بسم الله الرحمـٰن الرحيم

(وَفَوْقَ كُلِّ ذِي عِلْمٍ عَلِيمٌ)

Cytology & Molecular Biology | Lecture 11

Cell-Cell Interaction

Written by : DST

Reviewed by : NST

Cell-cell interaction

Cell Adhesion Molecules

Receptors/adhesion proteins interaction Found in

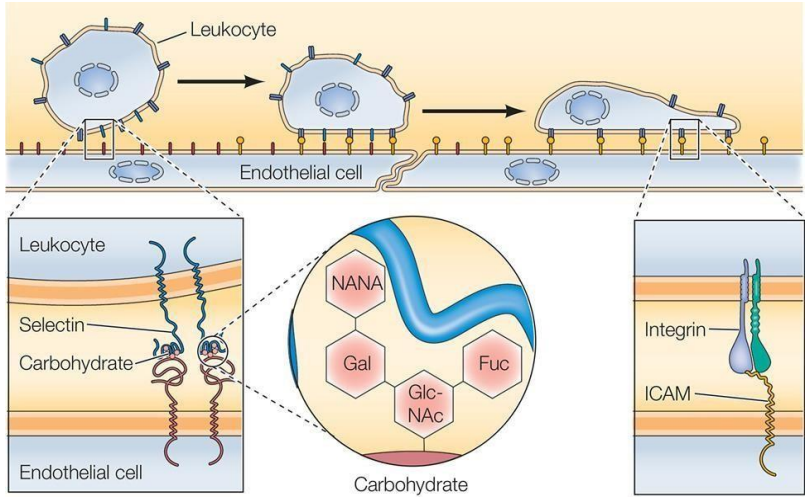
Family	Ligands recognized	Stable cell junctions
Selectins	Carbohydrates on the other cell line/cell type.	
Integrins	Extracellular matrix	Focal adhesions and hemidesmosomes
	Members of Ig superfamily	
Ig superfamily Ig=immunoglobulin	Integrins	
	Homophilic interactions can interact with each other(proteins from the same type).	
Cadherins	Homophilic interactions can interact with each other.	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.

On the endothelial cell surface

- The surface of the endothelial cells contains receptors and sugars.
- The carbohydrates on the endothelial cell surface are associated with transmembrane glycoproteins.



Further explanation regarding the previous slide:

- Initially, the **leukocytes** are swimming fast → then interaction happens between the **selectins** on the surface of the leukocyte and the **carbs** on the surface of the endothelial cells → so the **leukocytes** slow down → then another interaction takes place between the **integrins** on the surface of the leukocytes and the (**ICAMS**) on the surface of the endothelial cells.

- Note: all of these interactions are **heterophilic** (interactions between different types; selectins and carbs).

- Once this interaction takes place and **leukocytes stop**, they can **extravasate(**leave the vessels and move between the endothelial cells into the tissue to perform the function).

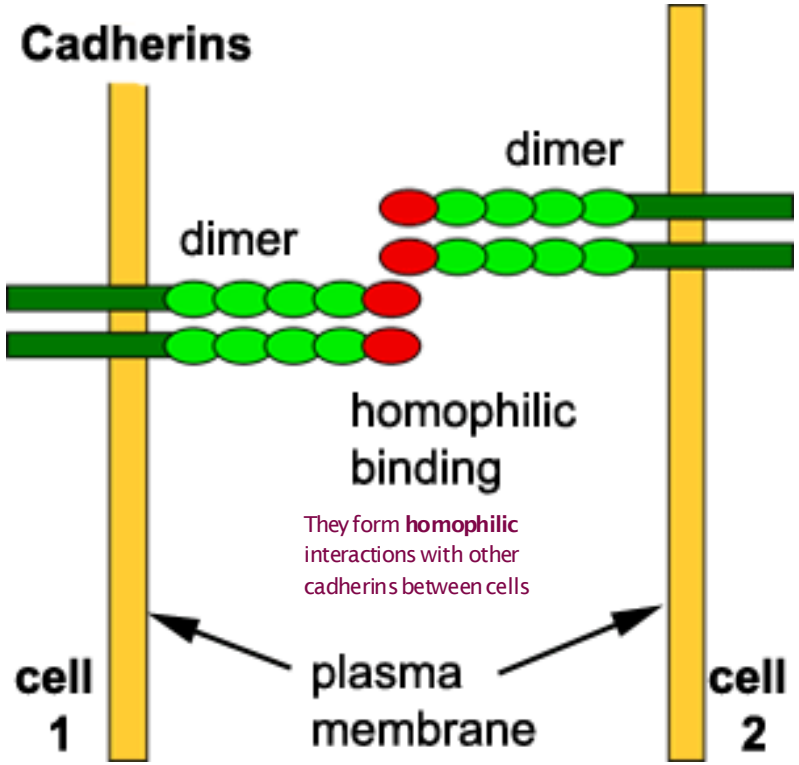
Cadherins

Cadherins interactions take place throughout development and throughout our life, so they are physiologically important.

- Cadherins are involved in selective adhesion
  - between **embryonic** cells **(development and differentiation)**
  - the formation of specific **synapses** in the nervous system,
  - for the maintenance of stable junctions between cells in tissue, they form(**adherens junctions and desmosomes**).
- Classic cadherins
  - **E**-cadherin: **e**pithelial cells
  - **N**-cadherin: **n**eural cells
  - **P**-cadherin: **p**lacental cells

Other types

- Desmosomal cadherins
- 7-Transmembrane cadherins



The importance of **E-cadherins**:

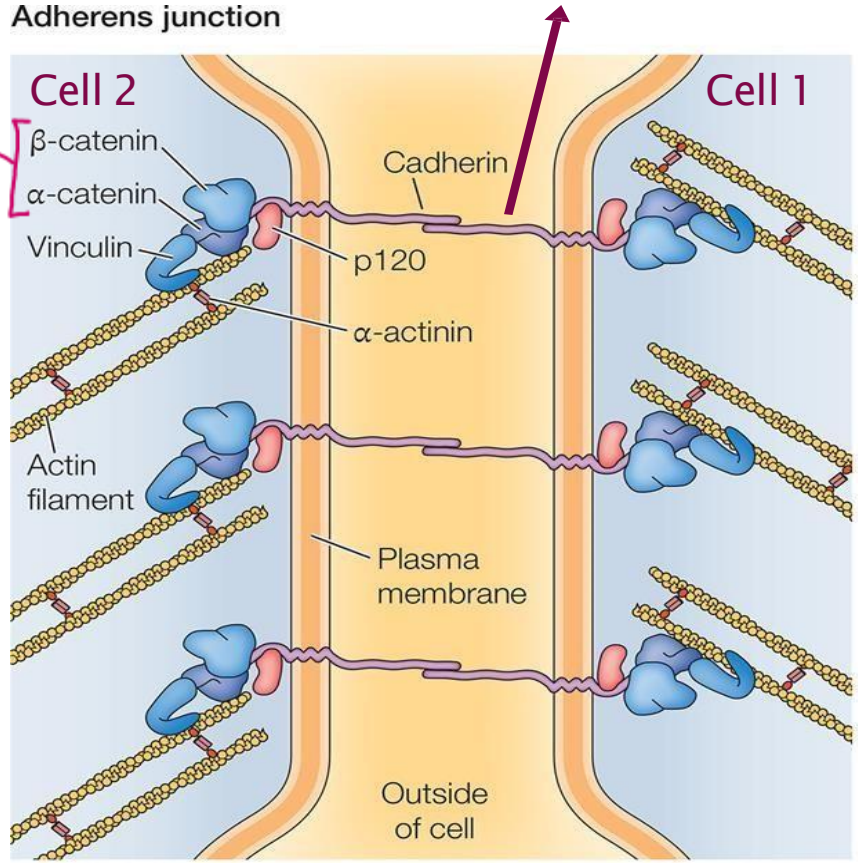
Connects epithelial cells together and stabilize them in place so they don't move, once they lose this interaction, they become mesenchymal like they become elongated and motile.

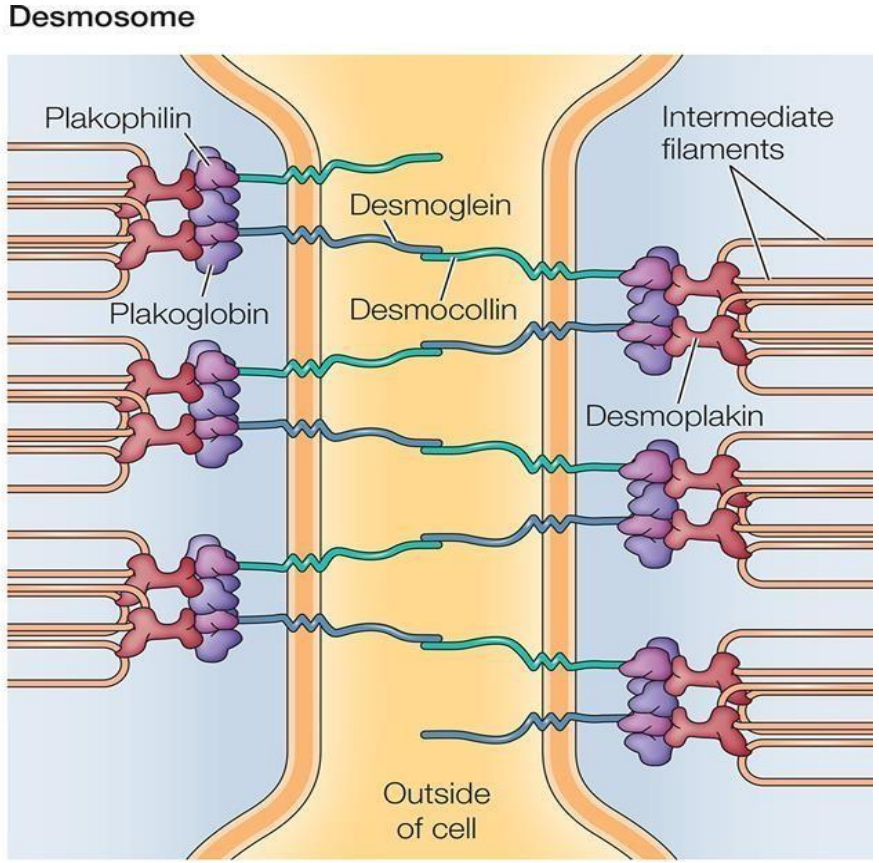
What happens in **cancer**(tumor mass) is that cells are interacting with each other(they aren't moving) they remain in their place and this is called **carcinoma** in situ(a tumor mass locked in place), but once they loose E-cadherins they become mesenchymal like, migrate and **metastasi**(Cancer that spreads from where it started to a distant part of the body).

Adherens junctions

Cadherin-cadherins interaction (**homophilic interaction).**

Catenins are one of the bio markers for cancer development.



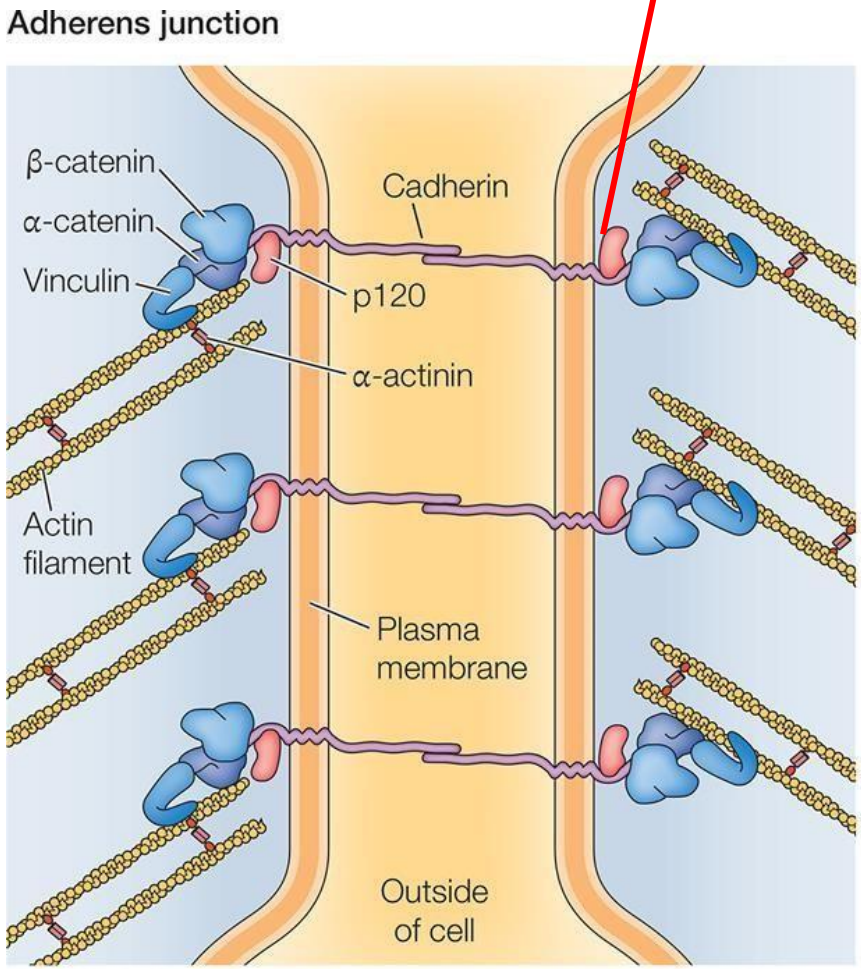


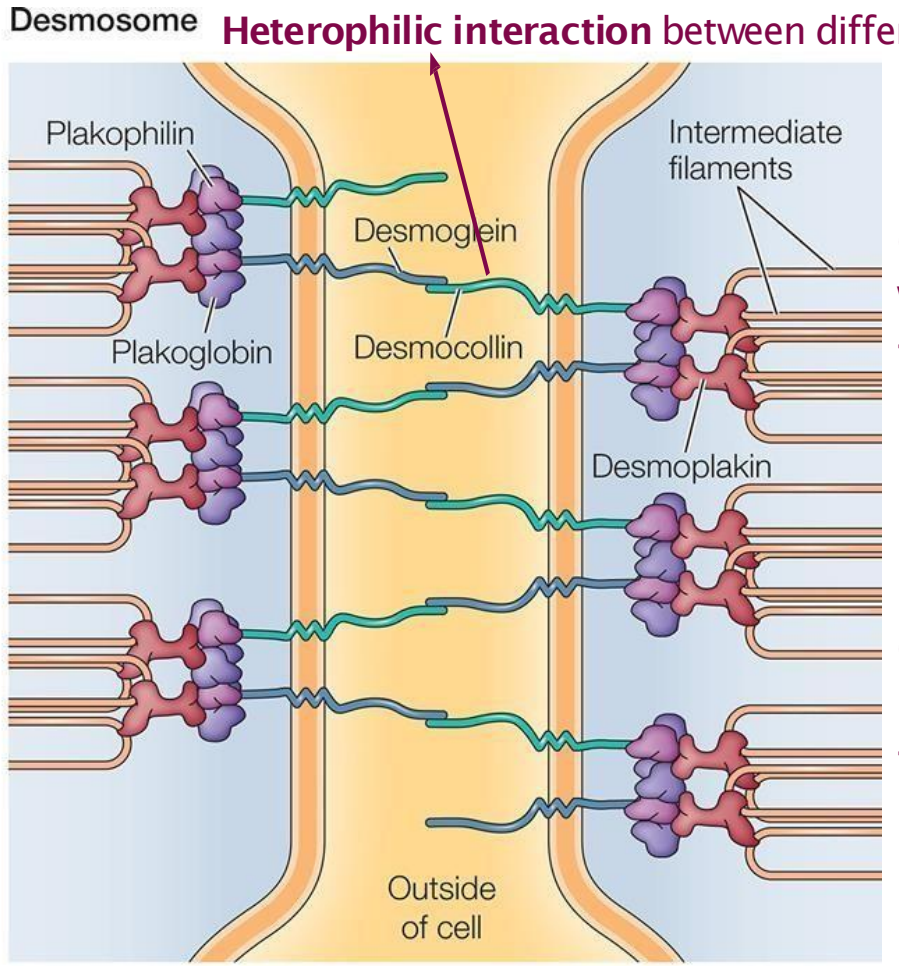
In **adherens junctions**, cadherins link the actin filaments of one cell to the **actin filaments** of an adjacent cell.

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

Further explanation regarding the previous slide:

The **cytosolic side** of the cadherin interacts with the catenins and actin binding proteins and these proteins interact with actin itself. Note from the image that cadherin connects the actin filaments of 2 neighboring cells.

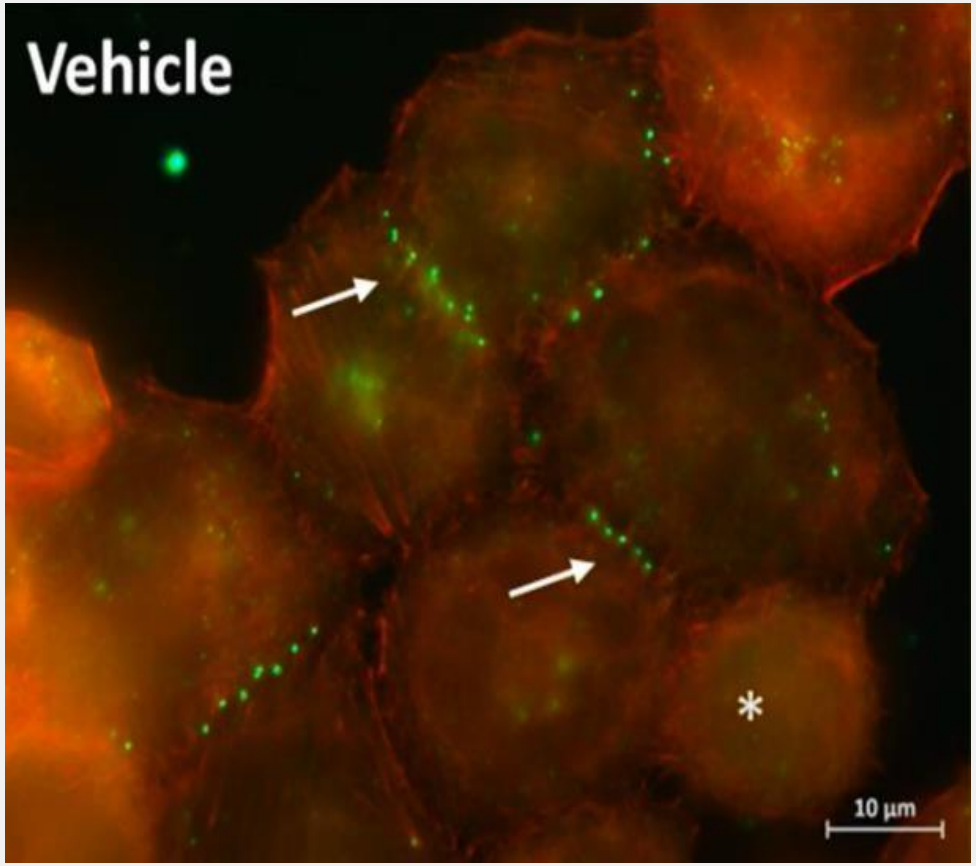


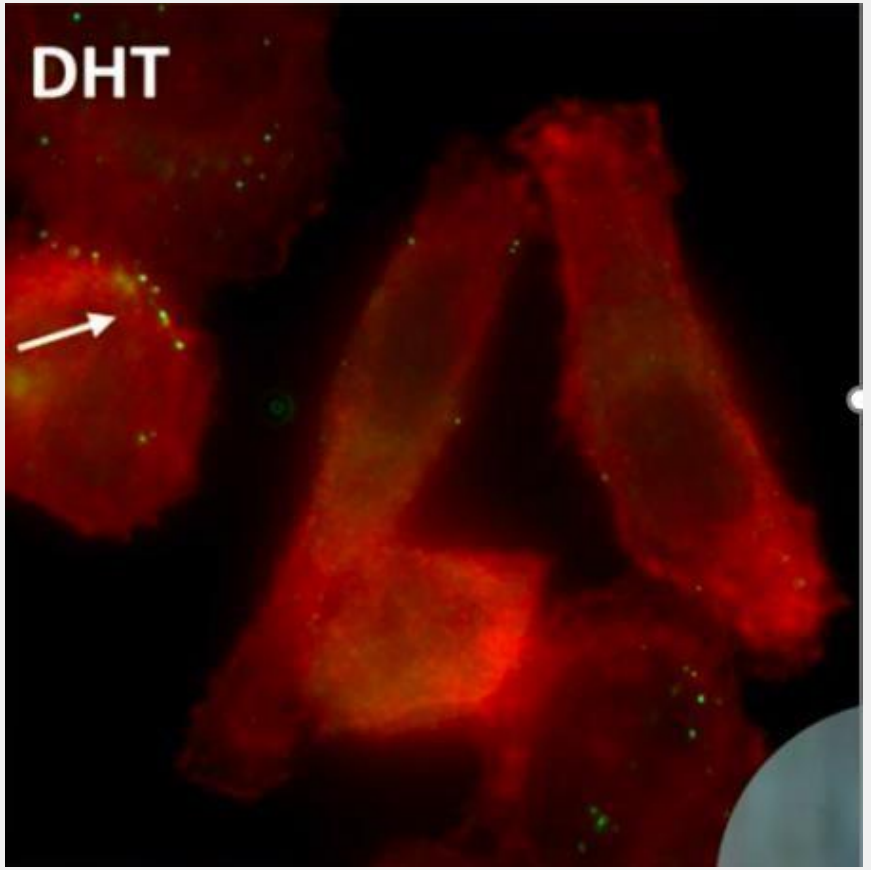


Heterophilic interaction between different desmosomal cadeherins.

Desmosomal cadherins (desmogleins and desmocollins) interact with intermediate filaments mediated by intermediate filament binding proteins.

Note from the image that desmosomal cadherins links the intermediate filaments of the 2 neighboring cells.

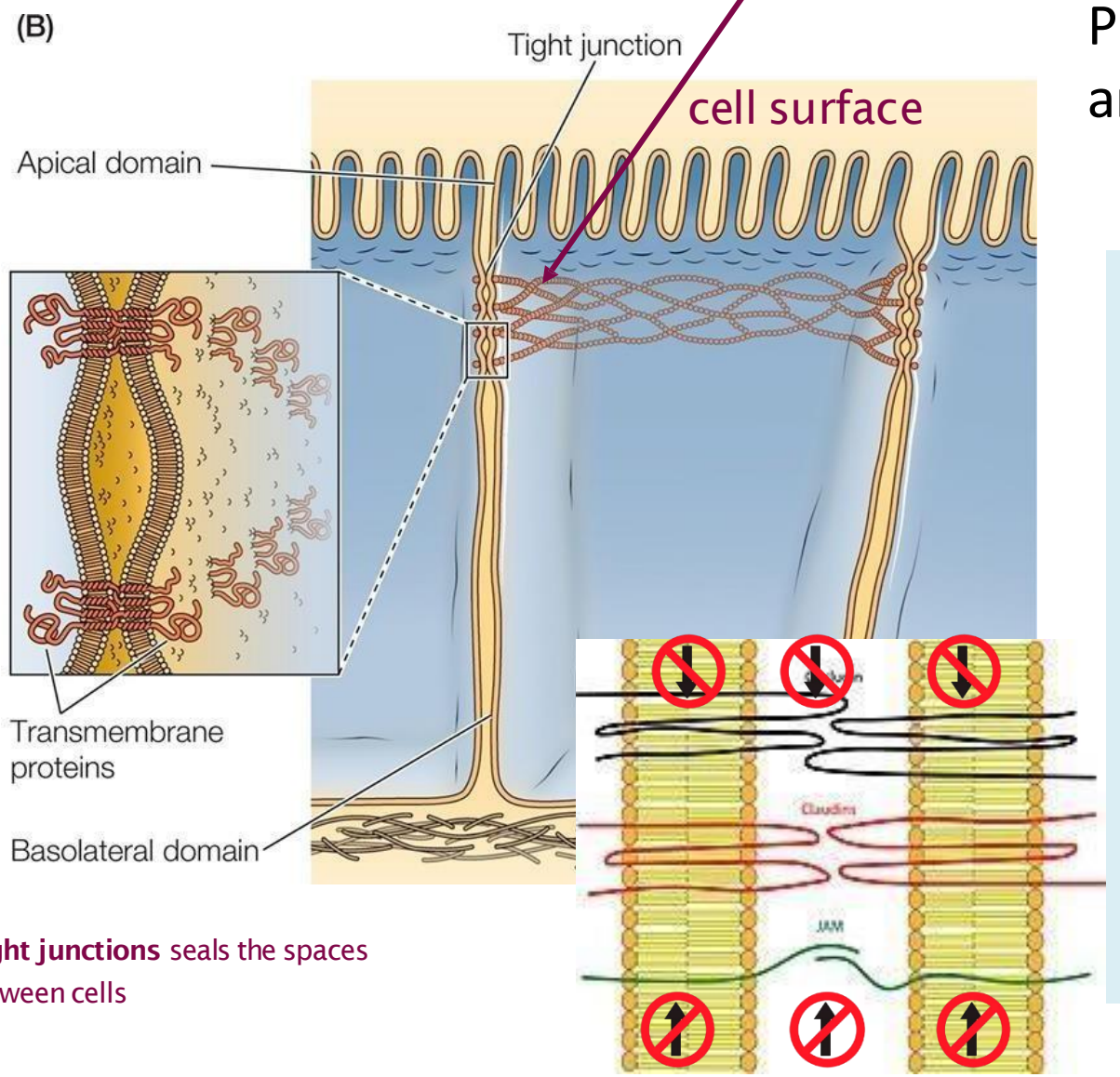




This slide is **not** required.
Watch the explanation of it for further understanding CLICK HERE.

Tight junctions

Strong, belt-forming interactions between proteins beneath the cell surface of adjacent cells.



Tight junctions seals the spaces between cells

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

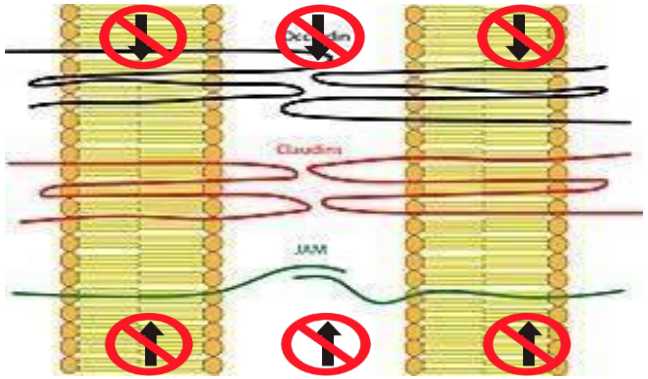
An example of a **tight junction protein**:

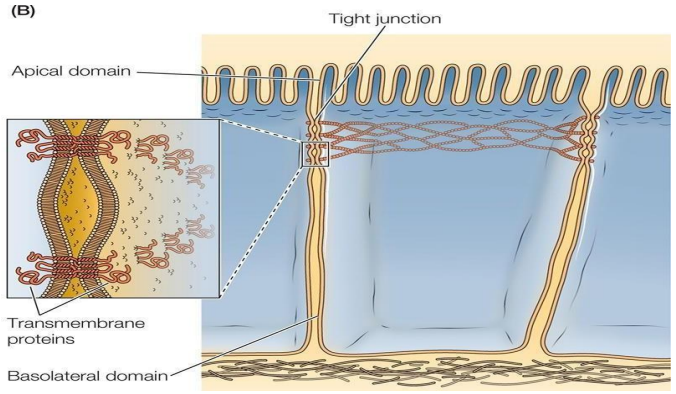
Claudin:

This protein can be associated with a cancer named: **Claudin-low breast cancer (**low expression of claudin) which is characterized by being **mesenchymal-like** (motile and elongated) with **low E-cadherin expression.**

Patients have **poor survival** (aggressive cancer) and **poor prognosis** (bad outcome; Death), **metastasis**, and younger age of onset.

Purposes of Tight Junctions:





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. Nothing in the lumen can pass to the basolateral surface.

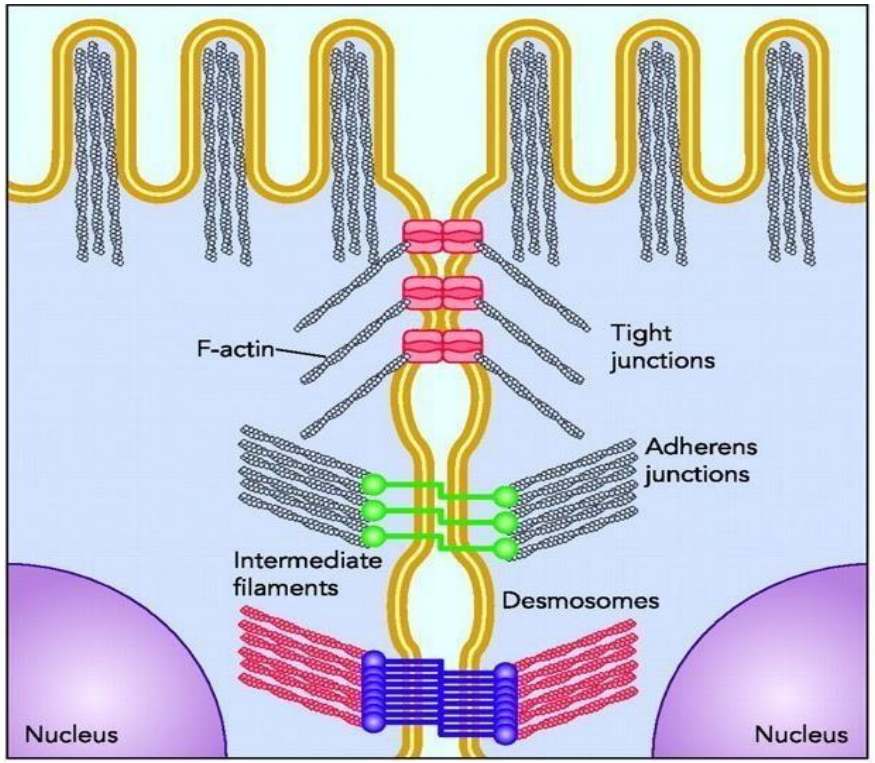
2. Separation of the apical and basolateral domains <u>inside</u> the cells:

Each surface (apical and basolateral) has distinct proteins. And since proteins are **dynamic** and move within the membrane, tight junctions act as **barriers** to keep apical proteins on the apical side and basolateral proteins on the basolateral side.

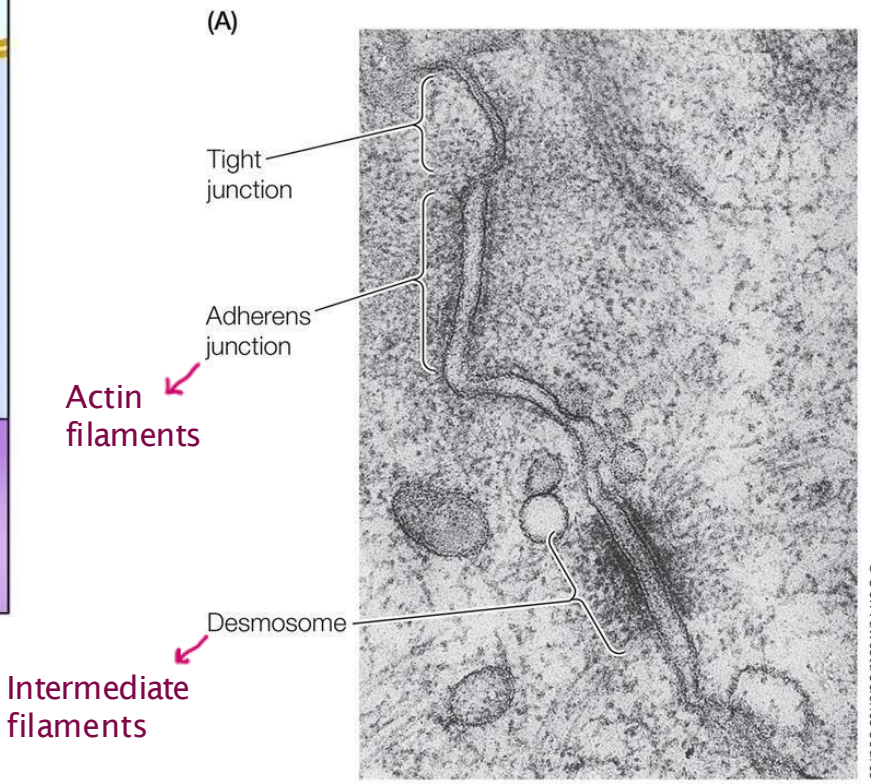
Tight junctions vs. adherens junctions vs. desmosomes

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

It's common to find them **all together.**



This is an image taken by an electron microscope (EM), showing different cell-cell junctions. Notice their order (Apically to basolaterally), tight are more apically and desmosomes more to the basement just as what we took in histology.

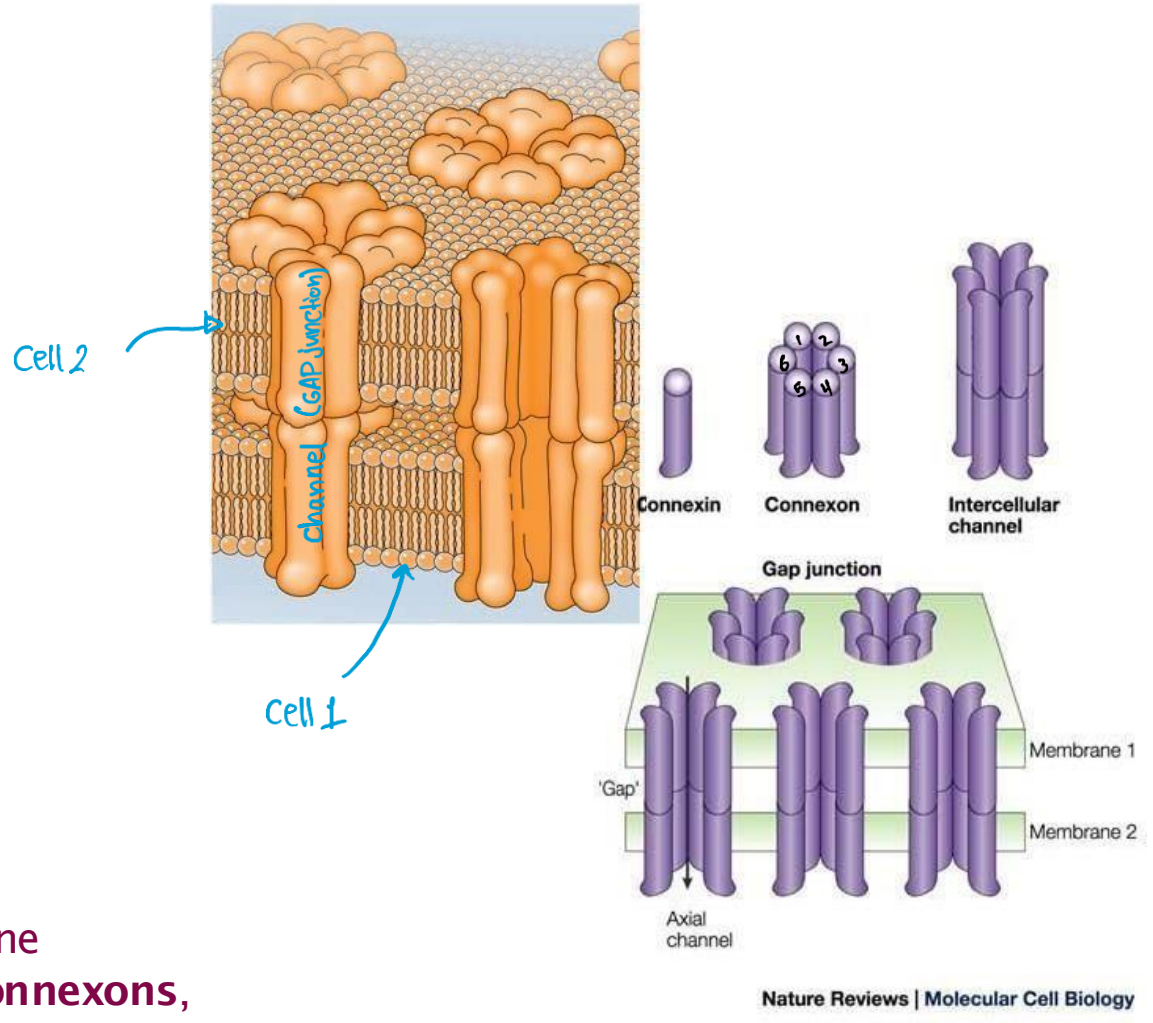


Gap junctions

Basically **channels** connecting 2 cells.

6 connexins = 1connexon
2 connexons (one from each cell) **= 1channel (Gap junction)**

- 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; entering from one cell and exiting into the other.
- **Connexons** are made of six transmembrane proteins (out of 21)called **connexins**.

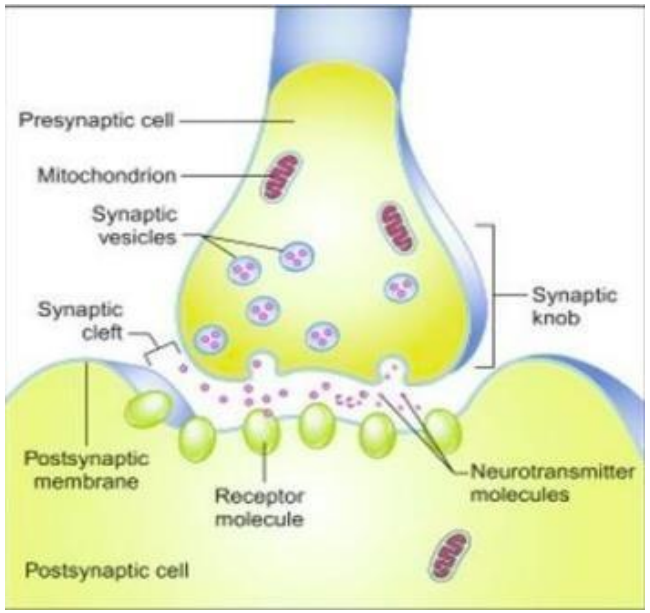


There are 21 different types of **connexins**, which are transmembrane proteins. These connexins can combine in various ways to form **connexons**, the structural units of **gap junction channels.**

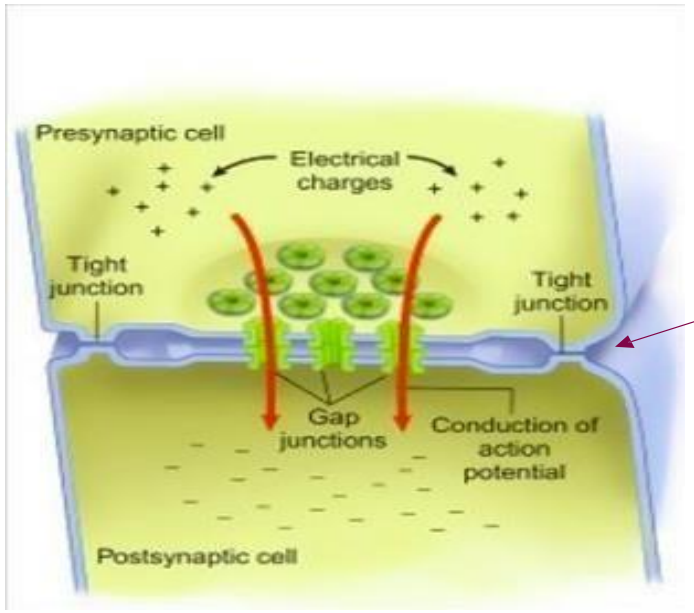
Interestingly, connexons can be homomeric, containing the same type of connexins, or heteromeric, with different types of connexins, allowing for a variety of channel properties.

Specialized connexon = electrical synapse (in Nerve cells)

A presynaptic cell can transmit a signal by either:



OR



Notice how tight junctions prevent passage by making a barrier.

A) Producing **neurotransmitters** that are then secreted by **exocytosis** into the synaptic cleft and bind to **receptors** on the postsynaptic membrane transmitting the signal (initiating a postsynaptic potential).

B) Through specific/ specialized **gap junctions**; as electrical charges can pass through them to the postsynaptic cells transmitting the signal.

Diseases caused by defective gap junctions and mutated connexins

Hereditary deafness can result from mutations in connexins, which disrupt cellular communication essential for hearing.

- Marie-Charcot-Tooth disease
- Deafness
- Skin disorders
- Cataracts

- **Although connexons are found in many tissues, only a limited number of tissues are affected.** For example, connexins in a tissue could be defective but on another one it is not; **Why?**
  - **Compensations by other connexins;** some tissues have the ability to compensate the connexin if it get down regulated or not expressed, while others doesn't.
  - **Requirement by affected tissues of a specific combination of connexins;** some tissues require a specific type of connexins while others don't need it; as it doesn't play a major role and doesn't provide a strong functional purpose.
  - **Mutations may affect proper assembly in the Golgi apparatus and/or export to the plasma membrane.**

The effects of a mutation depend on the specific **connexin** involved. A mutation in one connexin can disrupt the formation of **functional gap junctions and connexons** within a cell, leading to the accumulation of connexins in the Golgi apparatus instead of their proper integration into the membrane.

To sum up (CELL-CELL interactions):

There are various ways in which cells interact with each other and with their surrounding environment;

1) **Focal Adhesions:** where integrins bind to actin filaments within the cell and bind to the extracellular matrix.

2) **Hemidesmosomes:** in which specific proteins interact with integrins and are anchored to intermediate filaments, enhancing cell adhesion.

3) **Tight junctions:** which seal the space between cells.

4) **Adherens junctions:** in which cadherins form homophilic (like-with-like) bonds between cells and bind to actin filaments.

5) **Desmosomes:** in contrast to adherens junctions, link cells via desmosomal cadherins that bind to intermediate filaments and provide strong structural support.

6) **Gap junctions:** facilitate direct communication between cells by allowing small molecules and ions to pass freely between adjacent cells.

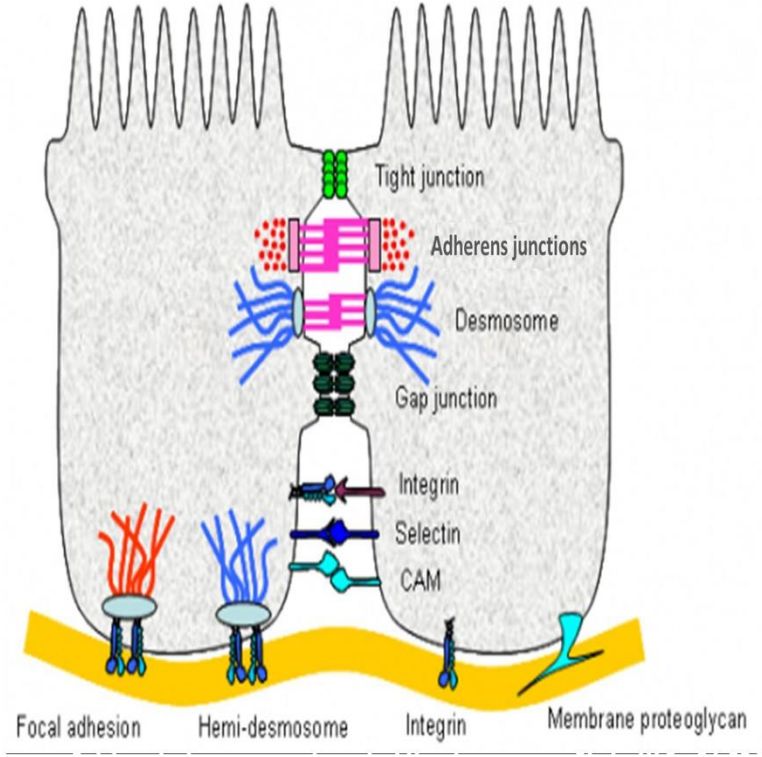


Table Attached by the Doctor

Junction	Tight Junction (Zonula Occludens)	Adherent Junction (Zonula Adherens)	Desmosome (Macula Adherens)	Hemidesmosome	Gap Junction (Nexus)
Major transmembrane link proteins	Occludins, claudins, ZO proteins	E-cadherin, catenin complexes	Cadherin family proteins (desmogleins, desmocollin)	Integrins	Connexin
Cytoskeletal components	Actin filaments	Actin filaments	Intermediate filaments (keratins)	Intermediate filaments	None
Major functions	Seals adjacent cells to one another, controlling passage of molecules between them; separates apical and basolateral membrane domains	Provides points linking the cytoskeletons of adjacent cells; strengthens and stabilizes nearby tight junctions	Provides points of strong intermediate filament coupling between adjacent cells, strengthening the tissue	Anchors cytoskeleton to the basal lamina	Allows direct transfer of small molecules and ions from one cell to another

QUESTIONS.

i) Which of the following filaments bind to the cadherin and catenin complex?
A) Myosin
B) Actin
C) Globulin
D) Albumin

ii) Which of the following protein is present in large amount in tight junctions?
A) Albumin
B) Globulin
C) Claudin
D) Elastin

iii) Which of the following types of junctions have protein that extends from one cell to another, thus "attaching" one cell to the other?

A) Gap junctions

B) Tight junctions

C) Desmosomes

iv) In the leukocyte-endothelial cell interaction, which molecule plays a crucial role in the initial "rolling" phase, and what type of interaction does it use?

A) Integrins; heterophilic interaction with ICAMs

B) Selectins; heterophilic interaction with carbohydrates

C) Cadherins; homophilic interaction with adjacent cells

D) Gap junctions; homophilic interaction with connexins

V) Which of the following best explains how loss of E-cadherin expression can contribute to cancer metastasis?

A) E-cadherin normally facilitates integrin binding to the ECM, and its loss leads to cell migration.

B) E-cadherin connects epithelial cells, stabilizing them; loss allows cells to become motile and invasive.

C) Loss of E-cadherin activates immune response, causing cancer cell spread.

D) E-cadherin mutations lead to loss of cell polarity, promoting angiogenesis and metastasis.

ANSWERS.

i) The answer is B.

The main function of adherens junction is to connect its cytoplasmic side with the actin filaments. The cadherins and catenin protein complex binds to the actin filaments.

ii) The answer is C.

iii) The answer is C.

iv) The answer is B.

v) The answer is B.

رسالة من الفريق العلمي:

اللهم يا رحيم، يا ناصرَ المستضعفين،
نسألك برحمتك الواسعة أن تحفظَ أهلَنا في غزّةَ والسودان،
اللهم كُن لهم ناصرًا ومعينًا،
اللهم ارفع عنهم البلاء، واجبر كسرهم، وآمِن روعَهم،
واشفِ جريحهم، وارحمْ شهداءَهم،
اللهم أنزِل عليهم سكينتَك، وبدّل خوفَهم أمنًا،
اللهم سخّر لهم من عبادِك من يمدّ لهم يدَ العَونِ والرحمة، اللهم احفظ أطفالَهم ونساءَهم وشيوخَهم من كلّ سوءٍ ومكروه،
اللهم عجّل بفرجِك ونصرِك، وكُنْ لهم وليًّا ونصيرًا يا ربَّ العالمين.

For any feedback, scan the code or click on it.

Corrections from previous versions:

Versions	Slide # and Place of Error	Before Correction	After Correction
V0 → V1	Slide 17		Table Attached by the Doctor
V1 → V2			