Lecture 7: the extracellular matrix and cell-cell interaction

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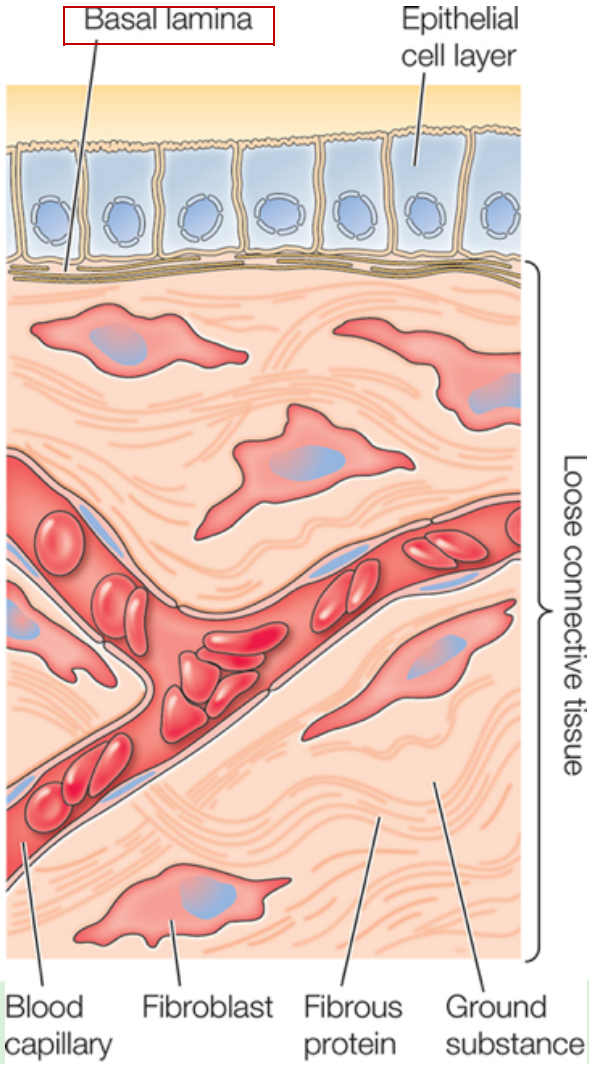
The extracellular matrix

What is it?

- The extracellular matrix fills the spaces between cells, binds cells, and forms tissues.
- Types:
  - Basal laminae: thin, sheet-like, structure upon which layers of epithelial cells rest
    - It supports the sheets of epithelial cells
    - It surrounds muscle cells, adipose cells, and peripheral nerves.
  - Connective tissues: Loose network of proteins and carbohydrates underneath the epithelial cell layers where fibroblasts are distributed.
    - Others: bone, tendon, and cartilage.

The basal laminae contain matrix components that differ from those in the connective tissues.

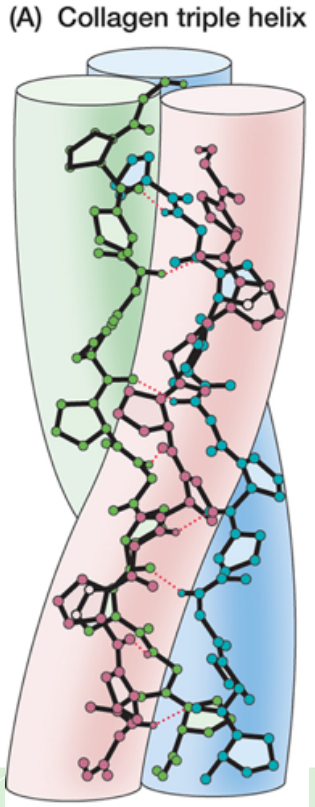


Components of ECM

- Matrix proteins
  - Examples: Collagen, elastin
    - Tough fibrous proteins embedded in a gel-like polysaccharide ground substance.
- Adhesion proteins
  - Examples: Fibronectin, laminin
    - These proteins link components of the matrix to one another and to the cells.
- Glycosaminoglycans.

The collagens

- The most abundant proteins in mammals (25% of the total protein mass).
- Long, stiff, triple-stranded helical structure made of three α chains
- A basic unit of mature collagen is called tropocollagen.
- Rich in glycine (33%), proline (13%), and hydroxyproline (9%)
- It contains hydroxylysine (attachment of polysaccharides)
- Crosslinking of chains via lysine and aldolysine via the action of lysyl oxidase



Types of collagens

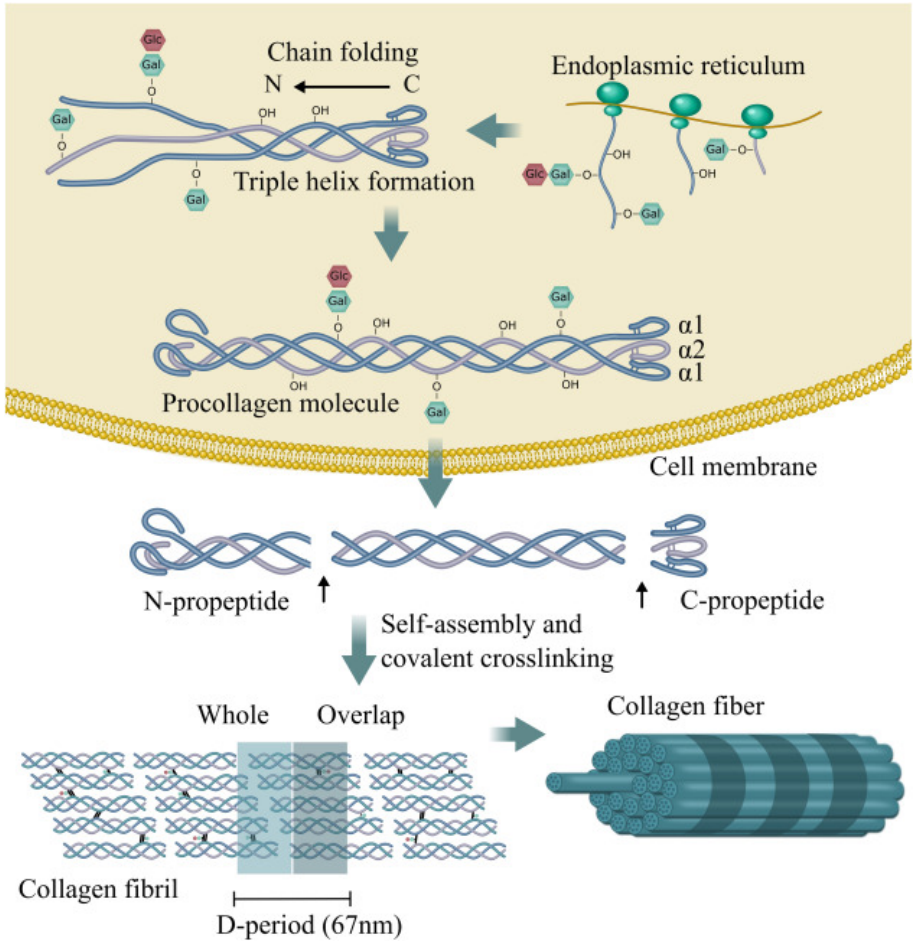
- More than 40 types of collagen that resist tissue stretching.
- Types:
  - Fibrillar collagens
  - Fibril-associated collagens
  - Network-forming collagens
  - Anchoring fibrils
  - Transmembrane collagens

Types of fibrillar collagens

- Type I: most connective tissues (long, aligned in parallel to each other in a regular staggered array to form fibrils), and rigid (fit to be in bone structure)
- Type II: cartilage and vitreous humor
  - Smaller in diameter than type I and oriented randomly in the viscous proteoglycan matrix
  - Rigid macromolecules, but compressible (to resist large deformations in shape and absorb shocks)
- *Type III: extensible tissues (skin and lung)*
- *Type XI: cartilage*
- *Type XXIV: bone and cornea*
- *Type XXVII: eye, ear, and lung*

Synthesis of collagen type I

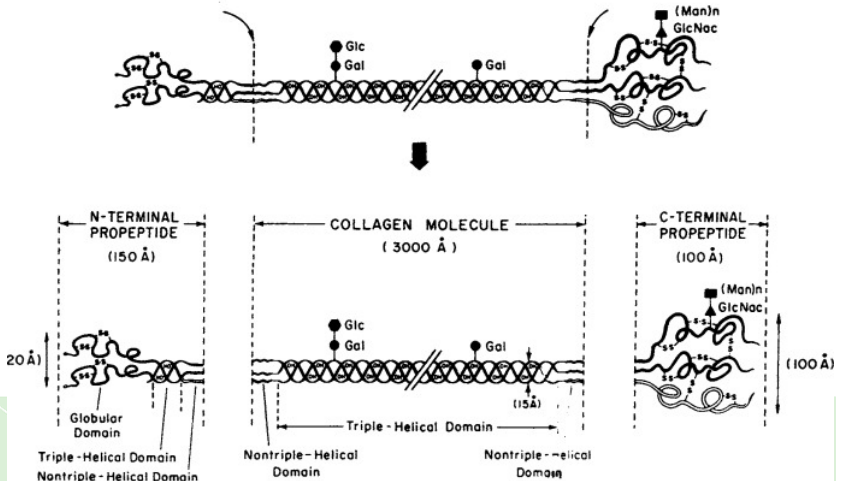
Synthesis of preprocollagen
Removal of pre-region during synthesis
Folding
Hydroxylation and glycosylation
Each chain is called protocollagen
Formation of a triple helical molecule
Vesicular exocytosis of procollagen
Now, it is called tropocollagen
Terminal propeptides are cleaved
Tropocollagen is now hydrophobic
Lysines are oxidized by lysyl oxidase
Copper is needed
Crosslinking of lysines and hydroxylysines
Fibril then fiber formation



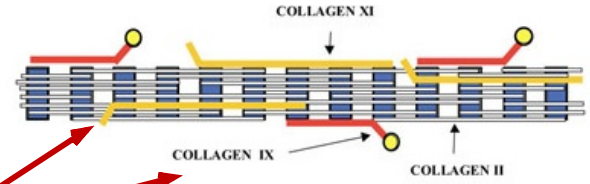
Synthesis of collagen

- Procollagen contains the N-terminal and C-terminal propeptides that inhibit <u>intracellular</u> fibril formation preventing the catastrophic assembly of fibrils within the cell.
  - Lysyl oxidase, which catalyzes the formation of reactive aldehydes, is an extracellular enzyme (another protective measure).
- Following exocytosis, the procollagen peptidases remove the propeptides.

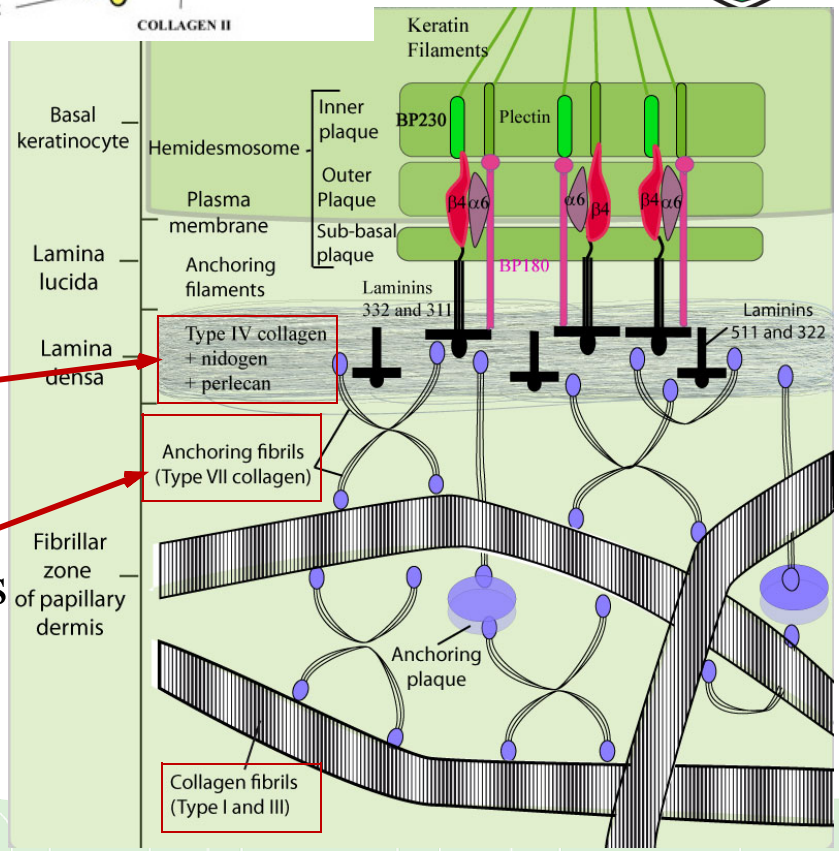
- Procollagen I Intact N-Terminal (PINP) is considered the most sensitive marker of bone formation, and it is useful for monitoring bone resorption therapies.



Others

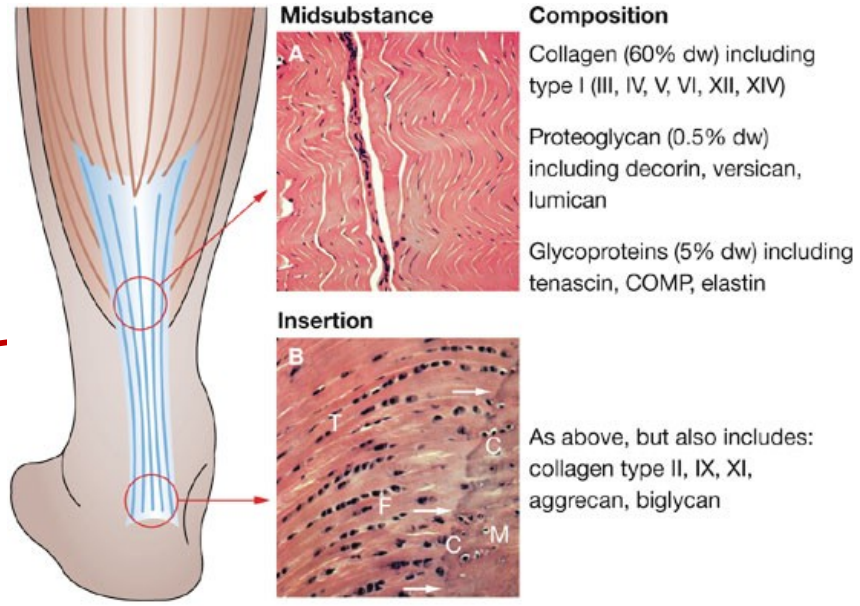


- Fibril-associated collagens
  - The Gly-X-Y repeats interrupted by short nonhelical sequences making it flexible.
  - Collagens type IX and XI link fibrils to one another and to other components in the ECM.
- Network-forming collagens
  - Types IV: constituent of the basal laminae.
- Anchoring fibrils (type VII): link basal laminae to underlying connective tissues (network-forming collagens to fibrillar collagens).



Collagen-related diseases

- Collagen is highly crosslinked in tissues where tensile strength is required such as in Achilles tendon.
- If lysyl oxidase is mutated and crosslinking is inhibited, the tensile strength of fibers is greatly reduced, collagenous tissues become fragile, and collagen structures tend to tear (skin, tendon, and blood vessels).

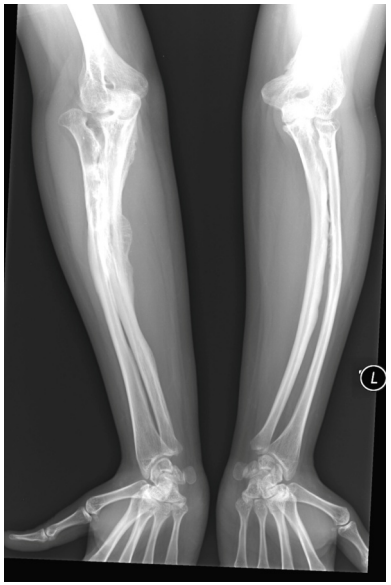


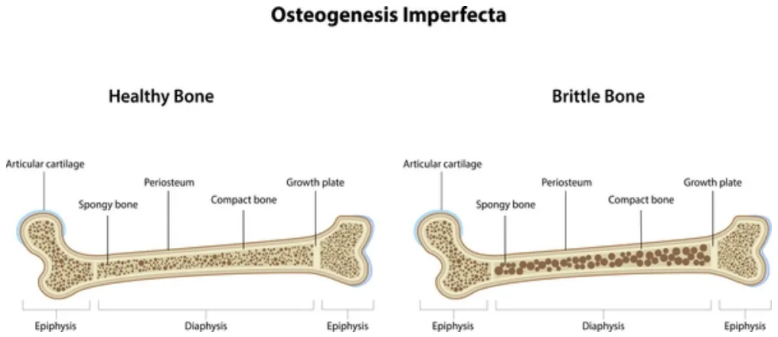
Osteogenesis imperfecta (Brittle-bone disease)

- "Osteogenesis imperfecta" = imperfect bone formation
- A genetic disorder of several forms that cause fragile, soft, brittle, and easily broken bones.
- Four types of osteogenesis imperfecta designated as type I through type IV
  - Type I: the mildest form of the condition.
  - Type II: the most severe form that results in death in utero or shortly after birth.
  - Milder forms generate a severe crippling disease.

Mutations of osteogenesis imperfecta

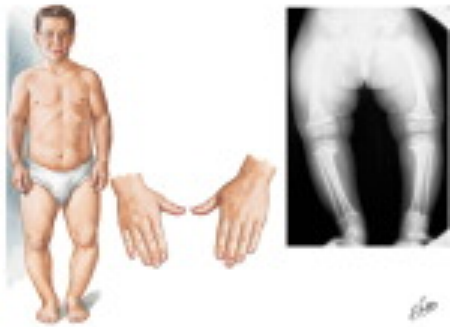
- Mutations in the COL1A1 and COL1A2 genes (and others) interfere with the assembly of **type I collagen**.
- Defective collagen weakens connective tissues, particularly bone, resulting in the characteristic features of OI.

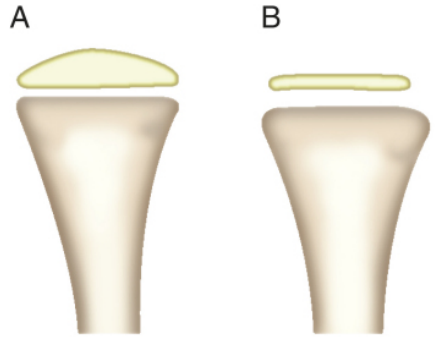




Chondrodysplasias

- Collagen type II is a spongy collagen that absorbs shock.
- It is formed by homotrimers of collagen, type II, alpha 1 chains.
- It makes up 50% of all protein in cartilage and 85–90% of the collagen of articular cartilage.
- Mutations affecting **collagen type II** cause chondrodysplasias, characterized by abnormal cartilage, which leads to bone and joint deformities.

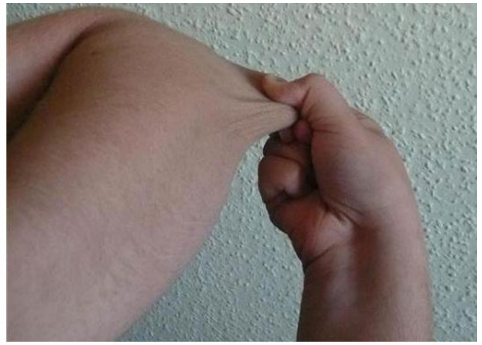




Ehlers-Danlos syndrome

- A heterogeneous group of disorders that affect the skin, bones, blood vessels, and other organs.
- The signs and symptoms vary from mild to life-threatening.
- All result from defects in collagen synthesis and/or processing.
  - Mutations in collagens type I, III, or V or in the collagen processing enzymes like procollagen N-peptidase or lysyl hydroxylase

Major manifestations are skin fragility and hyperextensibility and joint hypermobility.



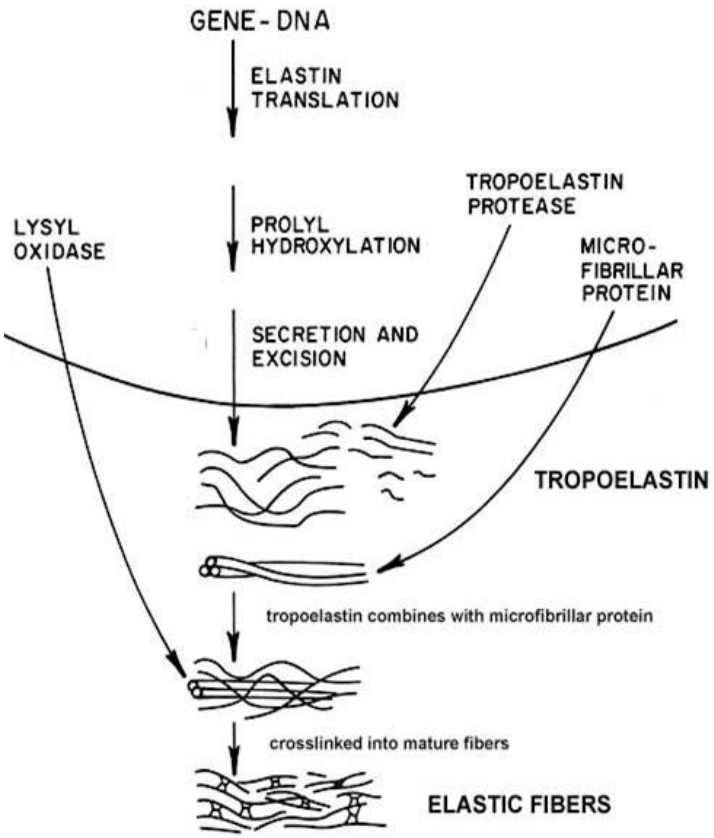
Type III EDS

- The most clinically important mutations are found in the gene of type III collagen.
- Since **type III collagen** is a major component of arteries, mutations affecting it result in fragile blood vessels.

- Other symptoms include stretchy skin and hypermobile joints.

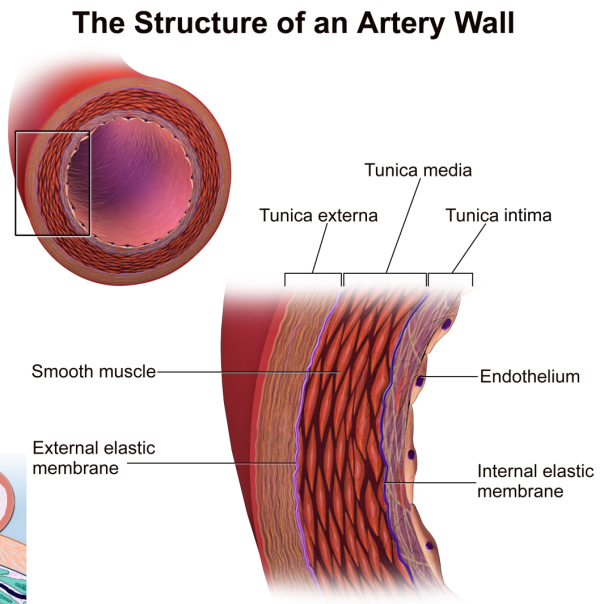
Elastin

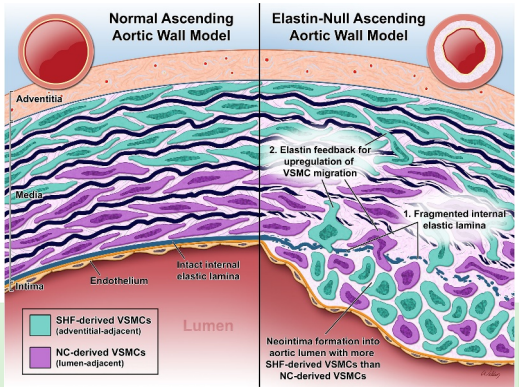
- The main component of elastic fibers is elastin
- Highly hydrophobic
- Rich in proline and glycine.
- Contains some hydroxyproline, but no hydroxylysine
- Not glycosylated
- Secretion of tropoelastin
- Assembly into elastic fibers
- Crosslinking via lysines



Function of elastic fiber

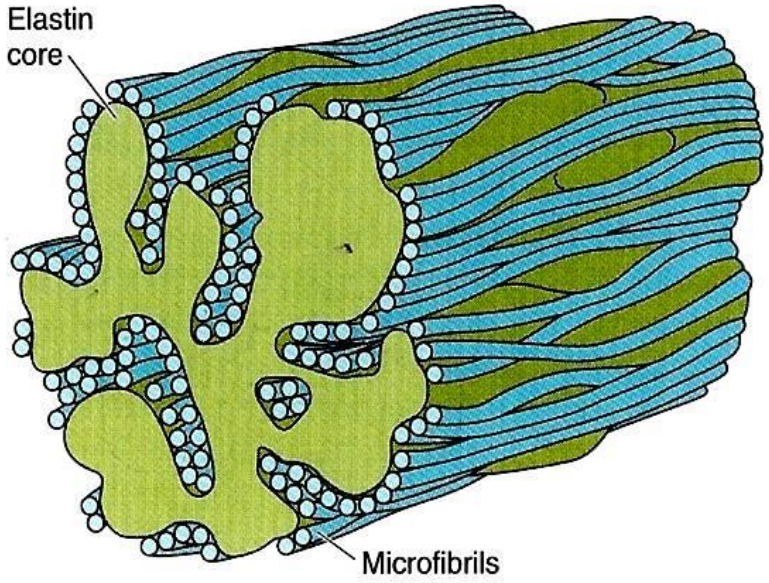
- Elastin is the dominant extracellular matrix protein in arteries.
- The normal elasticity of an artery restrains the proliferation of smooth muscle cells.
- Abnormal or deficiency of elastin results in excessive proliferation of smooth muscle cells in the arterial wall and narrowing of the aorta.





Microfibrils and fibrillin

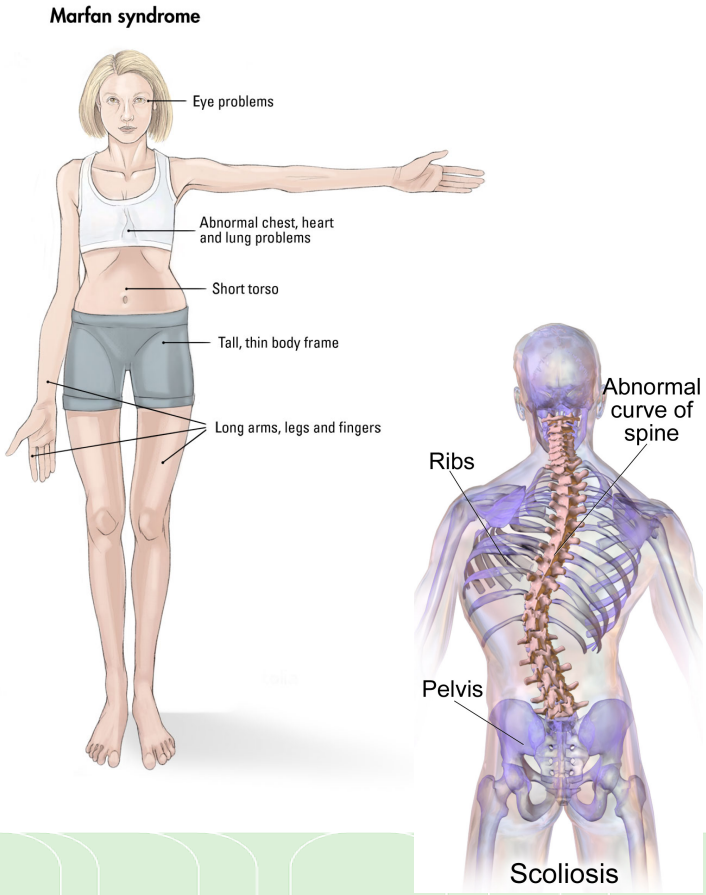
- The elastin core is covered with a sheath of microfibrils, which are composed of several glycoproteins, including the large glycoprotein fibrillin.
- Fibrillin binds to elastin and is essential for its integrity.
- The main job of microfibrils is to make the connective tissue strong and rigid.
- Their secondary job is to help control growth and development.



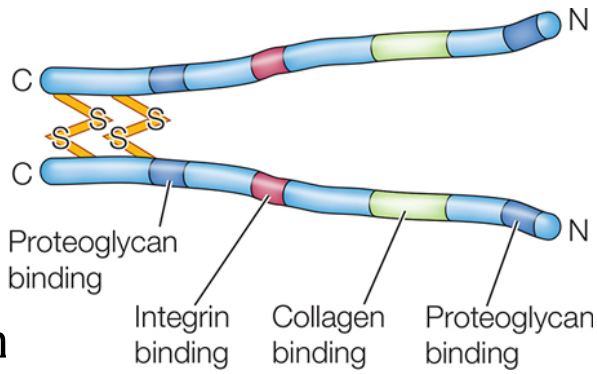
Marfan's syndrome

- Due to mutated fibrillin
- Rupture of aorta.

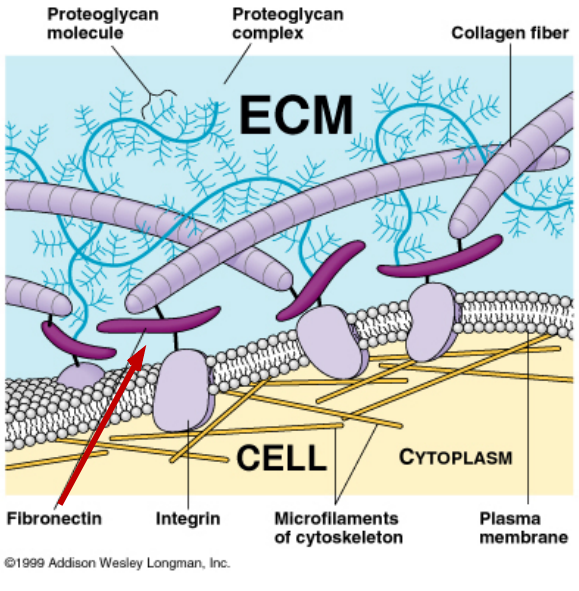
- Others: A tall, thin build; Long arms, legs, fingers, and toes and flexible joints; Scoliosis, or curvature of the spine; A chest that sinks in or sticks out; Crowded teeth; Flat feet.



Matrix adhesion proteins

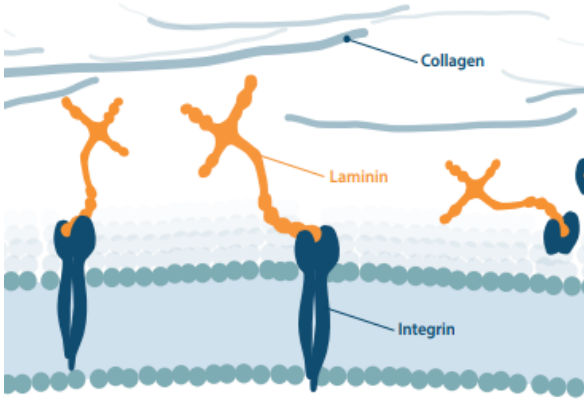


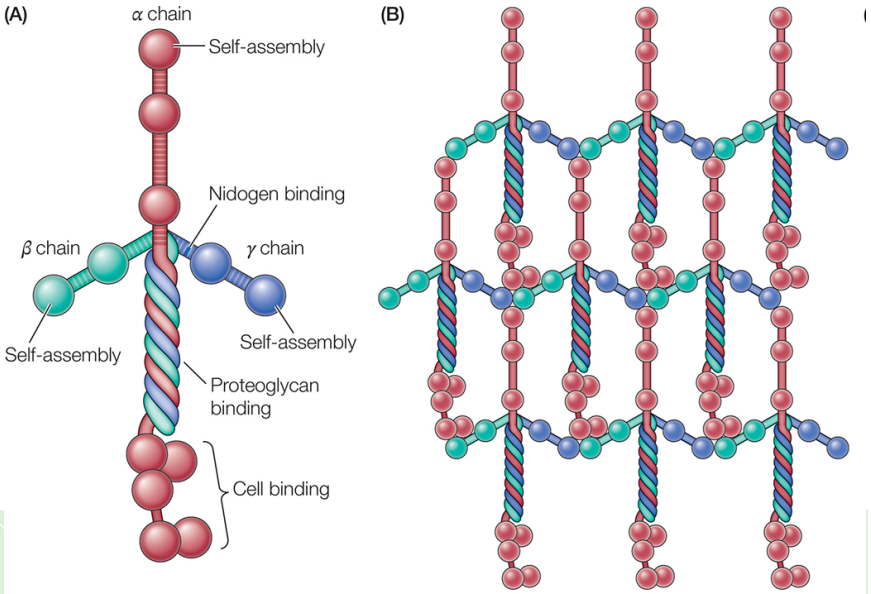
- They interact with collagen and proteoglycans and link matrix structural proteins with one another an to the surfaces of cells.
- Fibronectin: the principal adhesion protein of connective tissues.
  - A dimeric glycoprotein that is crosslinked into fibrils by disulfide bonds.
  - It binds to collagen and GAGs
  - It binds to cell surface proteins like integrins linking cells to the ECM



Laminin

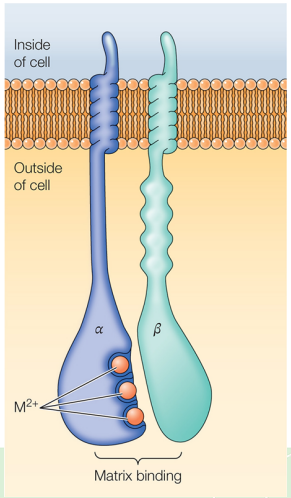
- It is found in the basal laminae.
- It forms T-shaped heterotrimers with binding sites for cell surface receptors such as integrins, type IV collagen, and GAGs.

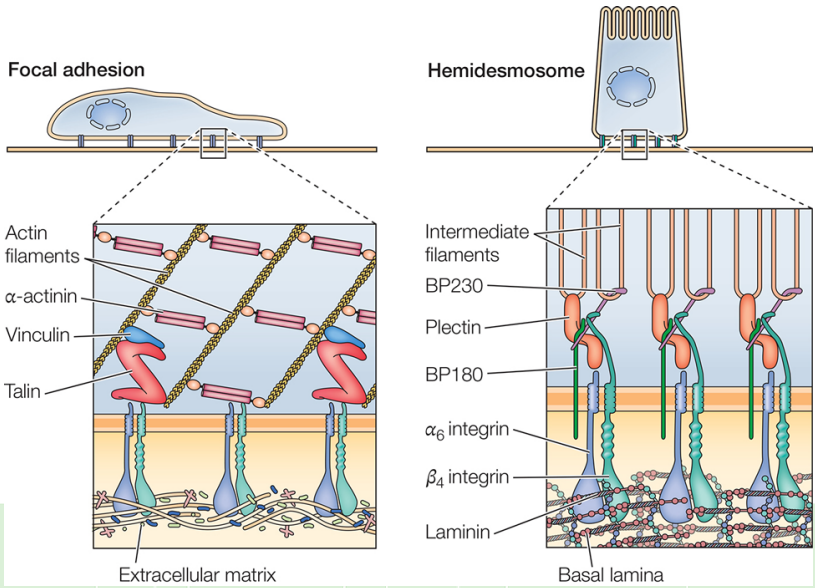




Cell-matrix interactions
Role of integrins

- integrins are a family of transmembrane heterodimers (α and β) that bind to short sequences of ECM proteins and attach cells to ECM.
- They also anchor the cytoskeleton at focal adhesions (cell-matrix interaction|) and hemidesmosomes (cell-basal laminae interaction).





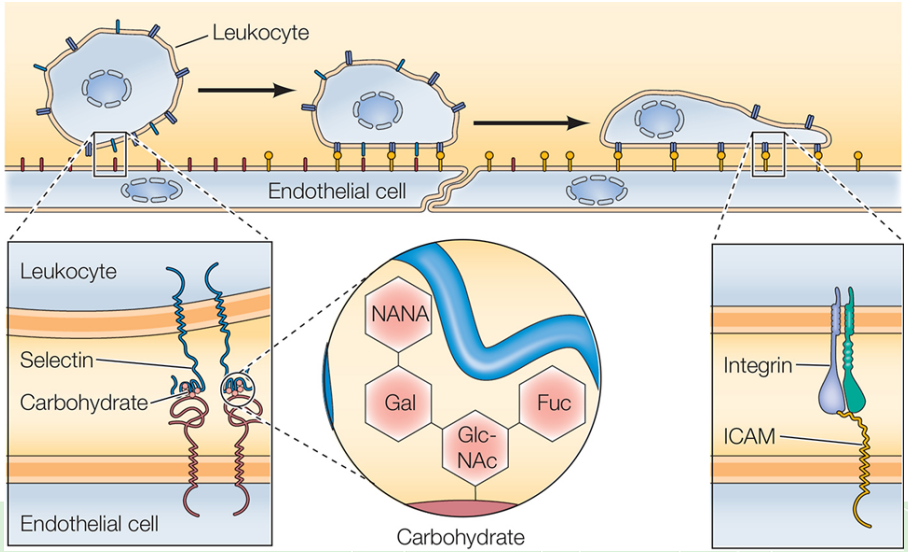
Cell-cell interaction

Cell Adhesion Molecules

Family	Ligands recognized	Stable cell junctions
Selectins	Carbohydrates	
Integrins	Extracellular matrix	Focal adhesions and hemidesmosomes
	Members of Ig superfamily	
Ig superfamily	Integrins	
	Homophilic interactions	
Cadherins	Homophilic interactions	Adherens junctions and desmosomes

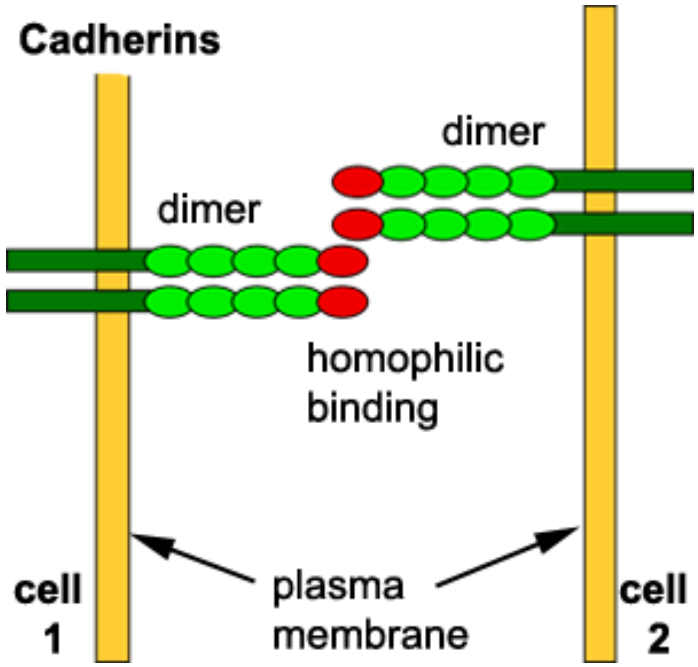
Role of Selectins in leukocyte-endothelial cell interaction

- Leukocytes interact with the endothelial cells via binding of leukocyte selectins to carbohydrates on the endothelial cell surface.
- This is followed by more stable interactions between leukocyte integrins and intercellular adhesion molecules (ICAMs)—members of the Ig superfamily.

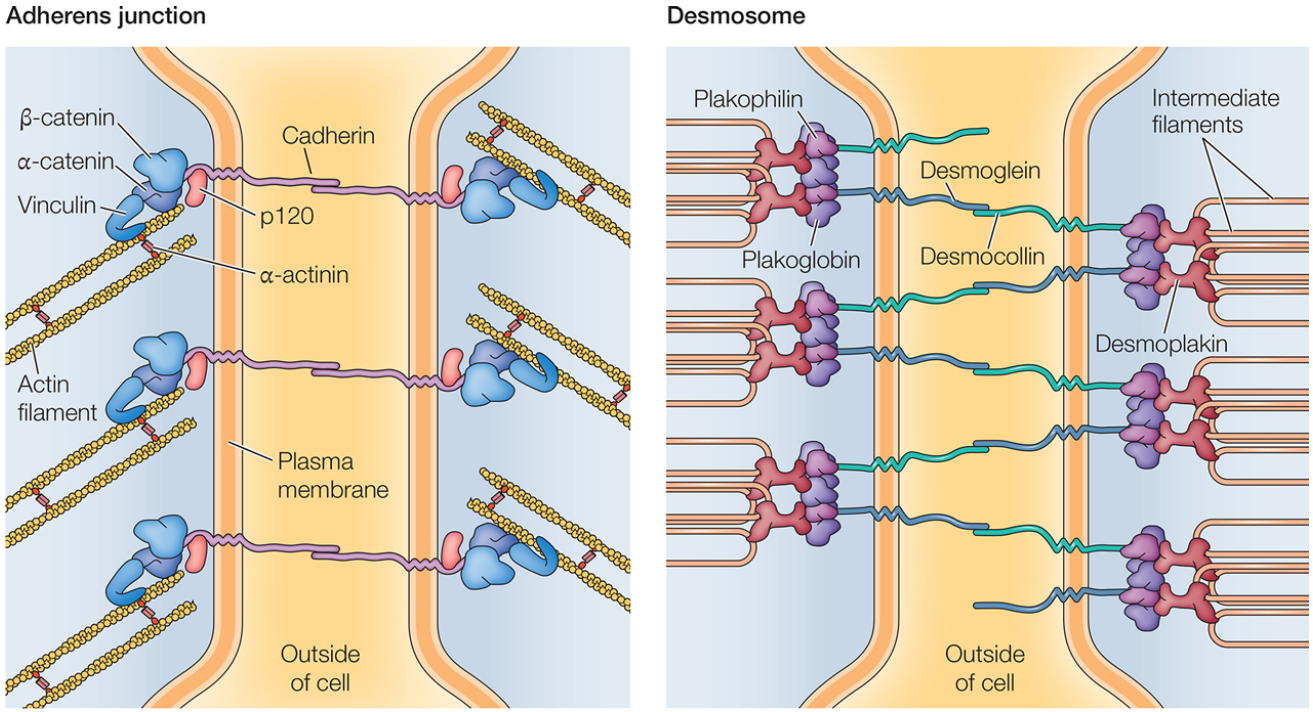


Cadherins

- Cadherins are involved in selective adhesion
  - between embryonic cells
  - the formation of specific synapses in the nervous system,
  - for the maintenance of stable junctions between cells in tissue (adherens junctions and desmosomes).
- Classic cadherins
  - E-cadherin: epithelial cells
  - N-cadherin: neural cells
  - P-cadherin: placental cells
  - Desmosomal cadherins
  - 7-Transmembrane cadherins

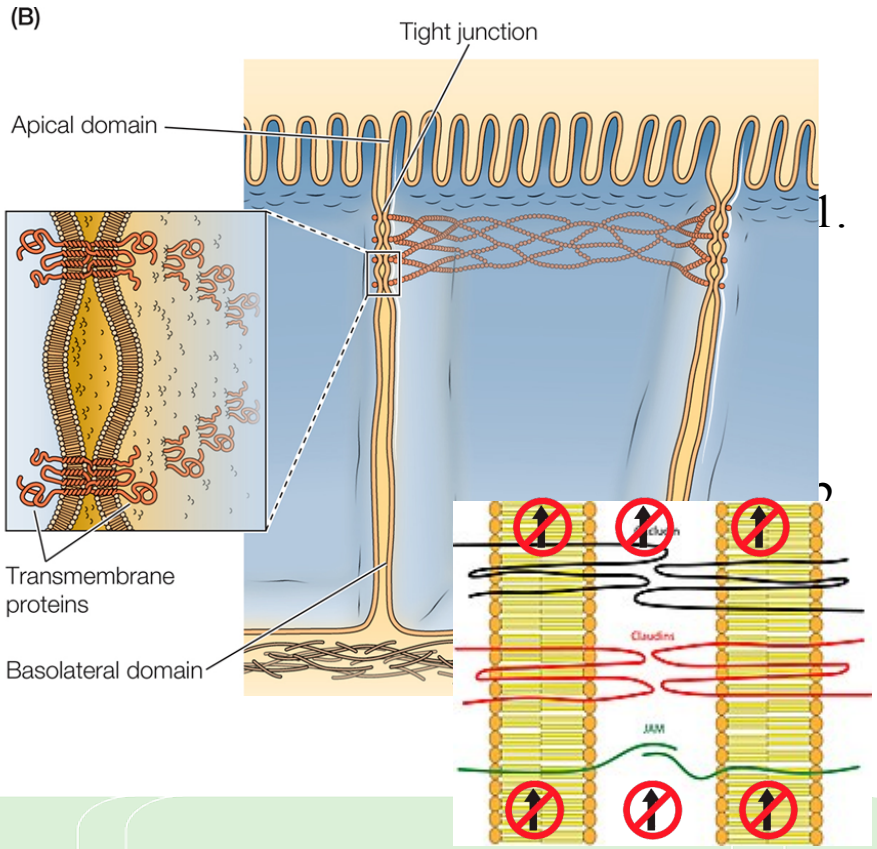


Adherens junctions vs. desmosomes



In adherens junctions, cadherins link the actin filaments of one cell to the actin filaments of an adjacent cell.	In desmosomes, desmosomal cadherins link the intermediate filaments of one cell to the intermediate filaments of an adjacent cell.

Tight junctions



Proteins form a barrier as a network belt around the entire circumference of the cell.

Purposes:

1. Separation of the two spaces <u>outside</u> the cells

   Example: lumen of the intestine from the underlying connective tissue

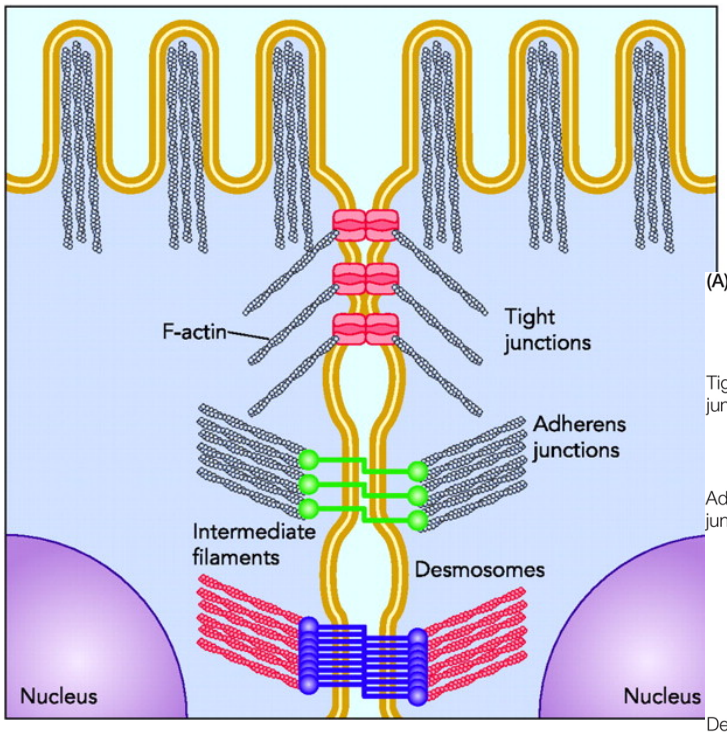
   They block free passage of molecules (including ions) between the cells of epithelial sheets.

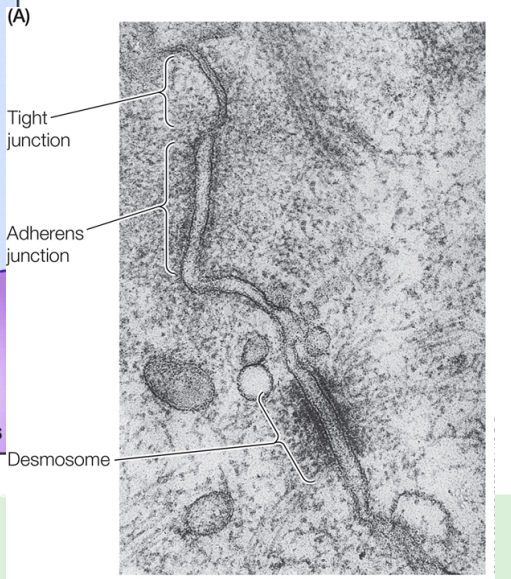
2. Separation of the apical and basolateral domains <u>inside</u> the cells.

Claudin-low breast cancer is characterized by being mesenchymal-like with low E-cadherin, poor survival and prognosis, metastasis, and younger age of onset.

Tight junctions vs. adherens junctions vs. desmosomes

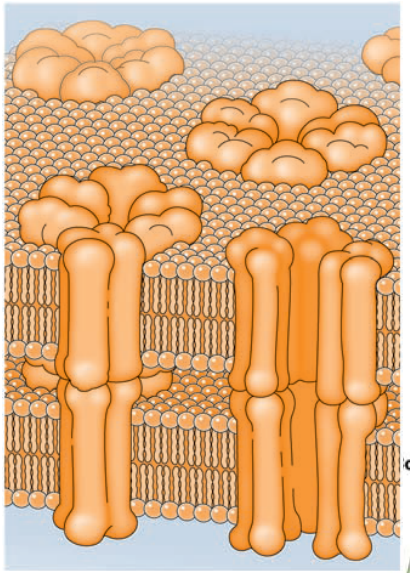
Tight junctions are usually associated with adherens junctions and desmosomes in a junctional complex.

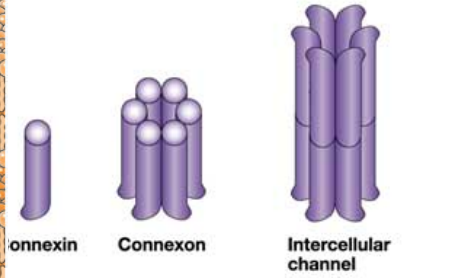


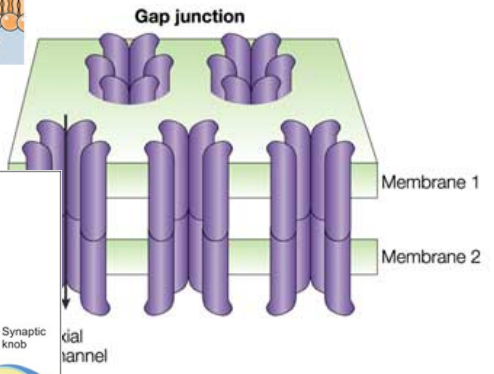


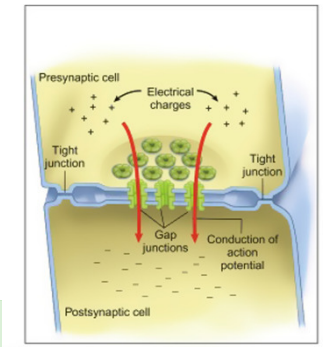
Gap junctions

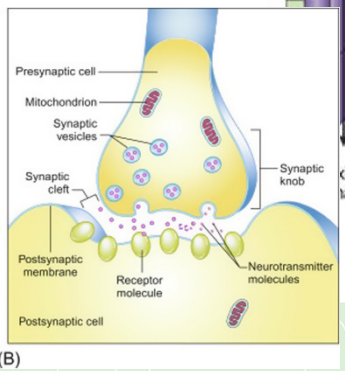
- Gap junctions are a cylinder with an open pore called **Connexons** that provide direct connections between the cytoplasms of adjacent cells.
- Ions, small molecules, and signaling molecules, *but not proteins and nucleic acids*, can diffuse between neighboring cells.
- **Connexons** are made of six transmembrane proteins (out of 21)called **connexins**.
- Specialized connexon = electrical synapse











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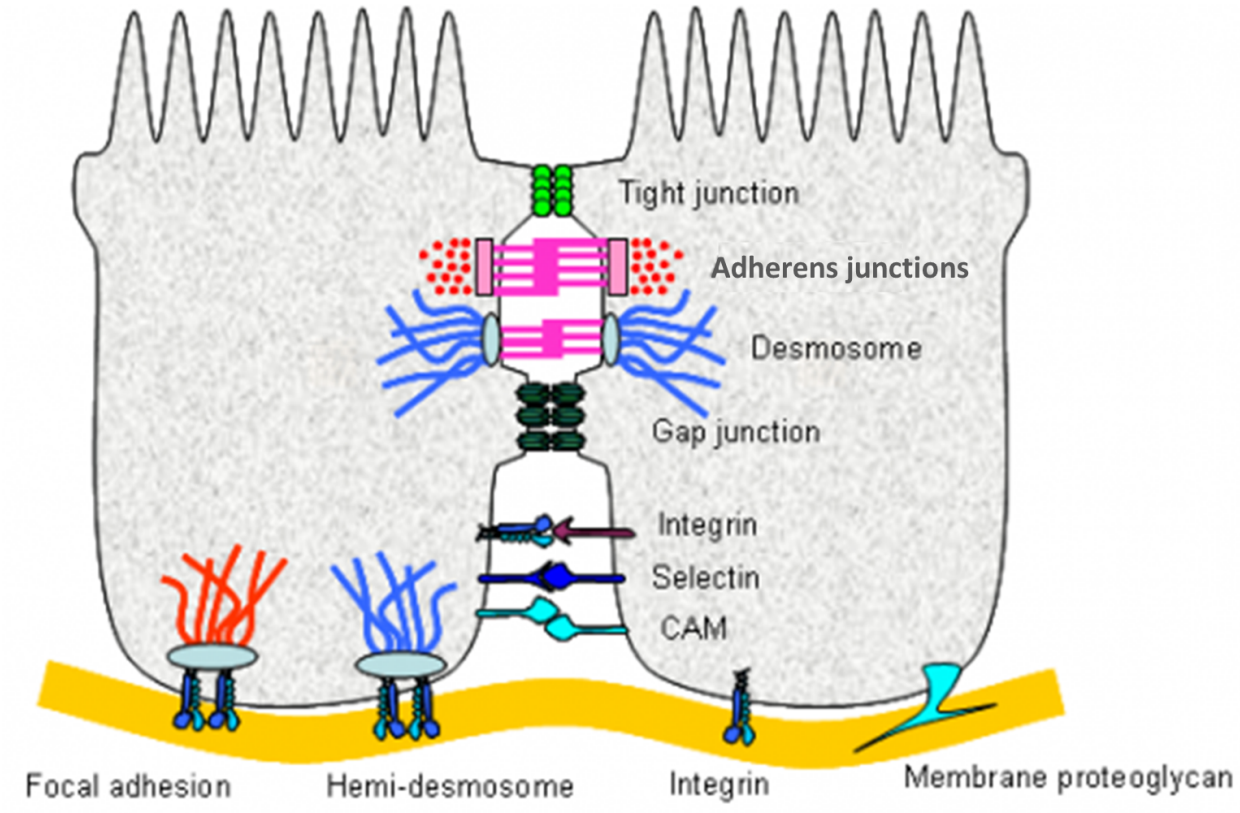
Diseases caused by defective gap junctions and mutated connexins

- Marie-Charcot-Tooth disease
- Deafness
- Skin disorders
- Cataracts
- **Although connexons are found in many tissues, only a limited number of tissues are affected. Why?**
  - Compensations by other connexins
  - Requirement by affected tissues of a specific combination of connexins.
  - Mutations may affect proper assembly in the Golgi apparatus and/or export to the plasma membrane.


Tight junction
Adherens junctions
Desmosome
Gap junction
Integrin
Selectin
CAM
Focal adhesion
Hemi-desmosome
Integrin
Membrane proteoglycan