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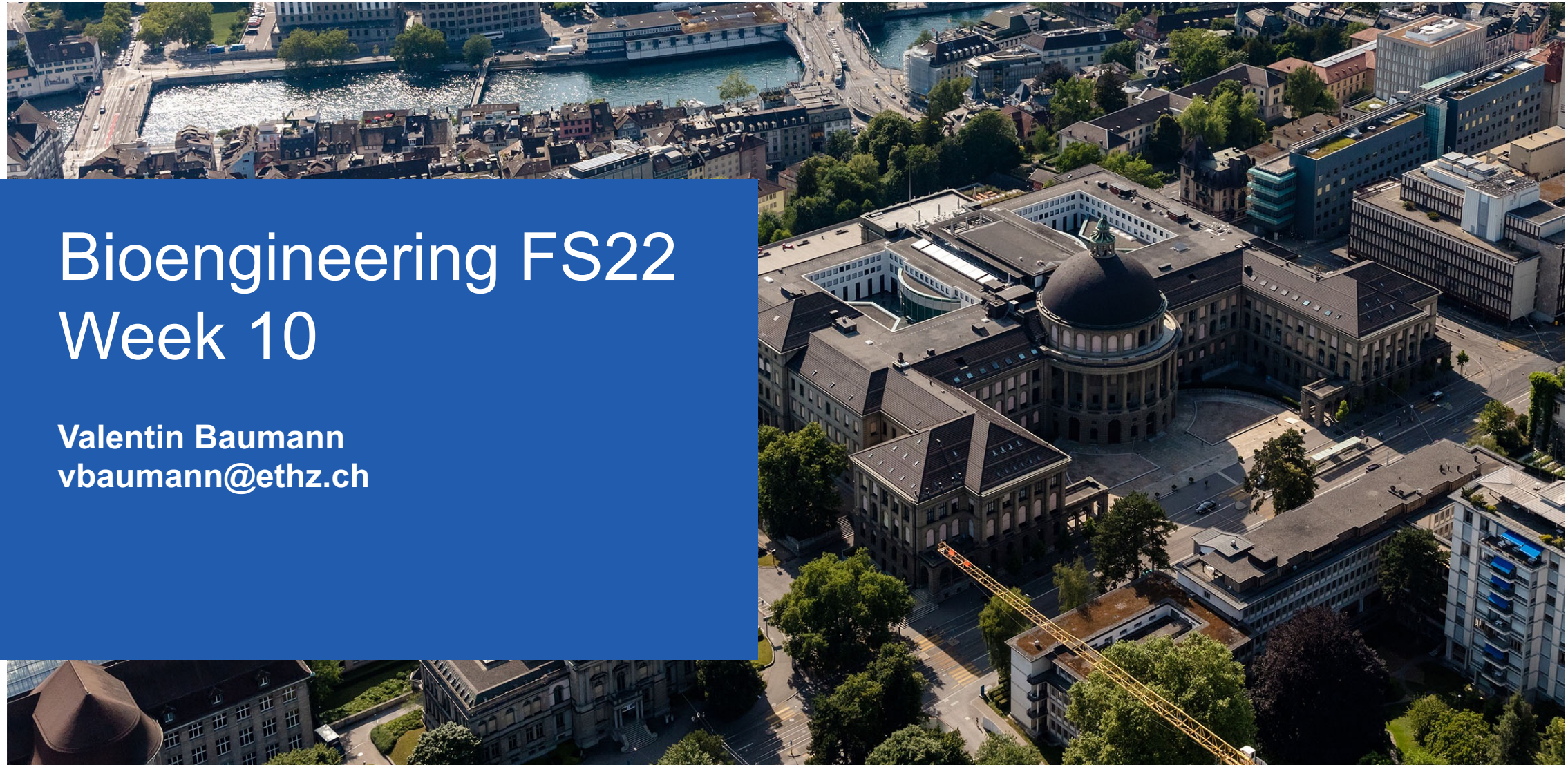

Bioengineering FS22
Week 10

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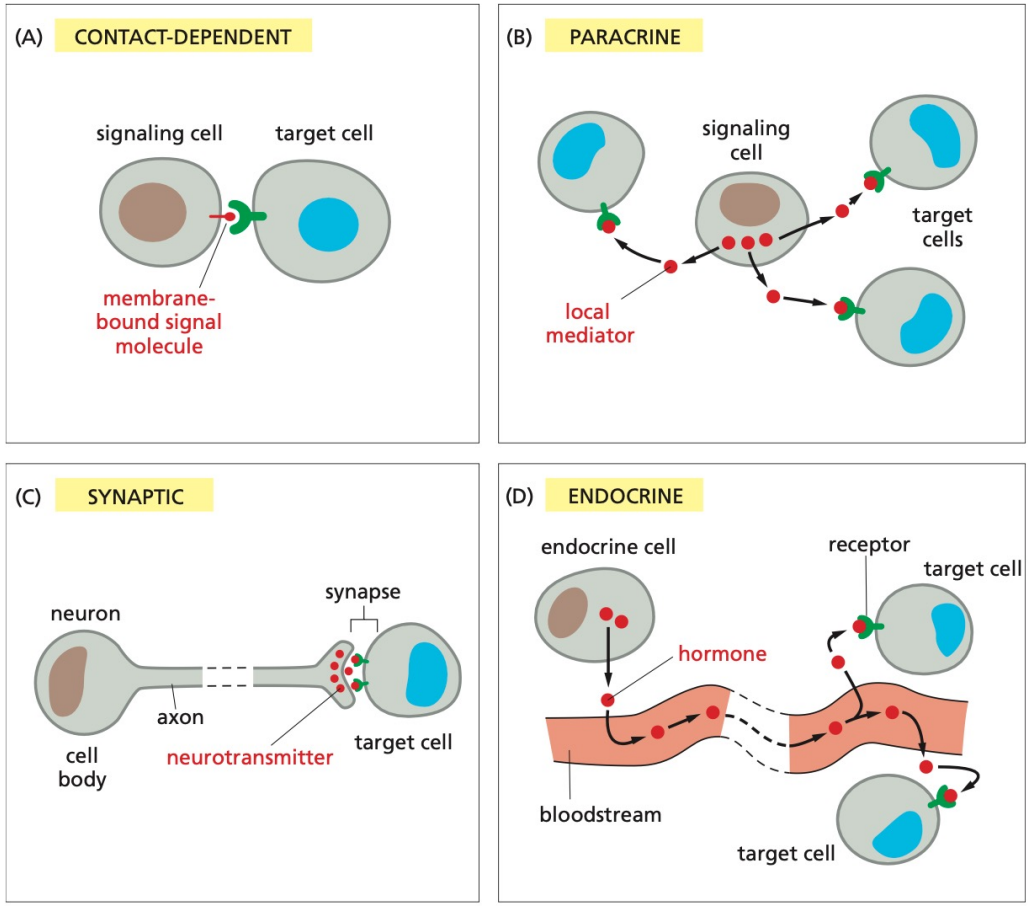
Agenda Today

1. **Cell Signalling**
    1. Intracellular Signalling
    2. Molecules, Receptors and Signals
    3. Signalling Proteins
    4. Characteristics
    5. Signal Responses
2. **Cell Matrix Signalling**
    1. ECM Interactions
    2. Tissue Basics
    3. Functional Parts
    4. ECM
    5. Cartilage and Wound Healing

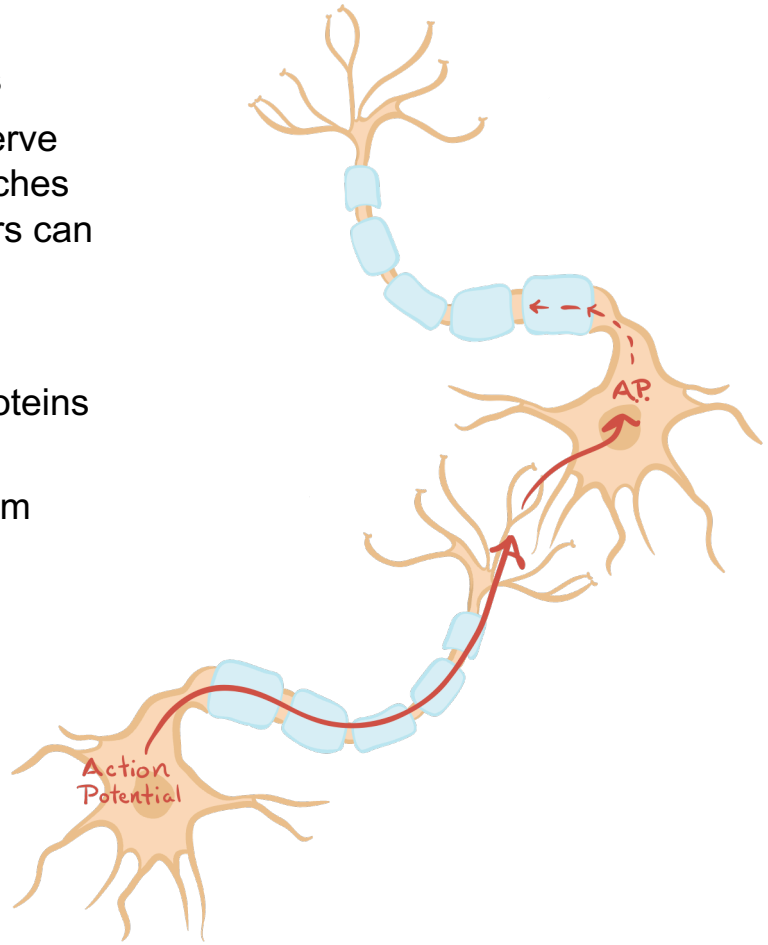
Cell-Cell Interactions – Intracellular Signalling

- Cell-cell interactions usually take place with the help of signalling molecules. But in some cases where cells are in direct contact with each other, the binding of a ligand to the receptor also acts to transmit signals. The signalling molecules depend on the type of signalling, but many are the same in all of the contact-less types of signalling, they do however differ int he speed and selectivity in which the signals reach their targets.
- There are four major types of intracellular signalling:
  - **Contact dependent signalling**
    direct cell contact
  - **Paracrine signalling**
    local signals released in extracellular space
  - **Synaptic signalling**
    performed by neurons, the signal is transmitted electrically along the axon up until the synapse, where neurotransmitters are released.
  - **Endocrine signalling**
    Requires endocrine cells that secrete hormones in the blood and allow the signal to be distributed throughout the whole body. Endocrine and neuronal cells work together to coordinate activities in the body.



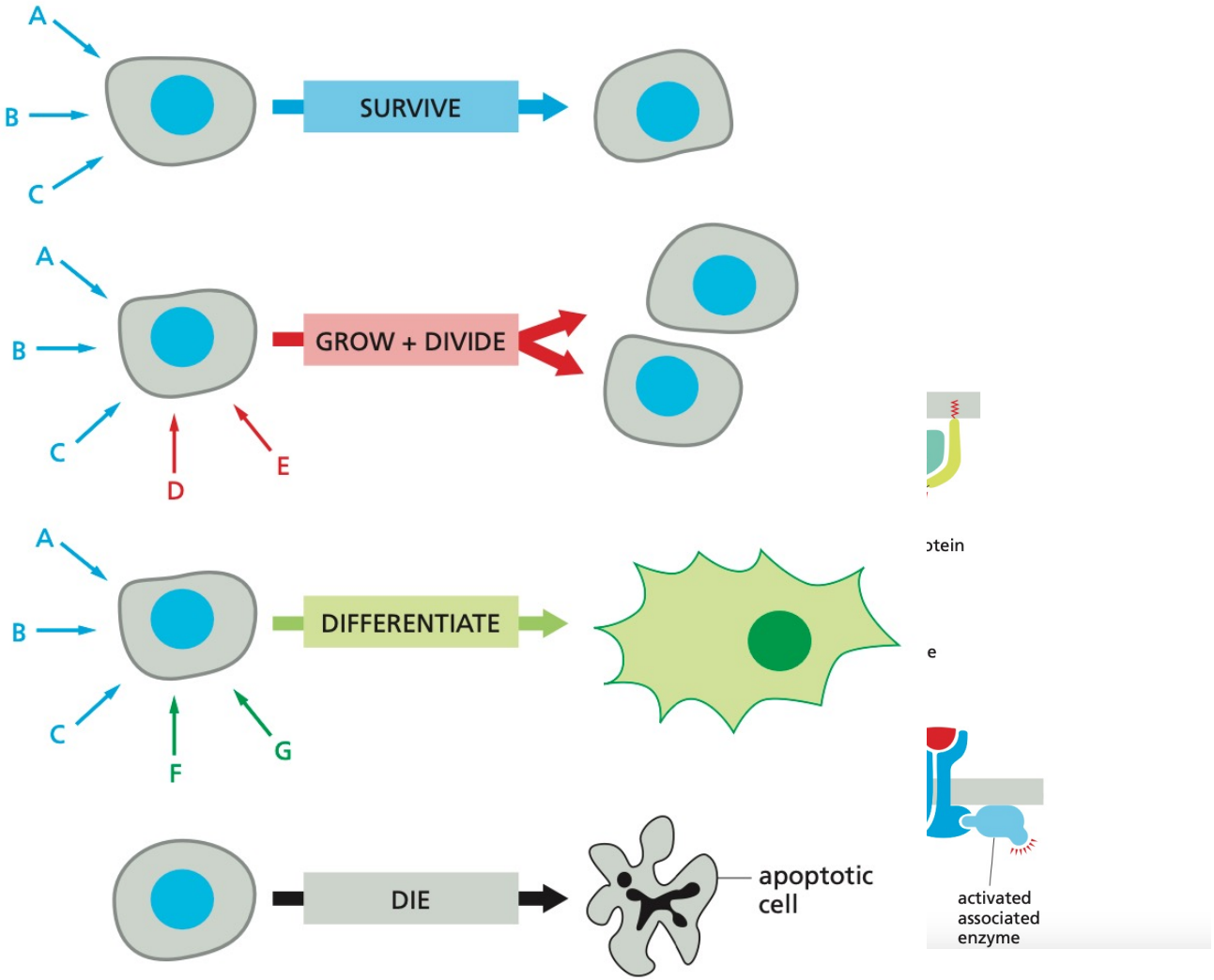
Cell-Cell Interactions – Intracellular Signalling

- Difference between synaptic and endocrine signalling:
  - **Endocrine** cells release hormone in the blood which then bind to suitable receptors
  - In **neuronal signalling**, specificity is determined by synaptic contacts between a nerve cell and a target cell. The neurotransmitter that is released by the synapse only reaches the target the cell that is in synaptic contact with the neuron. Some neurotransmitters can also act as local mediators (paracrine) on nearby target cells.
- **Signal Speed**
  - **Slow**: Signals that cause a change in gene expression and the synthesis of new proteins
    Cell growth and cell division
  - **Fast**: Signals that typically cause phosphorylation if effector proteins in the cytoplasm
    Changes in cell movement, secretion and metabolism
  - **Very Fast**: Signals that change the membrane potential
    Synaptic responses.

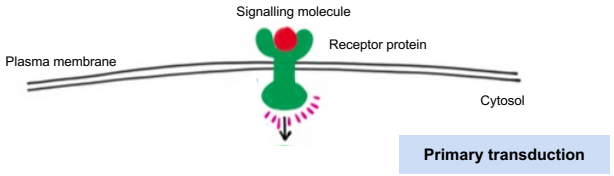


Cell-Cell Interactions – Molecules, Receptors and Signals

- Depeding on the nature of the signal molecule, the way the target cell receives a signal differs.
  - **Hydrophilic signalling molecule**: cannot pass the cell membrane which means that the molecule has to bind to receptors on the surface.
  - **Hydrophobic signalling molecule**: when the molecule is small, it can easily diffuse through the plasma membrane and can then bind to a receptor in the cytosol. These molecules have to be carried by carrier proteins, since they are water insoluble and are repelled by water – blood and other extracellular fluids are composed of water, amongst other things and thus the protein carrying them, protects them against interactions.
- **Cell surface receptors ->**
- **Receptors and Signals**
  Each cell has multiple receptors with specific purposes. The signalling molecules bind specifically to the receptors and when coordinated, regulate the cell behaviour in a certain way.



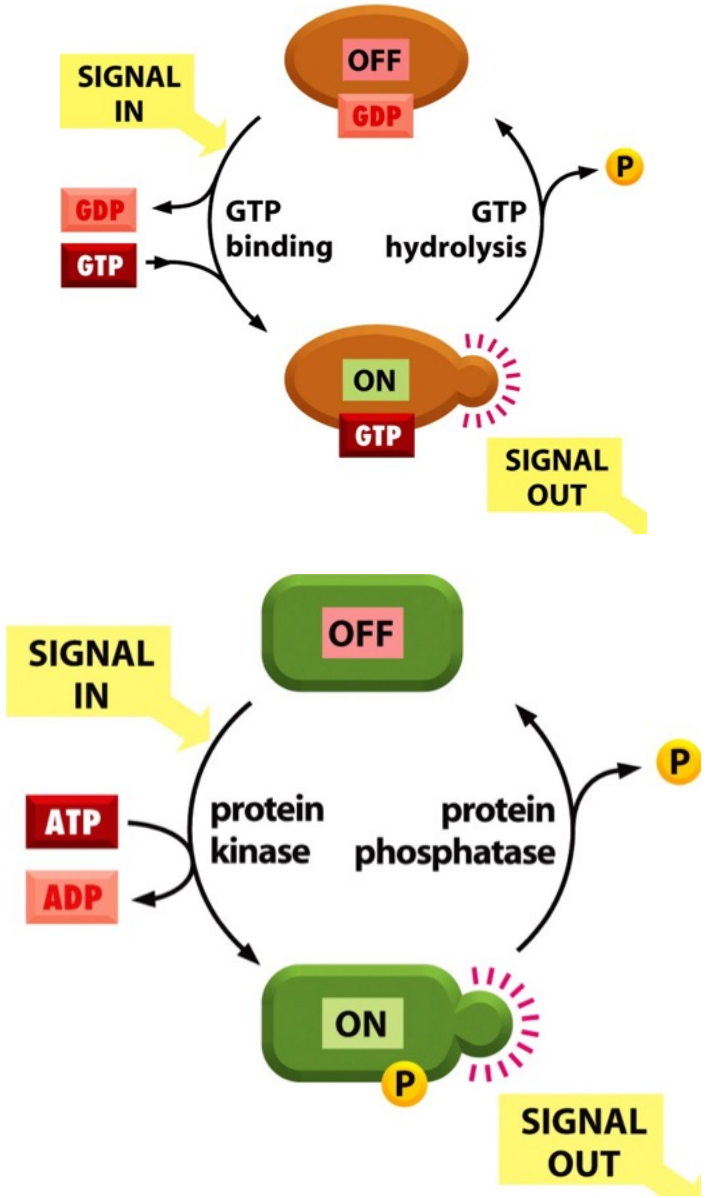
Types of Intracellular Signalling Proteins



- **Relay proteins** pass the signal to the next component
- **Scaffold proteins** combine multiple proteins for quick and efficient interaction -> building of signalling complex
- **Transducer proteins** transform the signal
- **Amplifier proteins** amplify the signal so that few signalling molecules can trigger a large response
- **Integrator proteins** integrate multiple signals into one response
- **Spreading** describes the connection of multiple signalling pathways
- **Anchoring protein** attach proteins to desired structure of the cell
- **Modulator protein** activate or inhibit the activity of signalling proteins – have an effect of the strength of a signalling pathway

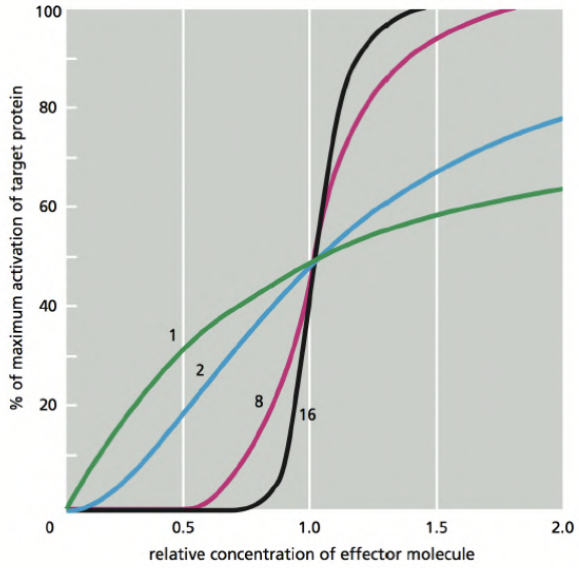
Intracellular Signalling

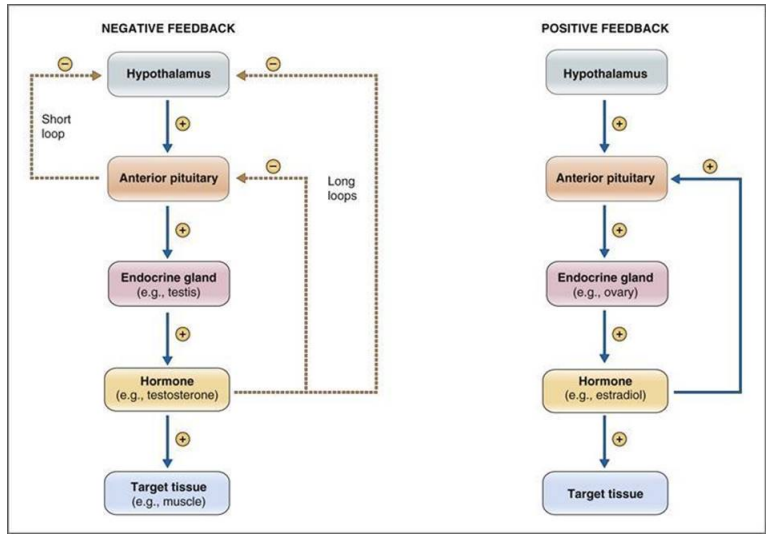
- **Molecular Clocks**
  - Signalling by phosphorylation and signalling by GTP-binding are both molecular clocks – meaning that a signal activtes the substrates. They remain active, until another process deactivates them again.
- **Integration of Signals**
  - Integrator proteins are one of the most crucial proteins in the cell, since they act as coincidence detectors that are only activated, when two or more converging signals are received simultaneously. Oftentimes cells need soluble signals and signals from the ECM to grow and proliferate.
  - A single signal usually activates a cascade of reactions inside the cell, so that a different reaction can be induced, for example a change in protein expression via the JAK.



Intracellular Signalling – Signal Responses

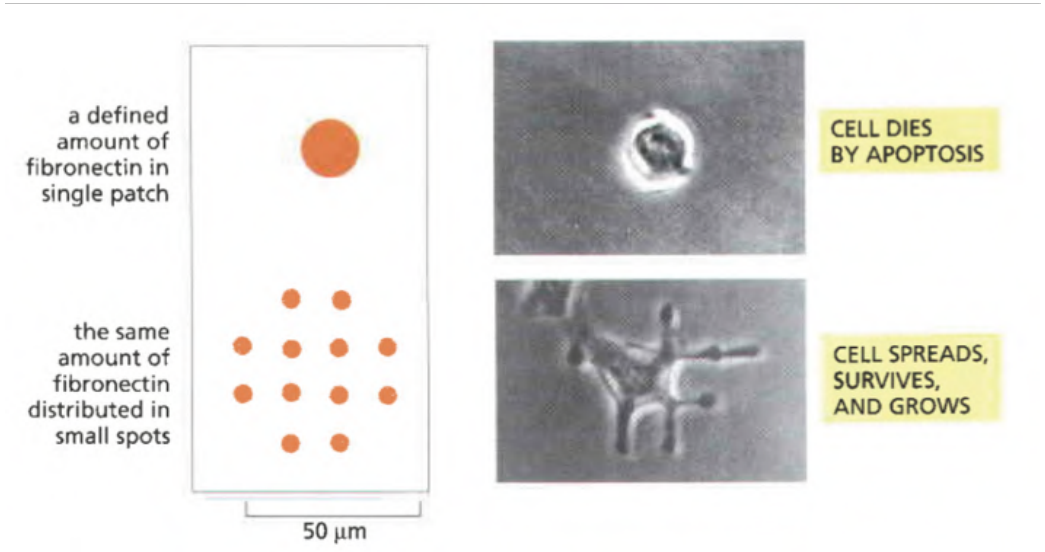
- **Cell response**
  - **Gradual** increase
  - **Abrupt** change (due to integration, phosphorylation, activation and simultaneous inhibition)
- **Positive and negative feedback**
  - Positive feedback: cells maintain the response to a signal (Blood clotting)
  - Negative feedback: cells reduce the response to a signal. This can also occur with a delay (remember the lac operon?)





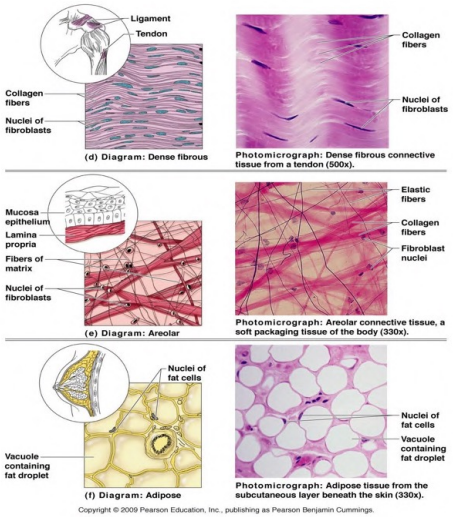
Cell-Matrix Signalling

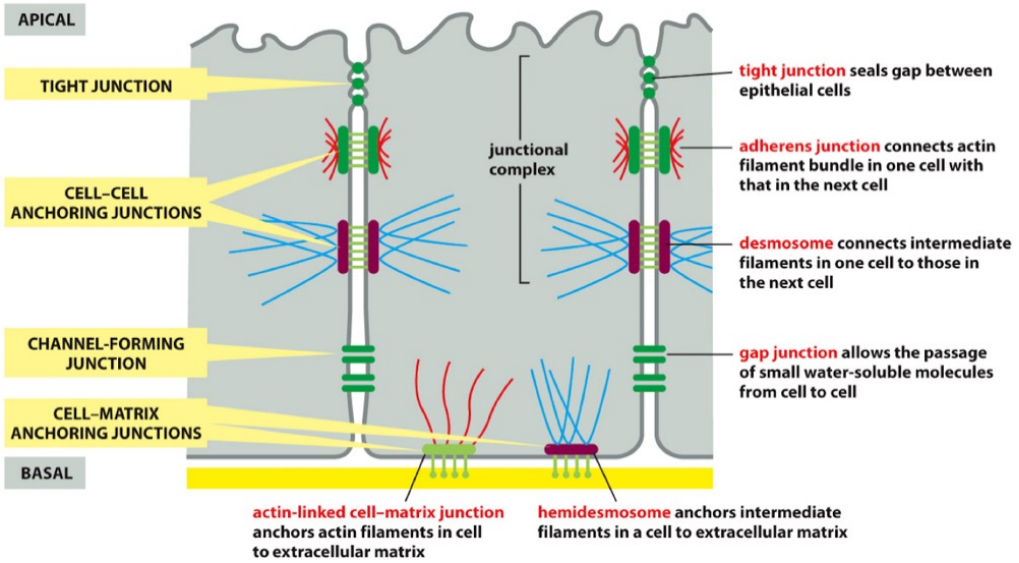
- **The interaction between cells and the extracellular environment**
  - Physical contact between cell and local environment strongly influences the behaviour of a cell
  - The environment is a prerequisite in order to engineer functional biomaterial interfaces.
  - Physical contact happens mostly via **cell-cell** contact or **cell-matrix** contact.
- **Signals**:
  - **Biochemical**: proteins or diffusible factors
  - **Mechanical**: hard/ soft/ elastic/ gel-like surface
  - **Topographic**: fibrils, meshes, pores



Cell-Matrix Signalling: Tissue Basics

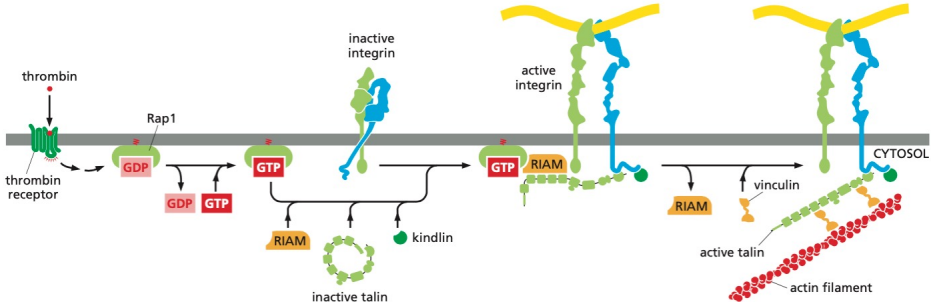
- **Basic tissues**
  - **Connective** - bone, cartilage, fat, fibrous tissue (MECHANICAL SUPPORT through the ECM)
  - **Epithelium** - Lines the inner and outer surfaces of the body (COVERING, cytoskeleton that is connected to the cells by anchoring junctions carries the load)
  - **Nervous Tissue** - Conducts electrical signals (COMMUNICATION)
  - **Muscle** - Produces mechanical force by contraction (MOVING)
- **Connections between cells**
  - **Anchoring junctions**: mechanical stability, sensing of physical forces
    - *Cadherins and integrins*
  - **Tight junctions**: physical sealant and barrier
    - *Cadherins*
  - **Gap Junctions**: fast intracellular transport
    - *Channels and pores*
  - **Signal transmission** (neuronal)



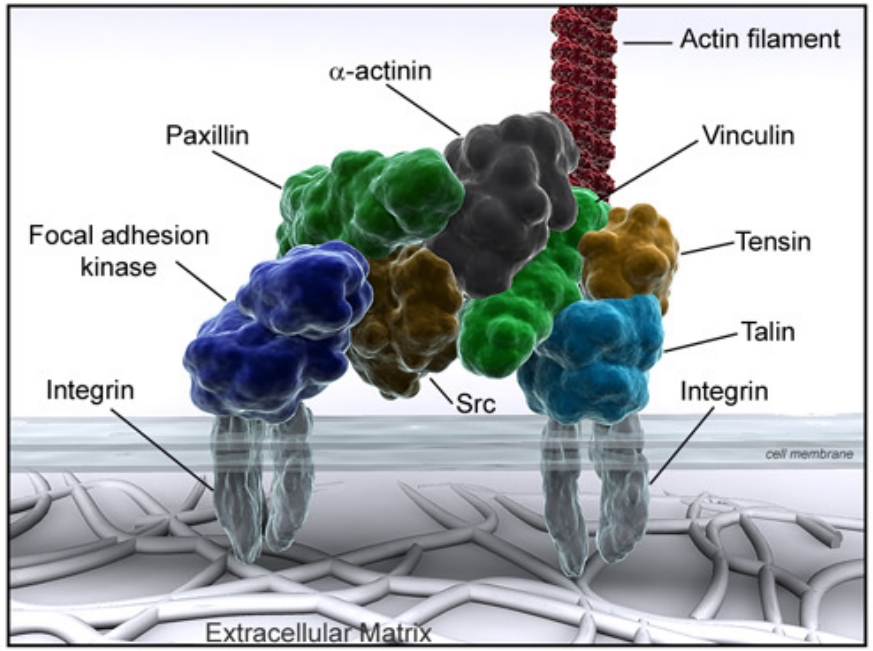


Cell-Matrix Signalling: Functional Parts

- **Integrins**
  - *Small transmembrane proteins that connect cell and ECM*.
    - Head of integrin molecule attaches to protein of the ECM (ex. Fibronectin)
    - Intracellular part binds to talin, which is connected to the cytoskeleton via actin.
    - The binding is strengthened by proteins such as vinculin and filamin.
  - **Mechanical principle**: *conformational changes at opposite end of the molecule are coupled AND tensile forces tighten the bond.*
    - In absence of ligand, integrin is tightly folded.
    - When interacting with an RGD sequence, the integrin unfolds into two units -> *Cells bind via integrins to the RGD sequence of ECM proteins.*
- **Focal Adhesions**
  - Anchoring cell connections that bind the actin cytoskeleton to the substrate. They allow the transfer of matrix forces to the cytoskeleton.



Composition of a focal adhesion



Cell-Matrix Signalling: Extracellular Matrix (ECM)

- The ECM is constructed from three major classes of macromolecules
  - **Glycosaminoglycans (GAGs)**: large and highly charged polysaccharides, that are usually covalently linked to proteins in the form of proteoglycans. They build the hydrated, gel-like ground substance of the ECM. GAGs are needed to resist compression.
  - **Fibrous proteins** which are primarily members of the collagen family and give the ECM its physical strength through elastin and collagen.
    - *Collagen and Fibronectin*
  - **Glycoproteins** which carry conventional, asparagine-linked oligo-saccharides. They produce the EMC and determine the local design.
    - *Proteoglycans, Laminins*
- **Basal lamina/ basement membrane**
  - Special form of ECM. It forms a thin layer between the epithelium and adjacent tissue and consists of *laminin, collagen, nidogen and perlecan*.
  - It provides mechanical stability, acts as a filter and creates „roads“ for cell migration.
- The combination of collagen and proteoglycans results in a stretchable and pressure resistant ECM.
- The viscoelasticity depends on the composition of a tissue, since proteoglycans are viscous and fibrous proteins are elastic,

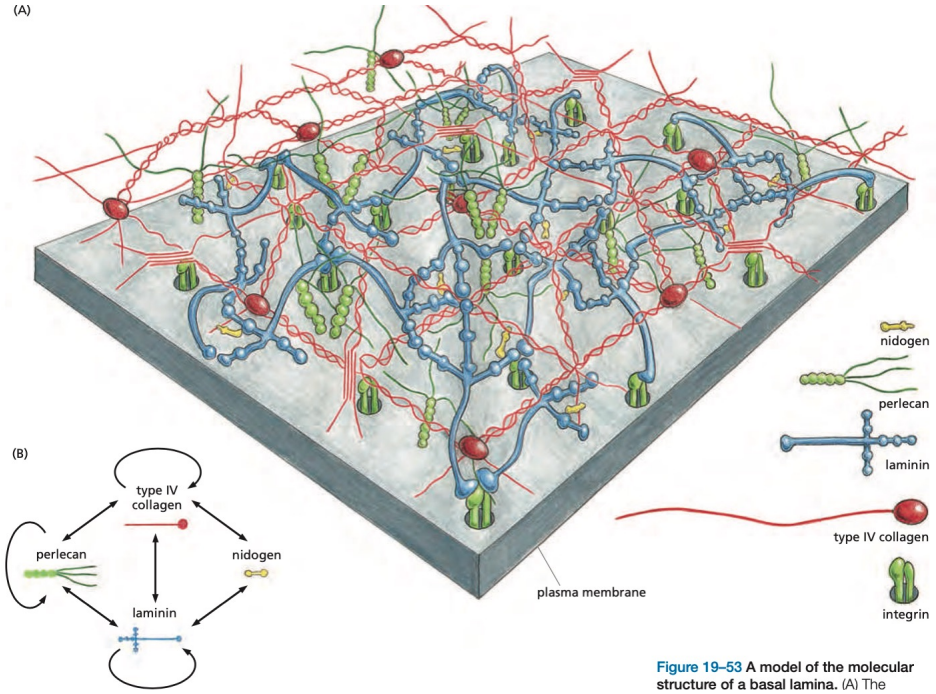


Figure 19–53 A model of the molecular structure of a basal lamina. (A) The

Cell-Matrix Signalling: Cartilage and Wound Healing

- **Cartilage**
  - The structure of the ECM is made of **collagen** (15-22%, primarily type II), **proteoglycans** (4-7%, primarily aggrecan), **water** (60-85%) and **chondrocytes** (< 10%, low density). There are no blood vessels and no innervation!
  - **Collagen** is the structural matrix component and is strong in tension, **proteoglycans/ GAGs** absorb water for swelling and **chondrocytes** are responsible for ECM maintenance!
- **Wound healing**
  - The composition of the ECM reflects the status of wound healing (inflammation, proliferation, remodelling)
    - Phase I: *Blood cell product*s, aka platelets, very *temporary matrix scaffold* (fibrin), *stimulatory proteins* which recruit vasular and other tissue related stem cells, macrophages and immune cells as well as fibroblasts.
    - Phase I-II: Granulation tissue forms (mixture of all required players: stem cells, immune cells, other cells, fibronectin, smaller collagens and proteoglycans)
      Key cellular players are stem cells, fibroblasts and myofibroblasts (= cranky fibroblasts)
    - Phase I-III: Revascularisation (vascular modelling) and vascular remodelling (layer collagens, laminin)
      Tissue remodelling is the process by which cells fine tune the tissue, ideally until it is restored to its pre- injury state.
    - Phase III: Scar tissue remodelling (towards normal tissue). Optimal cell types and optimal matrix (usually no or a small amount of fibronectin, fewer smaller and collagens and proteoglycans and more larger collagen and elastin) are used.