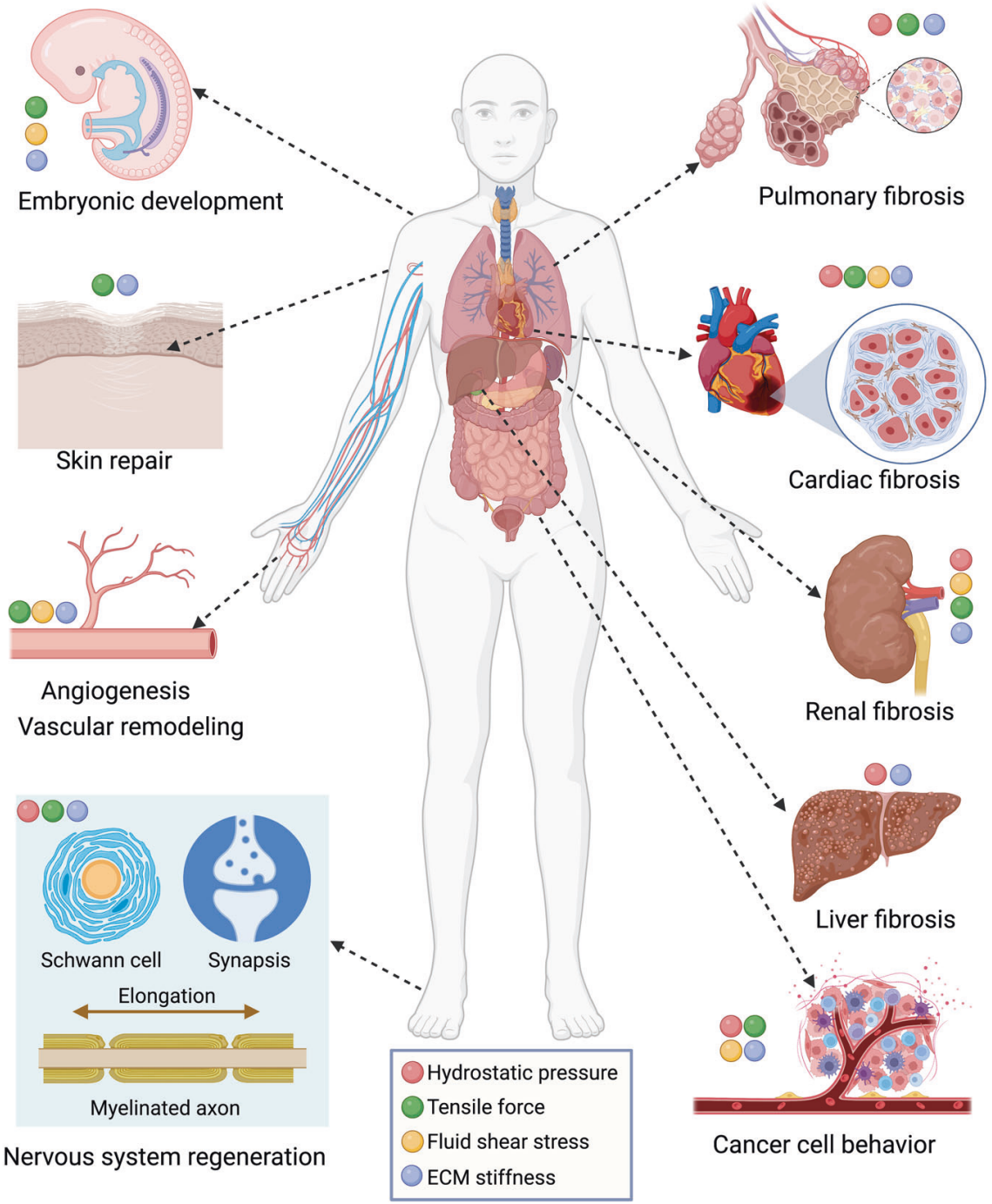
Mechanotransduction is cellular signal transduction in response to mechanical stimuli.

Physiological Conditions:

- **Tissue Development and Homeostasis**
- **Muscle Contraction**
- **Bone Remodeling**
- **Blood Flow and Vascular Mechanics**

Pathological Conditions:

- **Cancer Invasion and Metastasis**
- **Fibrosis**
- **Cardiovascular Diseases**
- **Neurological Disorders**
- **Osteoarthritis**

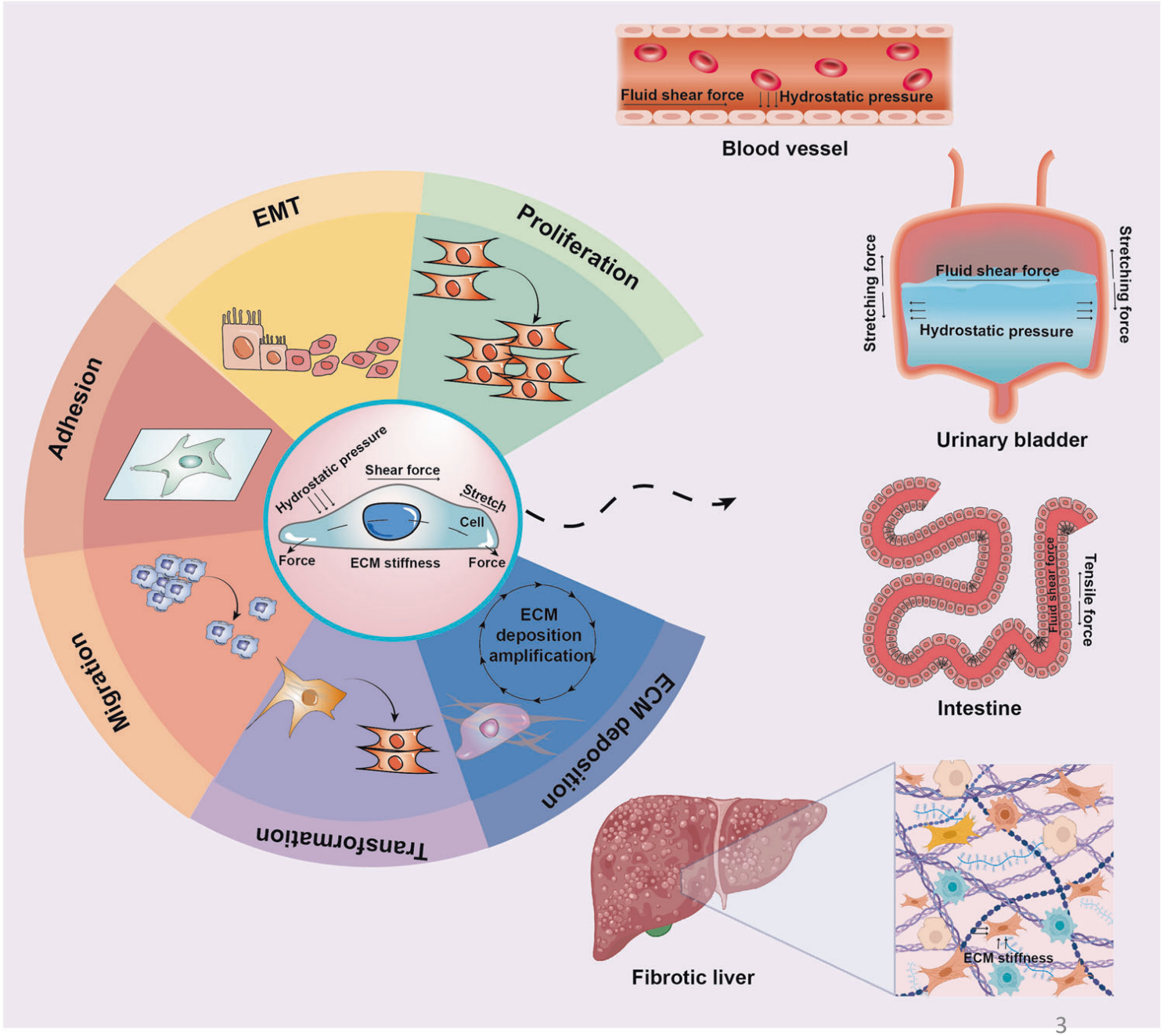


Signal Transduction and Targeted Therapy (2023)8:282

Cellular mechanotransduction in tissues and organs.

Mechanosensors are molecules or structures within cells that can detect mechanical cues.

- Hydrostatic pressure
- Tensile force
- Fluid shear stress
- ECM stiffness



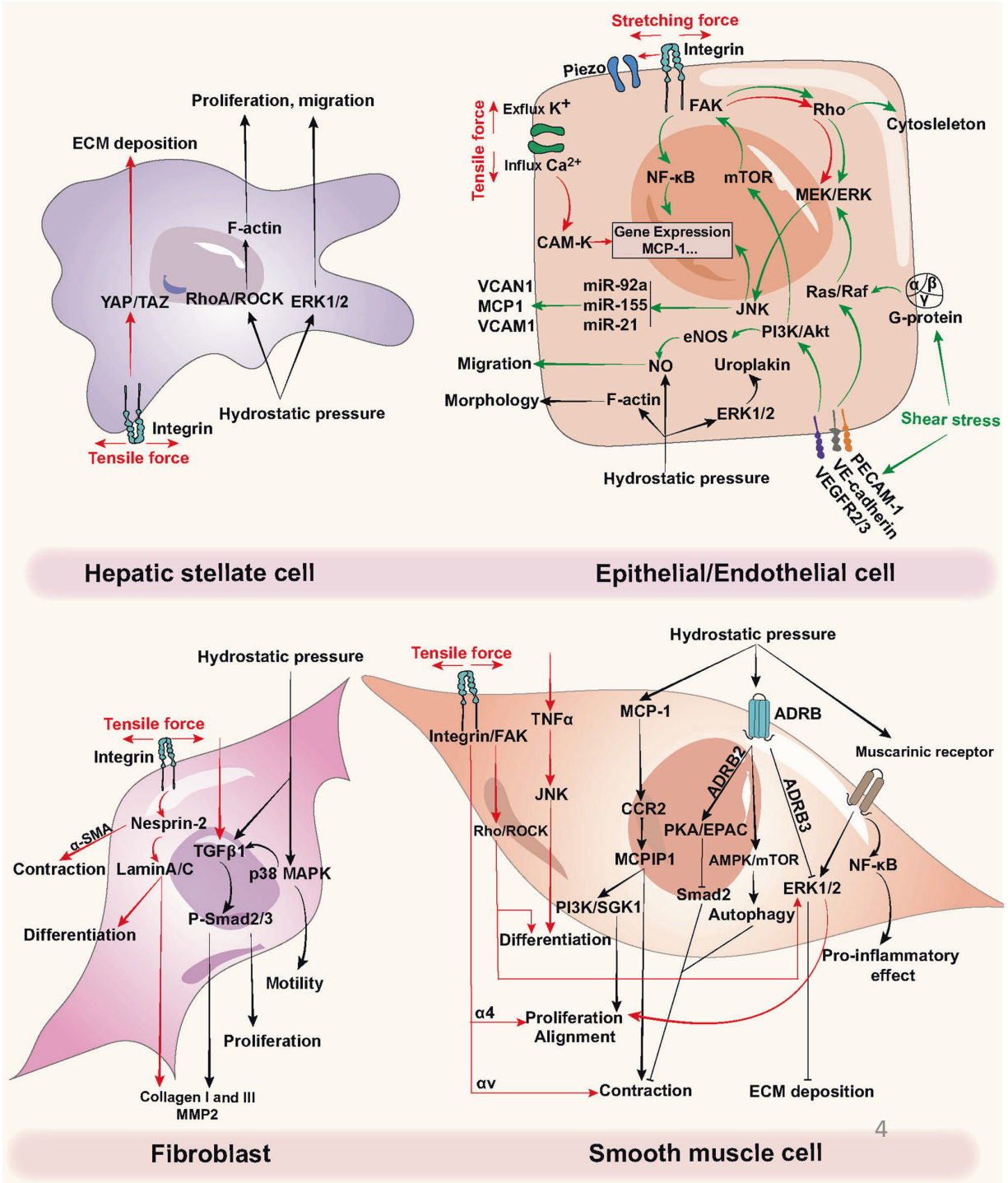
Signal Transduction and Targeted Therapy (2023)8:282

Regulatory mechanisms of tensile force, hydrostatic pressure, and shear stress on different cell types.

Different types of mechanosensors, such as integrins, focal adhesions, stretch-activated ion channels and membrane receptors.

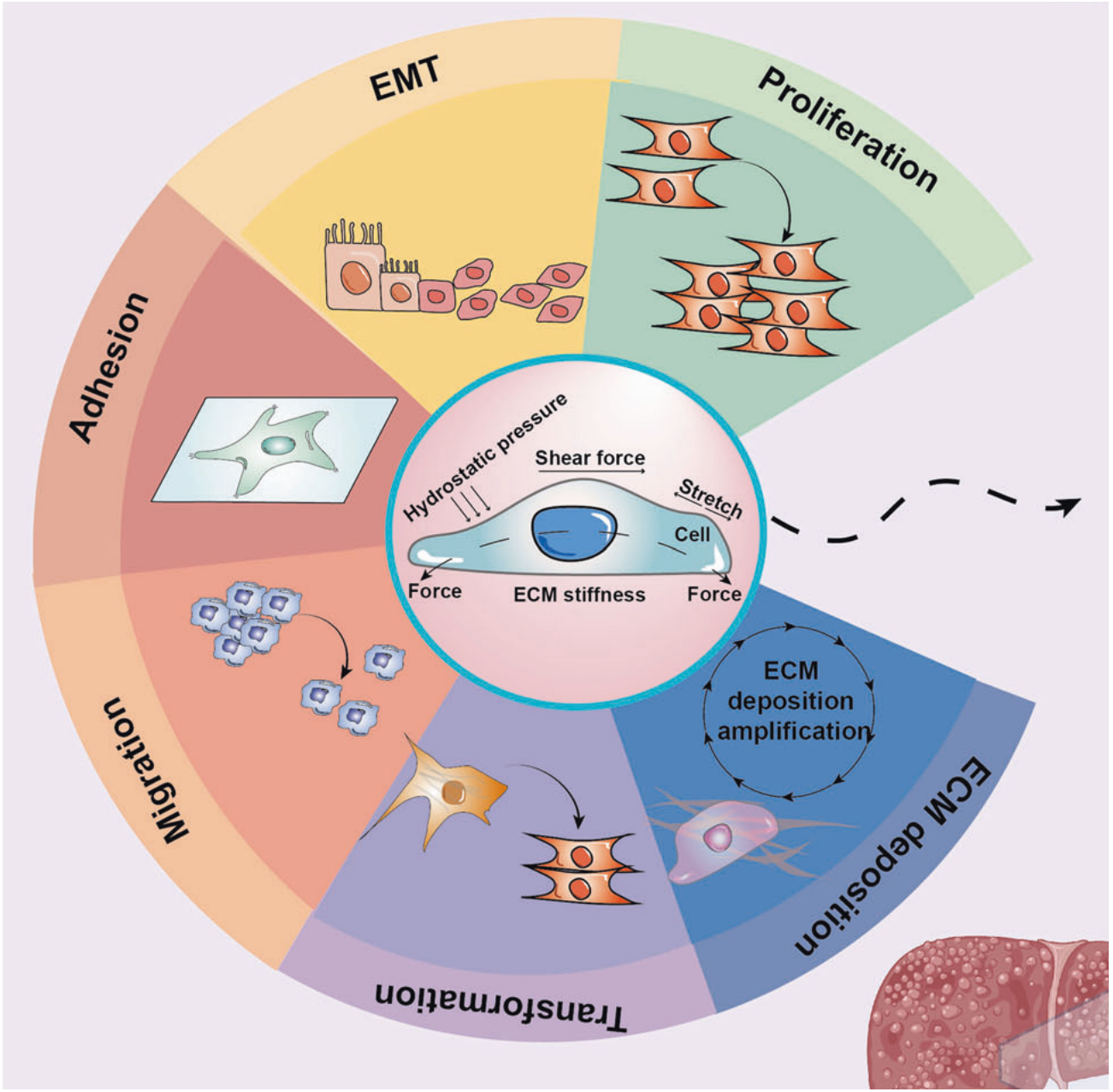
- Hydrostatic pressure
- Tensile force
- Fluid shear stress
- ECM stiffness

The importance of force magnitude, direction, and duration in influencing cellular responses.



Signal Transduction and Targeted Therapy (2023)8:282

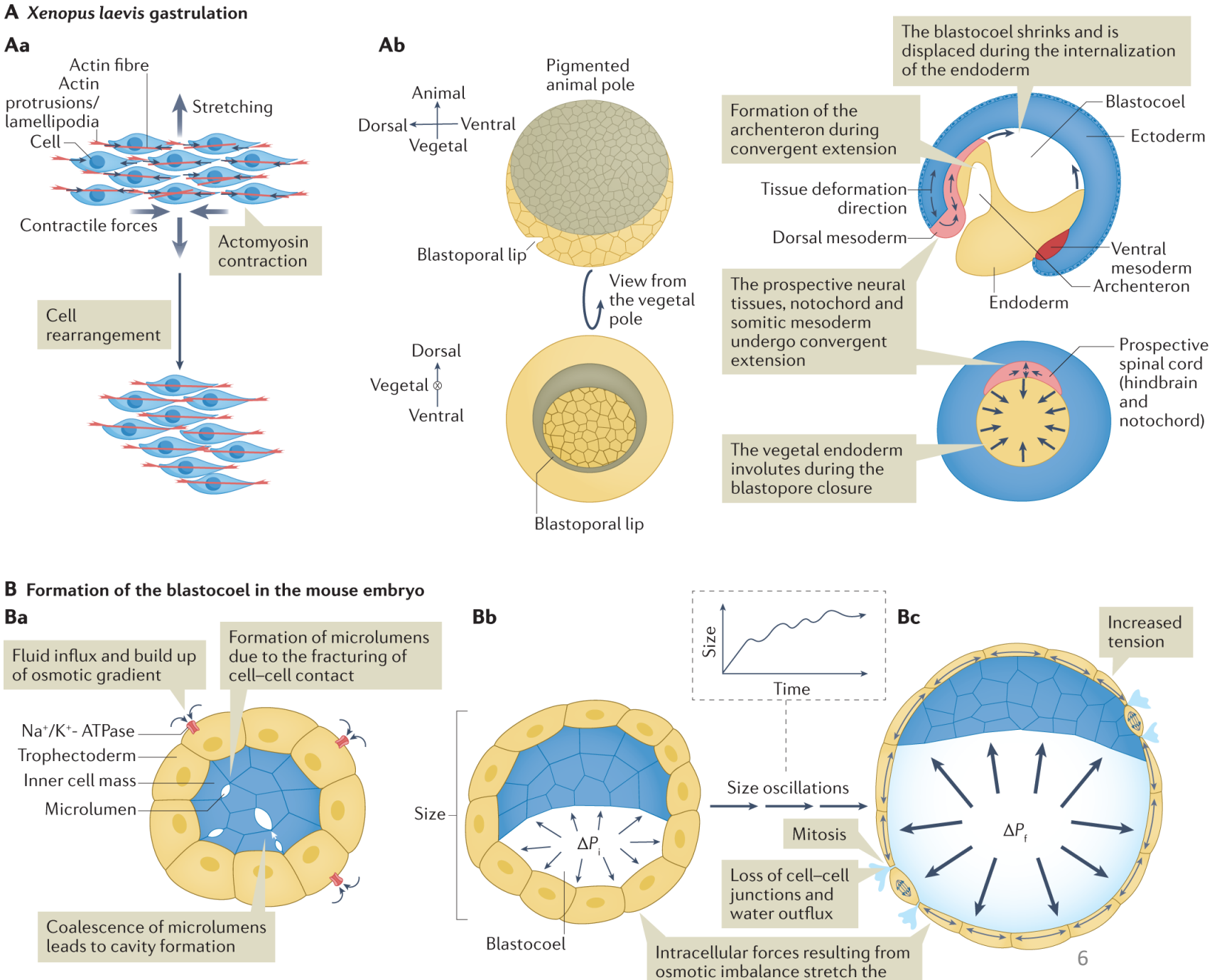
Various cellular responses are triggered by mechanical signals, such as changes in gene expression, cell migration, proliferation, and differentiation.



Signal Transduction and Targeted Therapy (2023)8:282

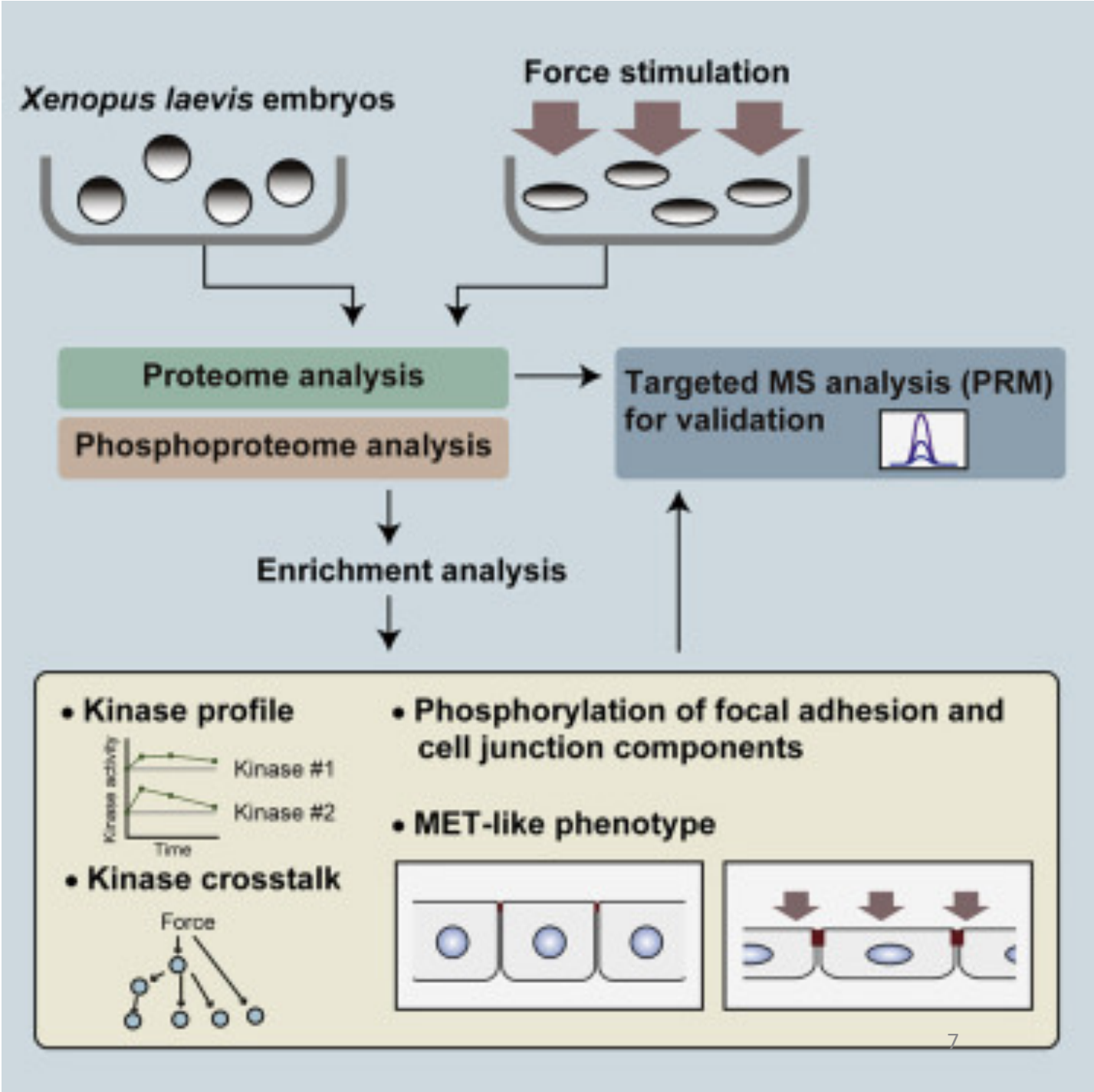
How mechanical cues can influence cell fate decisions and tissue development.

Tissue Development and Homeostasis: During embryonic development, mechanobiological cues guide cell differentiation, tissue patterning, and organ formation. In adult tissues, mechanical forces help maintain homeostasis by regulating cell renewal, differentiation, and proper tissue function.



Nature Reviews Molecular Cell Biology **23**, 169–184 (2022)

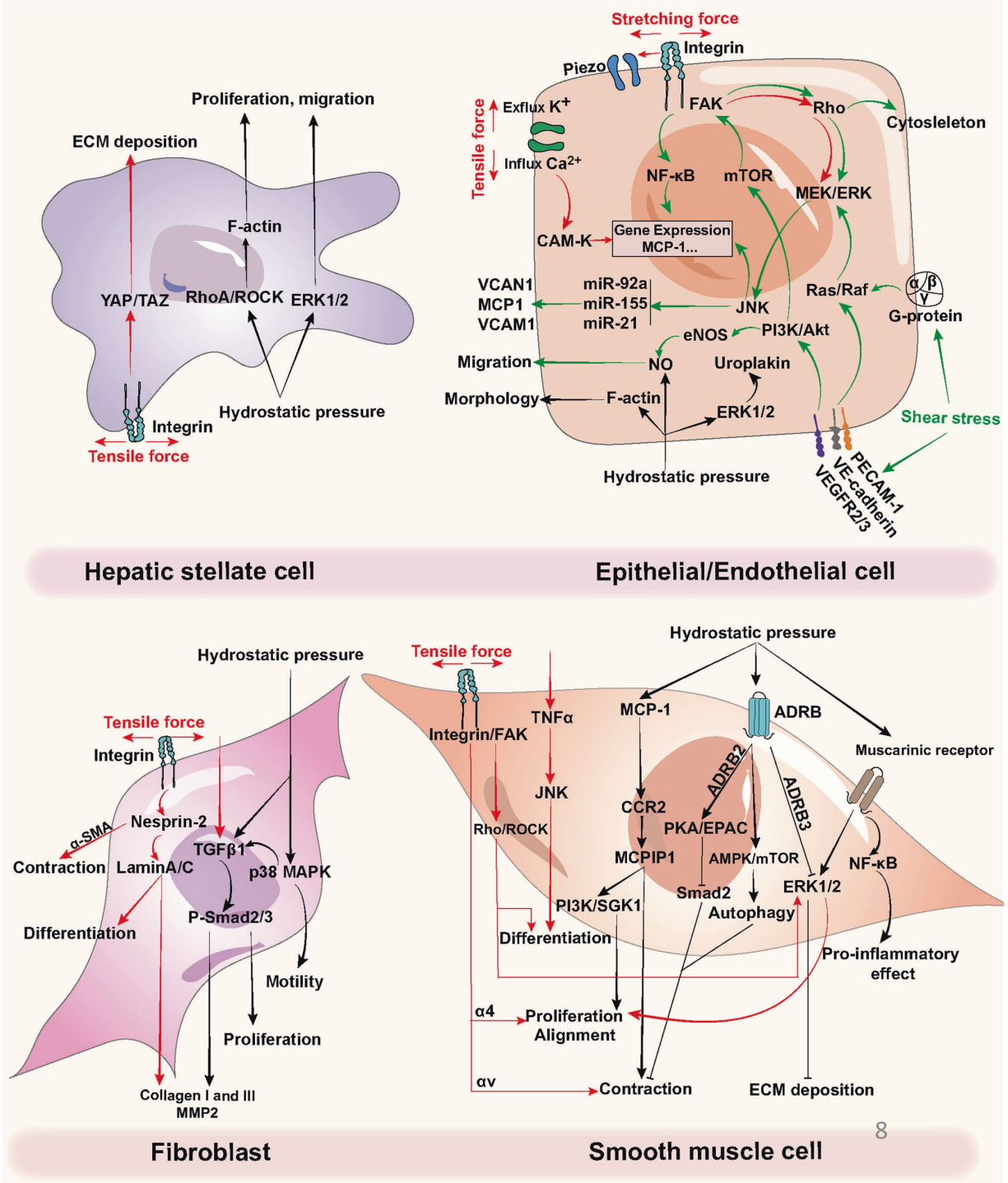
How mechanical cues can influence cell fate decisions and tissue development.



Cell Systems, 8, 226-241. (2019)

The signaling pathways involved in mechanotransduction, including focal adhesion kinase (FAK), Rho GTPases, and the Hippo pathway

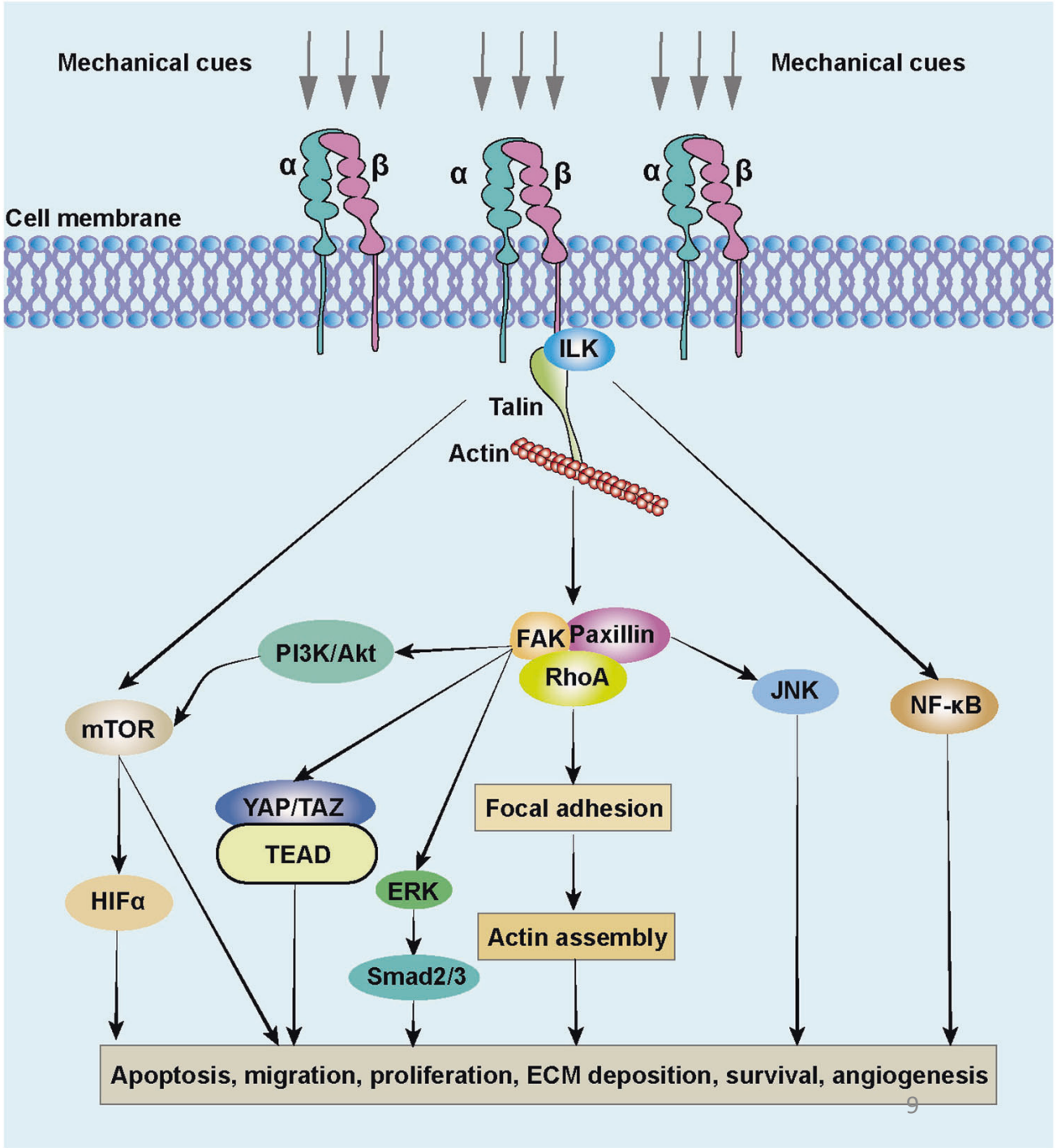
How these pathways regulate cellular functions in response to mechanical stimuli.



Signal Transduction and Targeted Therapy (2023)8:282

How these pathways regulate cellular functions in response to mechanical stimuli.

Mechanisms of integrins responding to mechanical stimulation. The β integrin interacts with ILK and talin to trigger downstream cascades. ECM extracellular matrix, ILK integrin-linked kinase

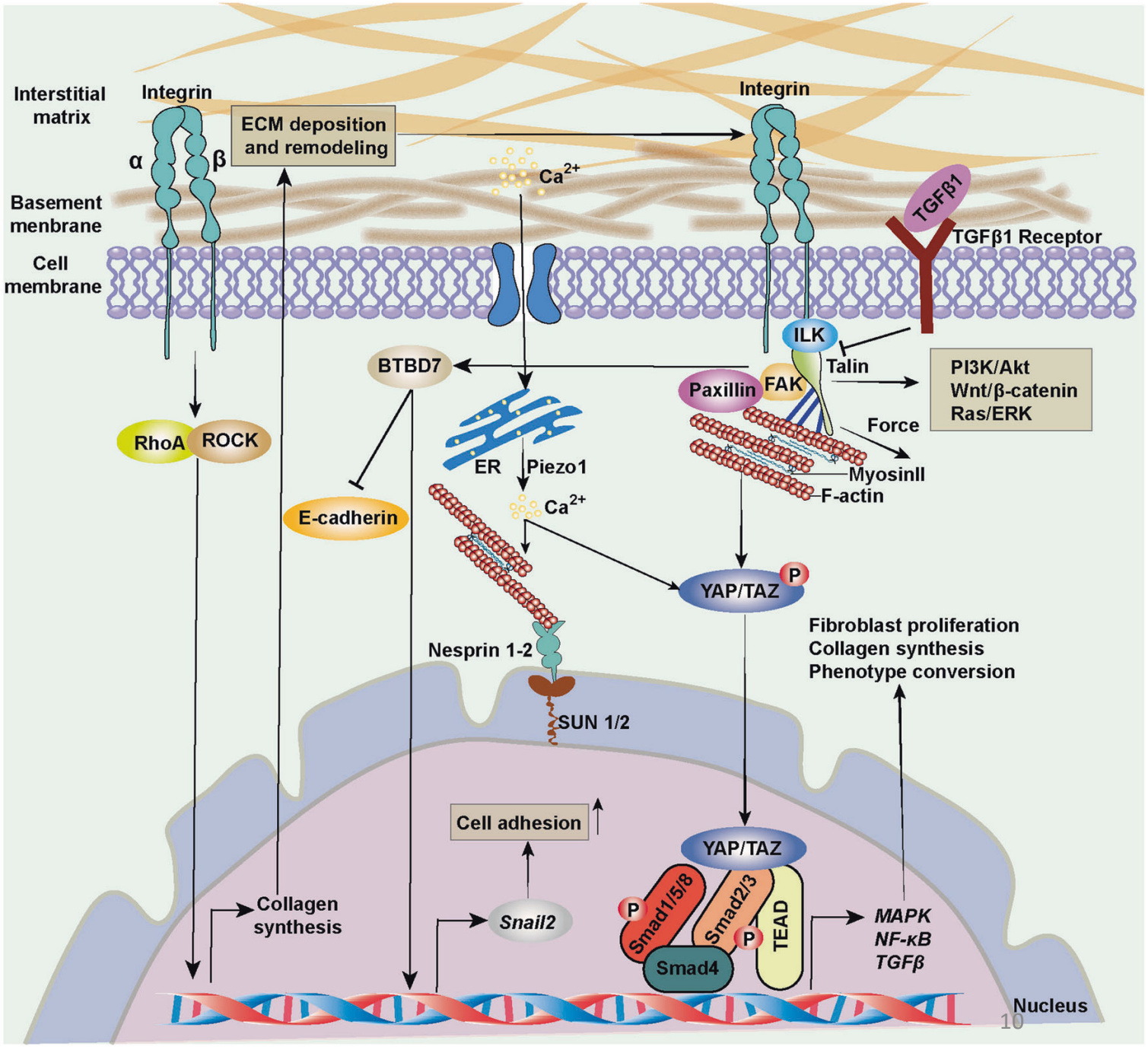


Signal Transduction and Targeted Therapy (2023)8:282

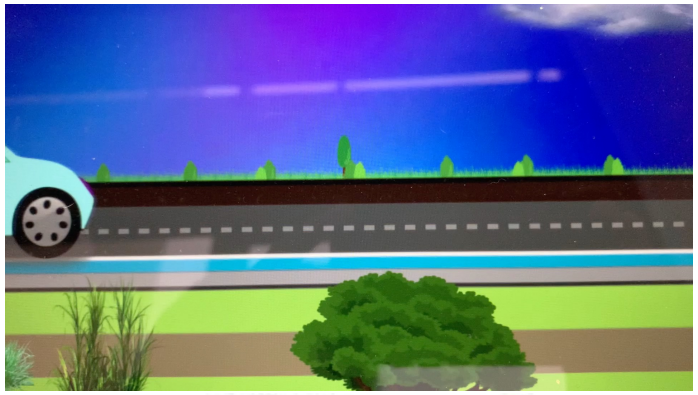
Cellular mechanotransduction of ECM stiffness.

- The integrins convey mechanical and biochemical signals from ECM into cells and facilitate cell proliferation, differentiation, migration, and invasion.
- The RhoA/ROCK pathway is activated, enhancing collagen and fibronectin accumulation.
- Talin/FAK facilitates the assembly of F-actin to promote signal transduction.
- The actin connects with myosin II and conveys the mechanical cues to the nucleus.
- YAP/TAZ is translocated into the nucleus to promote the transcription of downstream genes, collagen synthesis, and cell differentiation.

ECM extracellular matrix, **ER** endoplasmic reticulum, **ERK** extracellular signal-related kinase, **FAK** focal adhesion kinase, **ILK** integrin-linked kinase, **P** phosphate, **TGFβ** transforming growth factor β

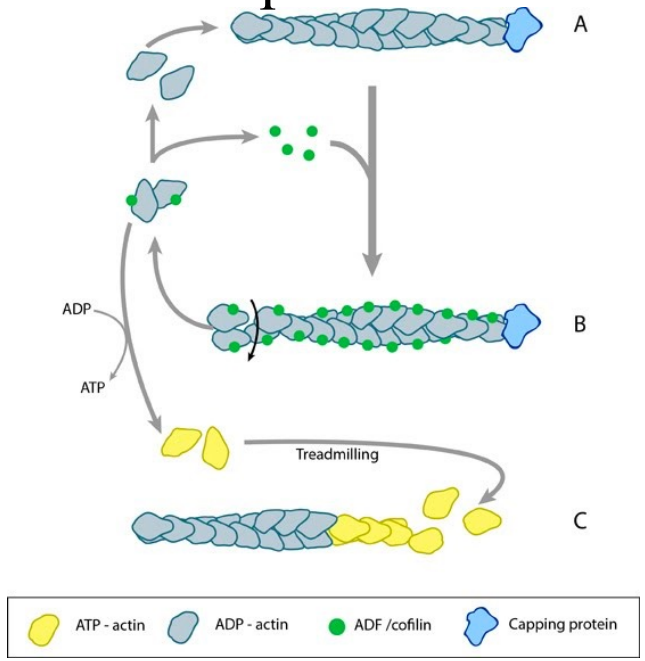


Signal Transduction and Targeted Therapy (2023)8:282

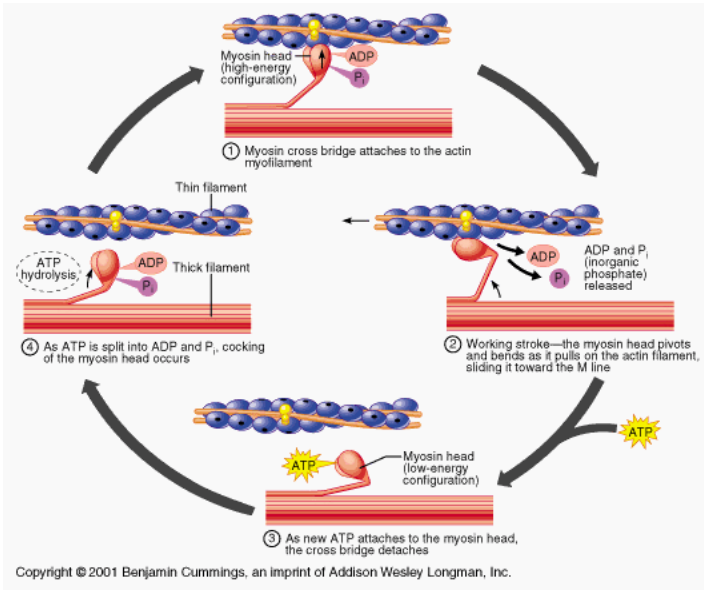


Cell engine

Actin polimerization

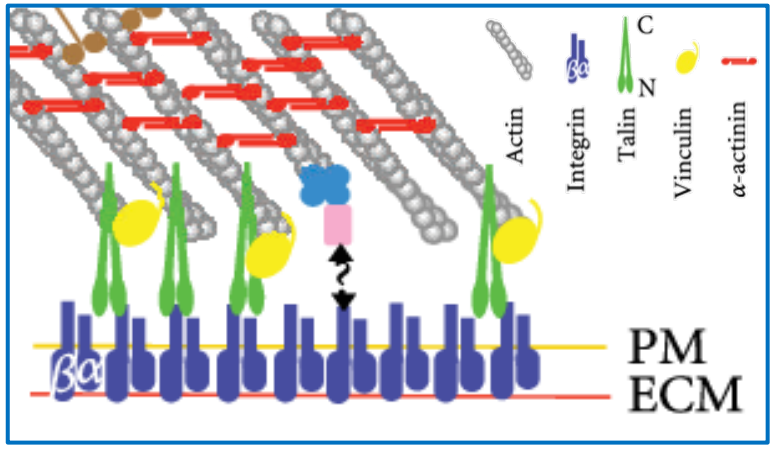


Actomyosin contractility



ATP → Forces

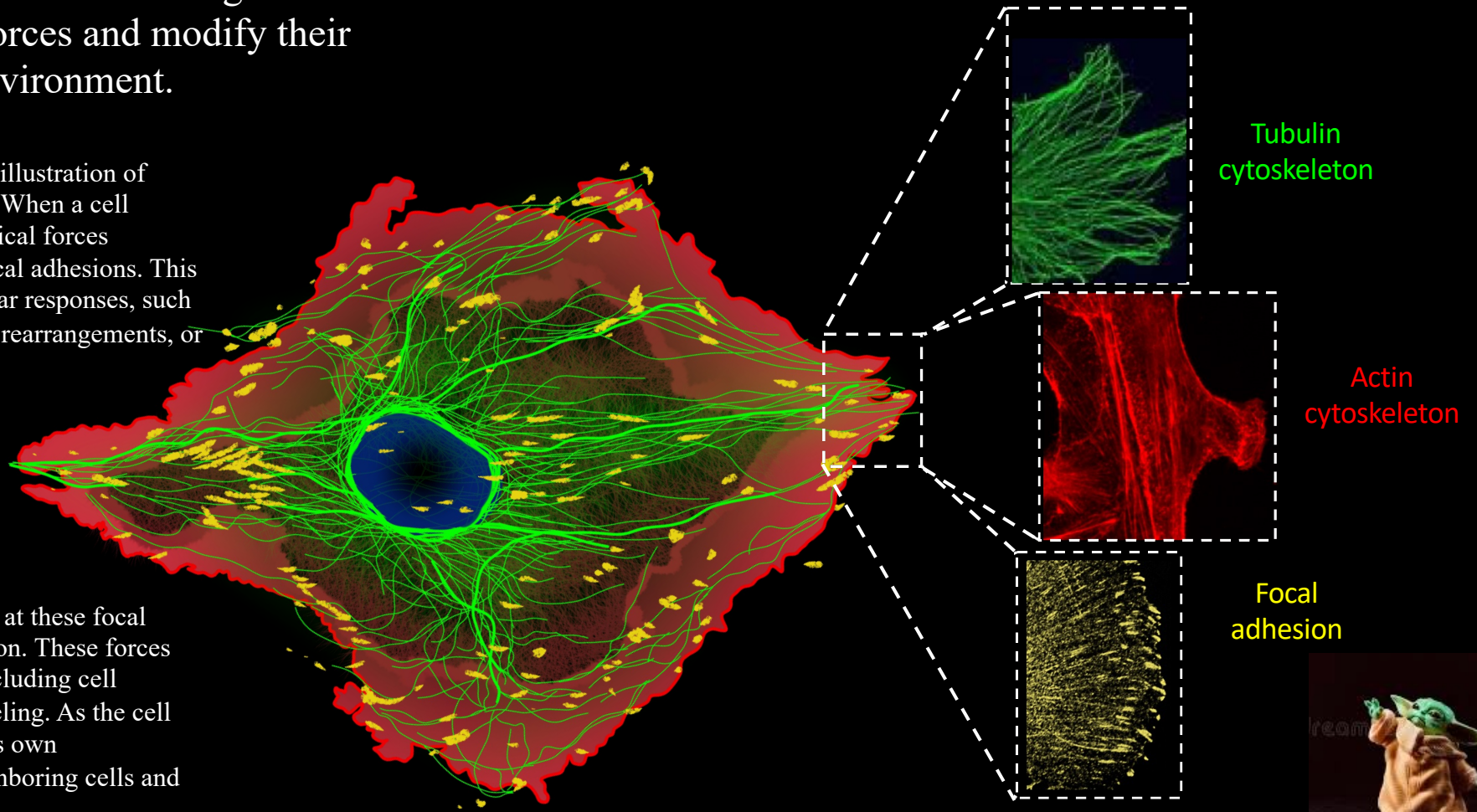
Adhesión Focal



Cell Migration

Mechanobiology is a dynamic and bidirectional process; cells not only respond to mechanical signals but also actively generate forces and modify their microenvironment.

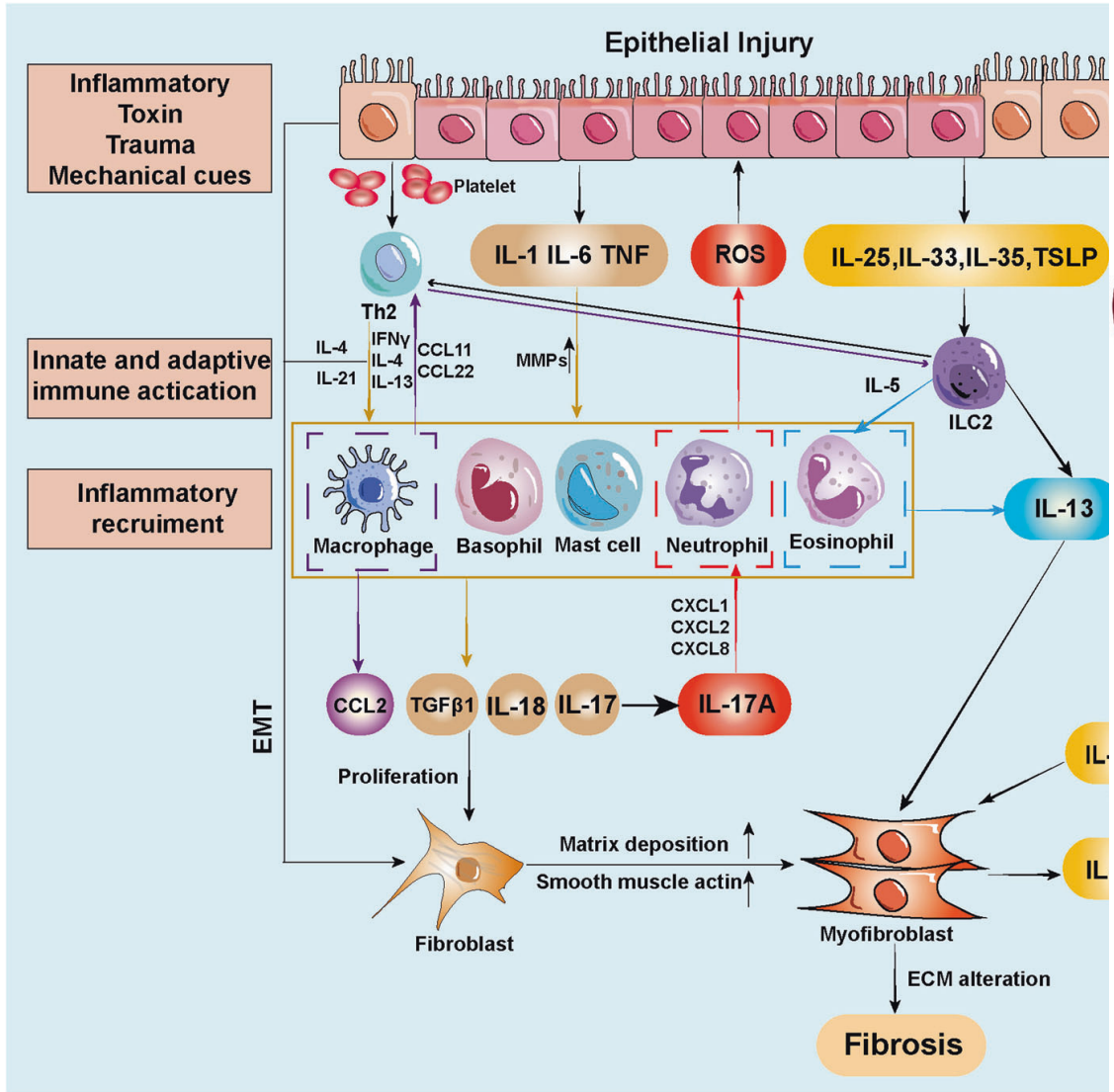
Example: Focal adhesions serve as a prime illustration of bidirectional mechanobiological processes. When a cell adheres to the ECM, it experiences mechanical forces transmitted through integrin receptors at focal adhesions. This mechanical signaling can trigger intracellular responses, such as changes in gene expression, cytoskeletal rearrangements, or cell migration.

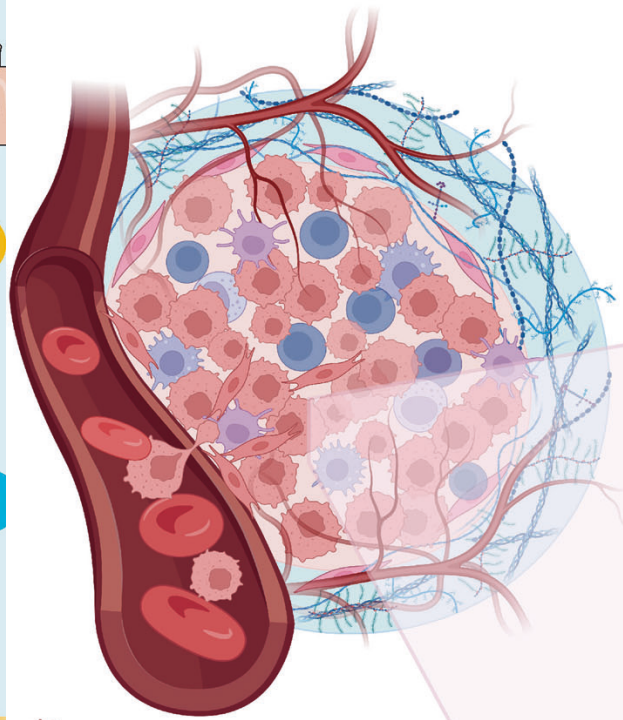


Conversely, the cell actively generates forces at these focal adhesions through the actomyosin cytoskeleton. These forces are involved in various cellular processes, including cell migration, tension sensing, and tissue remodeling. As the cell applies forces to the ECM, it can influence its own microenvironment, potentially affecting neighboring cells and the overall tissue architecture.

Villaseca ,S. Ph.D. Thesis

How mechanobiological processes are involved in various physiological and pathological conditions.





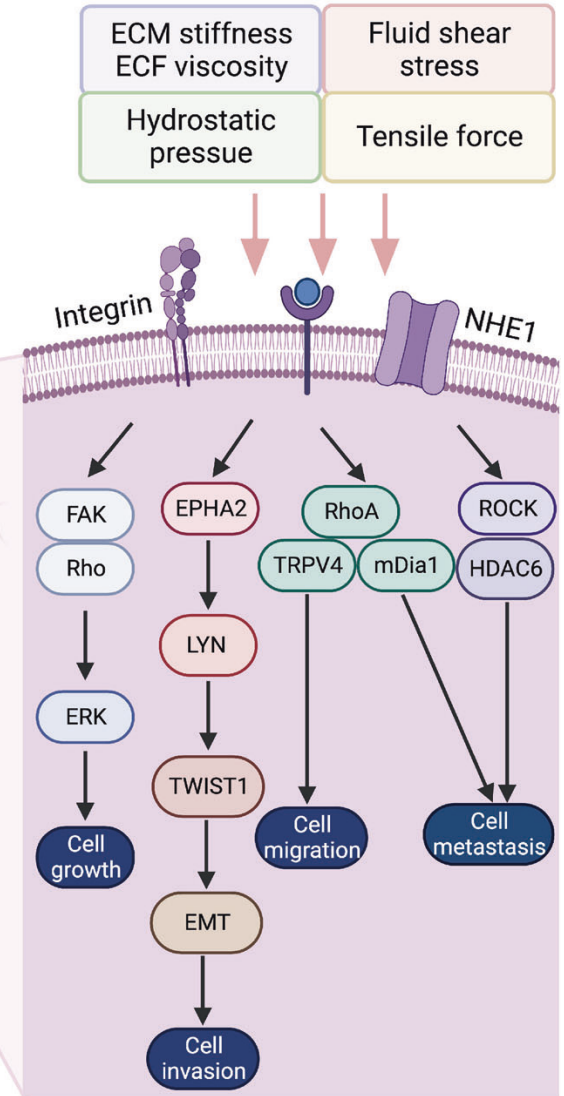


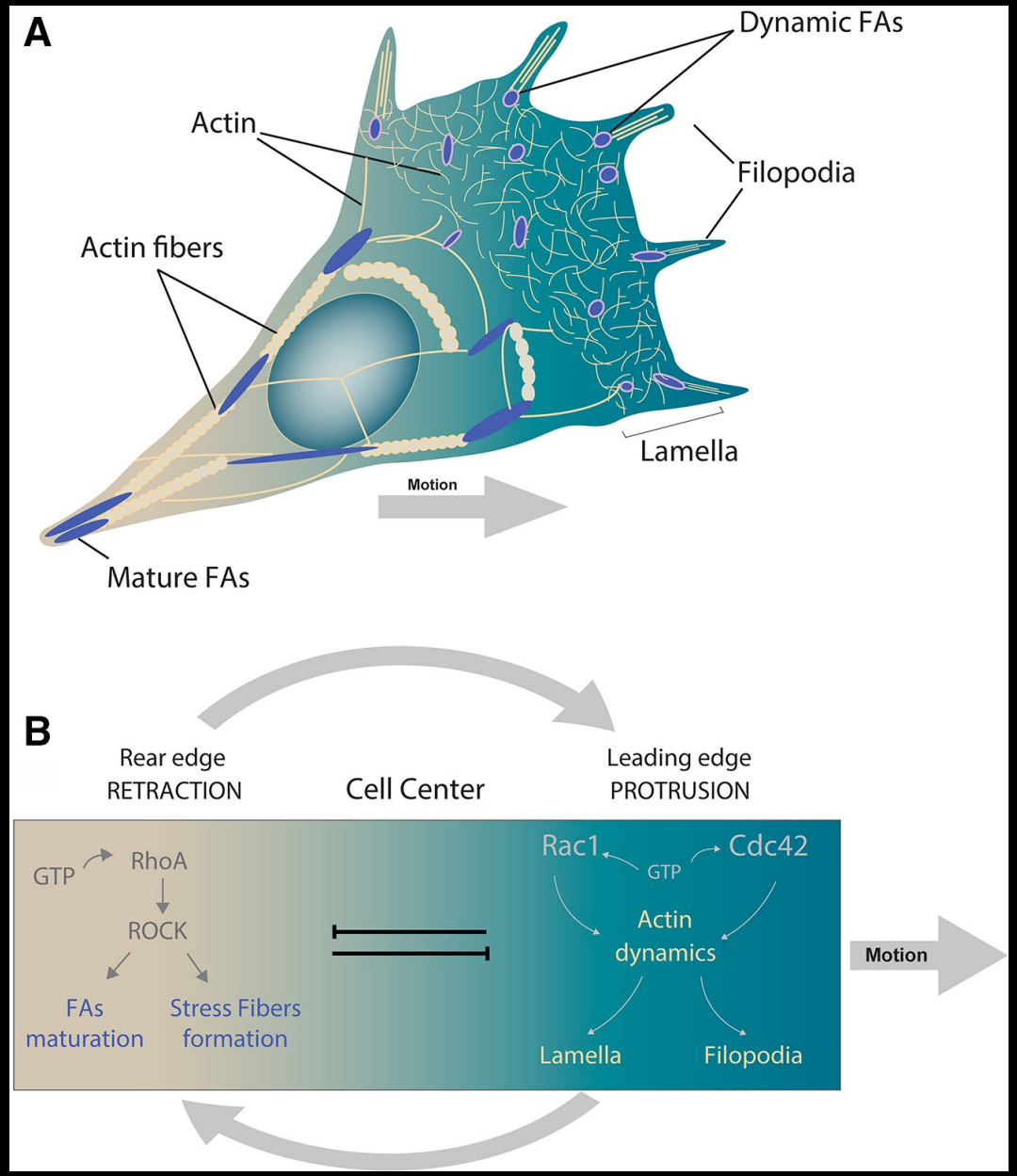
Table 2. Typical clinical trials targeting integrins

Integrin subtype	Intervention/treatment	Disease type	Phase	Current status	ClinicalTrials.gov identifier
α5β1	Volociximab	Metastatic renal cell carcinoma	2	Terminated	NCT00100685
		Pancreatic cancer	2	Completed	NCT00401570
		Ovarian cancer, primary peritoneal cancer	1/2	Completed	NCT00635193
α4β7	Vedolizumab	Ulcerative colitis	4	Recruiting	NCT05481619
		Crohn's disease; ulcerative colitis	Not applicable	Completed	NCT02862132
		Inflammatory bowel disease	Not applicable	Completed	NCT02712866
		Type 1 diabetes	1	Recruiting	NCT05281614
αvβ1; αvβ3; αvβ6	IDL-2965 oral capsule	Idiopathic pulmonary fibrosis	1	Terminated	NCT03949530
αvβ6; αvβ1	PLN-74809	Idiopathic pulmonary fibrosis	2	Completed	NCT04072315
αLβ2; α4β1	7HP349	Solid tumor	1	Completed	NCT04508179

Table 3. Typical clinical trials targeting YAP/TAZ

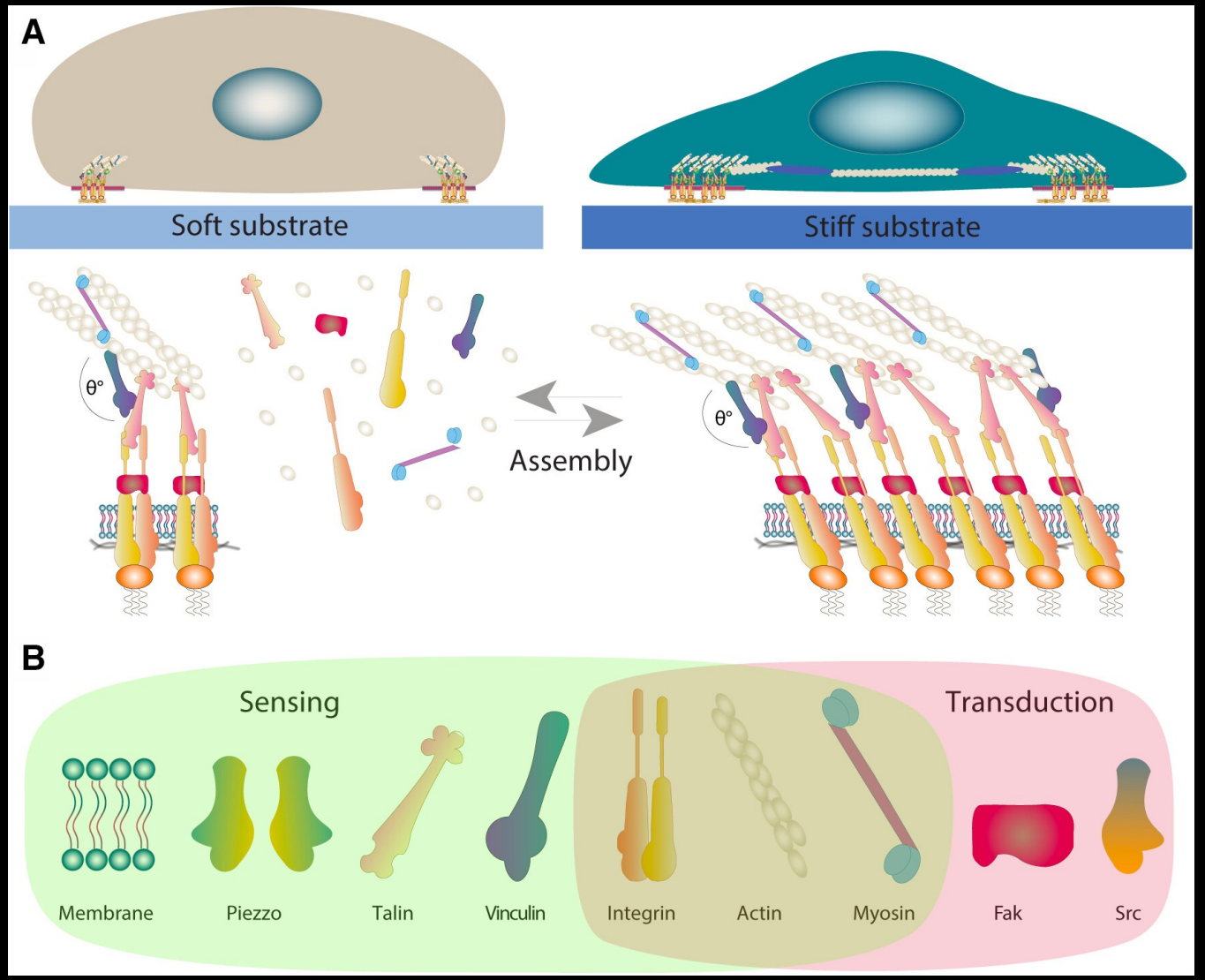
Target	Intervention/treatment	Disease type	Phase	Current status	ClinicalTrials.gov identifier
YAP	Simvastatin	Prostate cancer	2	Recruiting	NCT05586360
	ION537	Advanced solid tumors	1	Completed	NCT04659096
YAP/TAZ	Zoledronate	Breast cancer	2	Terminated	NCT02347163
TEAD	IK-930	Solid tumors	1	Recruiting	NCT05228015

Cell polarity and directed cell motion



Espina et al., 2021. The FEBS journal

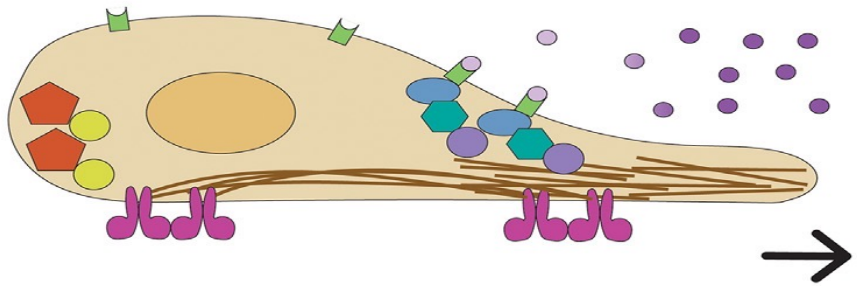
Mechanosensing in soft and stiff substrate



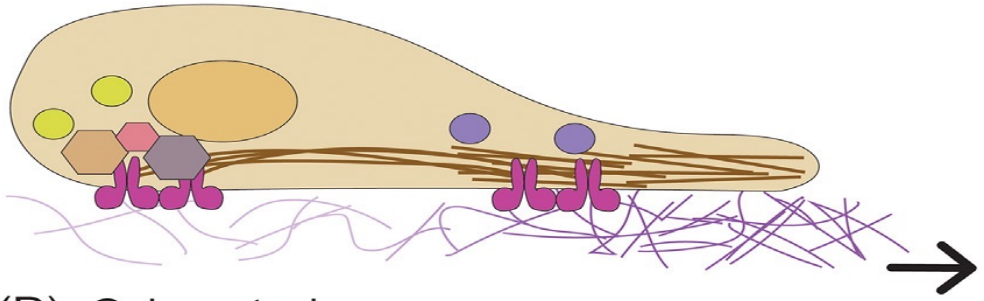
Espina et al., 2021. The FEBS journal

Mechanisms of Directional Migration

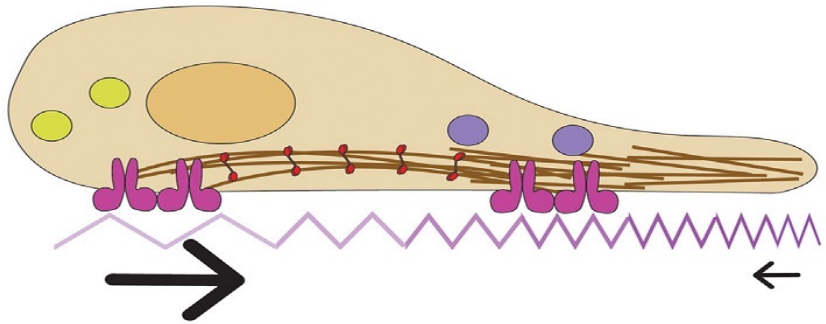
(A) Chemotaxis



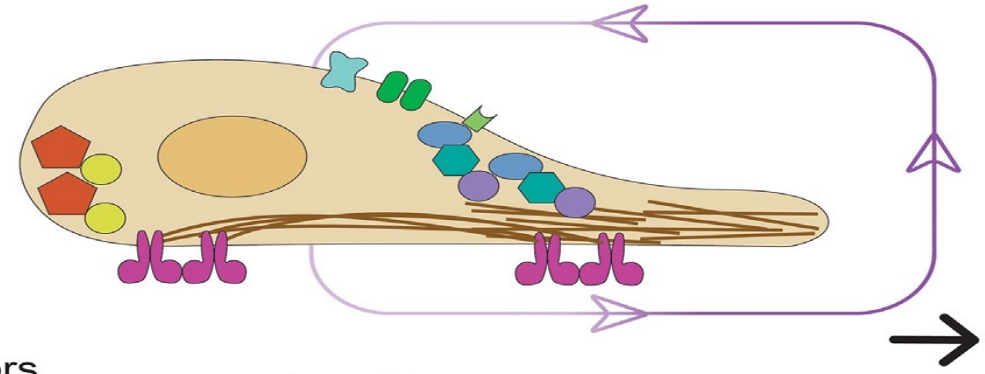
(C) Haptotaxis



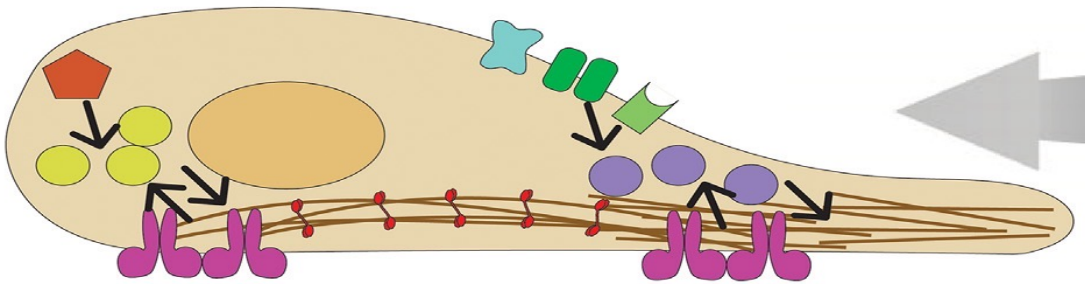
(B) Durotaxis



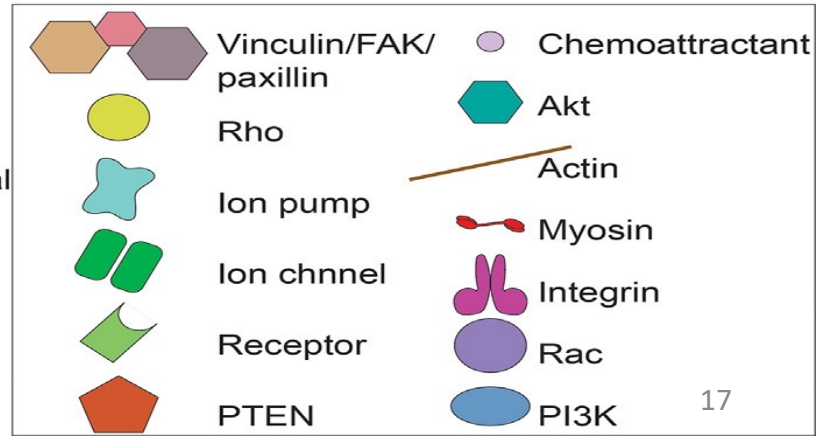
(D) Galvanotaxis



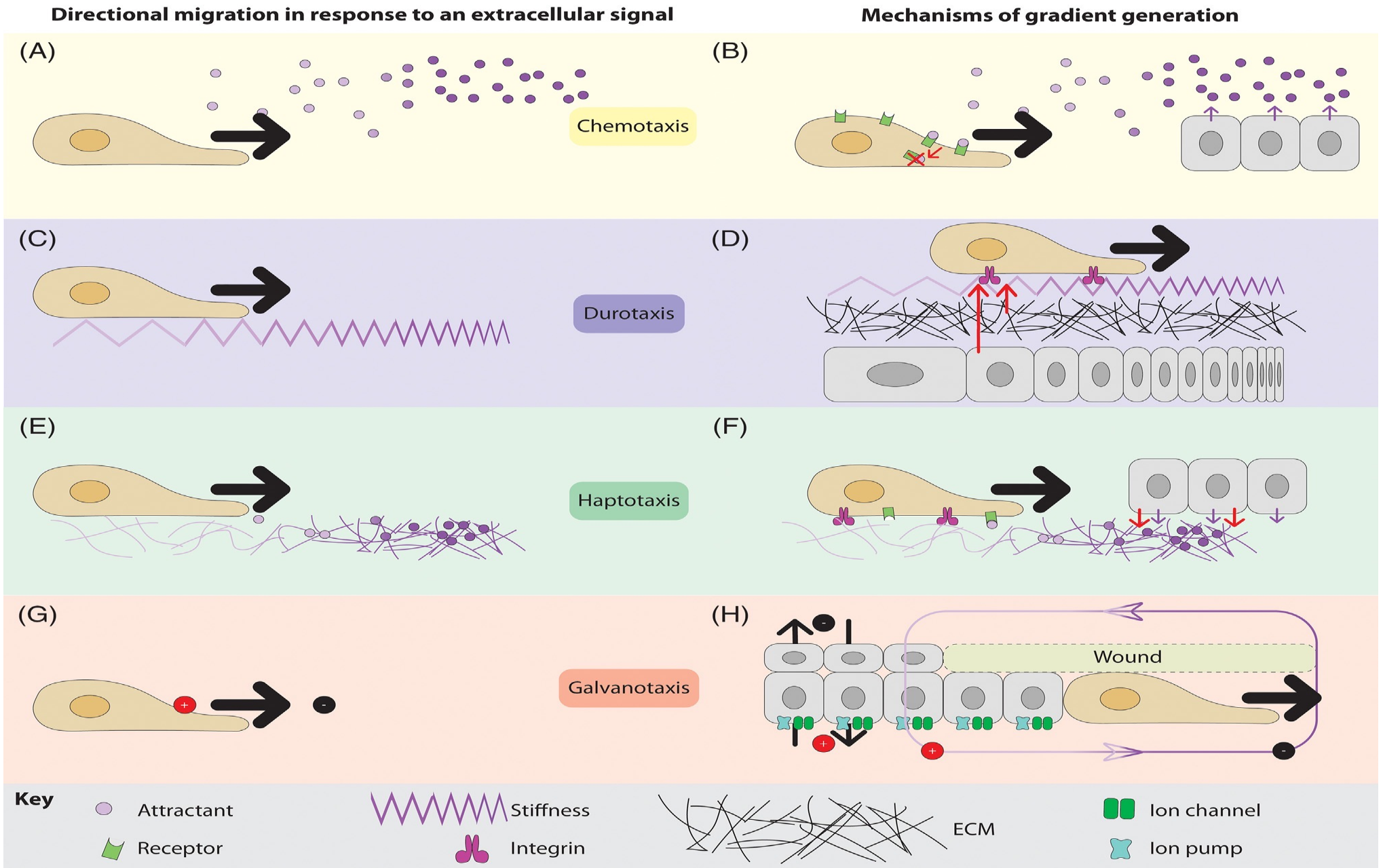
(E) Small GTPases and the actin cytoskeleton as central regulators



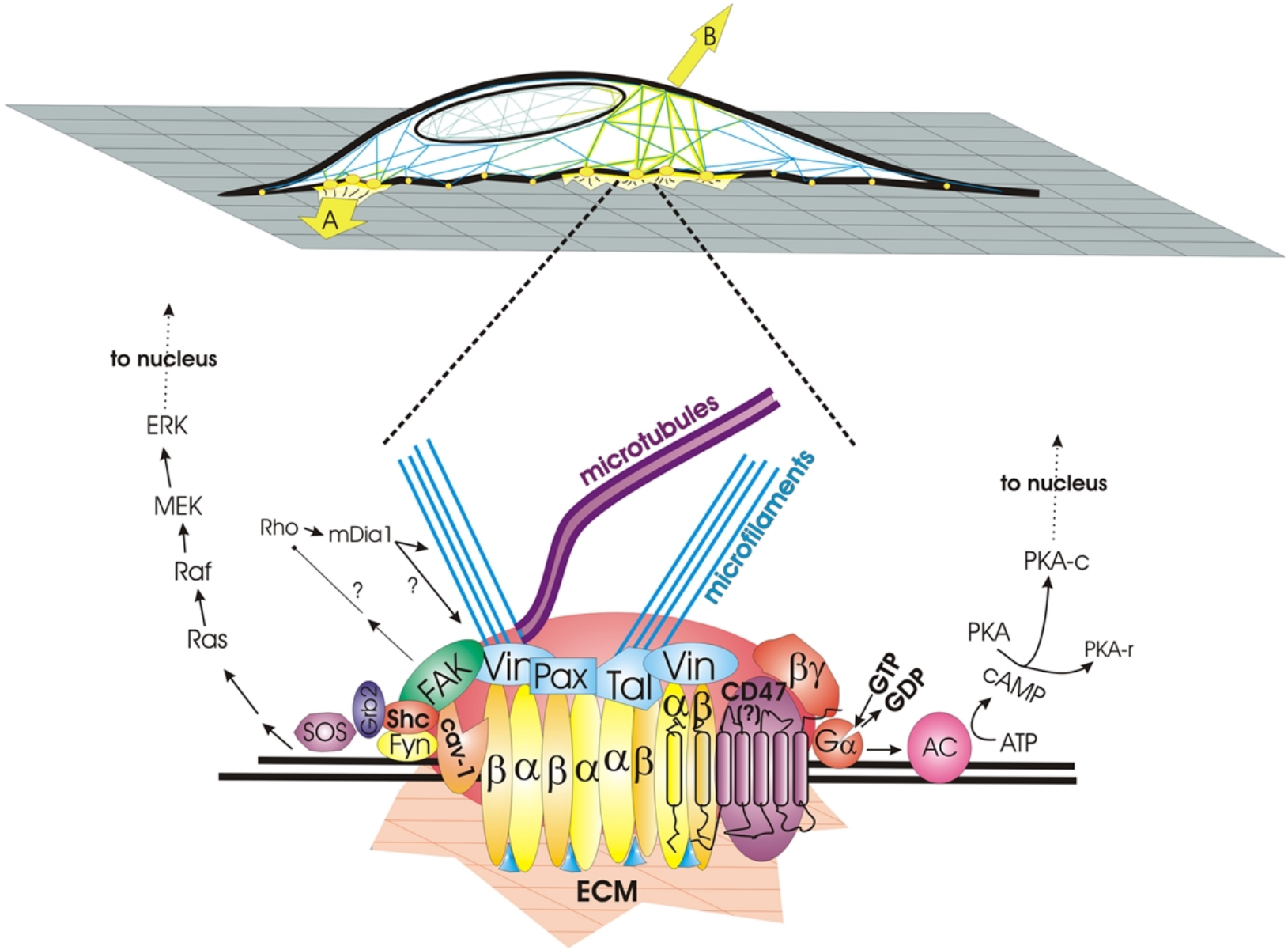
Chemical
Mechanical
Electrical

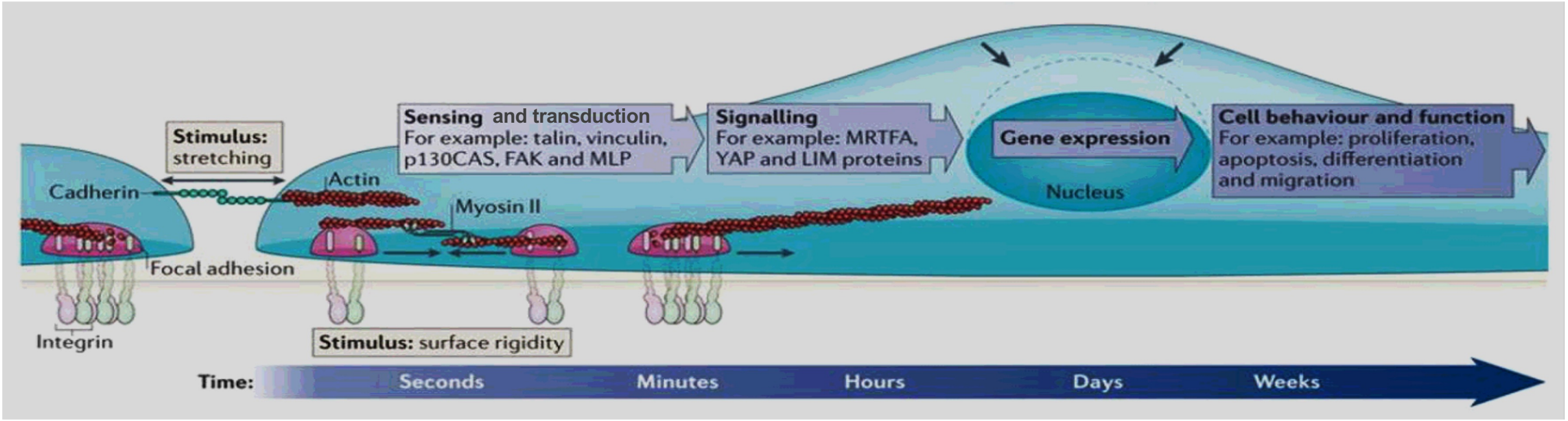


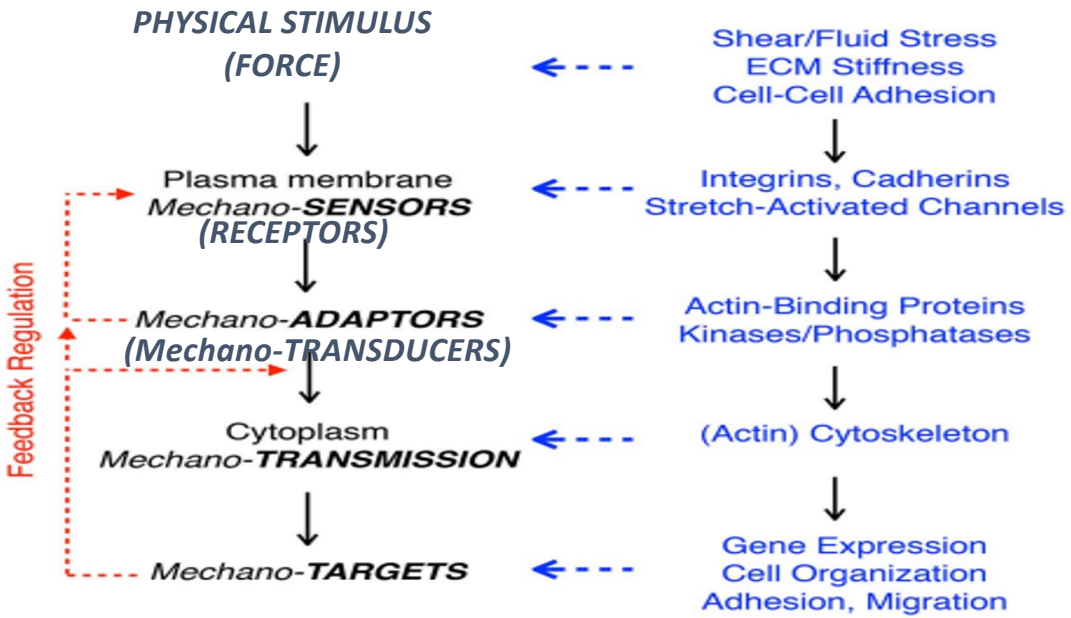
Gradient Formation of Migratory Cues



Schematic diagram of how forces applied through the ECM (**A**) or directly to the cell surface (**B**) travel to integrin-anchored focal adhesions through matrix attachments or cytoskeletal filaments, respectively.




Stimulus: stretching
Cadherin
Actin
Myosin II
Focal adhesion
Integrin
Sensing and transduction
For example: talin, vinculin, p130CAS, FAK and MLP
Signalling
For example: MRTFA, YAP and LIM proteins
Gene expression
Nucleus
Cell behaviour and function
For example: proliferation, apoptosis, differentiation and migration
Stimulus: surface rigidity
Time:
Seconds
Minutes
Hours
Days
Weeks

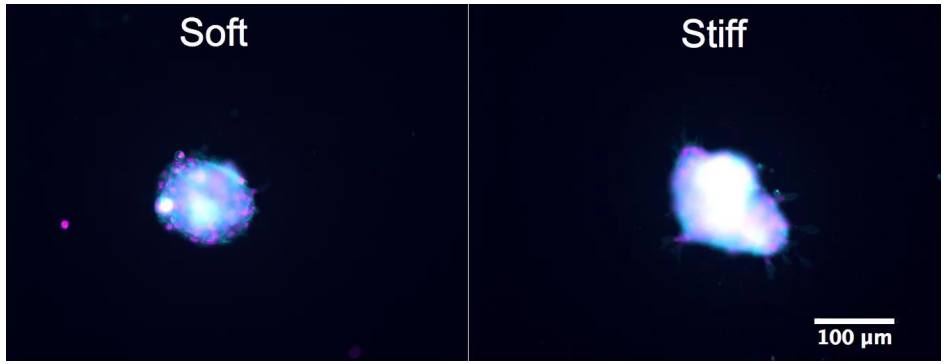

PHYSICAL STIMULUS (FORCE)
Shear/Fluid Stress
ECM Stiffness
Cell-Cell Adhesion
Plasma membrane
Mechano-SENSORS
(RECEPTORS)
Integrins, Cadherins
Stretch-Activated Channels
Mechano-ADAPTORS
(Mechano-TRANSDUCERS)
Actin-Binding Proteins
Kinases/Phosphatases
Cytoplasm
Mechano-TRANSMISSION
(Actin) Cytoskeleton
Mechano-TARGETS
Gene Expression
Cell Organization
Adhesion, Migration
Feedback Regulation


Extracellular forces
Force generating machinery

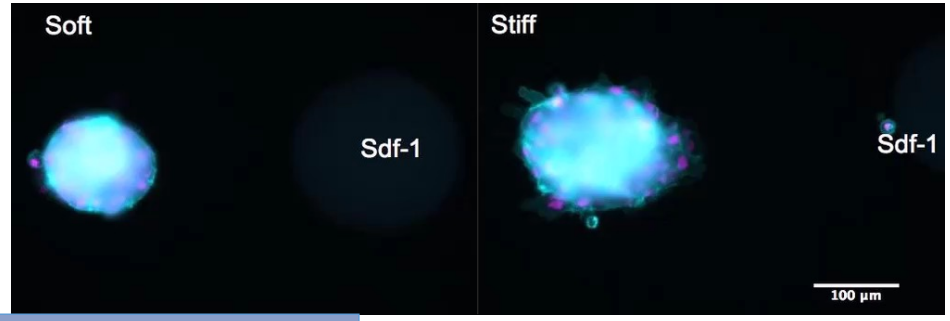
Techniques such as atomic force microscopy, traction force microscopy, and microfabrication tools that enable us to study mechanobiology at the cellular and molecular levels.

Migratory response to ECM stiffness

Cell spreading celular



Chemotactic migration

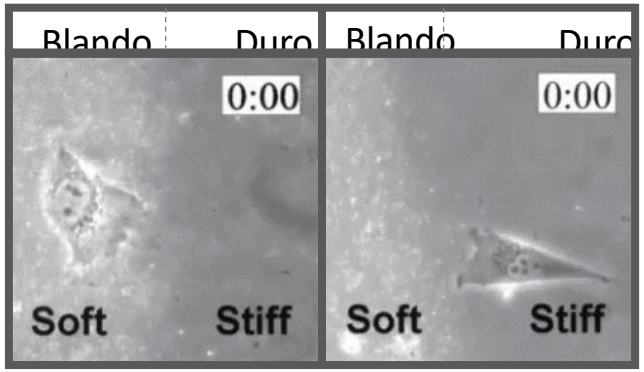


Sdf1 → CXCR4 (GPCR)

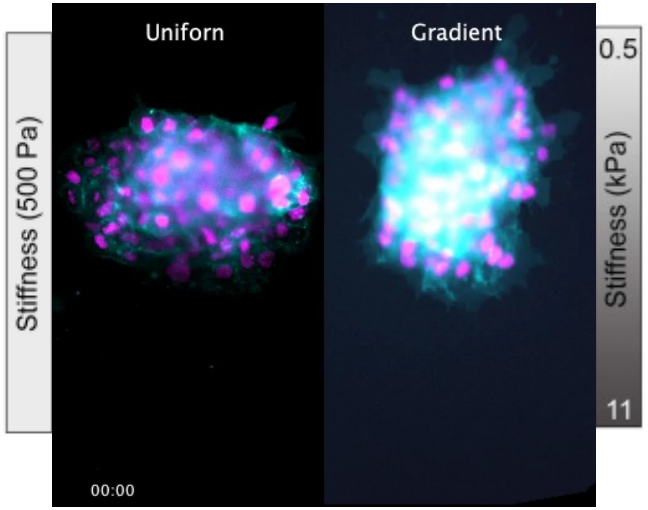
Craneal Neural crest Explants de Cresta Neural Craneal de *Xenopus*

[E. Barriga et al., (2018) Nature]

Durotaxis



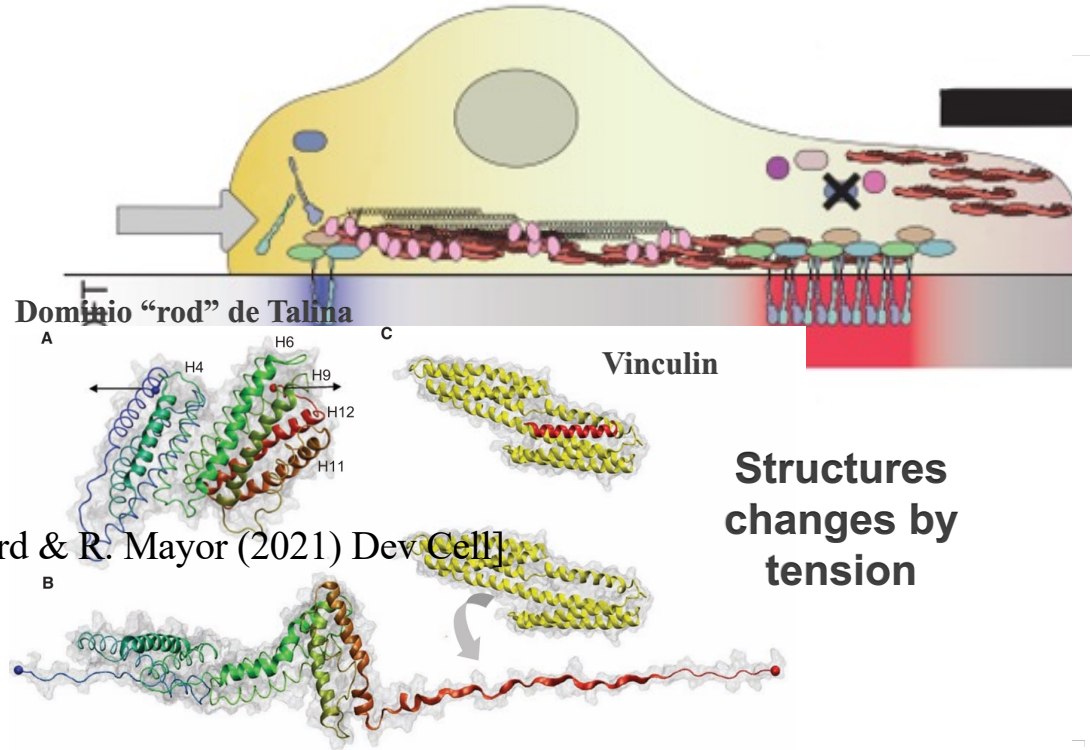
[Chun-Min Lo et al., (2000) Biophys J]



[Adam Shellard & Roberto Mayor (2021) Nature]

Mechanosensing by: 1) Cell adhesion tension

Mechanosensors as probes

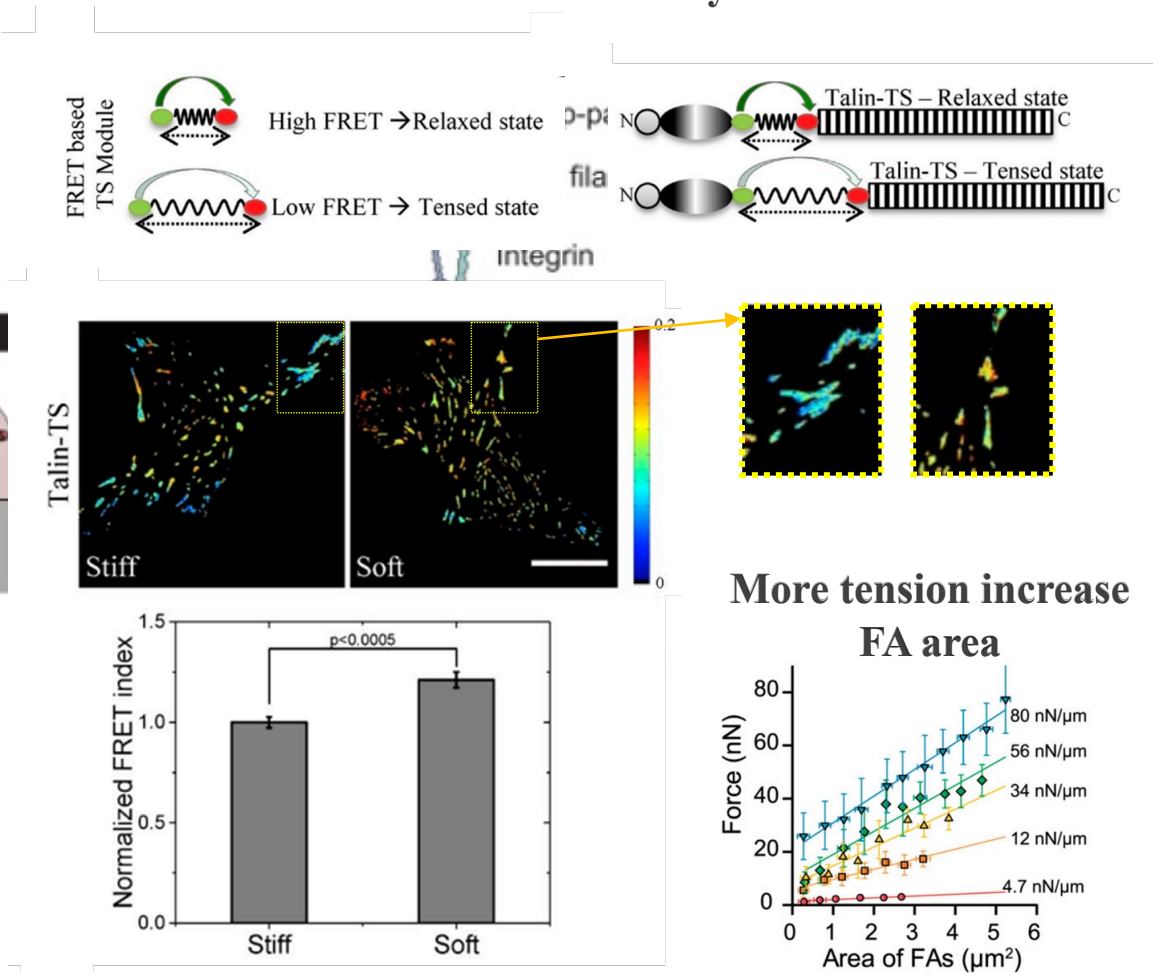


[A. Shellard & R. Mayor (2021) Dev Cell]

[Mingxi Yao et al., (2016) Nat Commun]

Focal adhesion or cell-cell adhesion

Talin tension is alterated by ECM stiffness

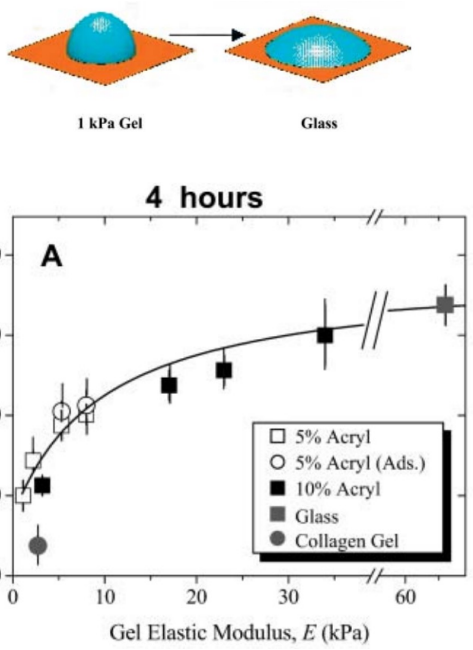


[A. Kumar et al., (2016) J Cell Biol]

[L. Trichet et al., (2012) Proc Natl Acad Sci USA]

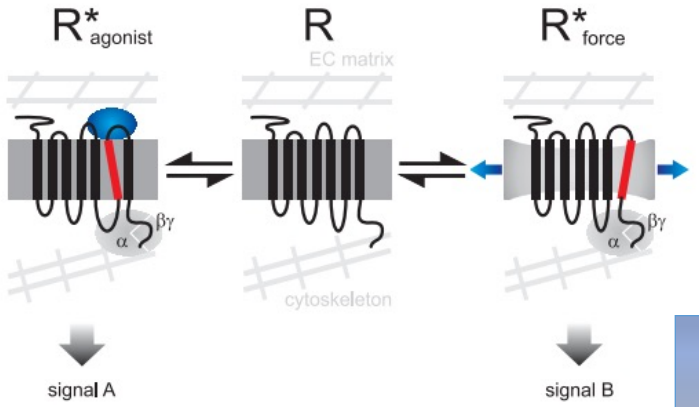
Mechanosensing by: 2) plasma membrane lateral stretching

Cellular Extension



[Adam Engler et al., (2004) Biophys J]

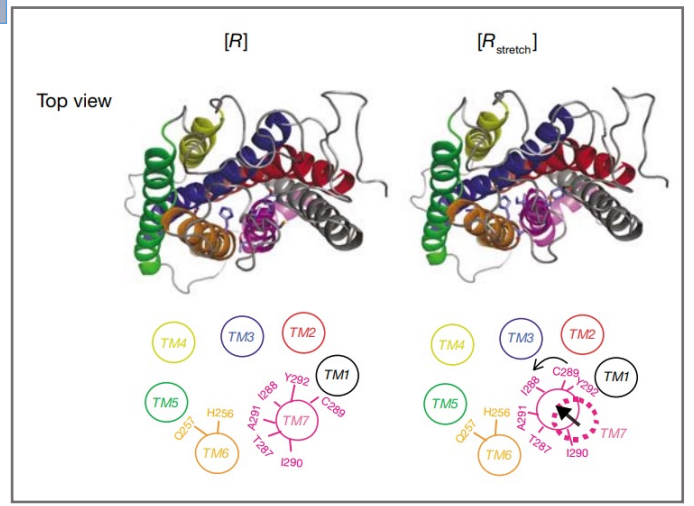
GPCR activated form chemical ligand or membrane tension



[U. Storch et al., (2012) Am J Physiol Heart Circ Physiol.]

GPCR

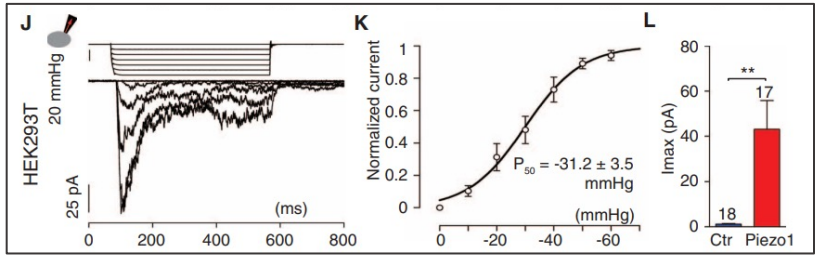
AT1R (activated by tension)



[N. Yasuda et al., (2008) EMBO Rep.]

Ion Channel

Piezo1 (activated by tension)



[B. Coste et al., (2010) Science]

Course “Optics, Forces & Development”

Heterotrimeric G protein Signalling in response to Mechanical cues

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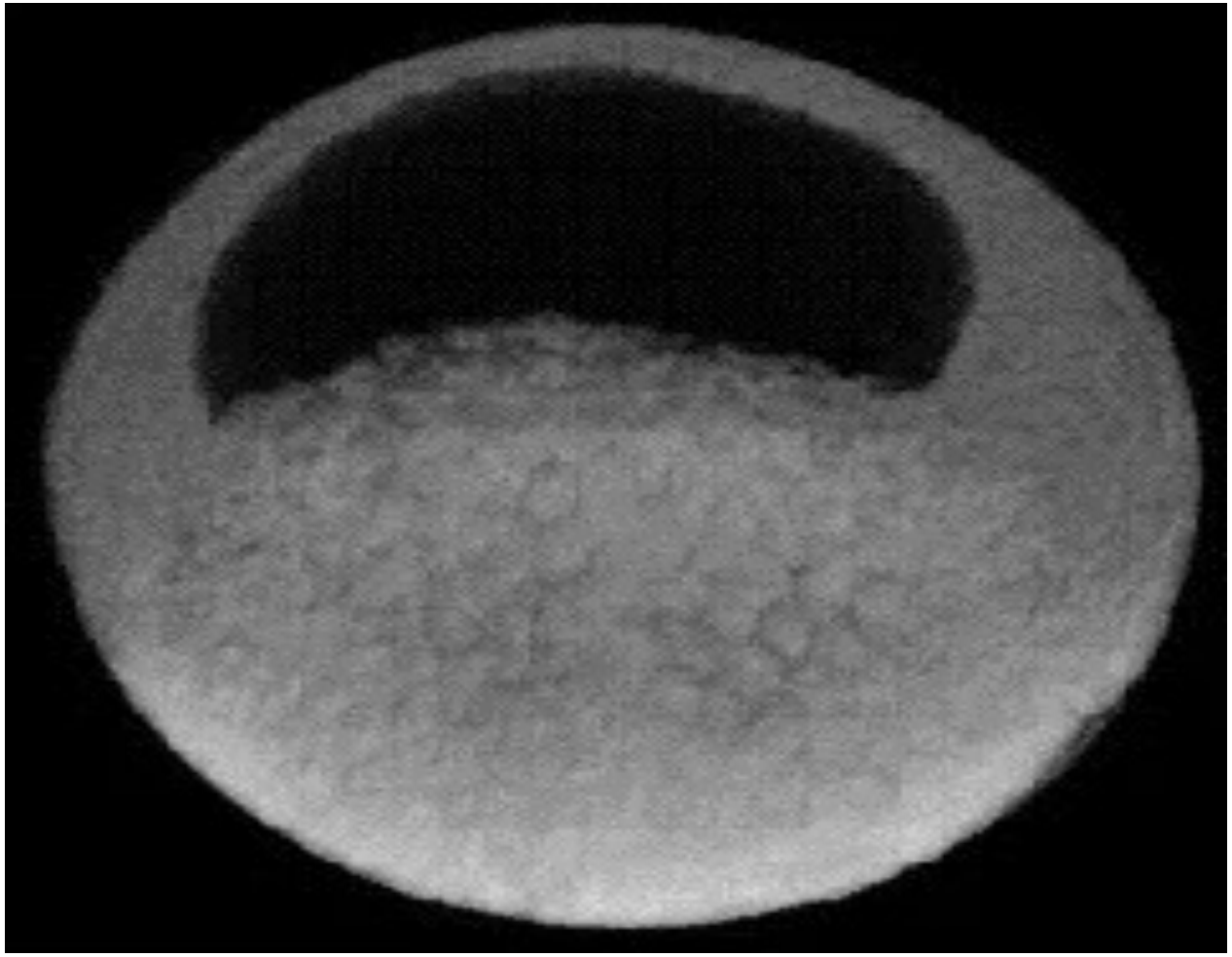
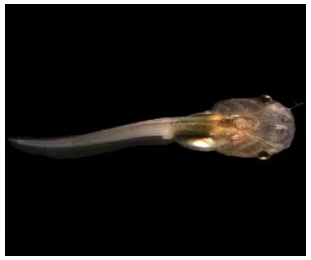
Facultad de Ciencias Biológicas
Universidad de Concepción

March 12th 2024

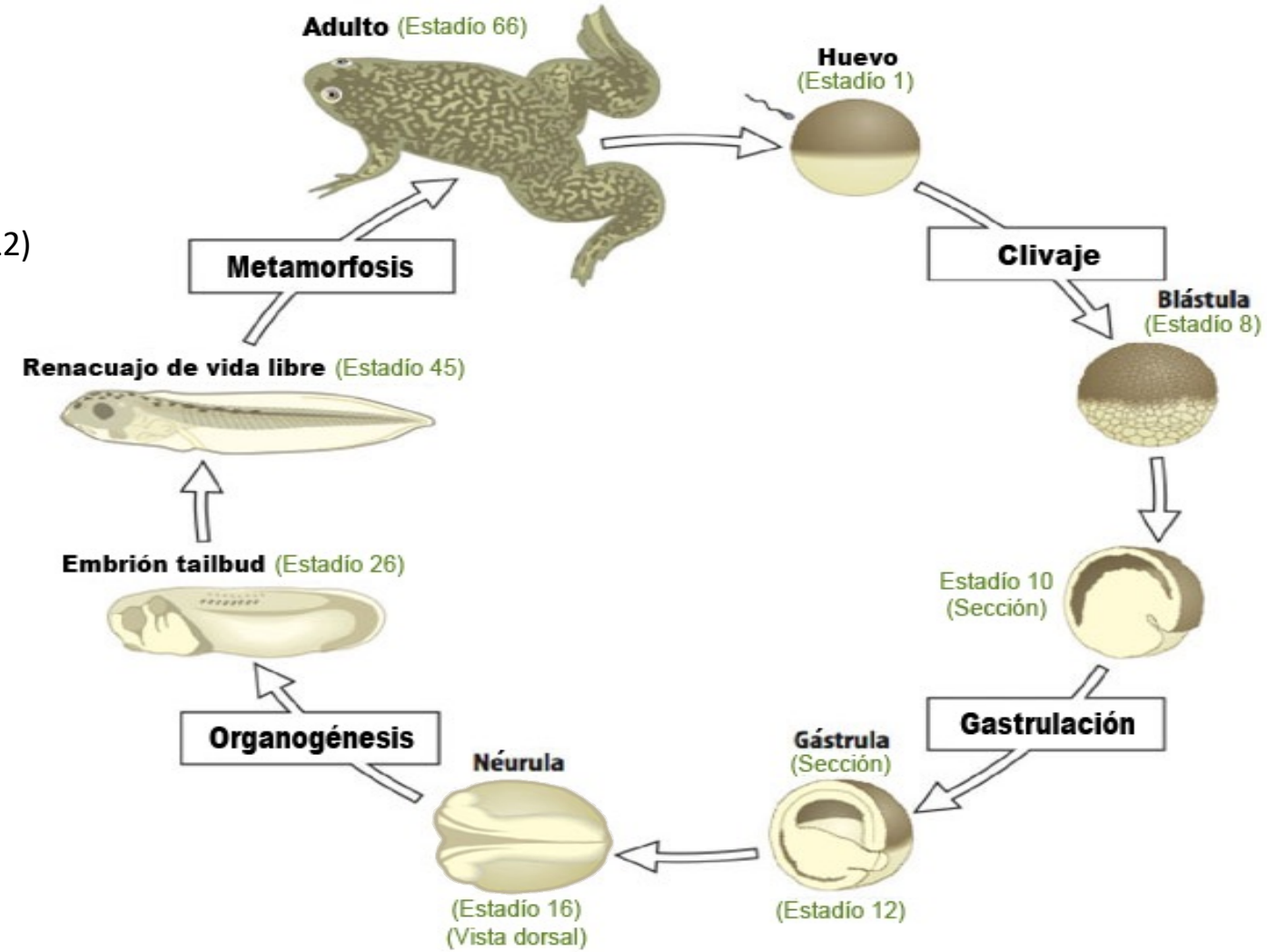
Gastrulation

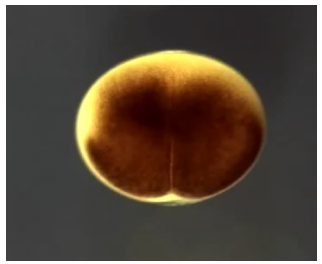


Xenopus tropicalis embryo development



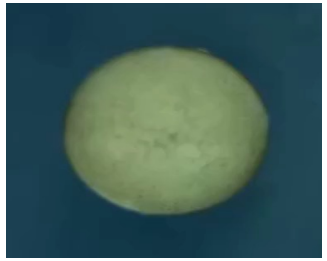
[Alexander Schreiber (2012) St. Lawrence University]





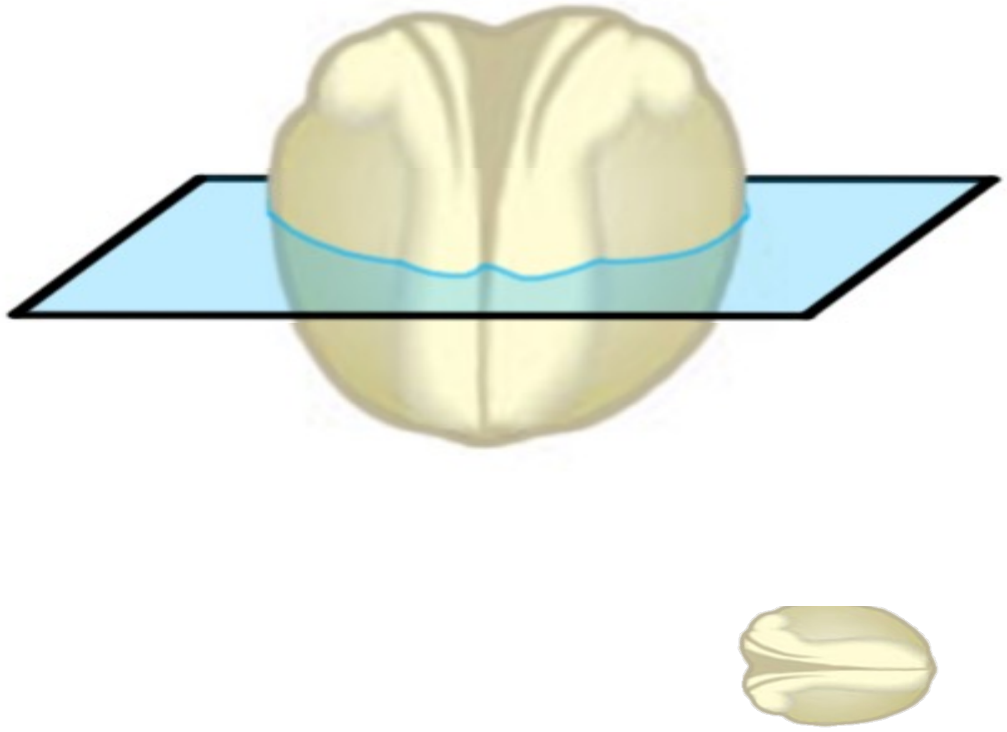
[H. Williams y J. Smith (2010), Xenbase]

[Dan Magliano (2016), Xenbase]

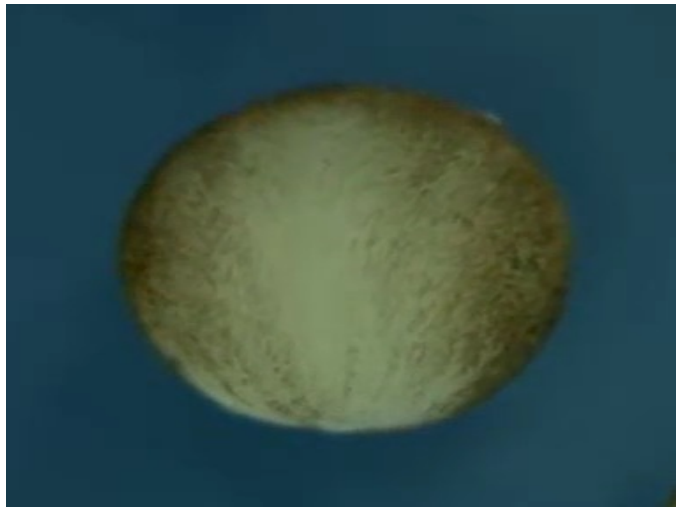


[TheDeepSci (2009), Xenbase]

Neural crest

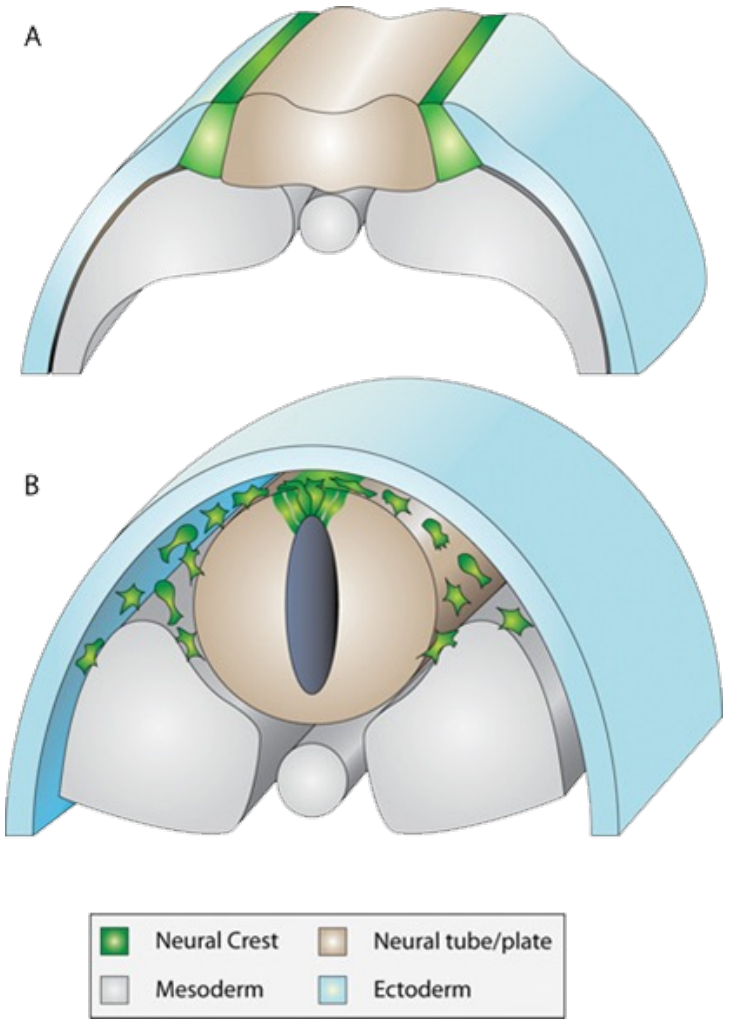


Neurulation

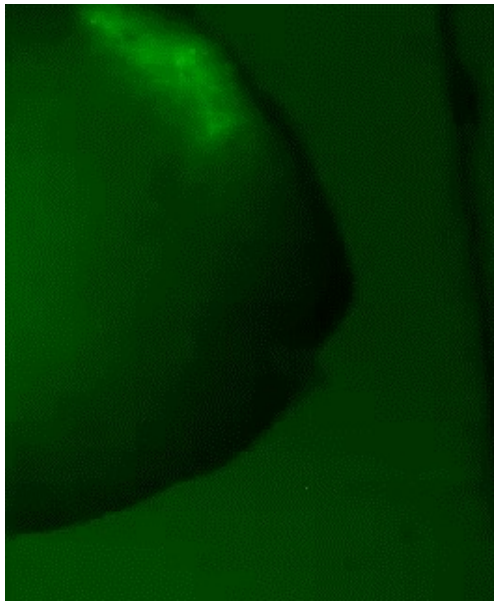


[TheDeepSci (2009), Xenbase]

Migration in Craneal Neural Crest (CNC)



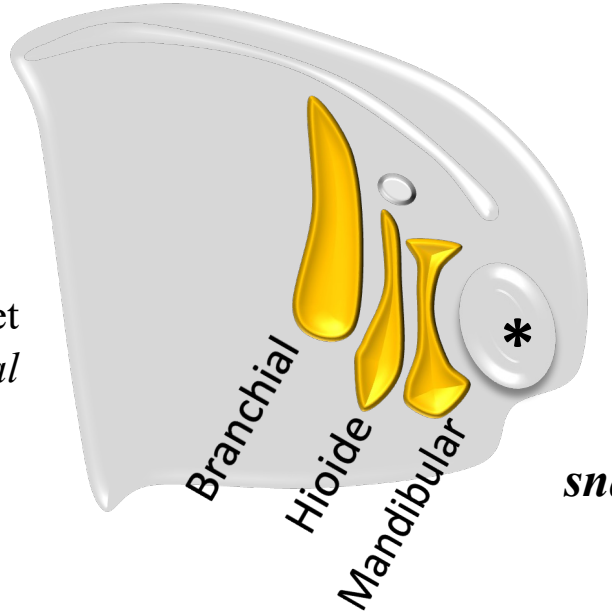
Mayor et al., 214, Biochem J.



GPCRs

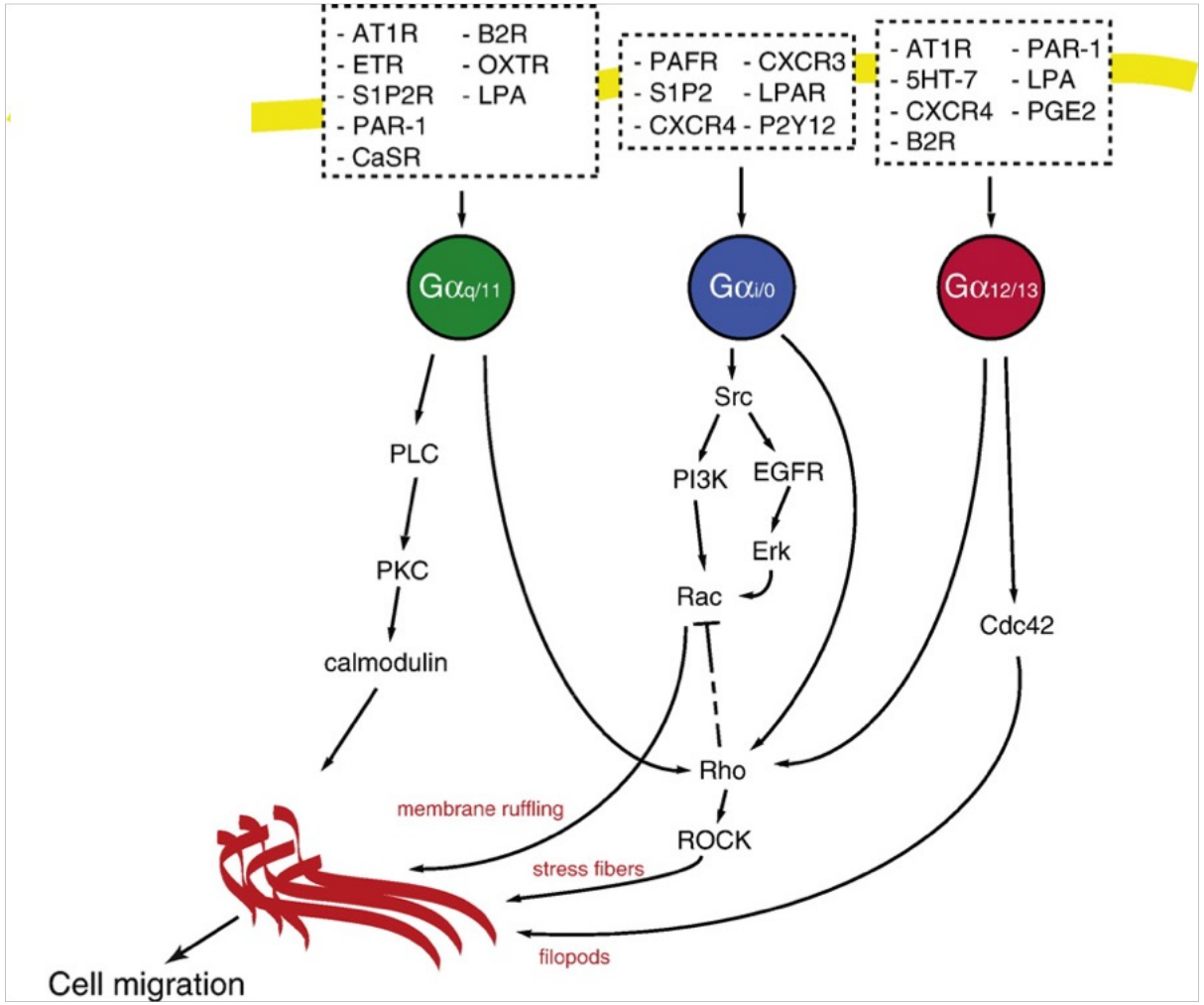
Cxcr4 [Theveneau et al. (2009), *Developmental Cell*]

C3aR [Carmona-Fontaine et al., (2011), *Developmental Cell*]

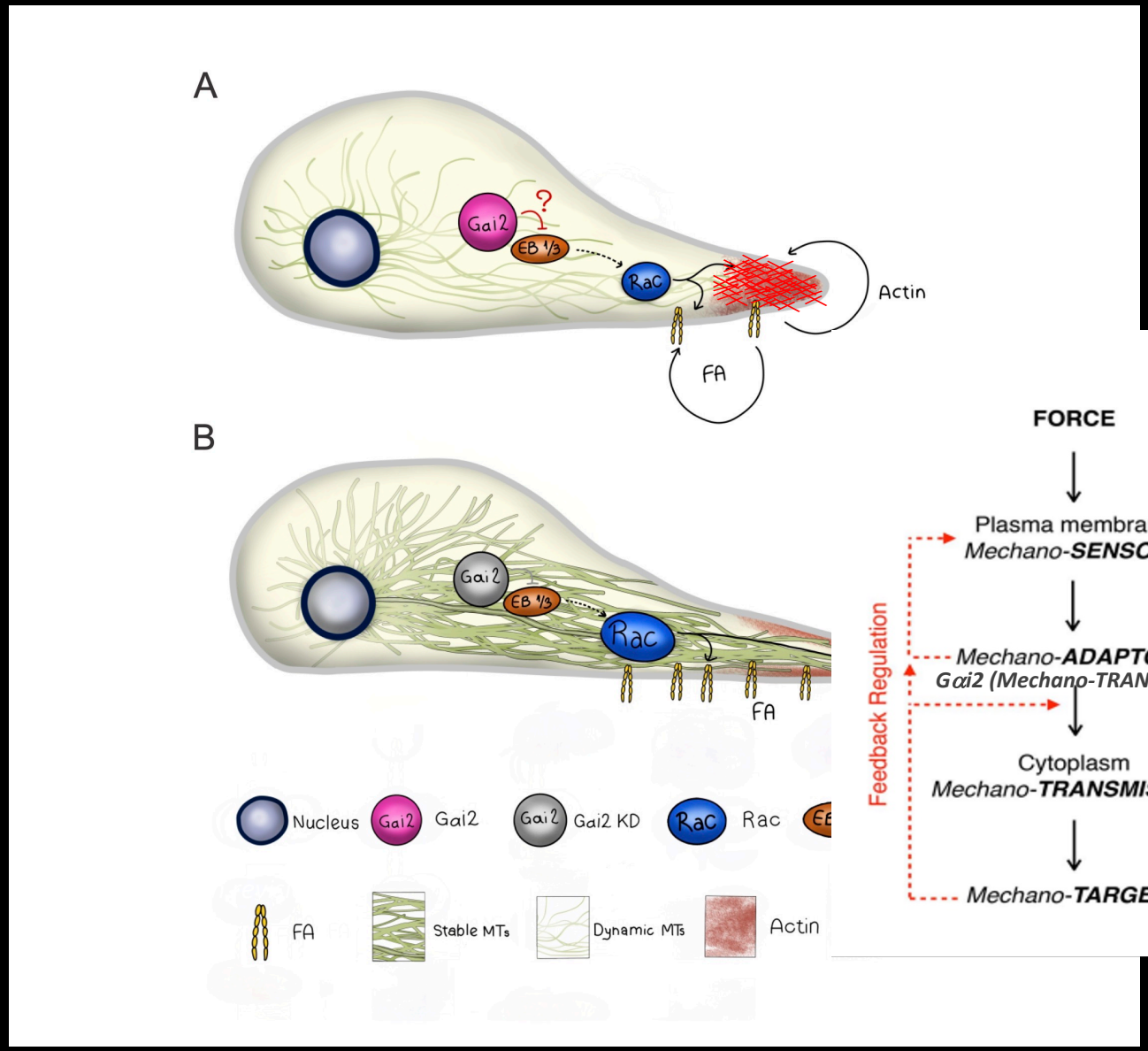


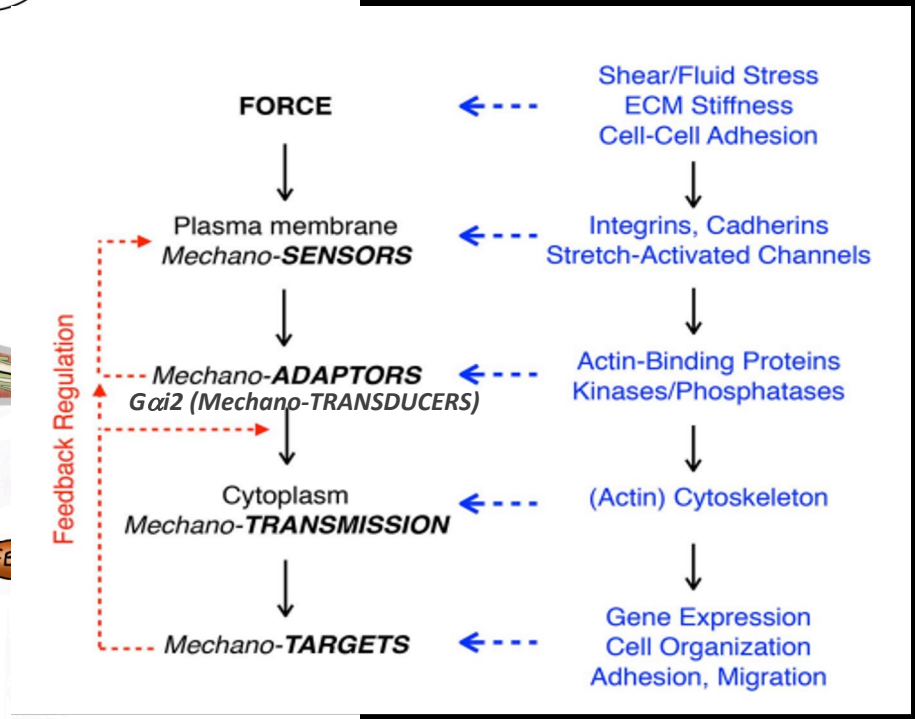
snail2 (st 25)

G-protein dependent cell migration



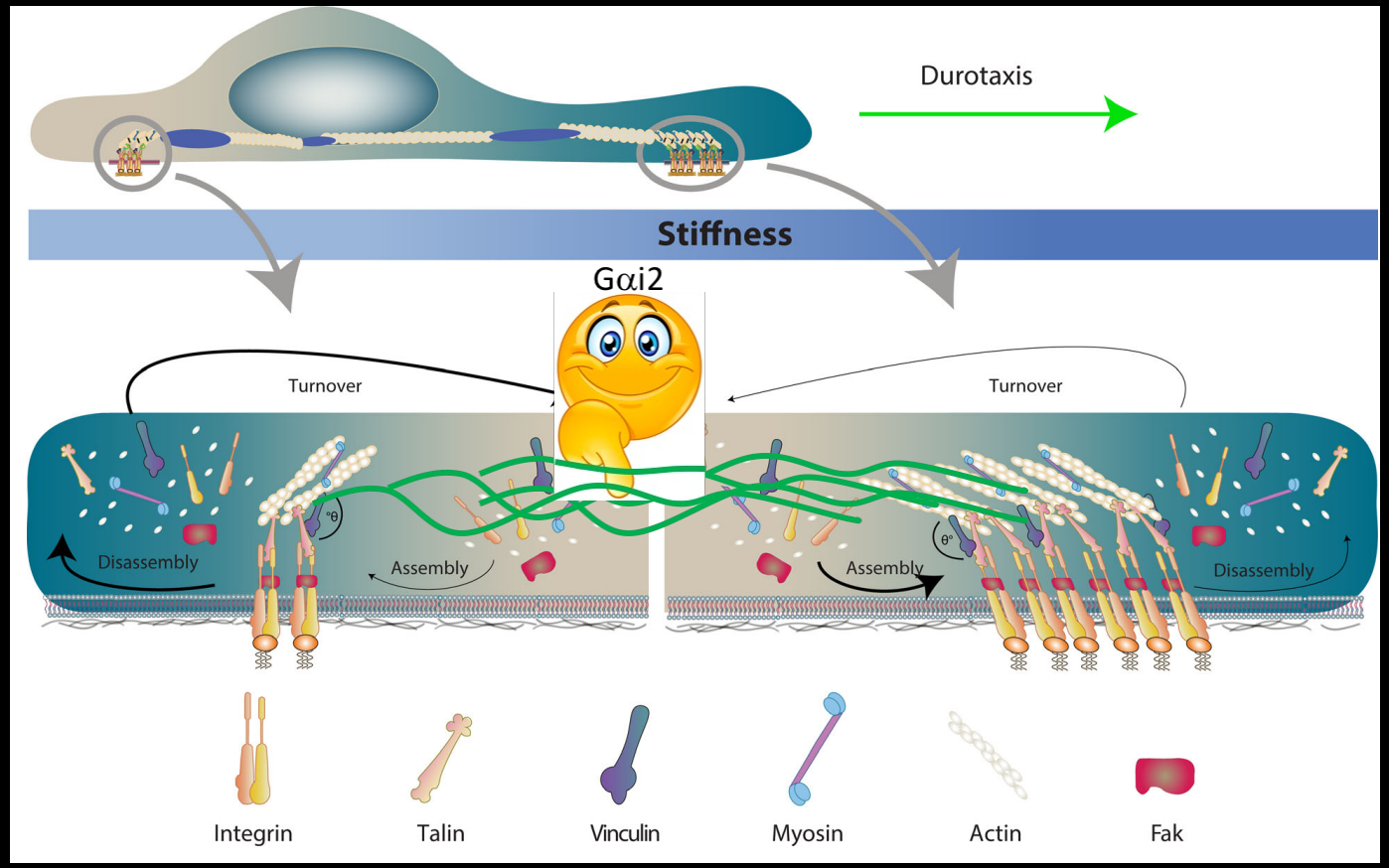
Gαi2 controls cranial NC migration by regulating mucrotubules dynamics





Modified from Pruit et al., 2014

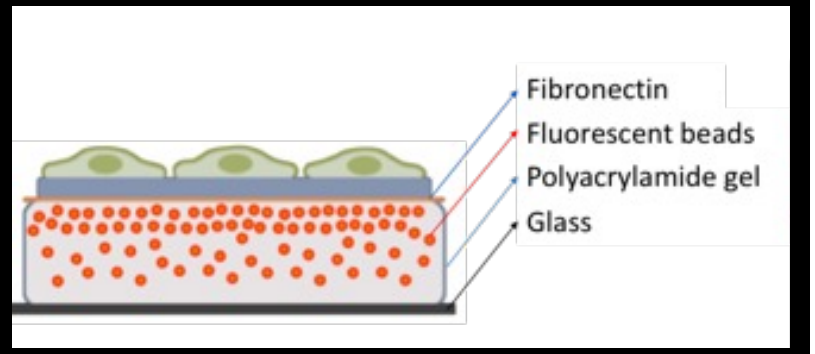
Does Gai2 function as a mechanotransducer?

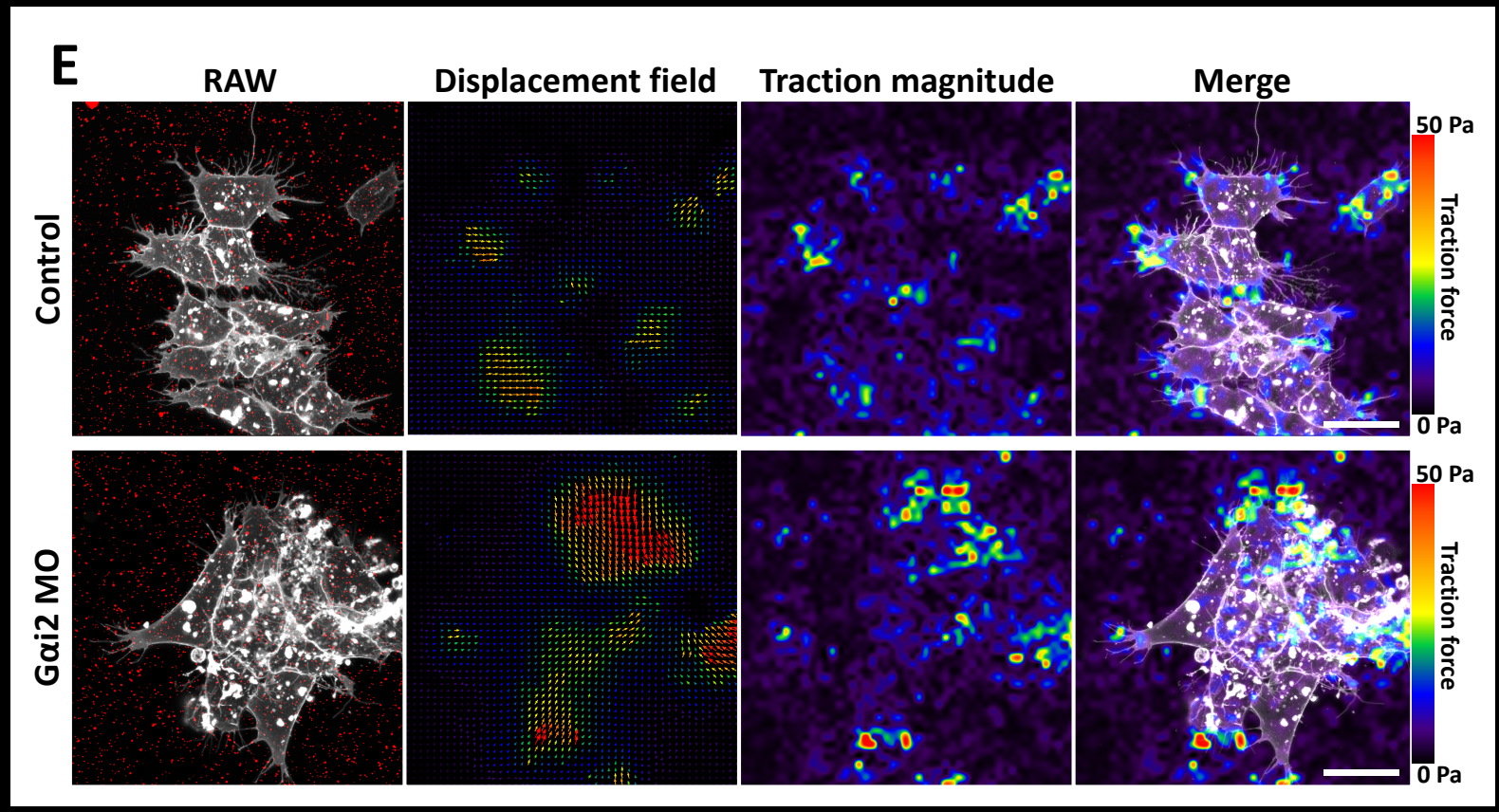


Forces transmission: mechanotransduction

Espina et al., 2021. The FEBS journal

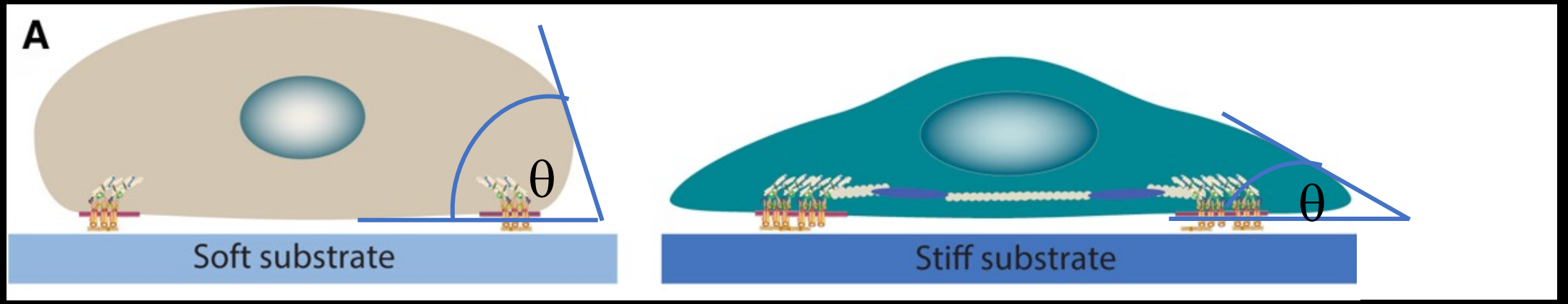
Traction force análisis in *Xenopus* cranial NC cells.

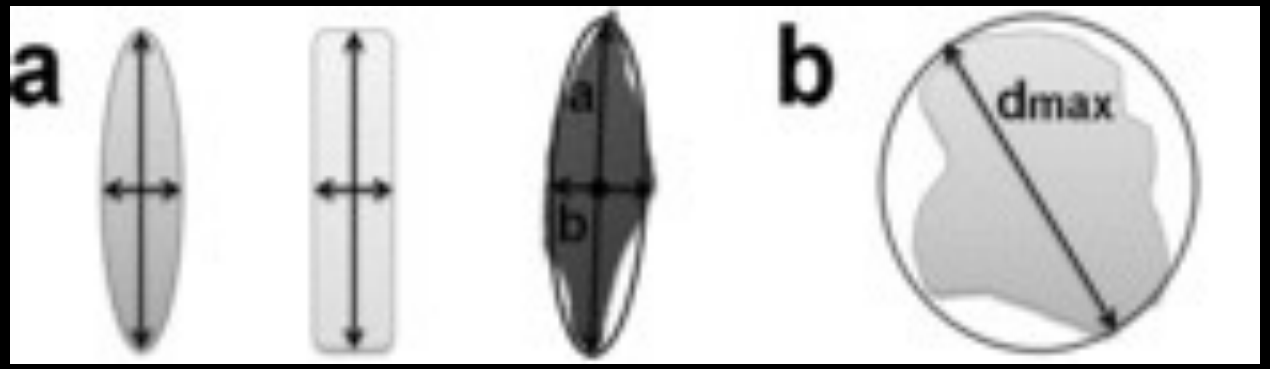




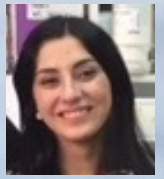
Leal JI, Ph. D. thesis

Cranial NC cells morphology inalysis in response to different stiffness





Laboratory of Signaling and Development



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