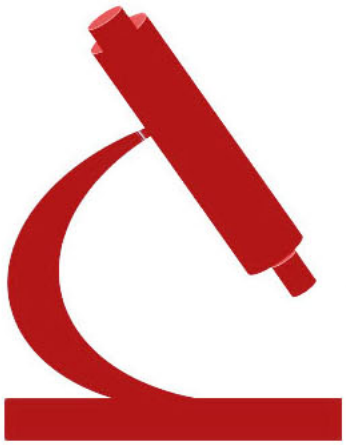

# CYTOLOGY

**Premed 2018 - JU**

◉ Sheet ○ Slides

Number

21

Done by:

Amneh Auben

Corrected by:

Abdulrahman Jabr

Doctor

Diala Abu-Hassan

# Matrix polysaccharides

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Extracellular matrix (ECM): It's a collection of components that fills the spaces outside the cell or between the cells.

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Its composed of two major components:

1- Proteins:

- fibers: can be either collagen or elastic.
- adhesion: to be discussed in this lecture……

2- polysaccharides:

-either sugars of glycoproteins that extend from the exterior of the cell or the part of proteoglycans (made of core protein and GAGs)

-Note: 1) elastic fibers don't have sugars in their components.

2) the collagen itself as a fibrous protein has a sugar component.

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**Glycosaminoglycans (GAGs)**: Polysaccharides of repeated disaccharides in which the fibrous structural proteins of the ECM are embedded.

They composed of <u>sugars that have amino group</u> (modified sugars) <u>so they are more hydrophilic and more polar than the original sugars.</u>

GAGs are converted into either N-acetylglucosamine or N-acetylgalactosamine in addition to sugars the modified by <u>different ways:</u>

1) By sulfate groups, e.g. dermatan sulfate, chondroitin sulfate, keratan sulfate, heparin sulfate.

2) by oxidation which makes them acidic (with carboxyl group).

-Sulfate and carboxyl have negative charges.

This makes these molecules very water attractive (hydrophilic).

They make the gel-like structure of proteoglycans.

-They contribute mainly to shock absorption.

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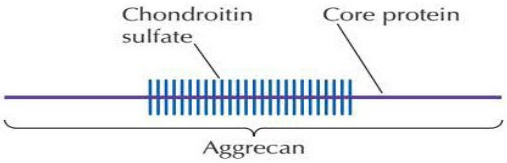
***Core proteins***: Some of them are cell surface proteins or anchored proteins which are going to interact with integrins as membrane proteins.

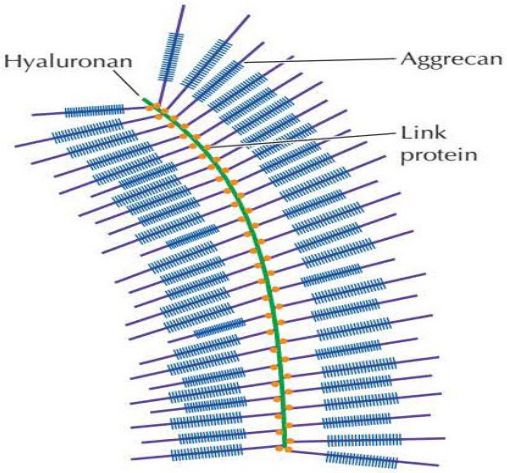
## There are different types to proteoglycans:

# Aggregan and hyalronan

Aggrecan is a large proteoglycan consisting of more than 100 chondroitin sulfate chains joined to a core protein.




Multiple aggrecan molecules bind to long chains of hyaluronan (green), that become trapped in the collagen network forming large complexes in the extracellular matrix of cartilage.



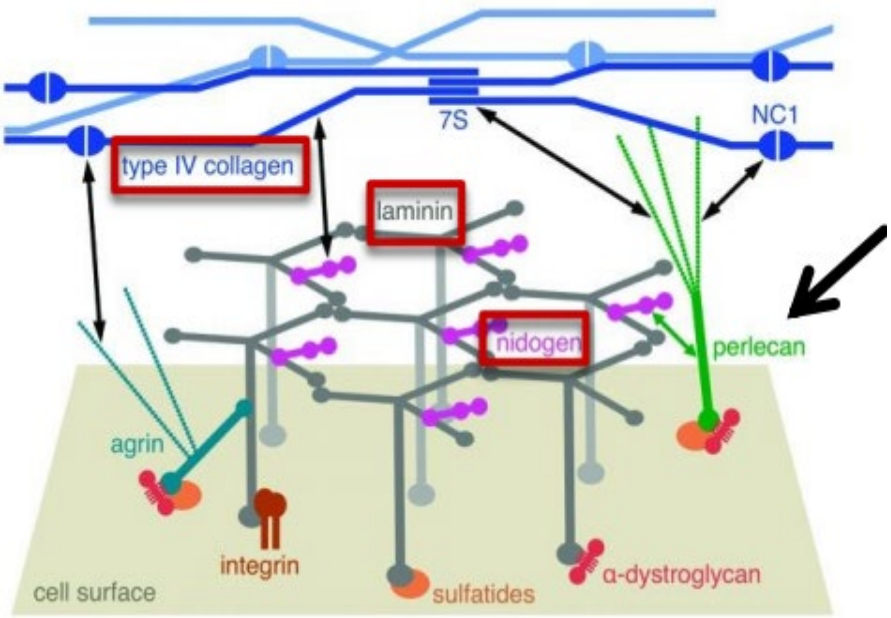

The presence of a large number of sugars around hyalronan helps to increase its interactions with water to be more hydrophilic as well as the sulfate group that has negative charge Which makes it more polar.

# Perlecan

Perlecen interact with molecules at cell surface and with molecules at the ECM . its binds to

1- collagen (e.g. type IV collagen)
2- the adhesion protein laminin.
3- Heparan sulfate proteoglycan of basal lamina. (nidogen)

It acts as connection between the cell surface and ECM mediated by different components such as fibrous components and other types of proteins.

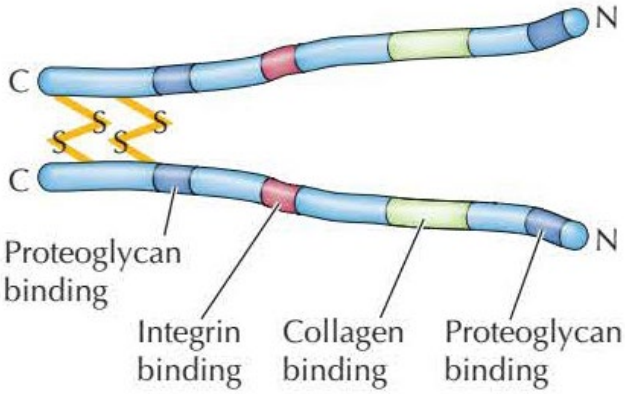



Proteoglycans bind to matrix proteins to form gel-like networks in which the fibrous structural proteins of the extracellular matrix are embedded.

# Matrix adhesion proteins

## Fibronectin

Fibronectin: the principal adhesion protein of connective tissues.
_ A dimeric (two units of protein interact with each other) glycoprotein that is crosslinked into fibrils by s-s bonds.
_ Binds to collagen and GAGs.
_ Binds to cell surface proteins like integrins linking cells to the ECM.
If we want to bind two molecules inside ECM, this process happens mainly through adhesion molecules.
***This is similar to the way in which the actin is linked to microtubules by linking them to the intermediate filament (one side of the intermediate filament to actin and the other side is linked to microtubules).***

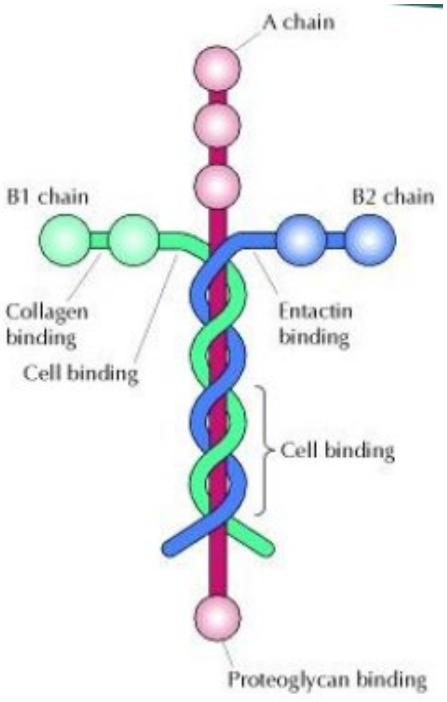



**At primary sequence it has specific region (stretch of amino acids), it can bind to collagen from one side and with proteoglycans from the other side. **

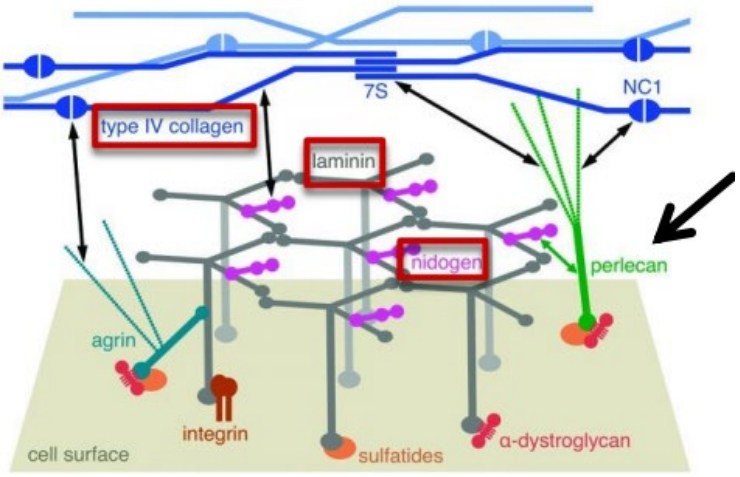
*They link matrix proteins with one another and to the surfaces of cells.
*They interact with collagen and proteoglycans and specify matrix organization and are major binding sites for cell surface receptors such as integrins.
**It binds ⟶ the cells and the fibers and the sugar components of ECM.**

## Laminin

Found in basal lamina.
T-shaped (or cross shaped) heterotrimers with binding sites for cell surface receptors (e.g. integrins), and ECM components, e.g. type IV collagen, and perlecan.
Laminins consist of three polypeptide chains designated:
- *A* chain: the main chain.
- *B*1 chain and *B*2 chain: they intertwined around *a* chain to give the final structure of the crossed shape.



Laminins (gray) are tightly associated with another adhesion protein, called **nidogen** (**Purple**), which also binds to type IV collagen, all of which form crosslinked networks in the basal lamina.




# Cell-matrix interactions
# Role of integrins

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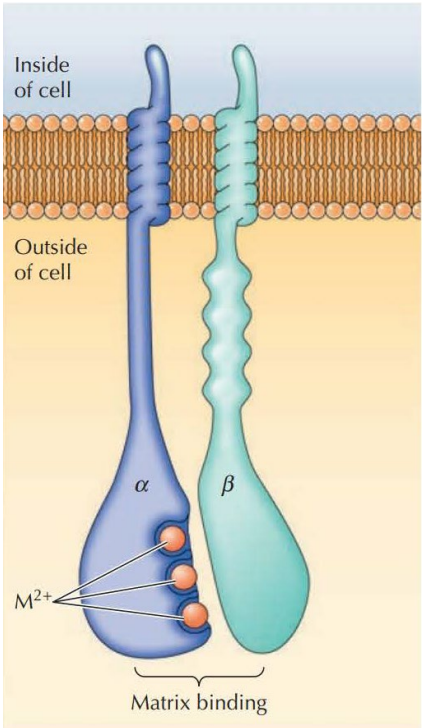
-The integrins are a family of transmembrane heterodimers proteins consisting of two subunits, designated *α* and *B.*

-They bind to short sequences present in ECM proteins including collagen, fibronectin, laminin and proteoglycans.

(Associated with proteins found on ECM; either to fibrous protein or to adhesion protein)




**Functions of integrins:**

1. The major cell surface receptors that attach cells to ECM.

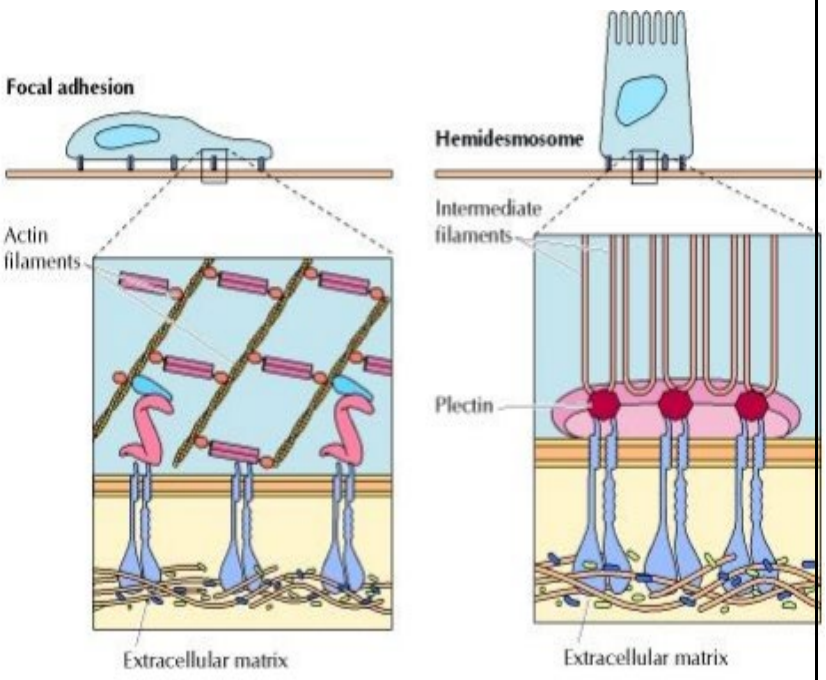
2. They anchor the cytoskeleton at focal adhesions and hemidesmosomes.

**Cell-matrix junctions mediated by integrins**

integrins mediate two types of stable junctions in which the cytoskeleton is linked to the extracellular matrix.

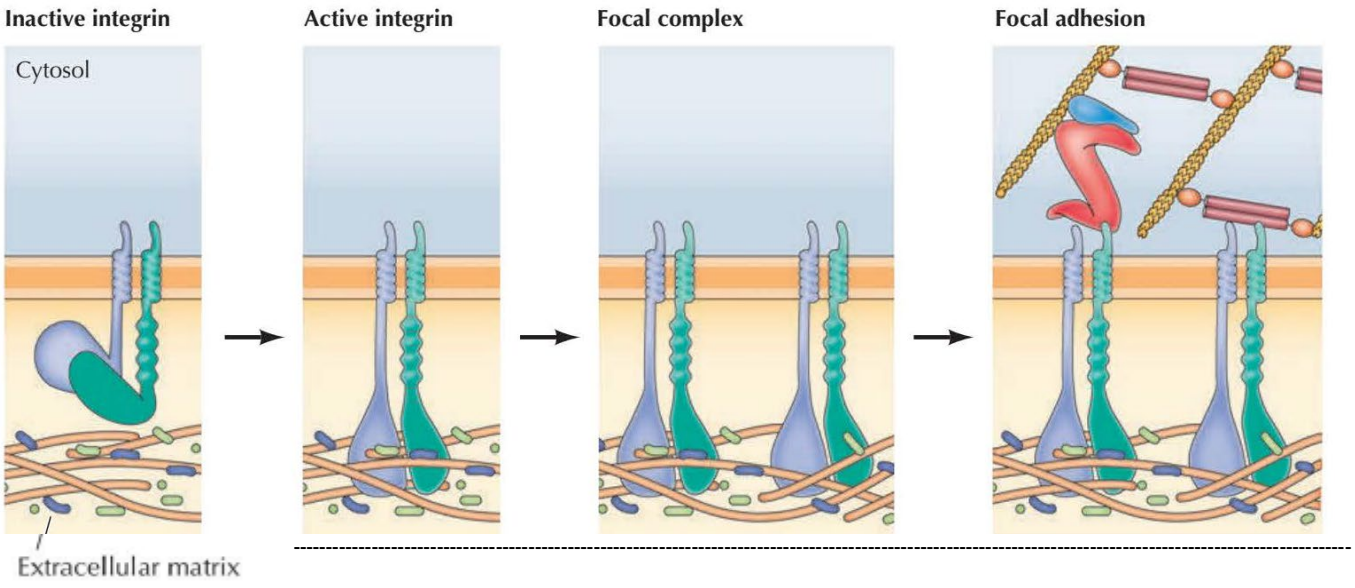
In **focal adhesions**:

bundles of actin filaments are anchored to the integrins via associations with a number of other proteins, including binding to a-actinin or by binding to talin then to vinculin.




In **hemidesmosomes**: integrins link the basal lamina layer of the extracellular matrix to intermediate filaments via plectin.

# Assembly of focal adhesions




*Regulated changes in integrin activity underlie the rapid assembly and disassembly of focal adhesions during cell movement.

The ability of integrins to reversibly bind matrix components is dependent on their ability to change conformation between inactive and active states.

In the inactivate state, integrin head groups are held close to the cell surface.
Signals from the cytosol activate integrins, extending the head groups and enabling them to bind to the ECM.
This leads to recruitment of additional integrins to form a focal complex, which develops into a focal adhesion.

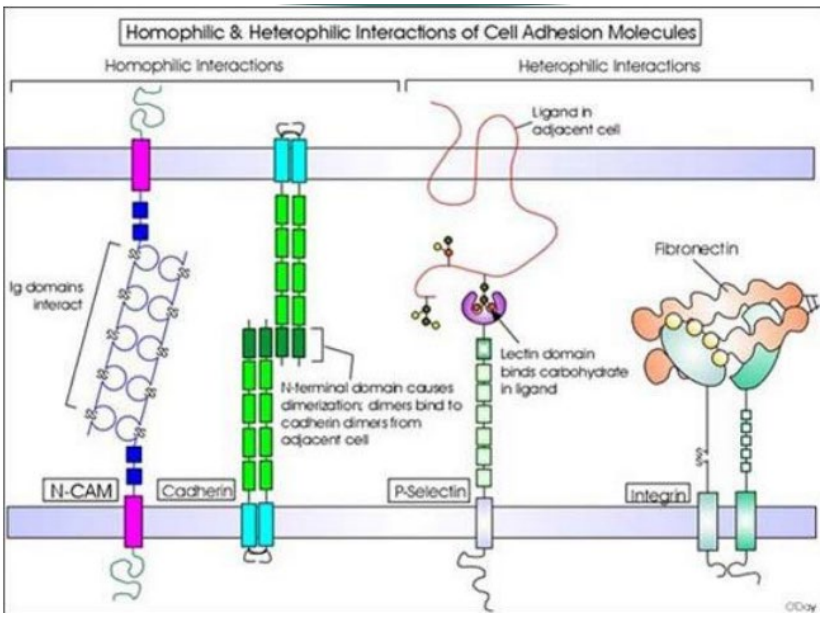
1. Activation of integrin and binding to ECM.
2. Recruitment of additional integrins forming focal complex.
3. Development of small integrin clusters called focal complexes.
4. Development of focal adhesions by the recruitment of formin, talin, vinculin and α-actinin.

# Cell-cell adhesion is a selective process
# Cell Adhesion Molecules

| Family | Ligands recognized | Stable cell junctions |
|---|---|---|
| Selectins | Carbohydrates | No |
| Integrins | Extracellular matrix | Focal adhesions and hemidesmosomes |
| | Members of Ig superfamily | No |
| Ig superfamily | Integrins | No |
| | Homophilic interactions | No |
| Cadherins | Homophilic interactions | Adherens junctions and desmosomes |

1. Interactions between proteins of the same kind (***hemophilic interactions***): e.g. In adherence junctions, the interaction is between two cadherin proteins.
2. Interactions between different types of proteins (***heterophilic interactions***).

Homophilic vs. heterophilic interactions




*u need only to know the difference not to remember the examples. ^^

# Selectin-mediated interaction between leukocytes and endothelial cells

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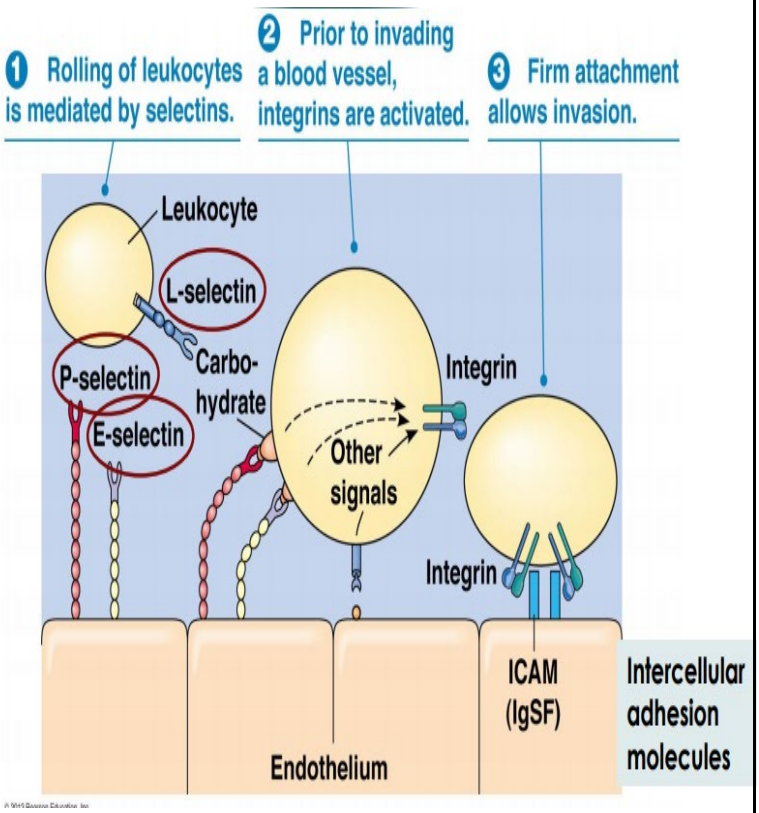
**Endothelial cells**: single cell layer that line blood vessels.

Leukocytes (white blood cell) are present in the blood circulation, but in case of Inflammation (can be caused by wound), they need to enter the tissue (extravasate). So, they are going to cross many layers including the endothelial layer of the blood until they reach the targeted site to **wound healing**.



This process starts by the interaction between the selectins present on the leukocyte surface (L-selectins) with a sugar molecule present on the surface of endothelial cells, and the selectins on the endothelium cell surface of blood vessels (simple squamous ☺) (E and P-selectins) interacting with sugar molecules on the leukocytes surfaces.

The actual extravasation process is mediated by an interaction between the integrins on the leukocytes and ICAM (part of the IG super family).
Once the ICAM and its substrate are in close proximity they bind together2 pulling the leukocyte inward between the cells. Then the leukocyte is able to move to the target site.

# Cadherins adhesion molecules

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υ **Selective** adhesion between embryonic cells and formation of stable junctions between cells in tissues.

***Classic cadherins***

υ E-cadherin: epithelial cells

υ N-cadherin: neural cells

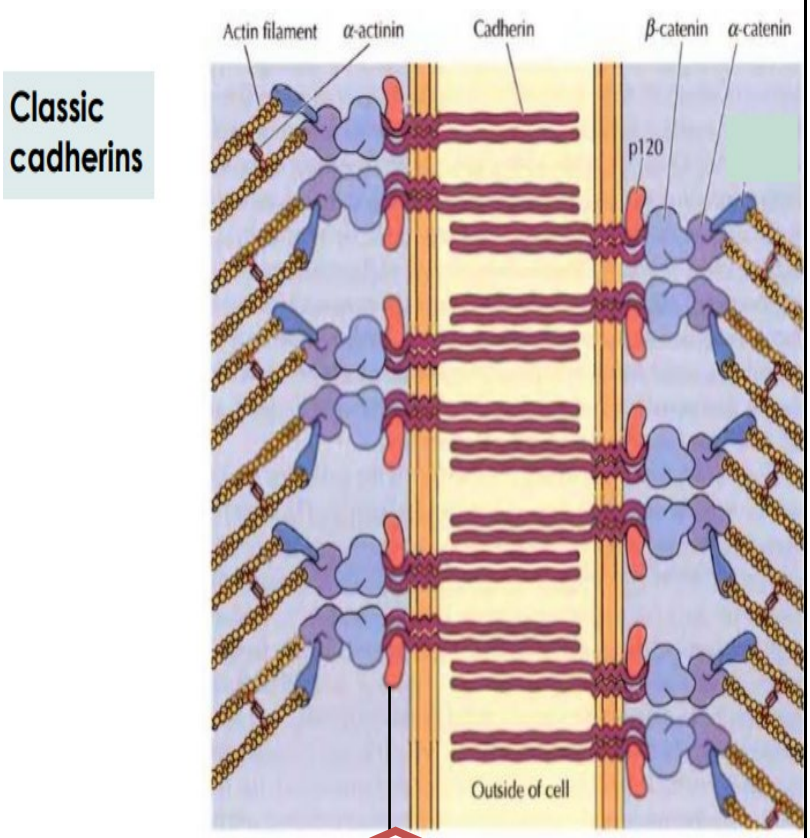
υ P-cadherin: placental cells

***Several subfamilies (non-classic)***

υ Desmosomal, fat-like and 7-Transmembrane cadherins.

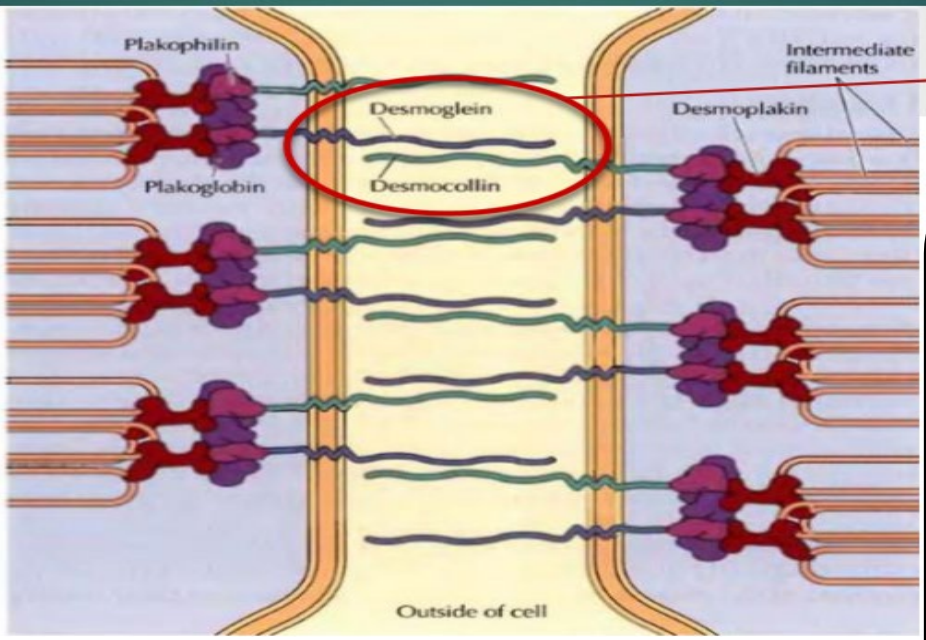
----- ***Several subfamilies (non-classic)*** They are different in characteristic and cell types.

---- ***Classical cadherins*** share structural characteristic although they found in different cell types.




Note that there are interactions with other proteins not to form (adhesion junction) but contribute to functions such as signaling (communication between cells)

# Desmosomes




**Desmosomal cadherins**

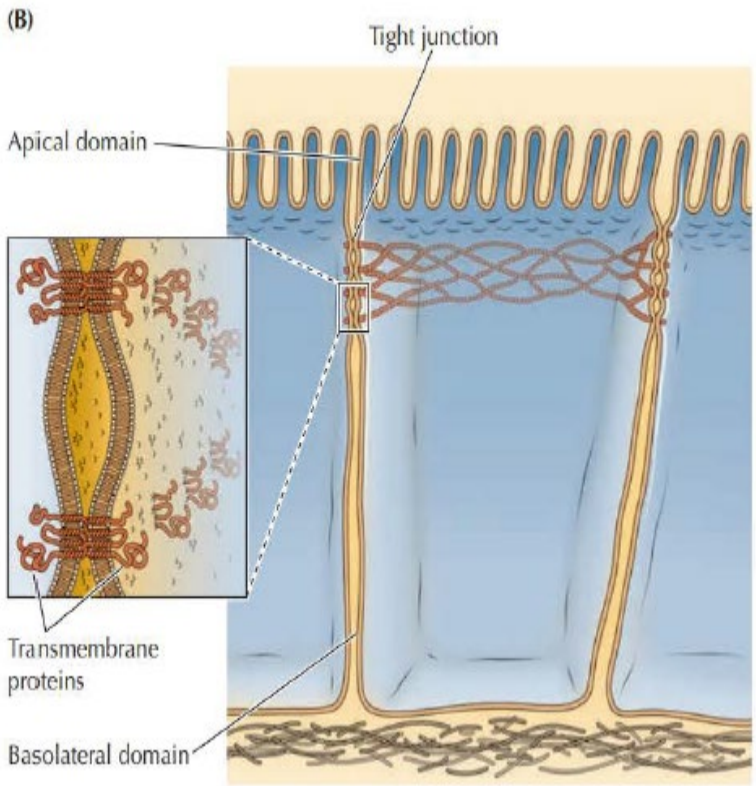
**heterophilic interaction**

What creates different types of Desmosomes?
Desmoplakin can interact with other types of protein such as plakoglobin, membrane proteins of different types and desmosomal cadherins of different types.

*This creates different types of desmosomes.

# tight junctions

From its name, it links the cells to each other in a way that makes it hard for the molecules to pass between those cells (impermeable).




υ A network of protein strands that continues around the entire circumference of the cell.

υ Each strand in these networks is composed of transmembrane proteins (claudins, occludin, and JAMs) that bind to similar proteins on adjacent cells (by connectors molecule that found in the cytoskeleton), thereby sealing the space between their plasma membranes.

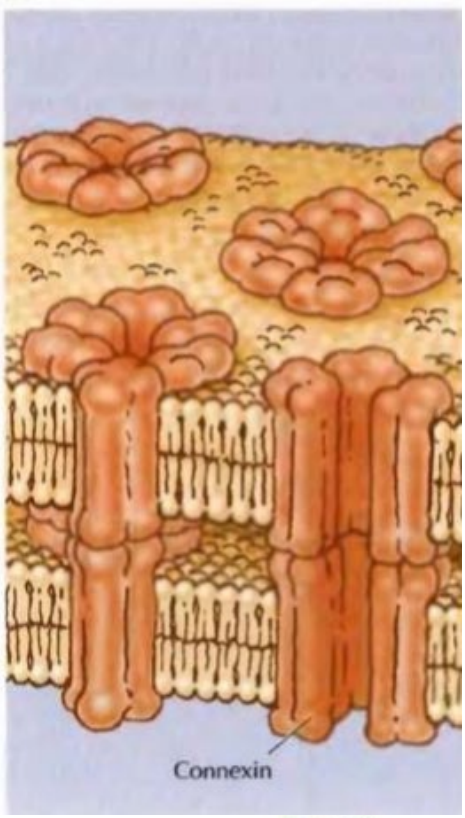
υ These proteins interact with the actin cytoskeleton via zonula occludens protein.

υ Separate the apical part from the basolateral part of membranes.

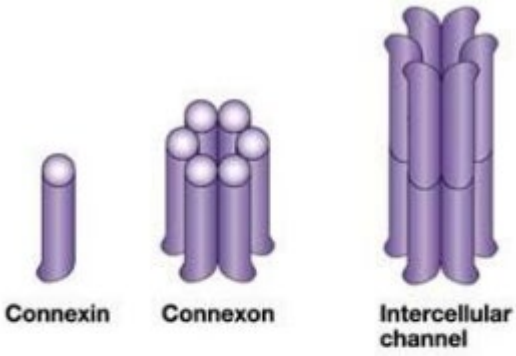
υ Prevent the passage of molecules (including ions) between epithelial cell.

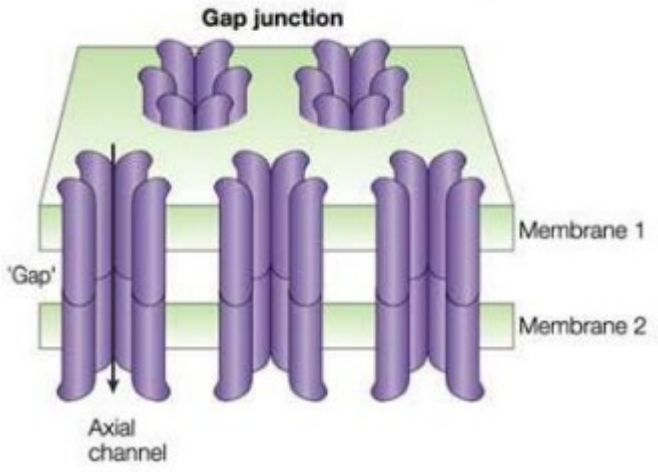
# Gap junctions

- They provide **direct connections** between the cytoplasms of adjacent cells as **open channels** allowing **limited movement of molecules** like ions and small molecules (<1000 Da) including signaling molecules between neighboring cells, but **preventing the passage of proteins and nucleic acids.**



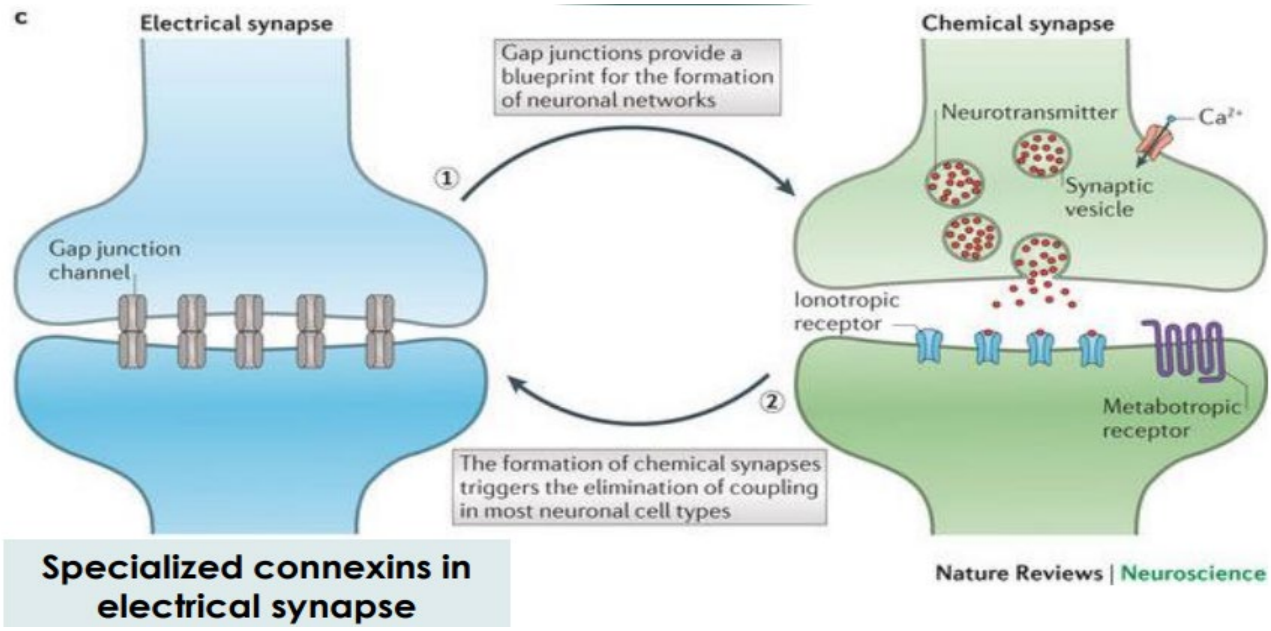

- Present in cells like epithelial cells, endothelia cells, cardiac cells and
smooth muscle cells.
- The two proteins that make up the gap junctions have extracellular domains.
-Those domains get in close proximity with each other, yet the plasma membranes of both cells are still not close to each other.
-This form a gap/ space between the two cells instead of them to be close to each other.
-This is why they're called gap junctions.
-Gap junctions are made of transmembrane proteins called **connexins.**
**-**Six connexins assemble to form a ***connexon*** (a cylinder with an open aqueous pore in its center).
**-** Two connexons (functional unit) on adjacent cells make a gap junction.



# Gap junctions and electrical synapses

During development and also in adulthood the synapses between neurons will develop. They start first by forming gap junctions that will act as blueprints that determine the future location of receptors on the post synaptic membrane of a neuron.




The pre-synaptic neuron on the other hand releases substances through vesicles and not through the gap junctions, **why?**

*An interaction or a stimulus is required for the stimulation of neuron rather than the continuous releasing of chemicals through gap junctions.

-Thus, the blueprinting of synapses is done by gap junctions.

-By changing the gap junctions, we are reducing the speed at which the signal is transmitted.

# Gap junction diseases

Mutations in different types of connexins result in many diseases such as:

- **Charcot-Marie-Tooth disease** (degeneration of peripheral myelinated nerves)
- **Deafness**: inability to rapidly exchange K+
- **Cataracts**: inability to obtain nutrients from the lens epithelial cells
- **Skin disease**