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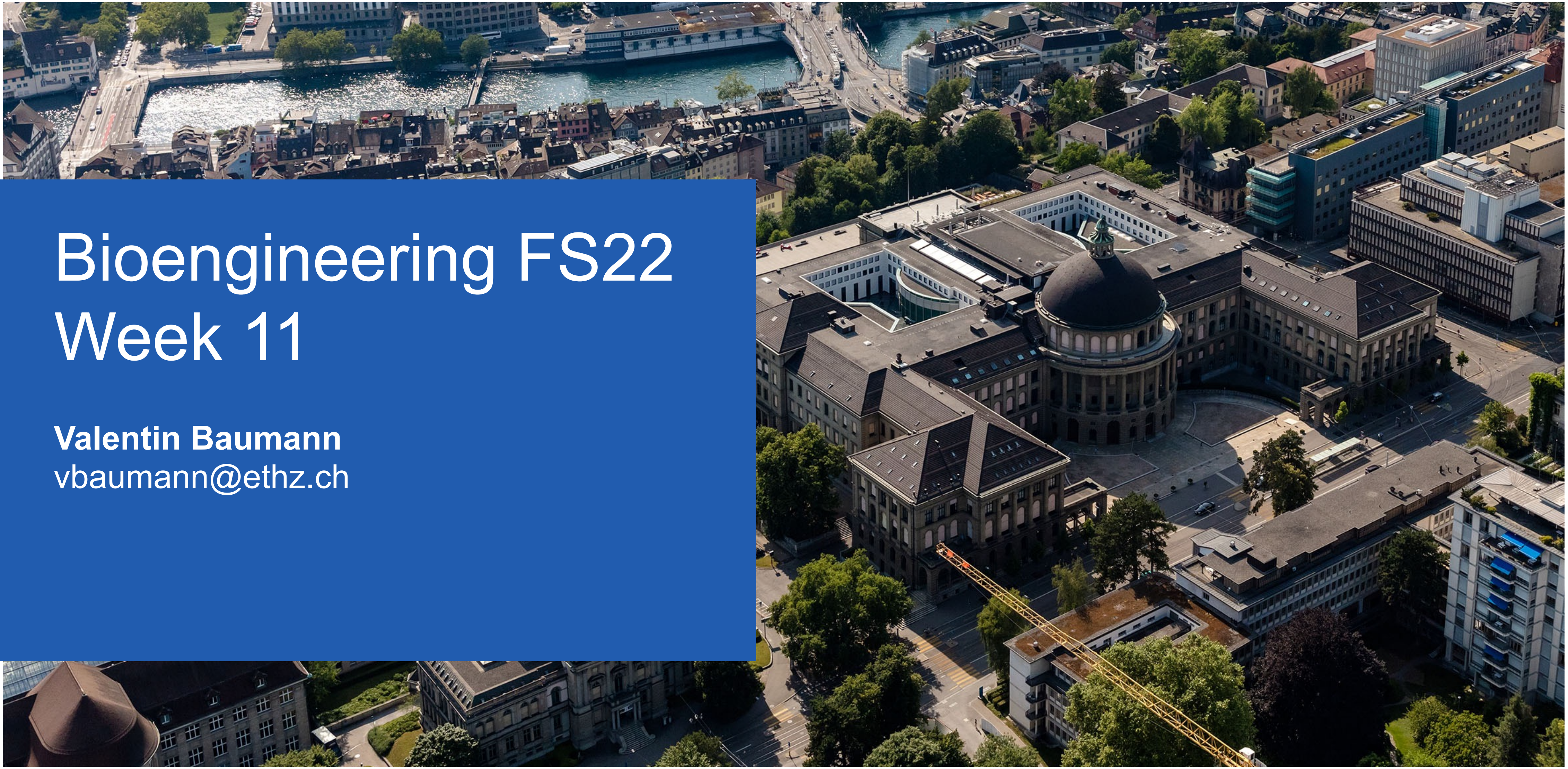

Bioengineering FS22
Week 11

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Agenda heute

1. Mechano-Biology
    1. Intro
    2. Wound healing – tissue differentiation
    3. Pseudoarthritis as an example for problems during bone healing
    4. Tissue and bone ingrowth vs. Stress shielding

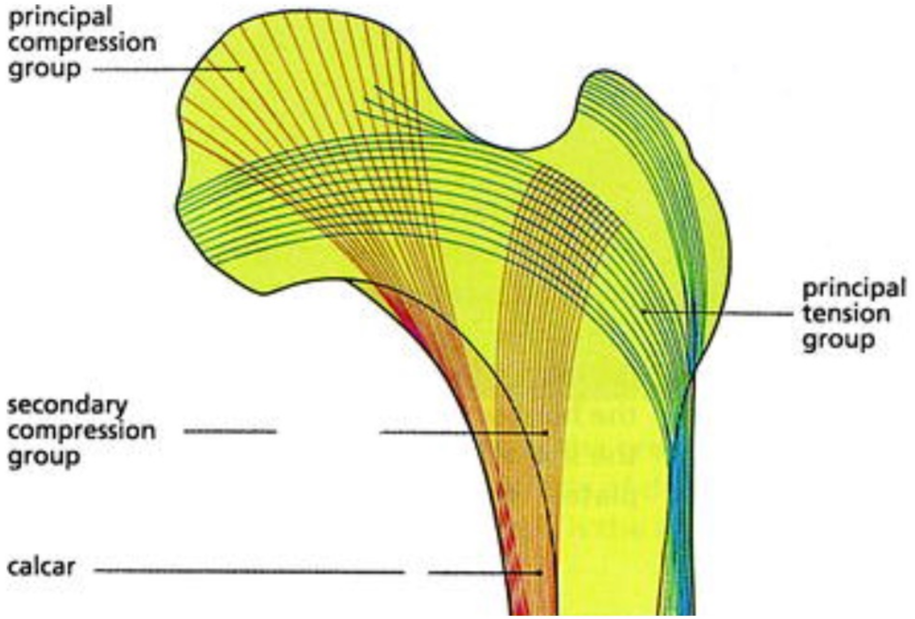
2. Mechanotransduction
    1. Intro & Process
    2. Imprtant vectors of mechanical signal transduction

Mechano-Biology

Mechano-Biology– Intro

- Physical forces and changes in stresses that act on cells and tissues contribute to development, physiology and disease inside an organism
- Changes in cell mechanics, ECM strucutre or mechanotransduction can contribute to the development of diseases (ex. Artherosclerosis, osteoporosis, heart failure, cancer)
- Already effective mechanical therapies in clinics today (ex. Tension application devices for bone fracture healing, pulmonary surfactant that promotes lung development, stents)

- Example 1: Bone tissue
  - Bone tissue develops differently depending on how much force and which way this force is applied to our bones.
  - Trabeculae of bone are oriented to best support the loads acting on the bone

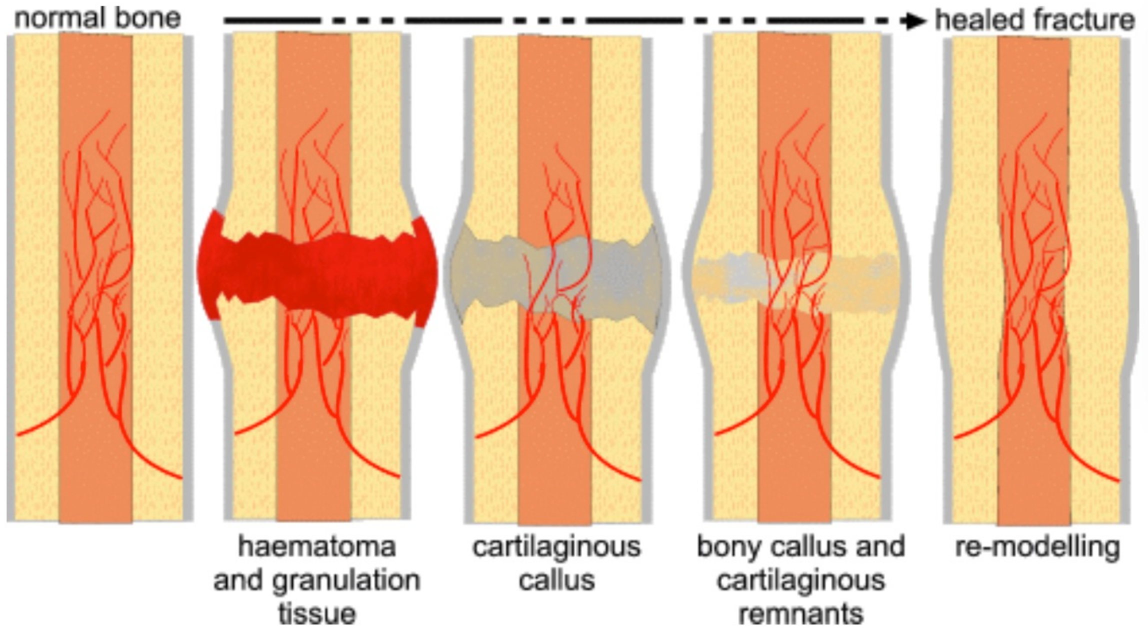


Mechano-Biology – Wound healing (ex. Bone fracture)

- Within short amount of time a lose aggreagte of cells (fibroblasts and stem cells) interspersed with small blood vessels forms → Granulation Tissue
- Over the next days, weeks and months this original new tissue is remodelled to best serve its purpose

Here: load bearing

- During this process cells are replaced and substituted, tissue is perfused to a specific level and tissue is generally oriented in a way to best serve load bearing purposes



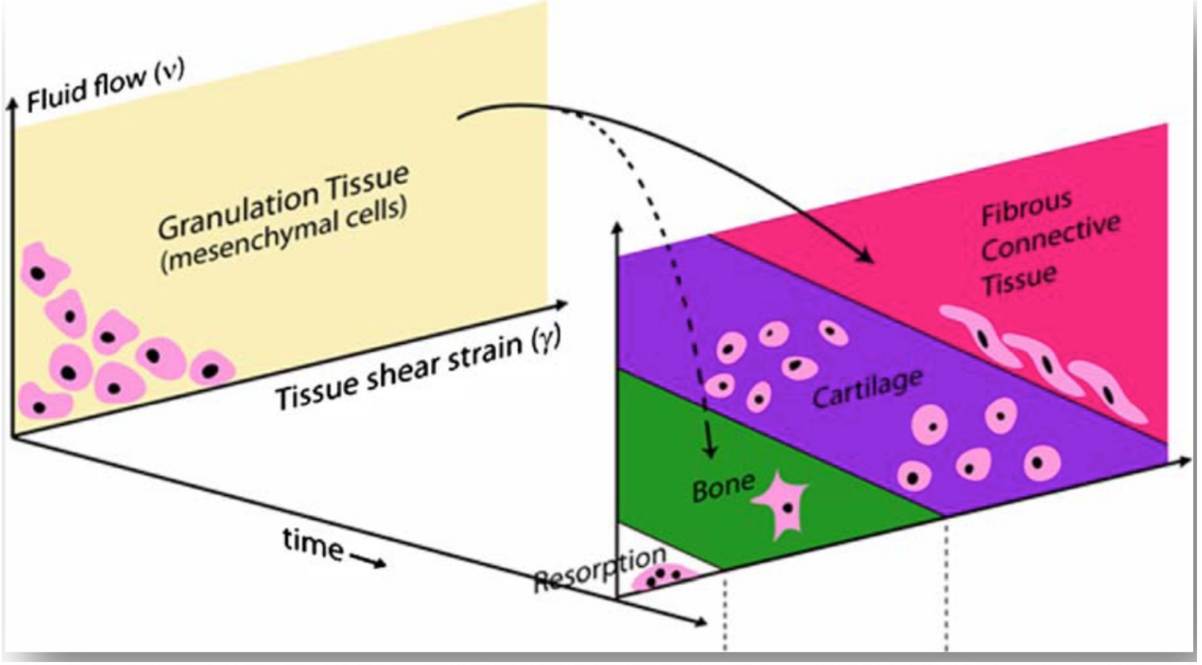
Mechano-Biology – Wound healing (ex. Bone fracture)

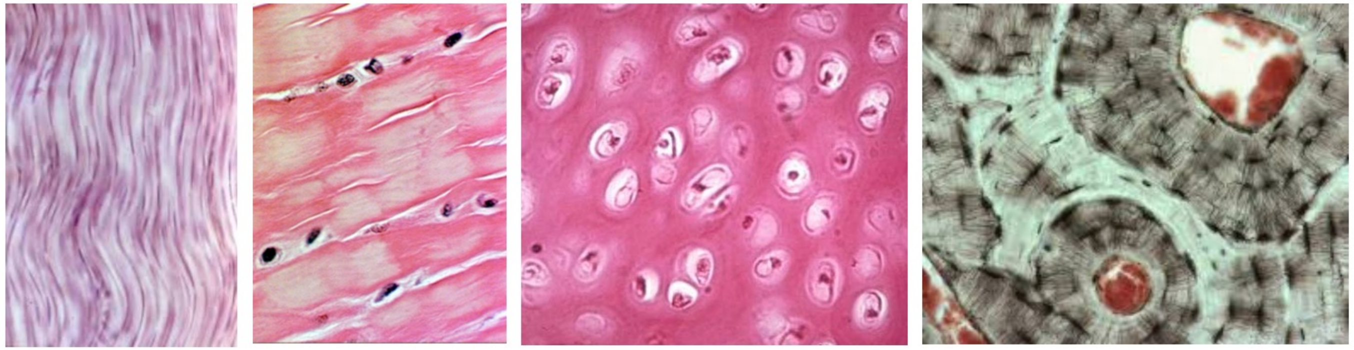
- This remodelling process is heavily governed by mechanical stresses (solid stresses and fluid shear stresses) in the tissue

- Depending on the amount of stress, cell differentiation, proliferation and matric formation is affected differently

→ tissue becomes connective tissue, cartilage or bone

- For bone, the tissue is slowly, step by step mineralised and ossified, until the tissue structure is correctly built to optimally resist external loads and stresses





Fibrous → Fibrocartilgenous → Cartilagenous → Ossified

Mechano-Biology – Wound healing (ex. Bone fracture) failure

- Too much load and the tissue is too stressed to heal correctly
- Too much motion and the tissue becomes more cartilaginous or fibrous than solid bone
- Too little load and the tissue has lack of necessary cues to guide correct bone tissue formation

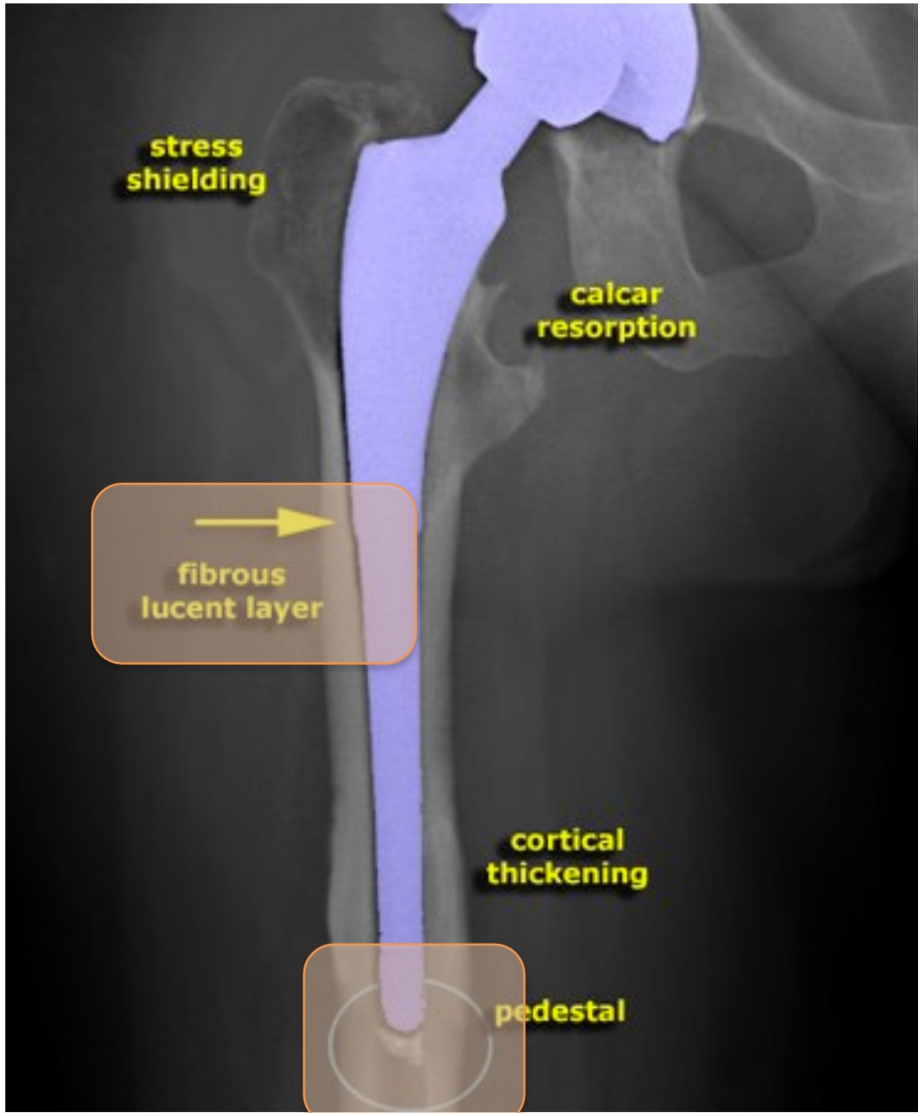
- Ex. For excessive tissue strains (too much motion):
    - Pseudoarthrosis → False joint that appears as a result of a fracture that has not been bridged by calcified tissue
        - This allows the two bone fragments to move
        - Often solved by using implants to fixate the bone fragments

Tibial midshaft non-union

Mechano-Biology – Tissue ingrowth into an implant (Or Not)

- In a stable, non-cemented joint, bone ingrowth and fibrous tissue ingrowth is wished for, in order to provide implant fixation
  - Fibrous tissue should be stable and well within a range of 1-2 mm

- Common implant problem: Stress shielding
  - If the material of the implant has properties that differ too much from the properties of bone, stress shielding can occur, meaning that the implant shields the bone from normal stress
  - This leads to the remaining bone tissue to be realtively unstressed, leading to bone resorption (according to Wolff's law) → osteoporosis like symptoms occur and there is thinning of the bone cortex → implant is not fixed in place by the bone



Mechanotransduction

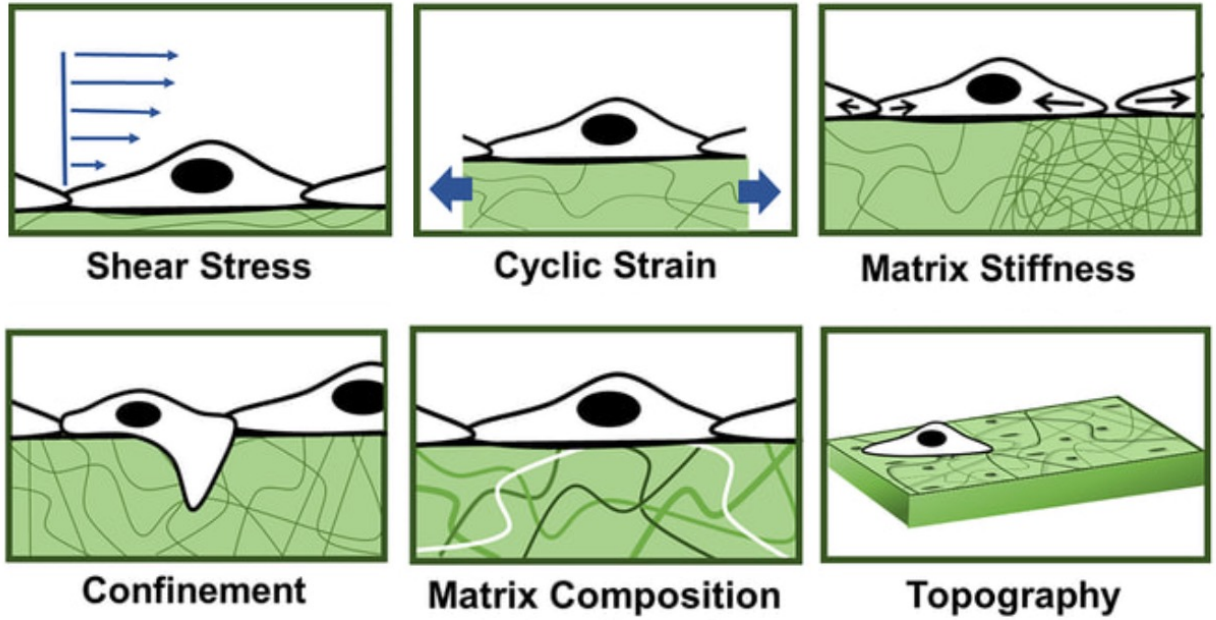
Mechanotransduction– Intro

- Cells can sense and respond to mechanical signals (ex. Stretch-activated ion channels)

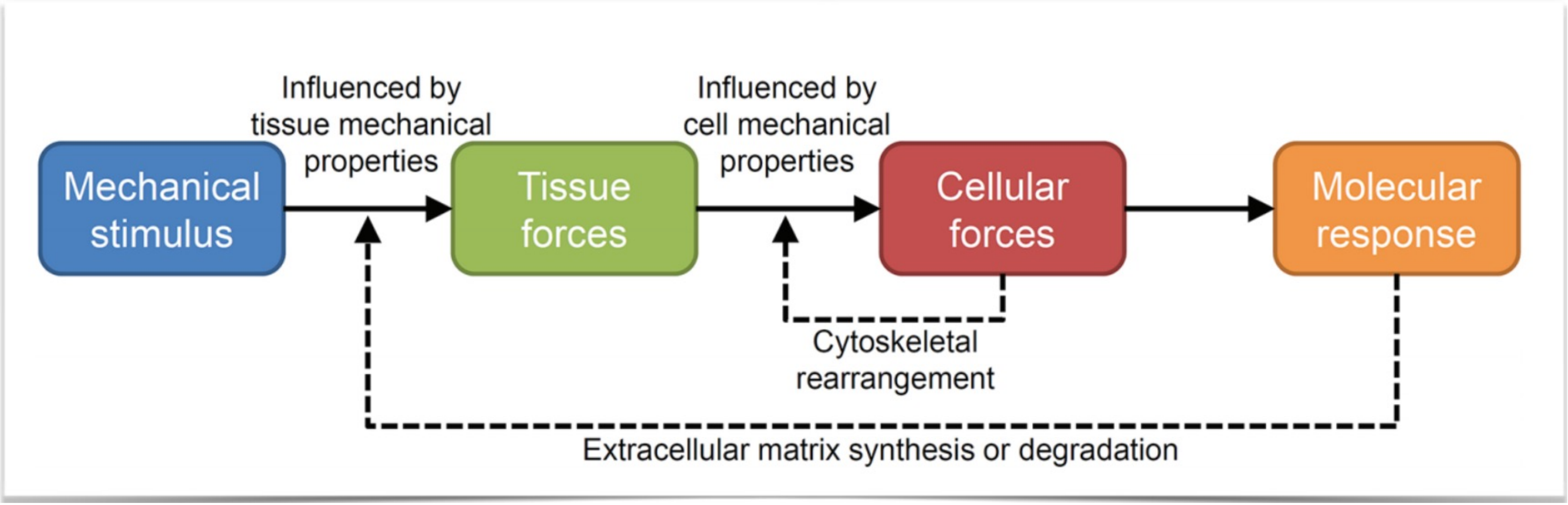
- Cells can generate traction and mechanical forces themselves, contributing to signal transduction and tissue behaviour around them.

- **Mechanotransduction** is thereby the sensation of mechanical signals and conversion to bio-chemical signals

- Cell architecture plays a crucial role in sensing and generating mechanical cues

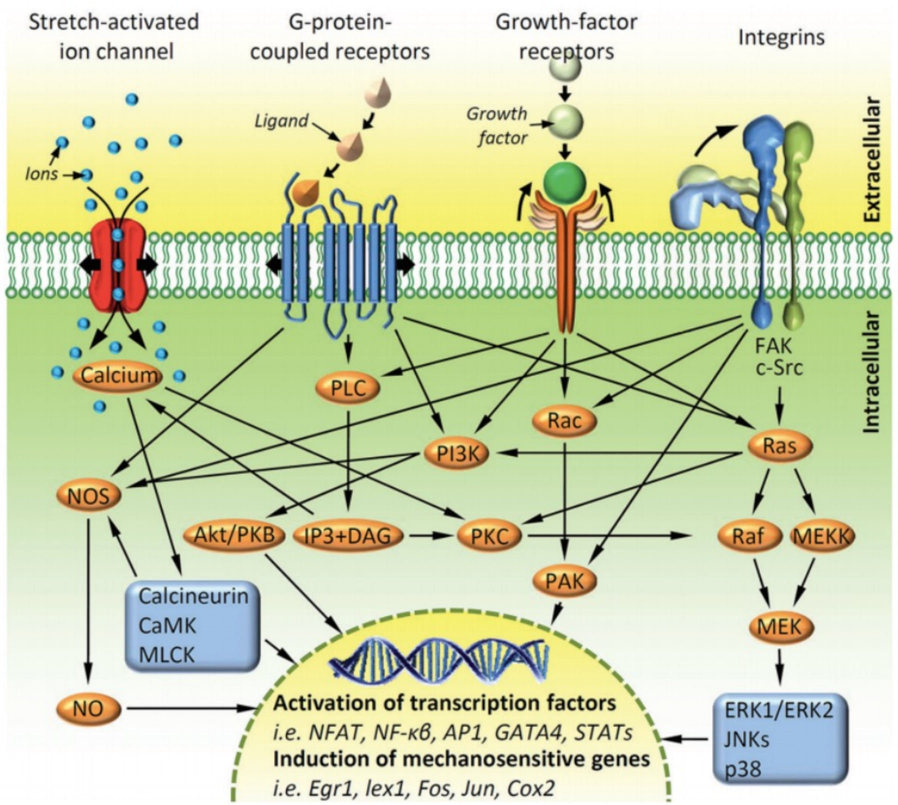


Mechanotransduction – Process



Mechanotransduction – Vectors of signal transduction

- Vectors are ways the mechanical signals can be sensed by cells, initiating cellular signalling, and eventually altering cell behaviour (external ECM forces incl. ion channels, focal adhesions, cytoskeletal forces to the nucleus)



Mechanical signal/force
(transmitted by the ECM)

Cellular force sensors

Calcium/ion influx + kinase assembly

Transcription factors shuttle in the nucleus

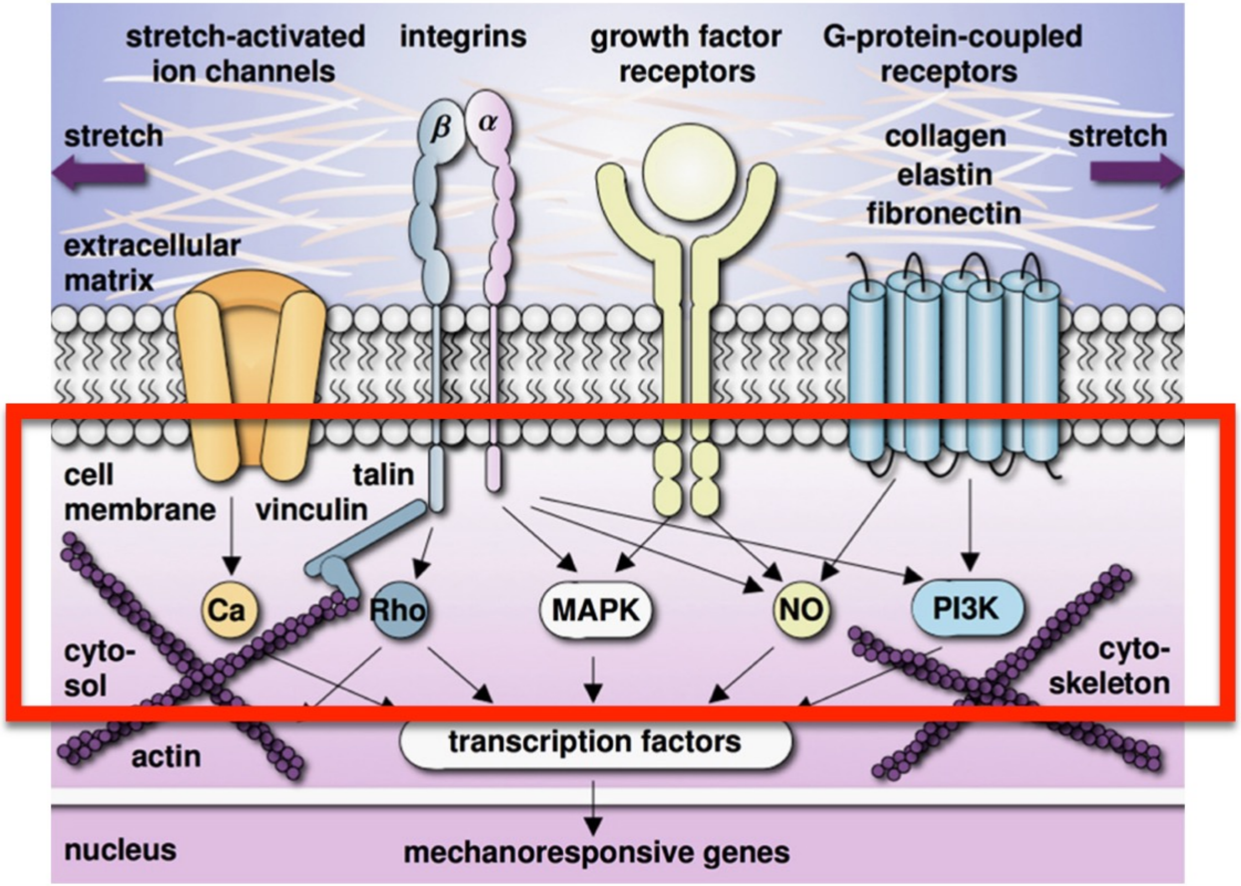
Gene regulation → tissue adaptation

Mechanotransduction – Vectors of signal transduction

- **External matrix forces** trigger various transmembrane sensors that in turn activate or deactivate signalling chains within the cell
  - **Integrin activation**
  - **Stretch-activated ion channels**

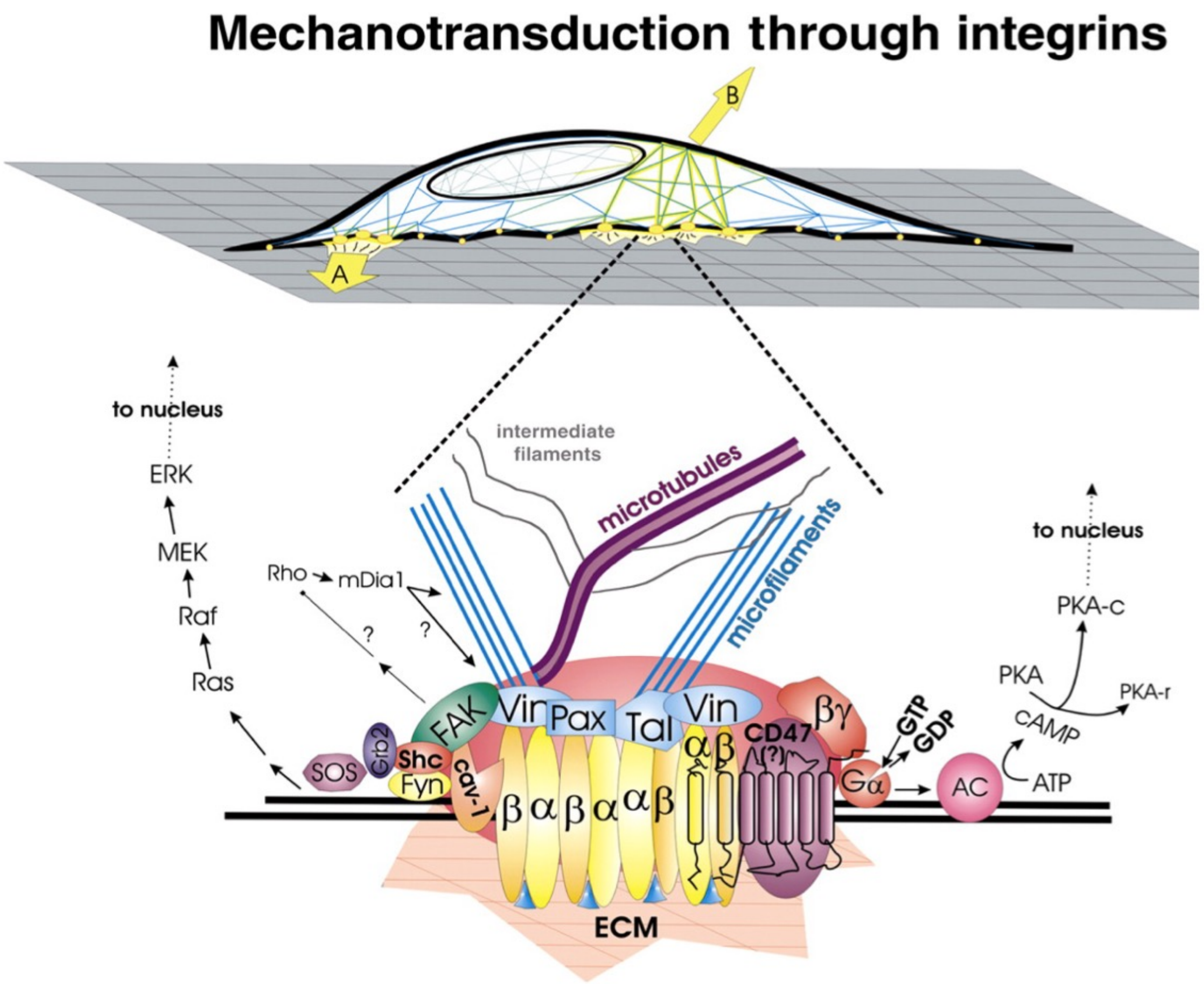
- Signalling chains often include the activation of Enzymes (ex. Kinases or Phosphotases), which in turn activate or deactivate signalling proteins by phsosphorylation or de-phosphorylation respectively

- Many of these signalling kinases are calcium dependent



Mechanotransduction – Vectors of signal transduction

- **Focal adhesion** are force sensitive protein complexes, where integrins binding to the ECM and receiving mechanical inputs, are concentrated
- Local forces and mechanical stretch change conformations of focal adhesion proteins, exposing their binding domains → This leads to intracellular signalling due to activation of kinases
- Focal adhesion Kinase (FAK) is a prominent example
    - Curcial for motility and cell survival (promotes turn-over of cell contacts) and has many downstream responses to mechanical signals (differentiation, ECM synthesis, apoptosis



Mechanotransduction – From cytoskeleton to the nucleus

- Forces are also transferred from focal adhesions via the cytoskeleton to the cell nucleus
  - Deformation of the nucleus can affect gene transcription by altering conformation of chromatin, which is anchored to the nuclear scaffold (inner lamina of the nuclear envelope)
  - Deformation can induce changes in chromatin organization (a), leading to **differential accessibility and binding of DNA regulatory factors** → changes in gene transcription for ex.
  - Deformation of specific chromatin regions can **modulate activities of** chromatin-associated transcription or spicing **factors** (b)
  - Mechanical pull of cytoskeleton connected to nuclear pores can **open or close pores, thus affecting nuclear transport** or influence post-transcriptional control of gene expression (due to altered mRNA transport) (c)