Cell Junctions : structure & role

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Contents

Plasma Membrane

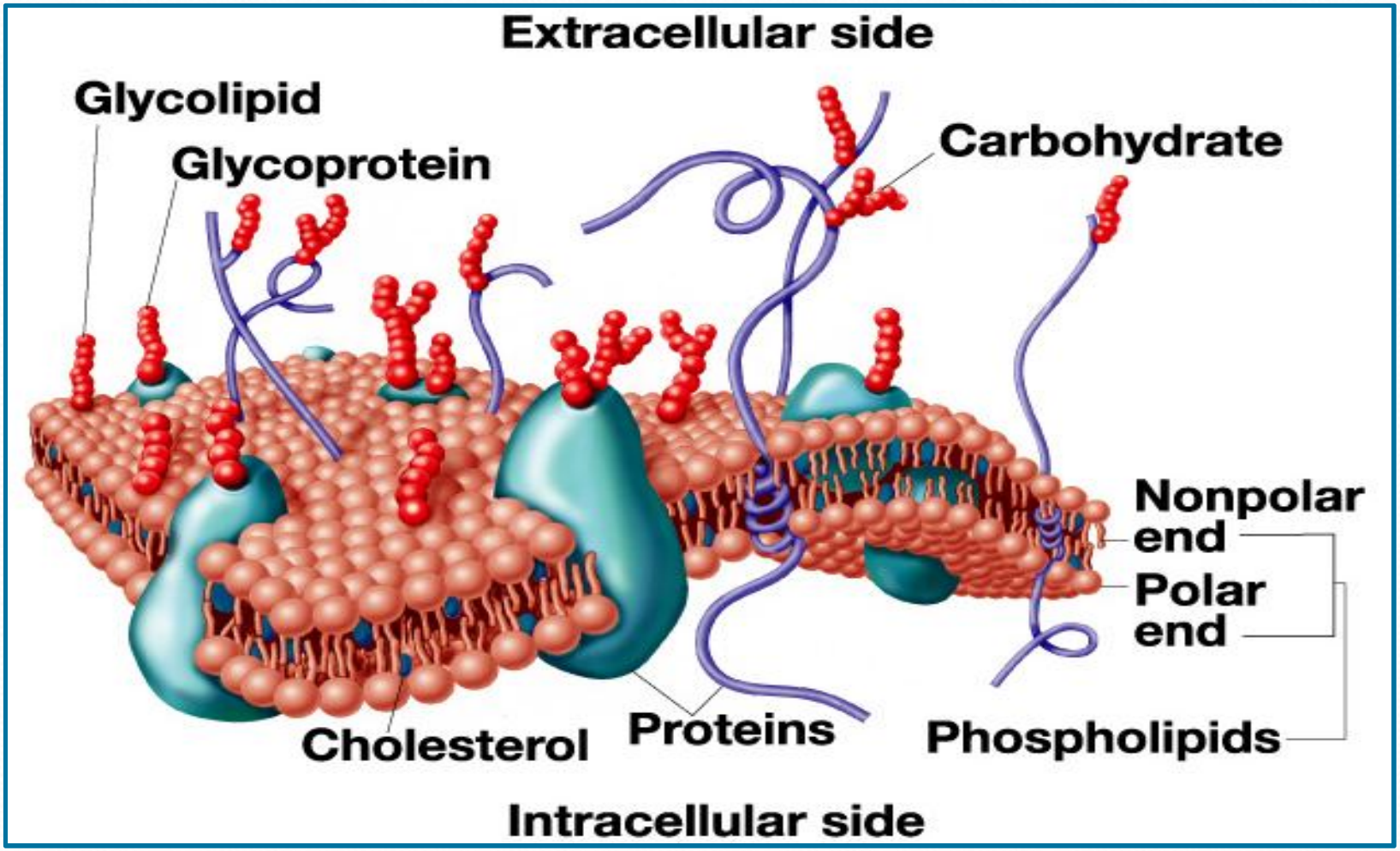
- **Definition:**

  The Plasma membrane is a thin bi- layered structure which surrounds each cell, consists of lipids (phospholipids 75%, cholesterol 20%,glycolipids 5%), proteins (partially or completely embedded), carbohydrates etc.,

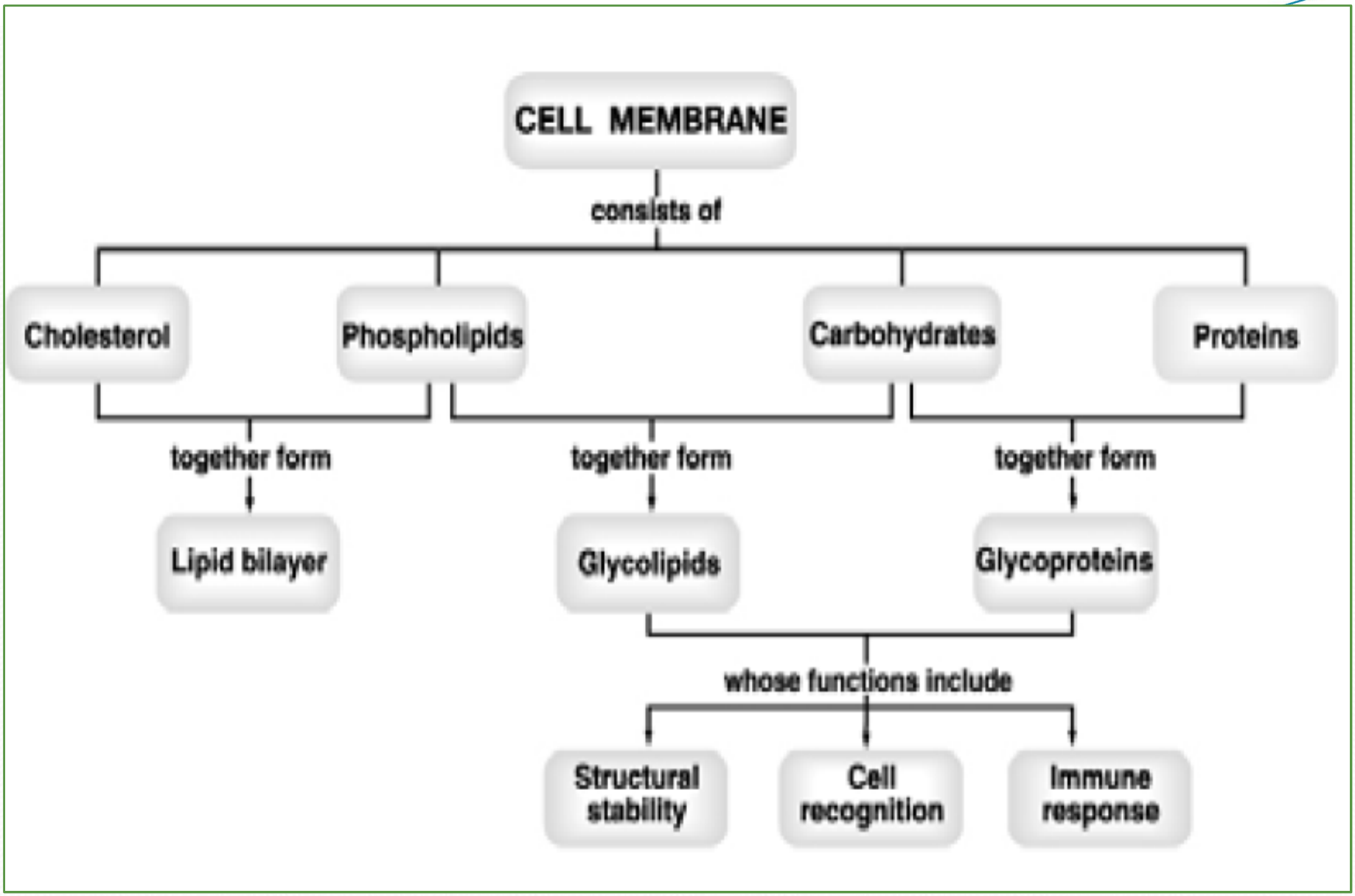
- It is usually 6-10 nm thick.

- It is always asymmetrical.

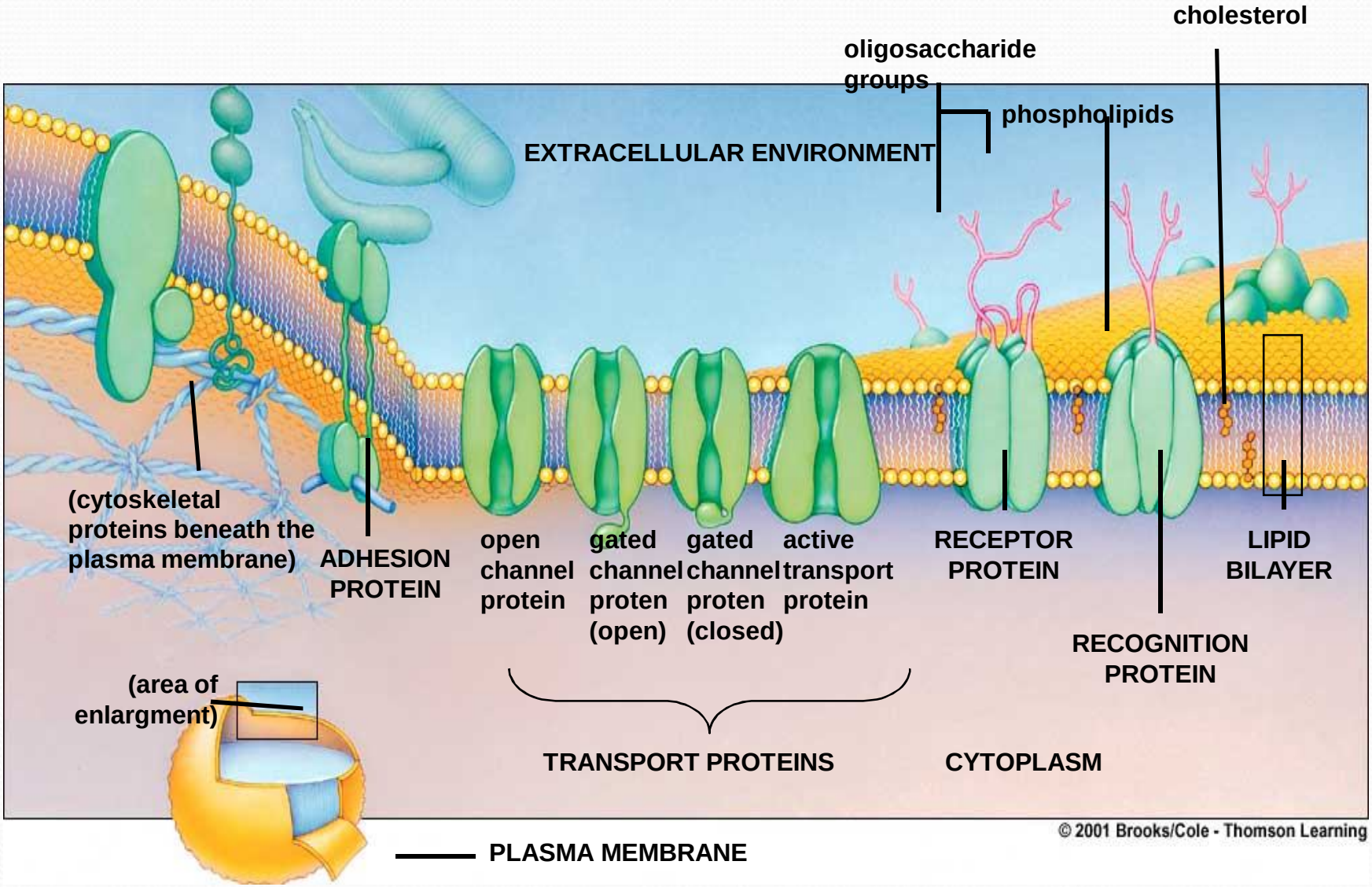
Plasma membrane structure



Plasma Membrane: composition

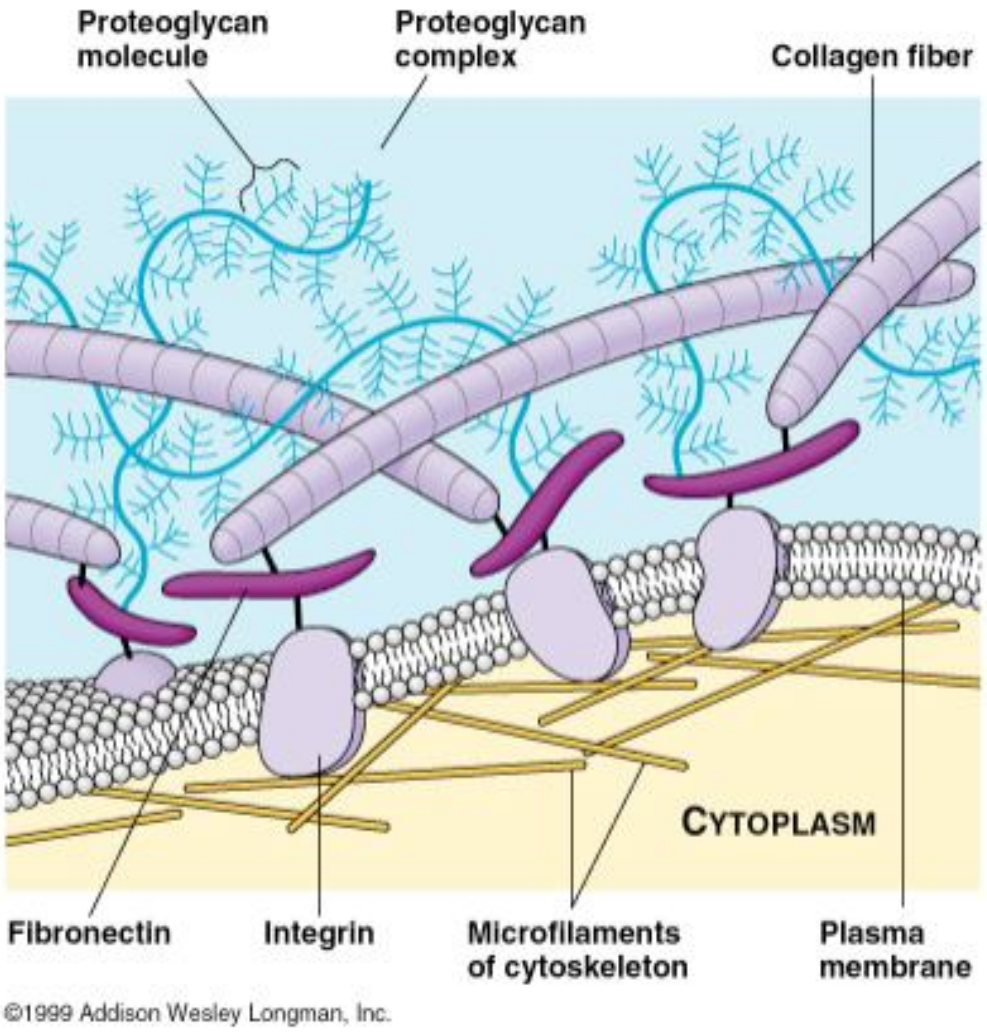


Proteins of Plasma Membrane



Extracellular matrix (ECM)

- Many animal cells are intrinsically linked to other cells and to the **extracellular matrix** (ECM).
- The ECM fills the spaces between cells and tissues together.
- Bone and cartilage are mostly ECM plus a very few cells. ECM is most abundant in Connective tissue, that surrounds glands and blood vessels, is a gelatinous matrix containing many fibroblast cells.
- The ECM contains three classes of molecules:
  1) Structural proteins (collagens and elastins);
  2) Protein-polysachharide complexes (proteoglycans)
  3) Adhesive glycoproteins to attach cells to matrix (fibronectins and laminins),



- Many types of glycoproteins
  - Form branched complexes
- Fibronectins act as docking site
  - Bound to Integrins
- Integrins(transmembrane proteins) and are bound to cytoskeletal filaments

Role of ECM

- Gives tissue stability by linking areas of cells together
- Allows communication between cells
- Fibronectin and integrins are involved in signal sending and receiving

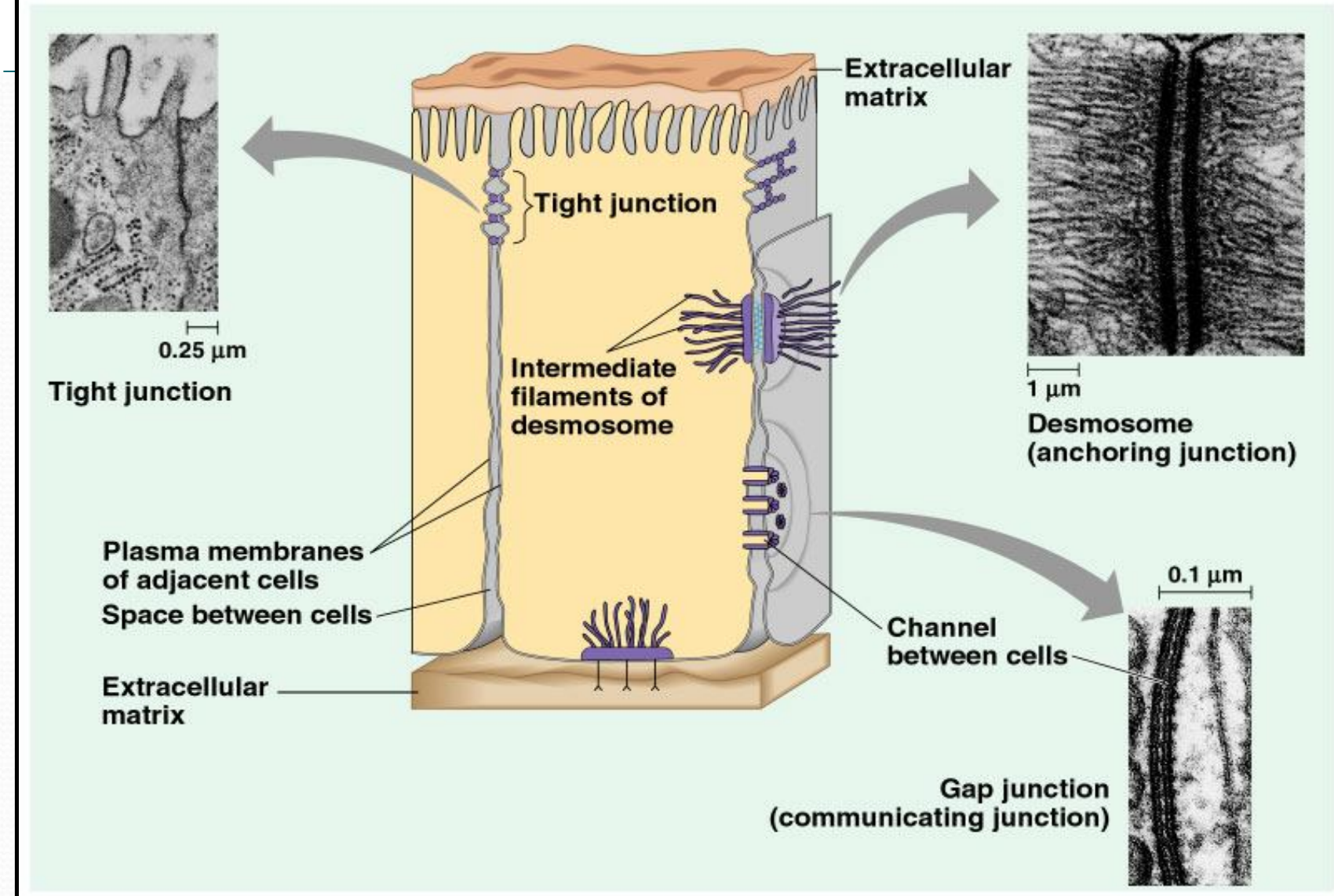
Cell junctions

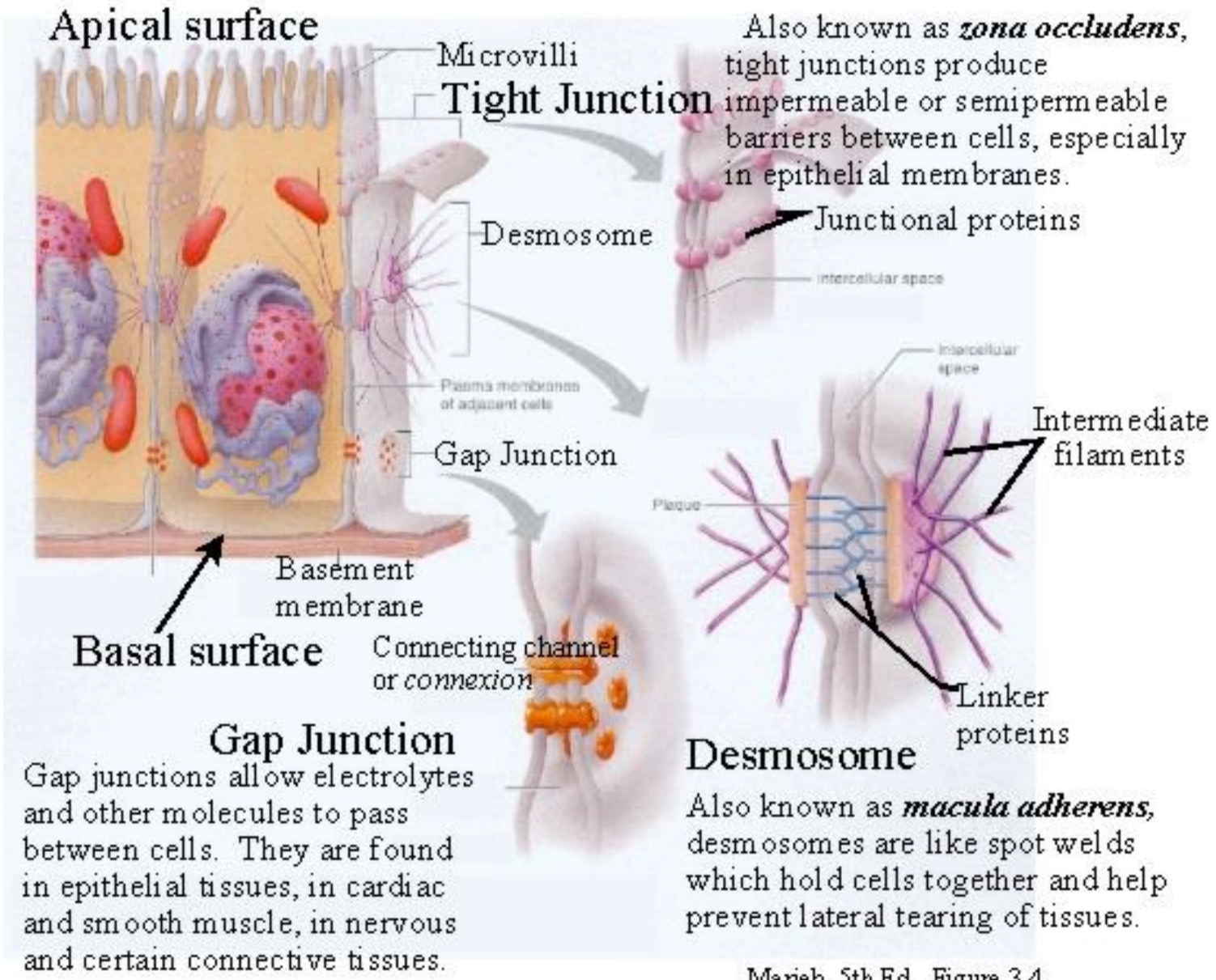
Definition

- *" Cell junctions are the contact points between the plasma membranes of tissue cells"*

- **i.e. Plasma membrane areas are specialized to provide contact between cells.**

- **Dense clusters of cell adhesion molecules (CAMs) on the outside linked to cytoskeleton on the inside through adapter proteins.**



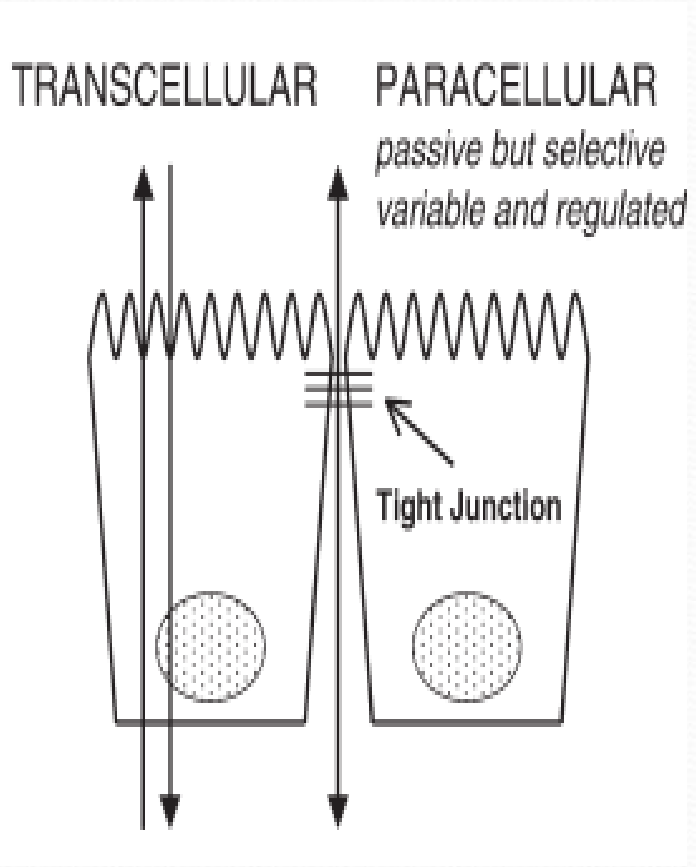


Marieb, 5th Ed. Figure 3.4

Transport across epithelial cells

Paracellular Pathway

- Transport is only passive driven by the gradients
- This physiological barrier exists to provide protection from the entry of toxins, bacteria,and viruses from the apical side to the basolateral side, and it allows the passage of selective molecules.



Transcellular Pathway

- Transport is both active & passive
- Transport is directional, energy dependent, and governed by the cell- specific profile of *transporters & channels* positioned on the apical & basolateral cell membranes.

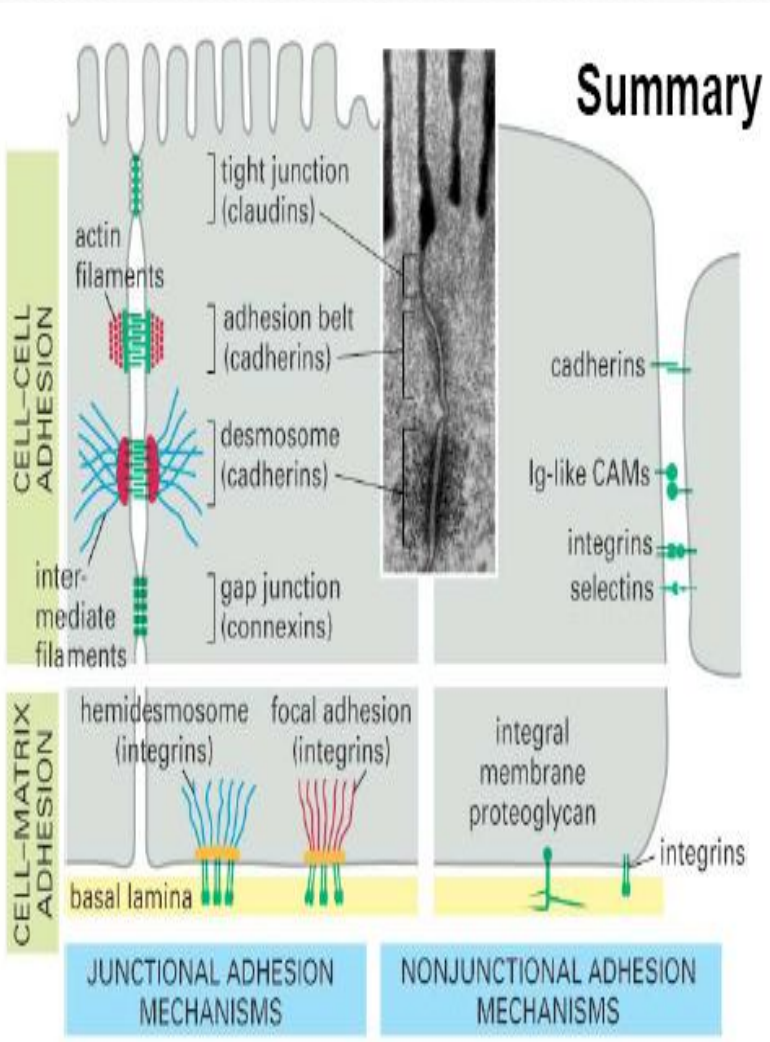
Cell junctions
(based on localization)

Between cells

- ***Tight junctions***
- ***Adherens junctions***
- ***Desmosomes***
- ***Gap junctions***

Between cells and matrix

- ***Hemidesmosomes***
- ***Focal adhesions***



Cell junctions
(based on function)

Occluding junctions

-Tight junctions

-Adhering junctions

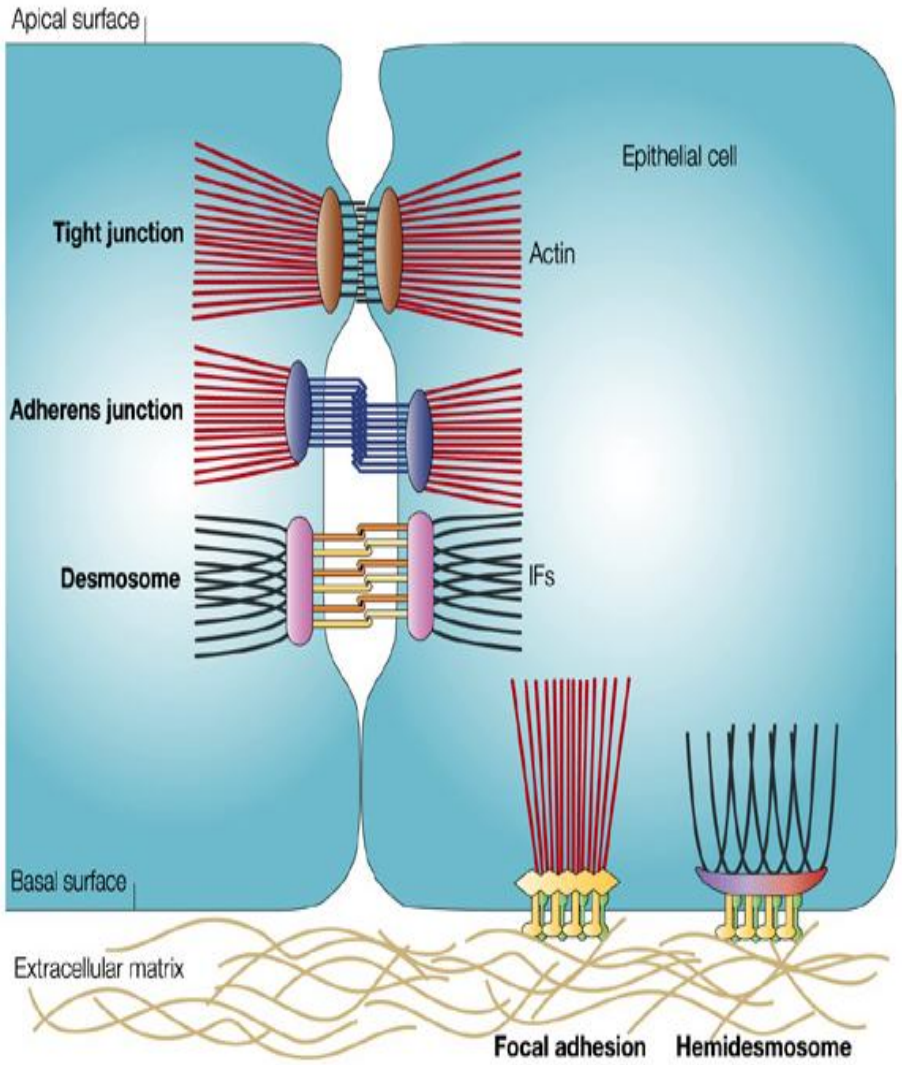
- Adherens junctions

- Desmosomes

- Hemidesmosomes

Communicating junctions

- Gap junctions

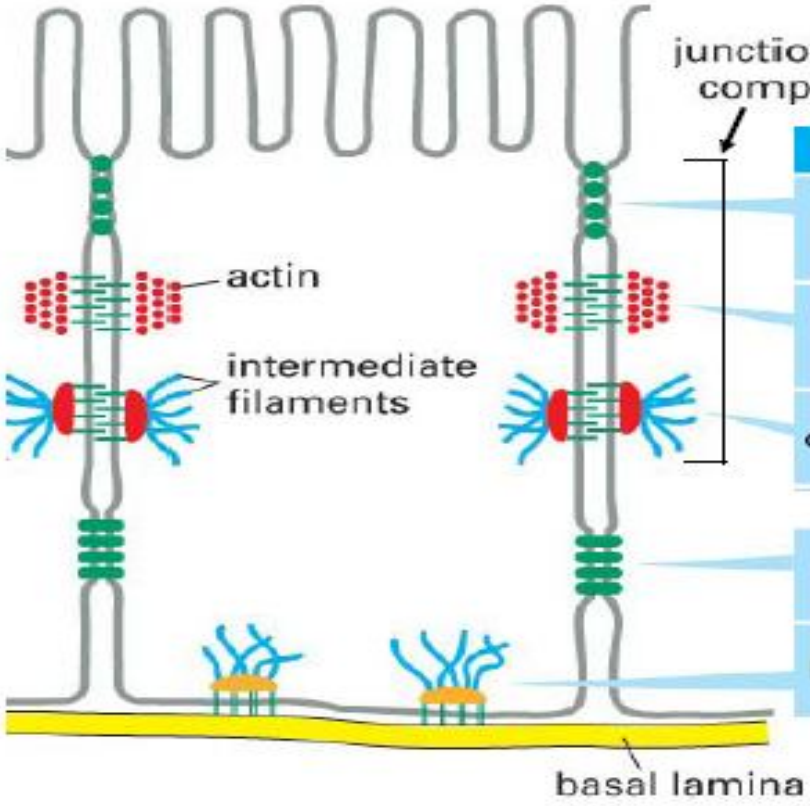


Functions of cell junctions

Cellular Junctions

Location
Function

Each junction consists of specific set of adhesion proteins



name	function
tight junction	seals neighboring cells together in an epithelial sheet to prevent leakage of molecules between them
adherens junction	joins an actin bundle in one cell to a similar bundle in a neighboring cell
desmosome	joins the intermediate filaments in one cell to those in a neighbor
gap junction	allows the passage of small water-soluble ions and molecules
hemidesmosome	anchors intermediate filaments in a cell to the basal lamina

Tight junctions (Zonula occludens)

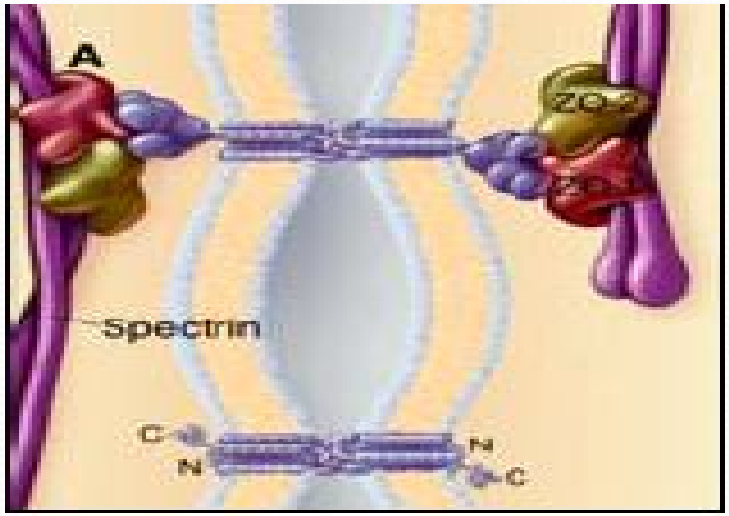
- Tight junctions consists of web like strands of transmembrane proteins (occludin and claudins) that fuse the outer surfaces of adjacent plasma membranes together.
- i.e. Belts of transmembrane proteins that close extracellular space between cells

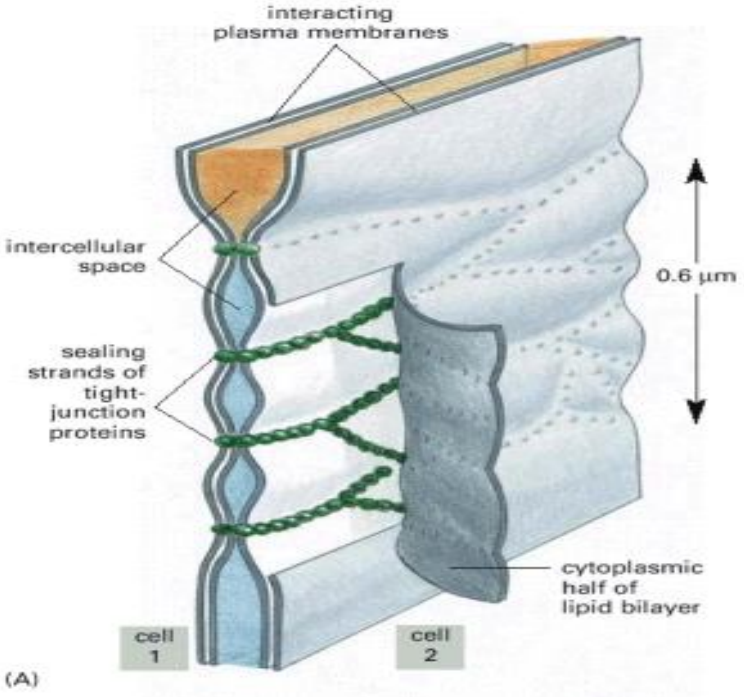
- Prevent passage of water and water-soluble substances
- Account for electrical resistance across epithelia

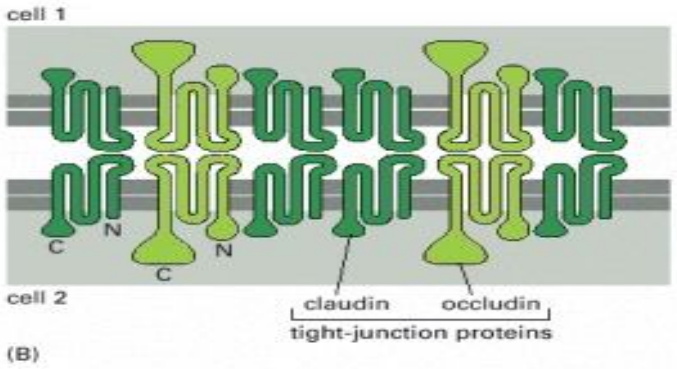
- Isolate parts of plasma membrane (Apical and Basolateral domains)

Molecular structure of tight junctions

- Claudins and occludins (membrane proteins) zip two membranes together
- Stabilized by spectrin
- Connected to spectrin by adapter proteins ZO1 and ZO2







Regulation of tight junctions

- The "tightness" varies according to the barrier needs.
- Leaky epithelia where there is need for some traffic.

- Hormones
- Vasopressin
- Cytokines
- Lack of ATP causes "leak"
- Extravasating leukocytes open tight junctions

Role of tight junctions :

- Tight junctions prevent the passage of water and solutes between the cells and are common between epithelial cells exposed to harsh chemicals / powerful enzymes
- E.g.: Tight junctions between epithelial cells lining the digestive tract keep digestive enzymes, stomach acids, or waste products from damaging underlying tissues
- Tight junctions constitute the main barrier to paracellular diffusion. The diameters of the tight junction pores are approximately 4-8 Å and 10-15 Å in humans and animals, respectively .
- Because in humans the paracellular route will not allow the passage of molecules with diameters greater than ~8 Å, this route is unlikely to play an important role in the absorption of most compounds of pharmaceutical interest.

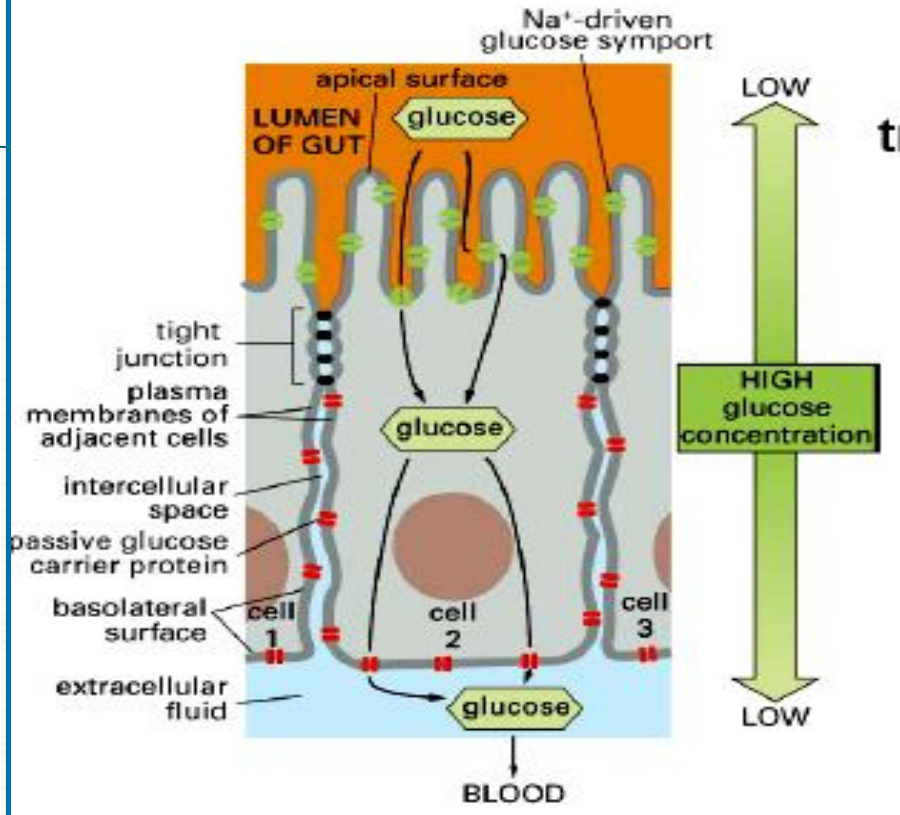


Figure 19–2. Molecular Biology of the Cell, 4th Edition.

One function of a tight junction is to promote transport through the cells

Occluding junctions provide a selective permeability barrier across epithelial cells.

Glucose can passively flow between cell membranes, but cannot pass across tight junctions.

Forces glucose to take an intracellular path, regulated by glucose receptors and glucose transporters.

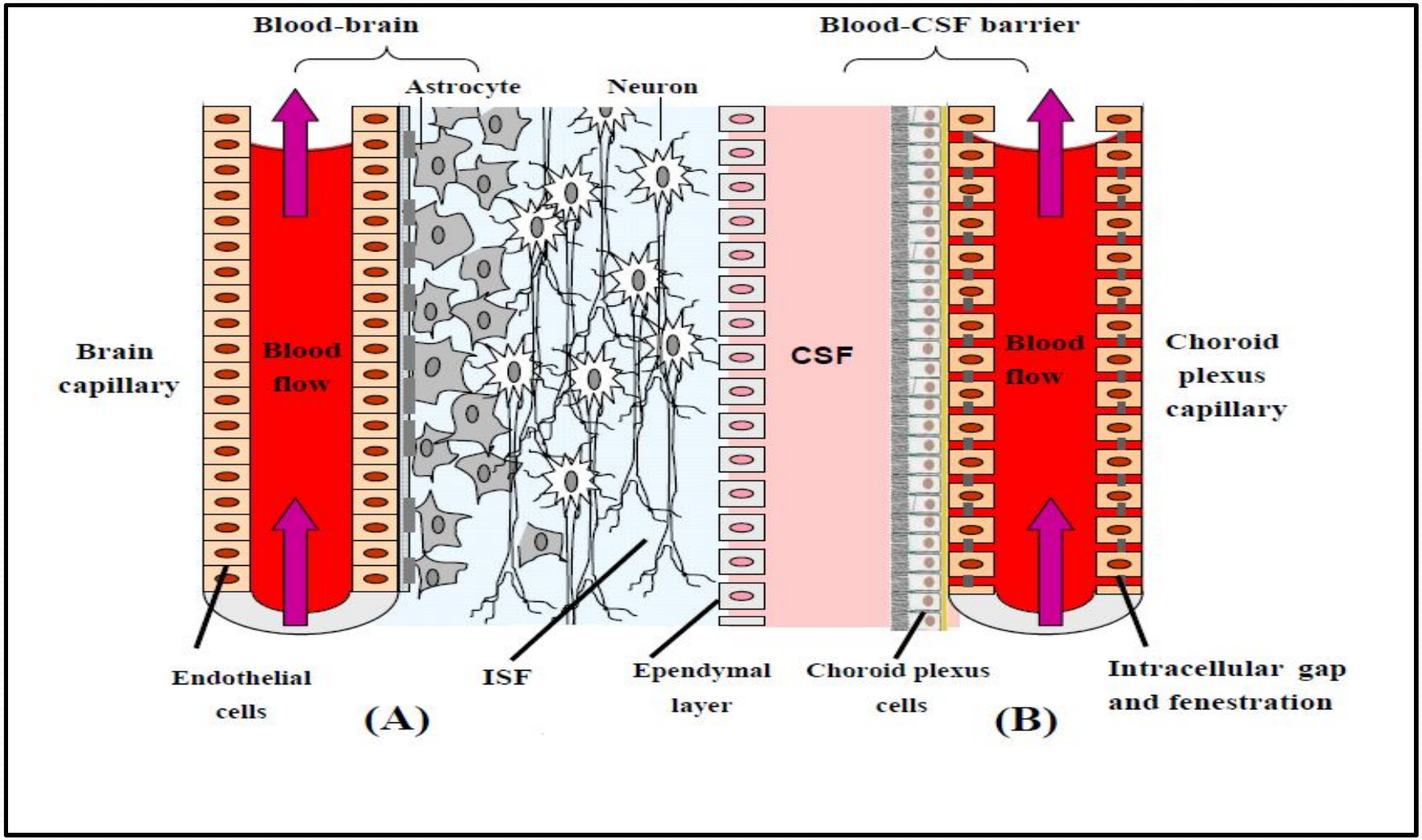
Transport may be directional

In intestinal epithelial cells transport of glucose from the intestinal lumen through the cell to the blood stream requires the uptake of glucose through apical surface sodium/glucose symport proteins and export by glucose transport proteins on the basolateral surface and tight junctions prevent the lateral movement of these transport proteins.

Blood brain barrier (BBB)

- The BBB is the major barrier to the passage of active molecules from the blood compartment to the brain.
- The BBB, which segregates the brain interstitial fluid (ISF) from the circulating blood, is located at the level of the brain capillaries, where there is a convergence of different cell types: endothelial cells, pericytes, astrocytes and microglia's (perivascular macrophages)
- The brain micro vessel endothelial cells (BMEC) that form the BBB, display important morphological characteristics such as the presence of tight junctions between the cells, the absence of fenestrations and a diminished pinocytic activity, that together help to restrict the passage of compounds from the blood into the extracellular environment of the brain.

The two main barriers in the CNS: blood-brain barrier (A) and blood cerebrospinal fluid barrier (B).



- Tight junctions provide significant Trans endothelial electrical resistance (TEER) to BMEC and impede the penetration of potential therapeutic agents such as oligonucleotides, antibodies, peptides and proteins.
- Under normal conditions the BBB acts as a barrier to toxic agents and safeguards the integrity of the brain.
- The BCSFB separates the blood from the cerebrospinal fluid (CSF) that runs in the subarachnoid space surrounding the brain.
- This barrier is located at the choroid plexus, and it is formed by epithelial cells held together at their apices by tight junctions, which limit paracellular flux.

Adhesive/Anchoring junctions

- Adhesive junctions (Adherens junction , desmosomes & hemidesmosomes) link adjoining cell to each other and to the ECM.

- Although adhesive junction types are similar in structure and function, they contain distinct

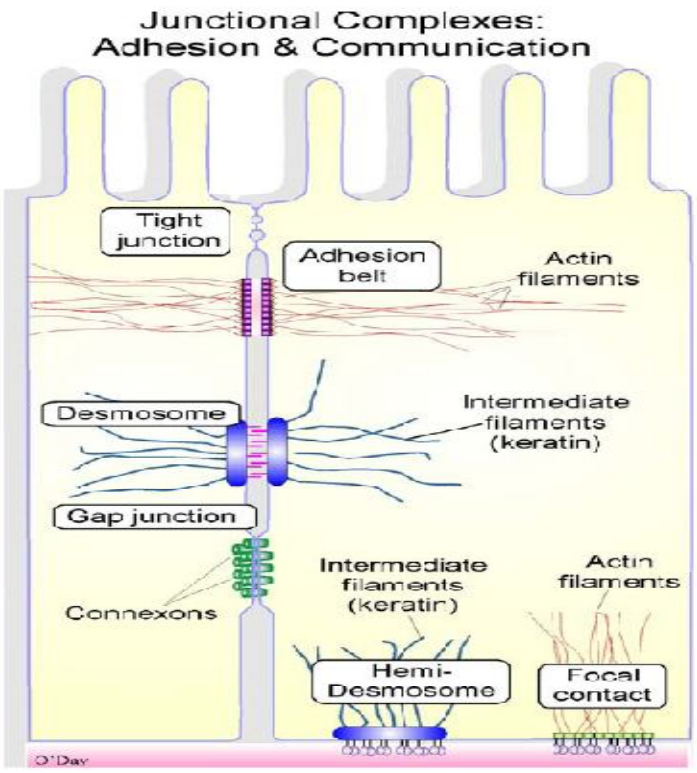
1) intracellular attachment proteins and

2) transmembrane linker proteins.

Anchoring Junctions

TABLE 19-2 Anchoring Junctions

JUNCTION	TRANSMEMBRANE ADHESION PROTEIN	EXTRACELLULAR LIGAND	INTRACELLULAR CYTOSKELETAL ATTACHMENT	INTRACELLULAR ANCHOR PROTEINS
Cell–Cell				
Adherens junction	cadherin (E-cadherin)	cadherin in neighboring cell	actin filaments	α- and β-catenins, vinculin, α-actinin, plakoglobin (γ-catenin)
Desmosome	cadherin (desmoglein, desmocollin)	desmogleins and desmocollins in neighboring cell	intermediate filaments	desmoplakins, plakoglobin (γ-catenin)
Cell–Matrix				
Focal adhesion	integrin	extracellular matrix proteins	actin filaments	talin, vinculin, α-actinin, filamin
Hemidesmosome	integrin $\alpha_6\beta_4$, BP180	extracellular matrix proteins	intermediate filaments	plectin, BP230



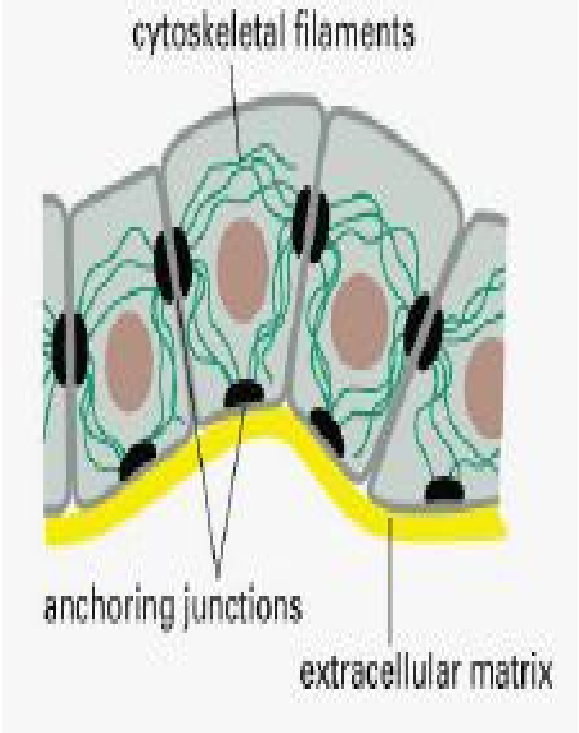
- The intracellular attachment proteins form a thick layer of fibrous material on the cytoplasmic side of the plasma membrane called a plaque which binds actin microfilaments in adherens junctions and intermediate filaments in desmosomes and hemidesmosomes.

- The *transmembrane linker proteins* are anchored to the plaque by the cytoplasmic domain and binds the ECM or to the same proteins on other cells.

ADHERENS JUNCTIONS

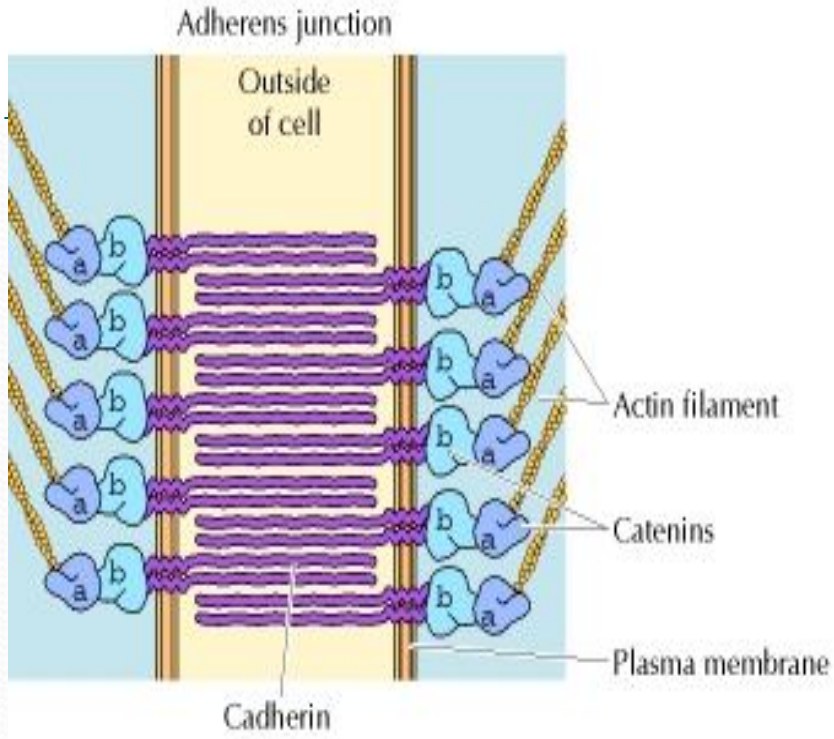
•Adherens junctions resemble desmosomes except two adjoining cells are separated by a thin space of 20-25 nm and connect to actin microfilaments in the cytoplasm.

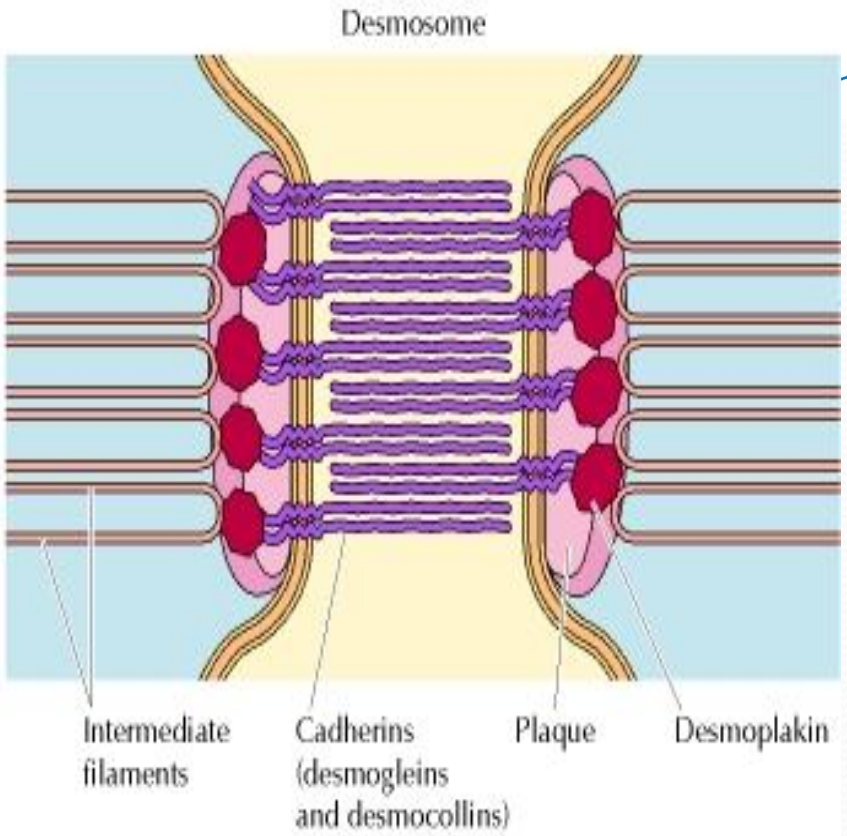
• Contain plaque- a dense layer of proteins on the inside of plasma membranes that attaches to both membrane proteins & to microfilaments of the cytoskeleton



- **Actually transmembrane glycoproteins called *cadherins* that join the cells.**

- Each cadherin inserts in to the plaque form the opposite side of the plasma membrane, partially crosses the inter cellular space & connects to cadherins of an adjacent cell.
- In epitelial cells adherens junction often form extensive zones called ***Adhesion belts***





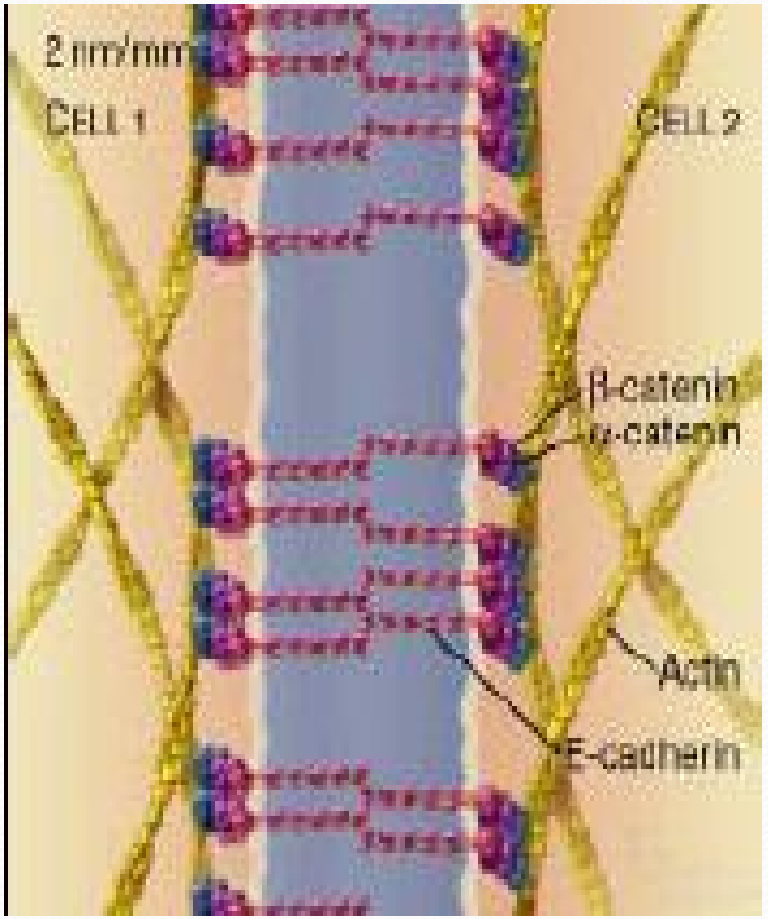
Role *: help epithelial surfaces resist separation during various contractile activities, as when food moves through the intestines.*

- Hold cells tightly together
- Confer mechanical strength

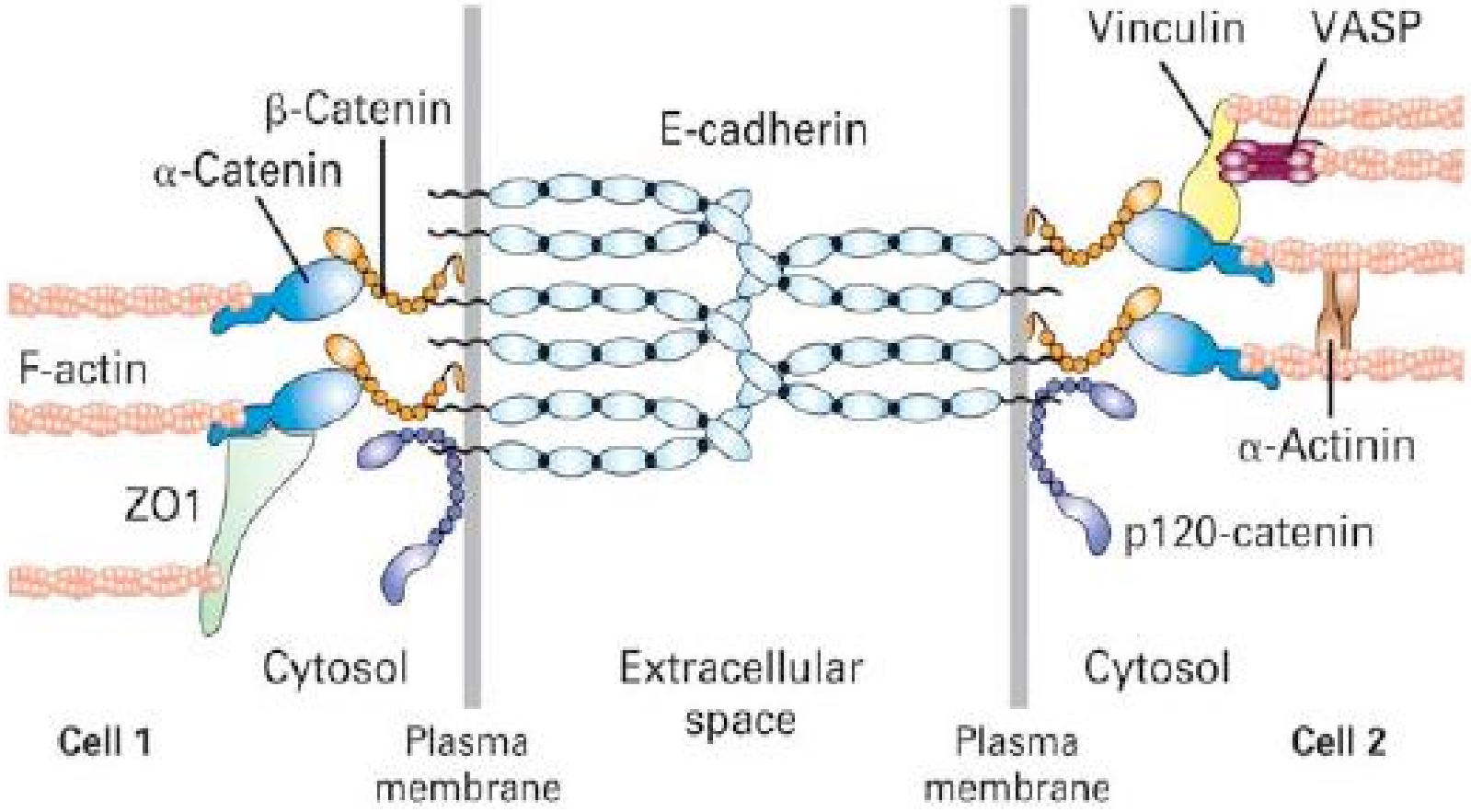
Molecular structure of Adherens junctions

Belt like junctions located just below tight junction.

Homophilic pairing of E-cadherins, Adapter proteins (plakoglobin and α and β catenins) link cadherins to the belt of actin filaments.



E-cadherin junctional proteins



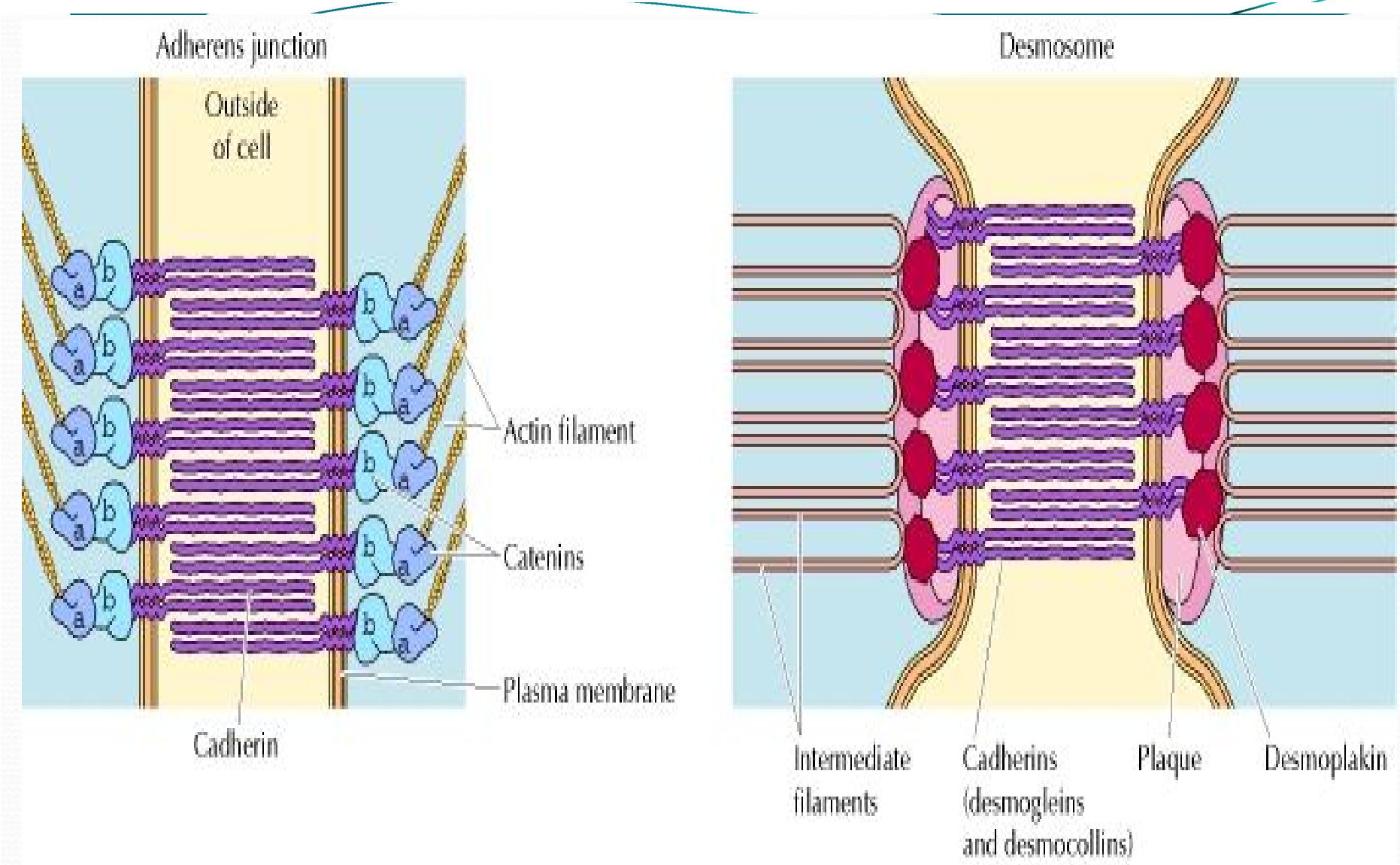
Desmosomes

•Desmosomes form strong points of adhesion between cells in a tissue such that two adjoining cells are separated by a thin space of 25-35 nm, the desmosome core, in which cadherin molecules mediate cell-cell adhesion

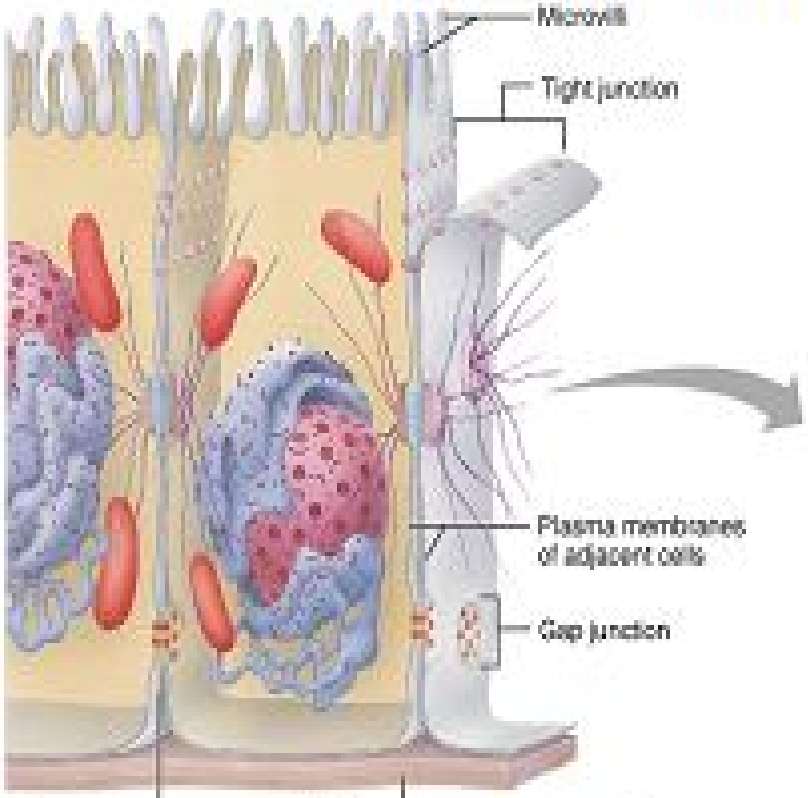
• Like adherent junctions desmosomes contain plaque & transmembrane glycoproteins**(*CADHERINS***) that extend in to the inter-cellular space between adjacent cell membranes & attach cells to one another

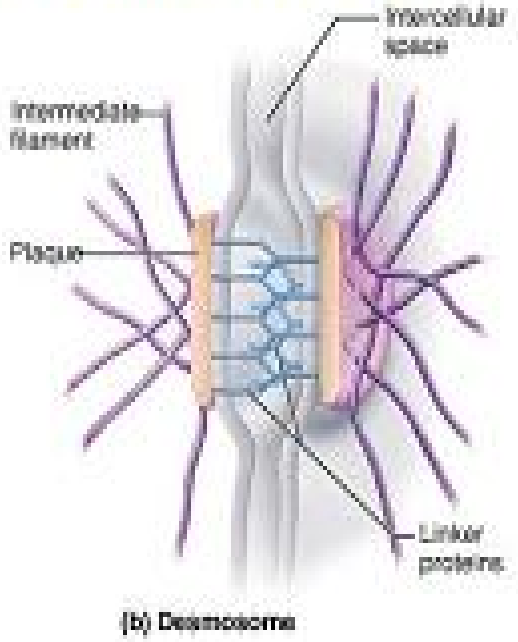
• Unlike adherens junction , the plaque of desmosomes does not attach to micro filaments. Instead, a desmosome plaque attachs to intermediate filaments of the cytoskeleton that consist of the protein ***keratin***

Figure 12.64


Adherens junction
Outside of cell
Actin filament
Catenins
Plasma membrane
Cadherin
Desmosome
Intermediate filaments
Cadherins (desmogleins and desmocollins)
Plaque
Desmoplakin

Anchoring Junctions: Desmosomes





Desmosomes are *Intermediate Filament-associated* adhesion complexes that stabilize epithelial sheets mechanically

Desmo ('bound'), soma ('body')

- Intermediate filaments extend from desmosomes on one side of the cell across the cytosol to desmosomes on the opposite side of the cell.
- This structural arrangement contributes to the stability of the cells & tissues.
- These Button like /spot-weld-like junctions are common among the cells that make up the *epidermis, cardiac muscle cells in the heart*

- ***Role*** :-Desmosomes prevent epidermal cells from separating under tension & cardiac muscle cells from pulling apart during contractions.

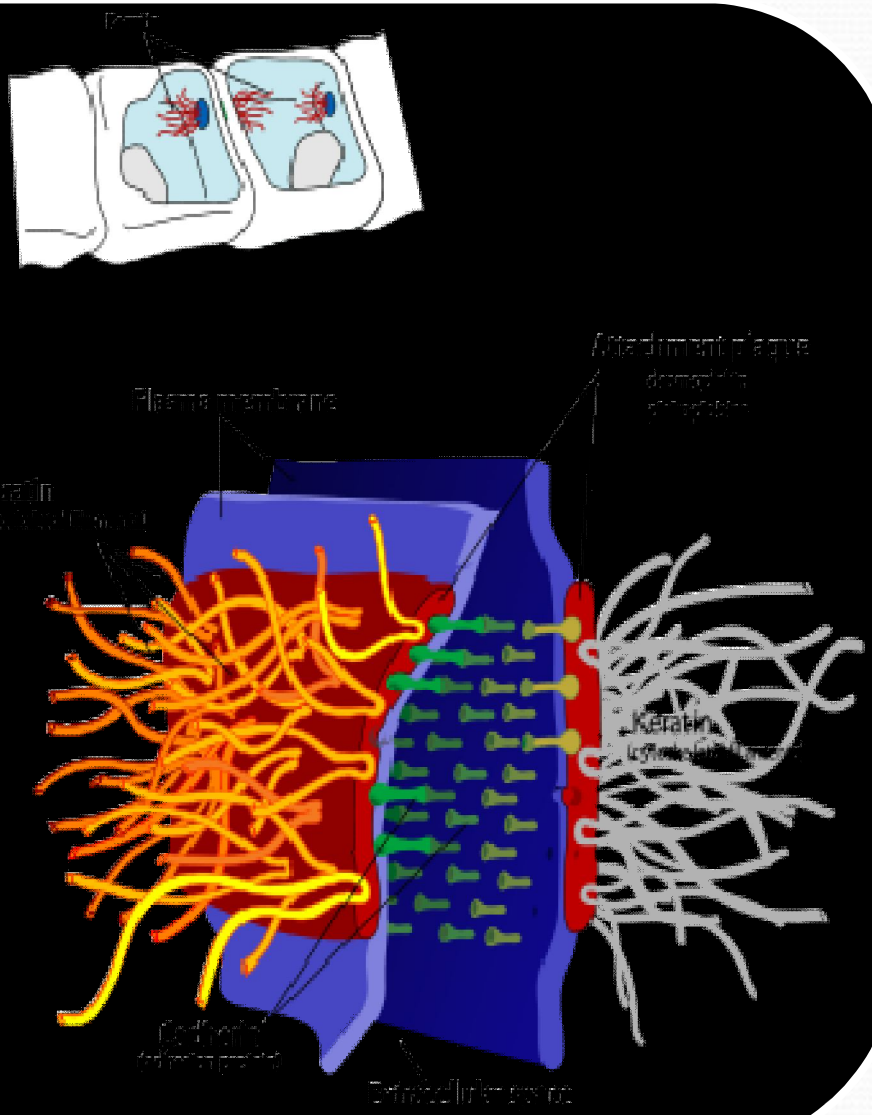
Molecular structure of Desmosomes

Two cadherins

- Desmoglein
- Desmocollin

Adapter proteins

- Plakoglobin and desmoplakin Linked to epidermal keratins
- Cadherins bind the membranes of adjacent cells in a way that gives strength and rigidity to the entire tissue.



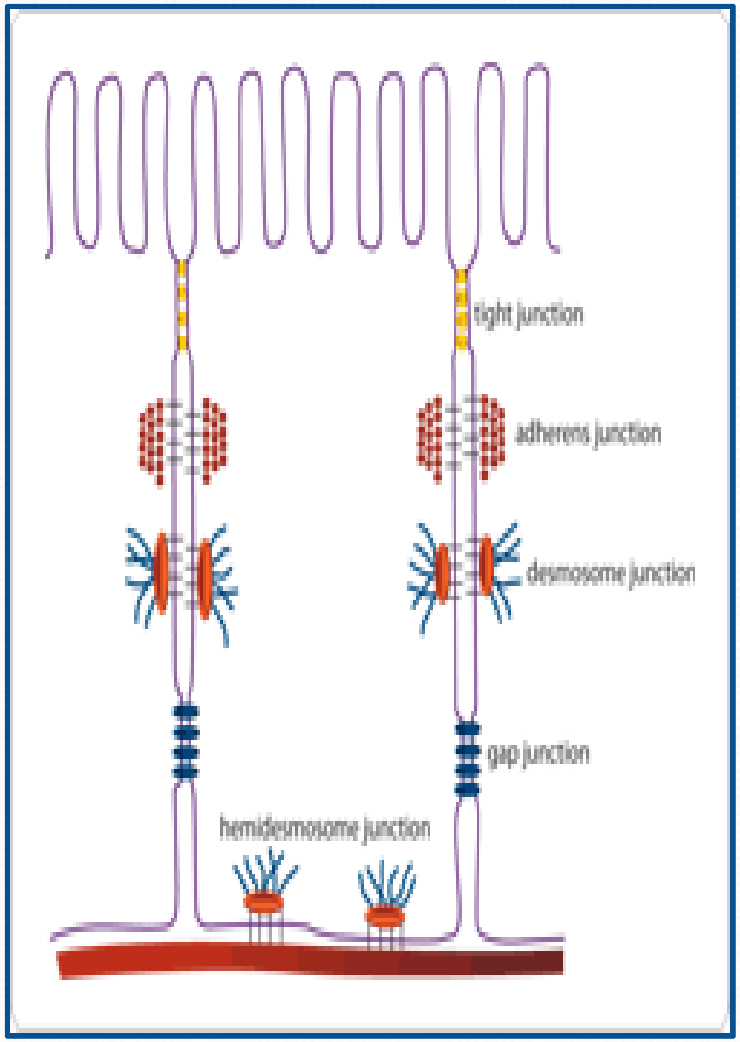
- The plaques on the inner surfaces of cells joined by desmosomes have a mixture of intracellular attachment proteins (desmoplakins and plakoglobin) which interact with the tonofilament intermediate filaments(Keratins).
- **Desmosomes are very strong, and the connection can resist *stretching & twisting***
- **In the skin, these links are so strong that dead cells are usually shed in thick sheets, rather than individually.**

Hemidesmosomes

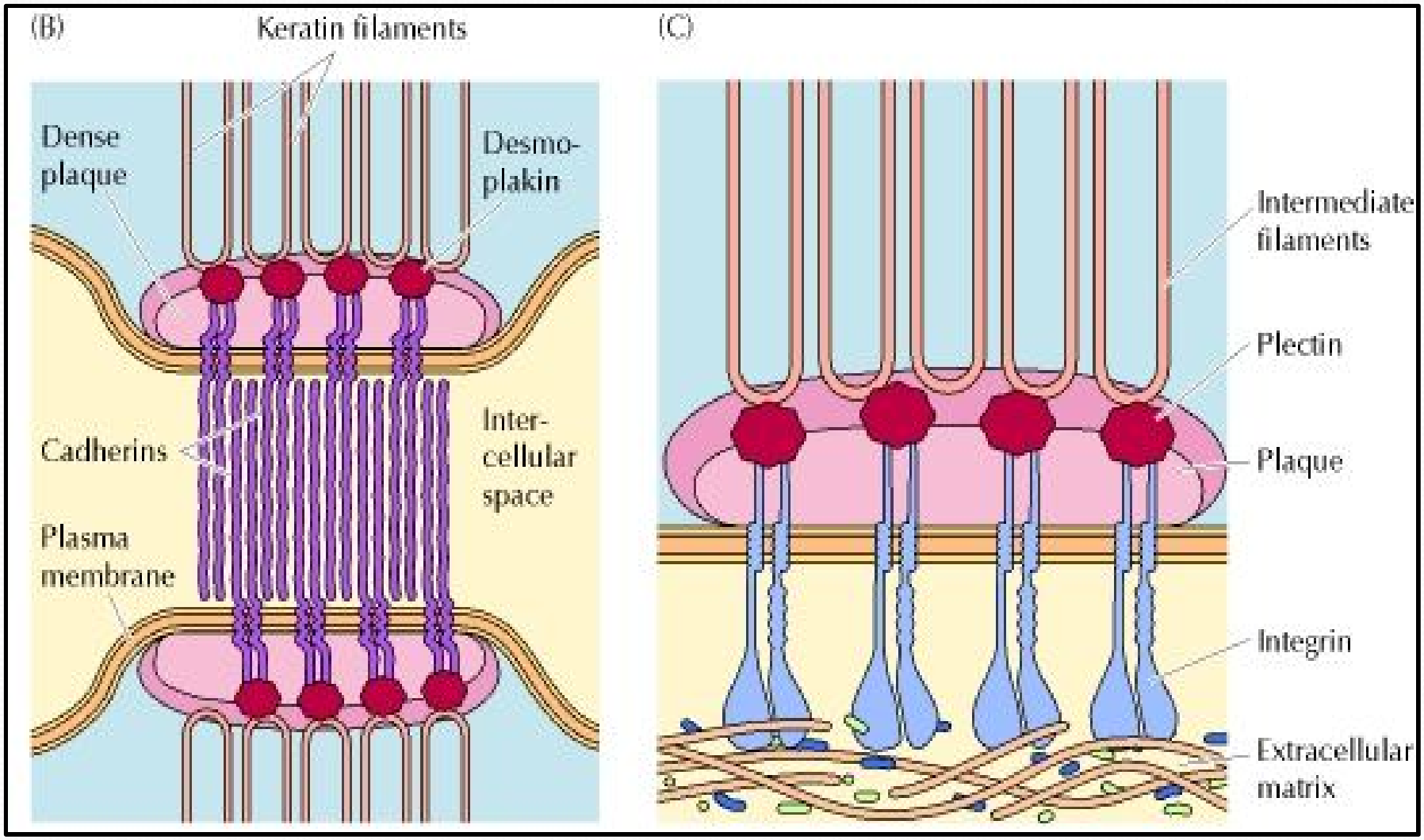
- Similar to desmosomes but they do not link adjacent cells, name arises from the fact that they look like half of a desmosome

- Has totally different molecular structure, because the transmembrane glycoproteins in hemidesmosomes are *INTEGRINS* rather than cadherins

- On the inside of the plasma membrane , integrins attach to intermediate filaments made of the protein *keratin*



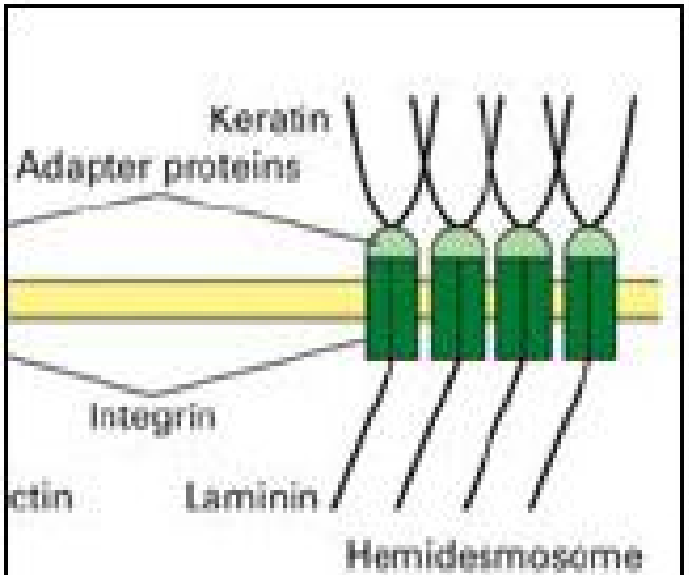
Desmosome (B) Hemidesmosome (C)



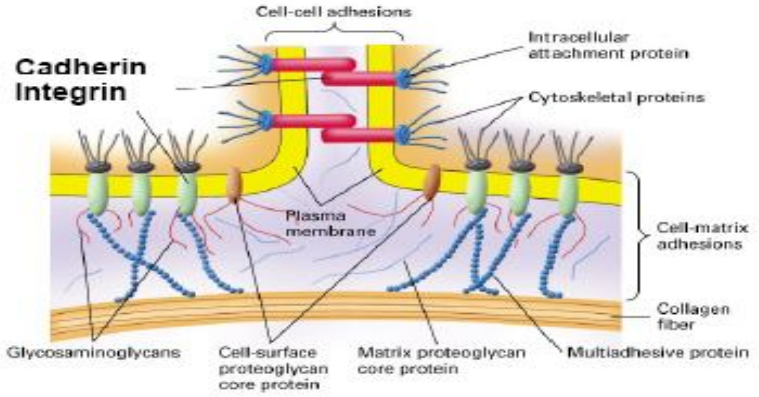
Molecular structure of Hemidesmosomes

Composed of integrins (outside) that bind to collagen and laminin-5(present in ECM)

Cytosolic side consist of a plaque composed of adapter proteins (plectin) attaching integrins to keratin filaments

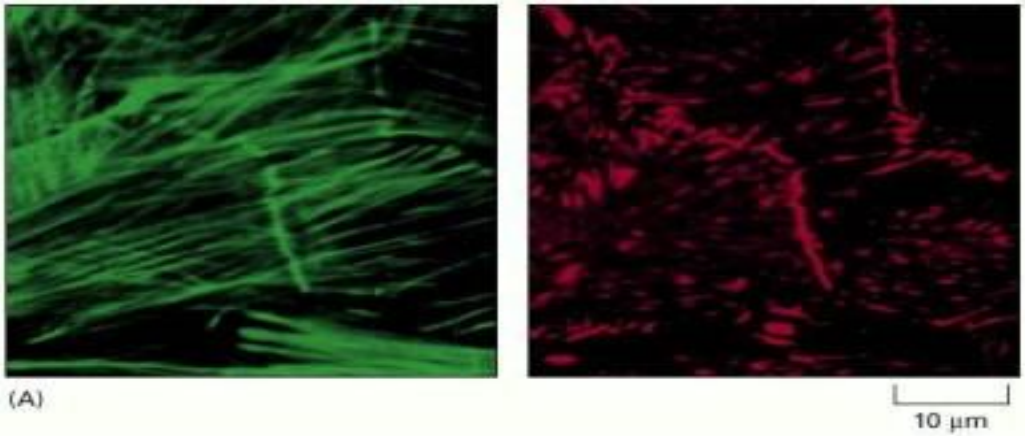


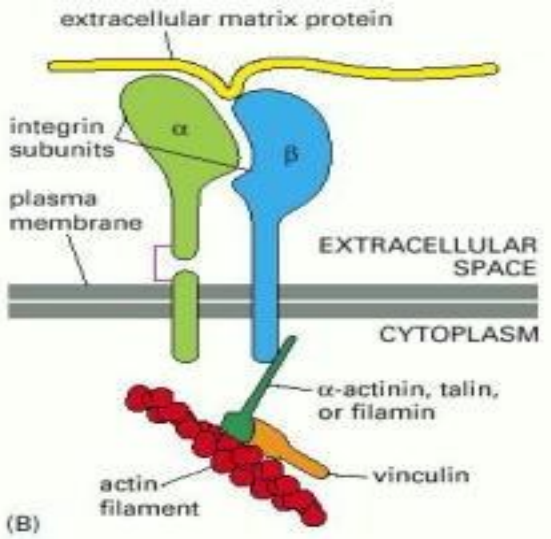
Hemidesmosome (green)



Focal adhesions

- It is the cell to matrix junctions, which connects the actin filaments of the cell to the ECM.
- The transmembrane proteins, which hold the cell membrane and the matrix, are called ***INTEGRINS***
- ***ROLE:-*** ***Attach cells to 1) basal lamina***
  2) extracellular matrix
- **Example; different epithelial cells**





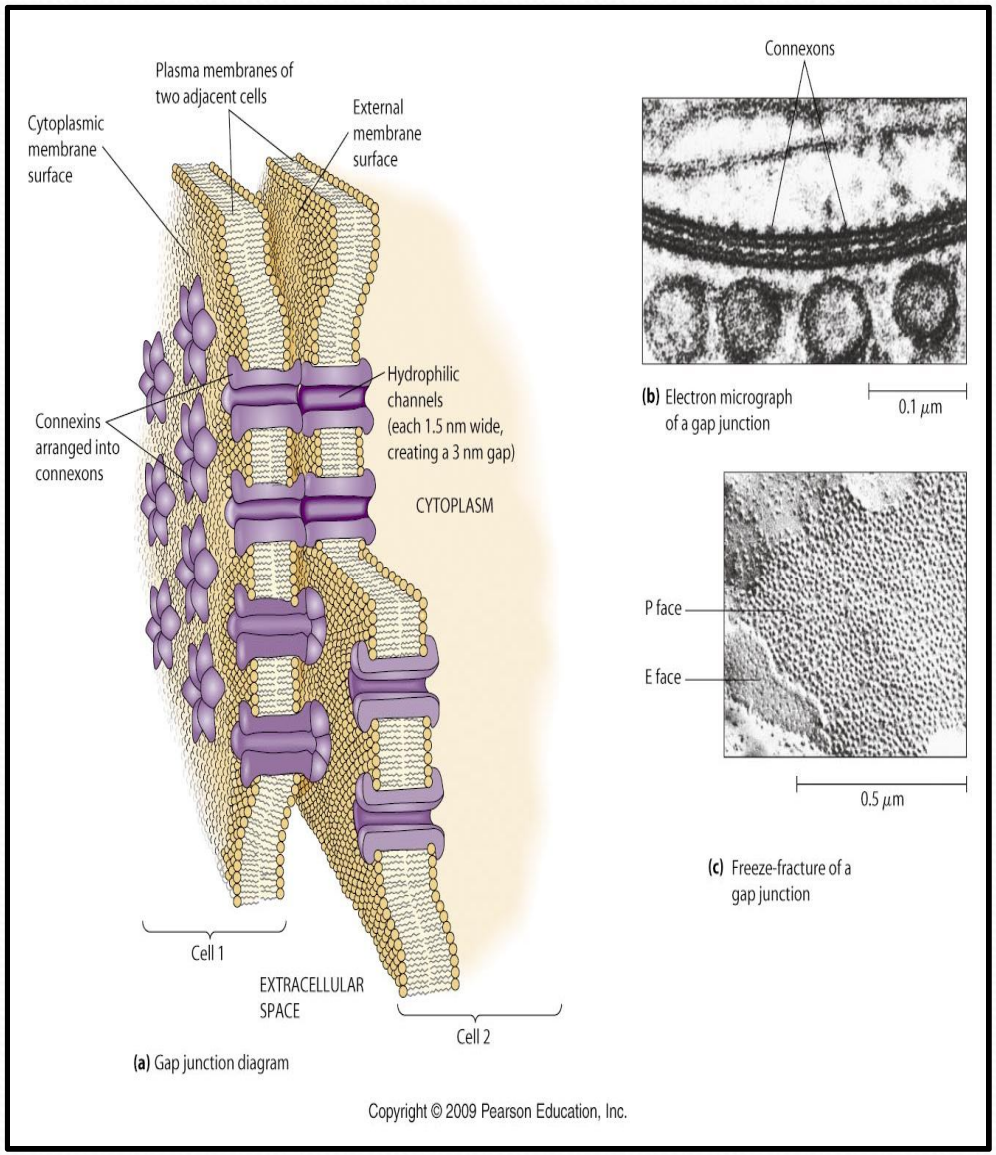
Gap junctions

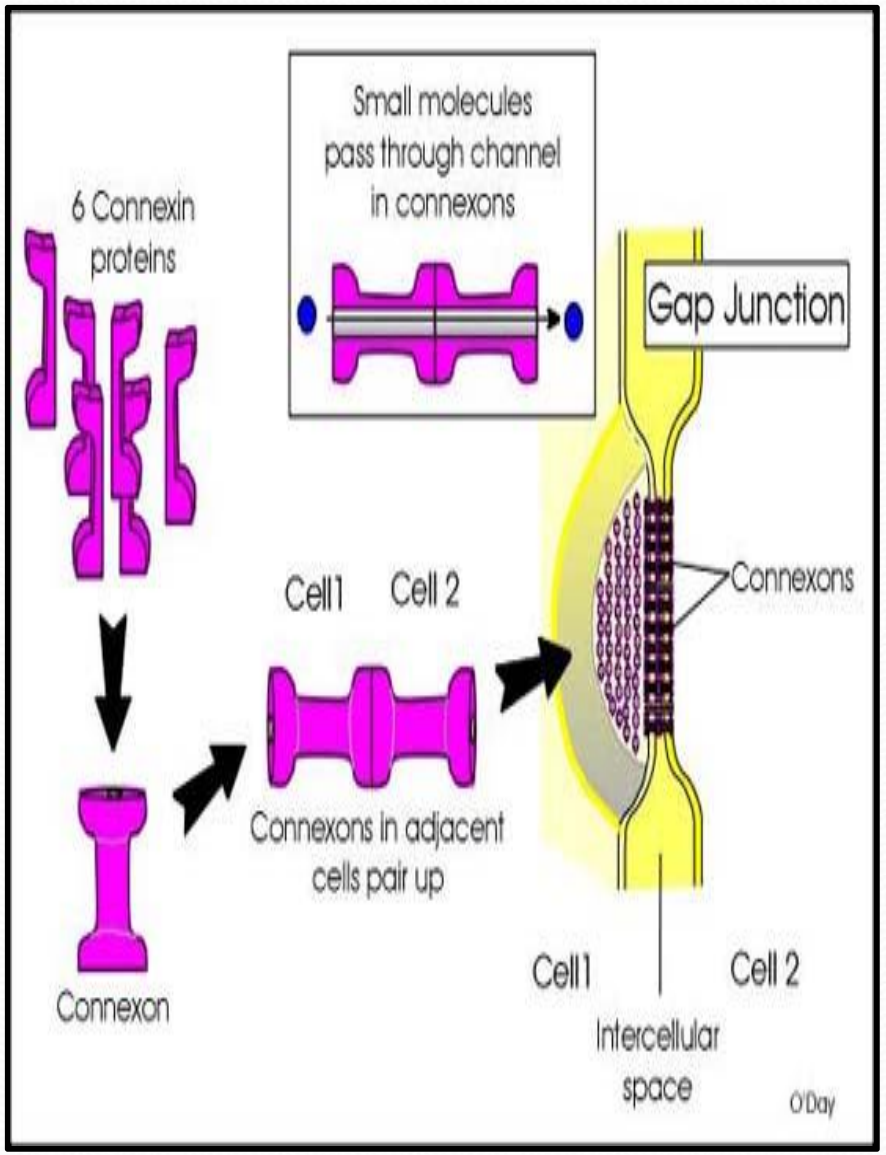
- At gap junctions, membrane proteins called ***connexins*** form tiny fluid filled tunnels called connexons that connect neighboring cells

- Plasma membranes of gap junctions are not fused together as tight junctions but are seperated by a very narrow inter cellular gap(space)
- It has a diameter in the range of 2- 4 nm

- Hence forms Junctions that provide direct connections (door) between cells.

Forms Channels or pores through the membranes of two cells and across the intercellular space


Plasma membranes of two adjacent cells
Cytoplasmic membrane surface
External membrane surface
Hydrophilic channels (each 1.5 nm wide, creating a 3 nm gap)
Connexins arranged into connexons
CYTOPLASM
Cell 1
EXTRACELLULAR SPACE
Cell 2
(a) Gap junction diagram
Connexons
(b) Electron micrograph of a gap junction
0.1 μm
P face
E face
0.5 μm
(c) Freeze-fracture of a gap junction
Copyright © 2009 Pearson Education, Inc.


6 Connexin proteins
Small molecules pass through channel in connexons
Gap Junction
Connexons
Cell1
Cell 2
Connexons in adjacent cells pair up
Connexon
Cell1
Cell 2
Intercellular space
O'Day

- **These channels are usually in an *open state* but will close when the cells *become leaky* or when the *metabolic rate is depressed*.**
- **Form electrical synapses - Direct transmission of action potential without transmitter, receptors etc.**
- **Allow the passage of small molecules such as *metabolites & inorganic* ions.**
- **The transfer of nutrients & perhaps wastes , takes place through gap junctions in avascular tissues such as lens & cornea of the eye.**

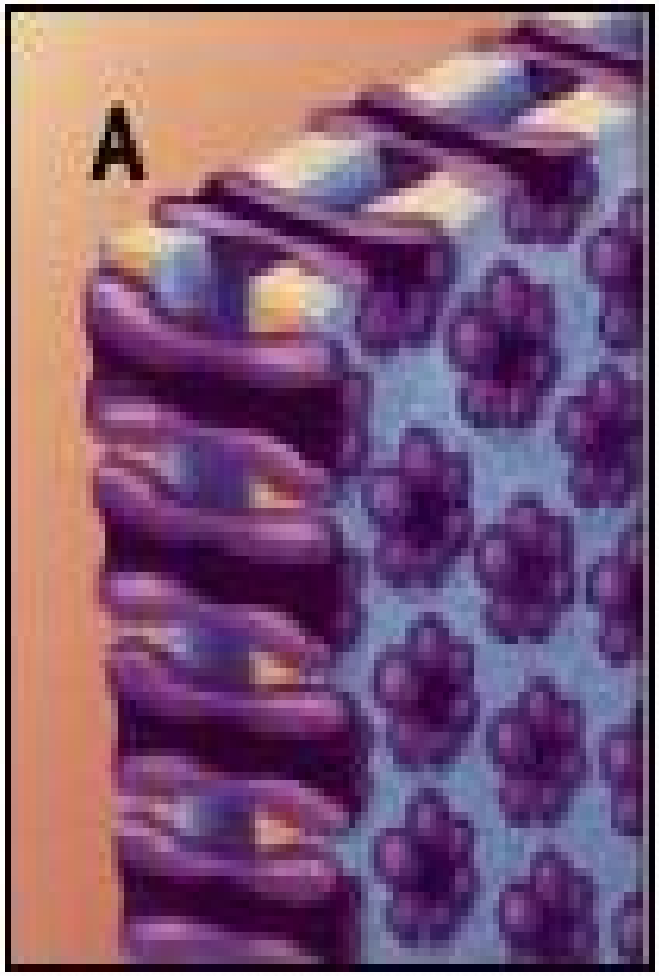
- **Integrate the metabolism of the cells**
- **They allow cells in a tissue to communicate with one another**
- **In developing embryo, some of the *chemical & electrical signals* that regulate growth & cell differentiation travel via gap junctions.**
- **Gap junctions also enable *nerve/muscle impulses to spread rapidly among cells- A process that is crucial for the normal operation of some parts of the nervous system & for the contraction of muscles in the heart , GIT & uterus.***

Molecular Structure of Gap junctions

A ring of 6 membrane proteins called connexins
- connexons

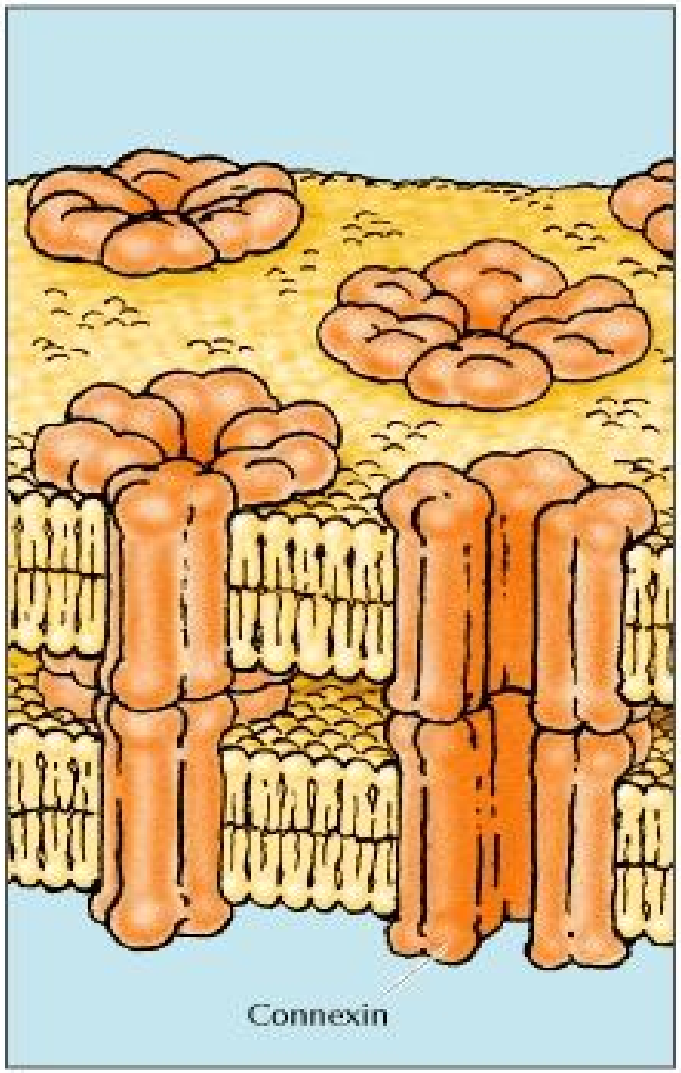
Two connexons on neighboring membranes form a transmembrane channel that interconnects the cytoplasms of two cells

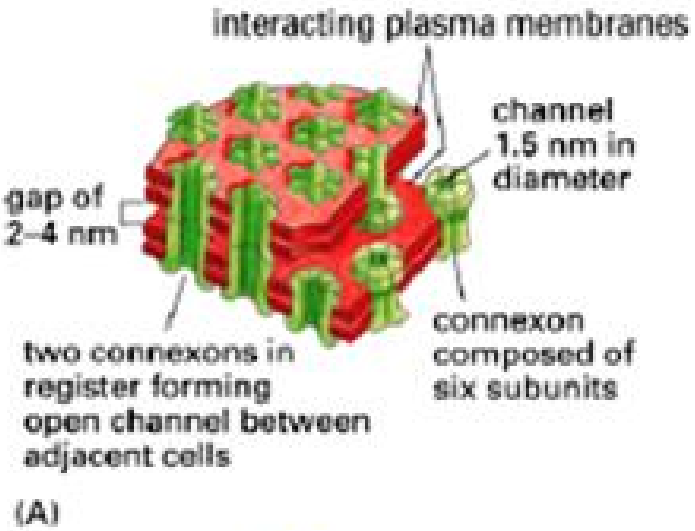
Connexons are size filters

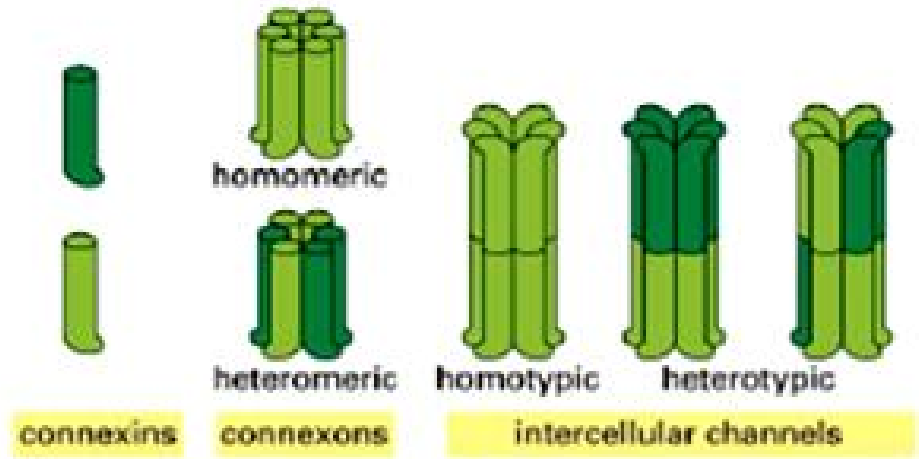


***Gap junctions* separate cells by 2-3 nm and allow direct electrical and chemical communication.**

Connexons are tightly packed 7 nm wide hollow cylinders in two adjacent cell membranes that form a 3 nm thin hydrophilic channel that allows the passage small molecules and ions.







Gap Junctions

- Gap Junctions are made up of units called connexons.
- A connexon is made up of 6 transmembrane connexin subunits
- Connexins are pass through membrane proteins. Form a continuous aqueous channel between 2 cells
- Most cells have more than 1 type of connexin.
- These form homotypic and heterotypic connexons.

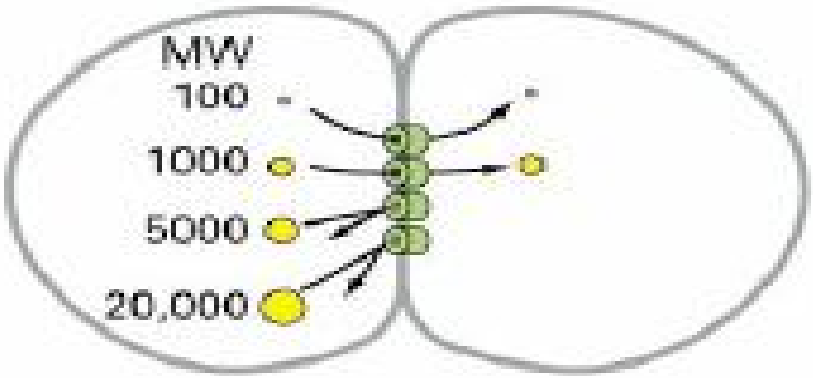
Regulation of Gap junctions

- Cytoplasmic levels of Ca^{2} (increased levels)
- P^{H} (acidification)
- Phosphorylation of the channel
- Oleamide – closes gap junctions and induces sleep

Cells that use Gap junctions

- Skin epithelium
- Endocrine glands
- GI epithelium
- Smooth muscle
- Cardiac muscle
- Osteocytes
- Glial cells

Functions of gap junctions



The type of connexin in the connexon determines the size of molecule that can pass through.

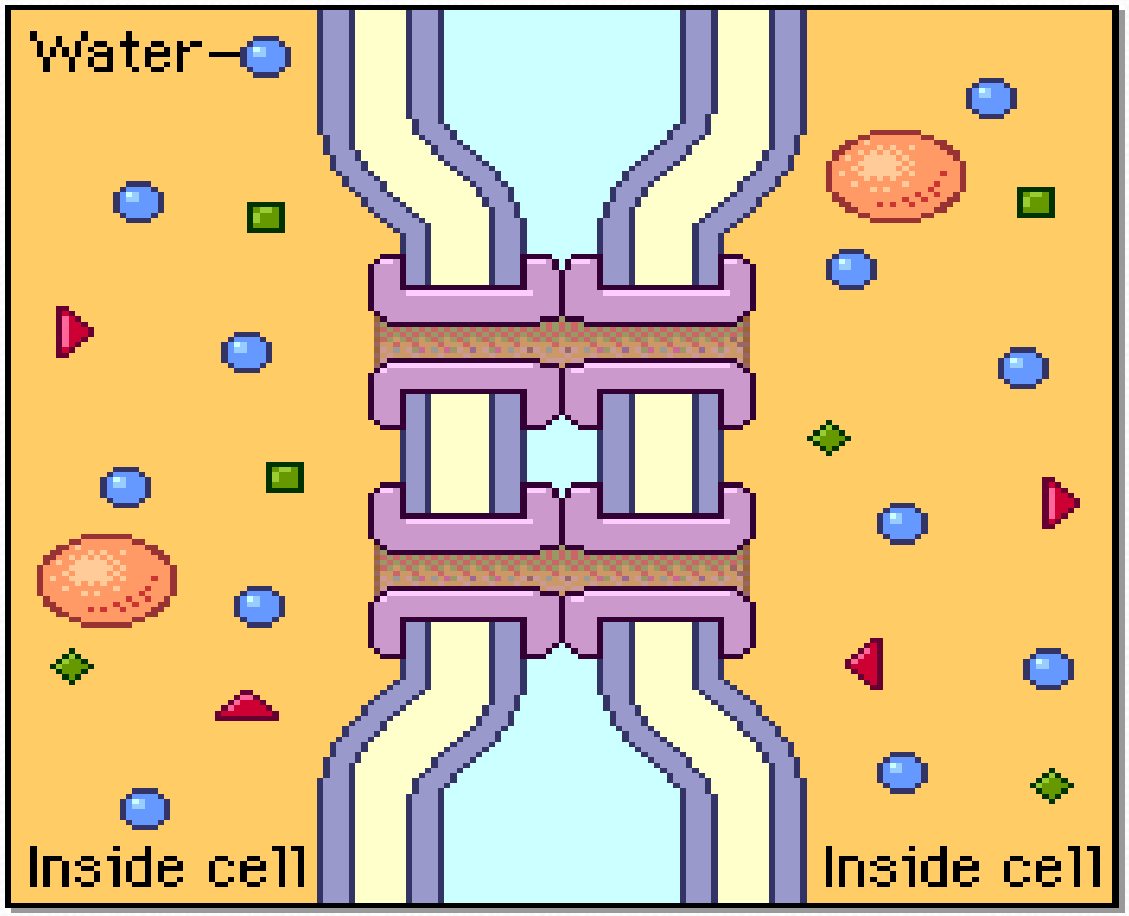
- They provide open channels through the plasma membrane, allowing ions and small molecules (less than approximately a *thousand Daltons*) to diffuse freely between neighboring cells, but preventing the passage of *proteins* and *nucleic acids.*

- Consequently, gap junctions couple both the metabolic activities and the electric responses of the cells they connect.
- Most cells in human/animal tissues—including epithelial cells, endothelial cells, and the cells of cardiac and smooth muscle—communicate by gap junctions

- In electrically excitable cells, such as heart muscle cells, the direct passage of ions through **gap junctions** couples and synchronizes the contractions of neighboring cells.

- **Gap junctions** also allow the passage of some intracellular signaling molecules, such as cAMP and Ca^{2+}, between adjacent cells, potentially coordinating the responses of cells in tissues.

Gap Junctions



Three types of cell junctions:

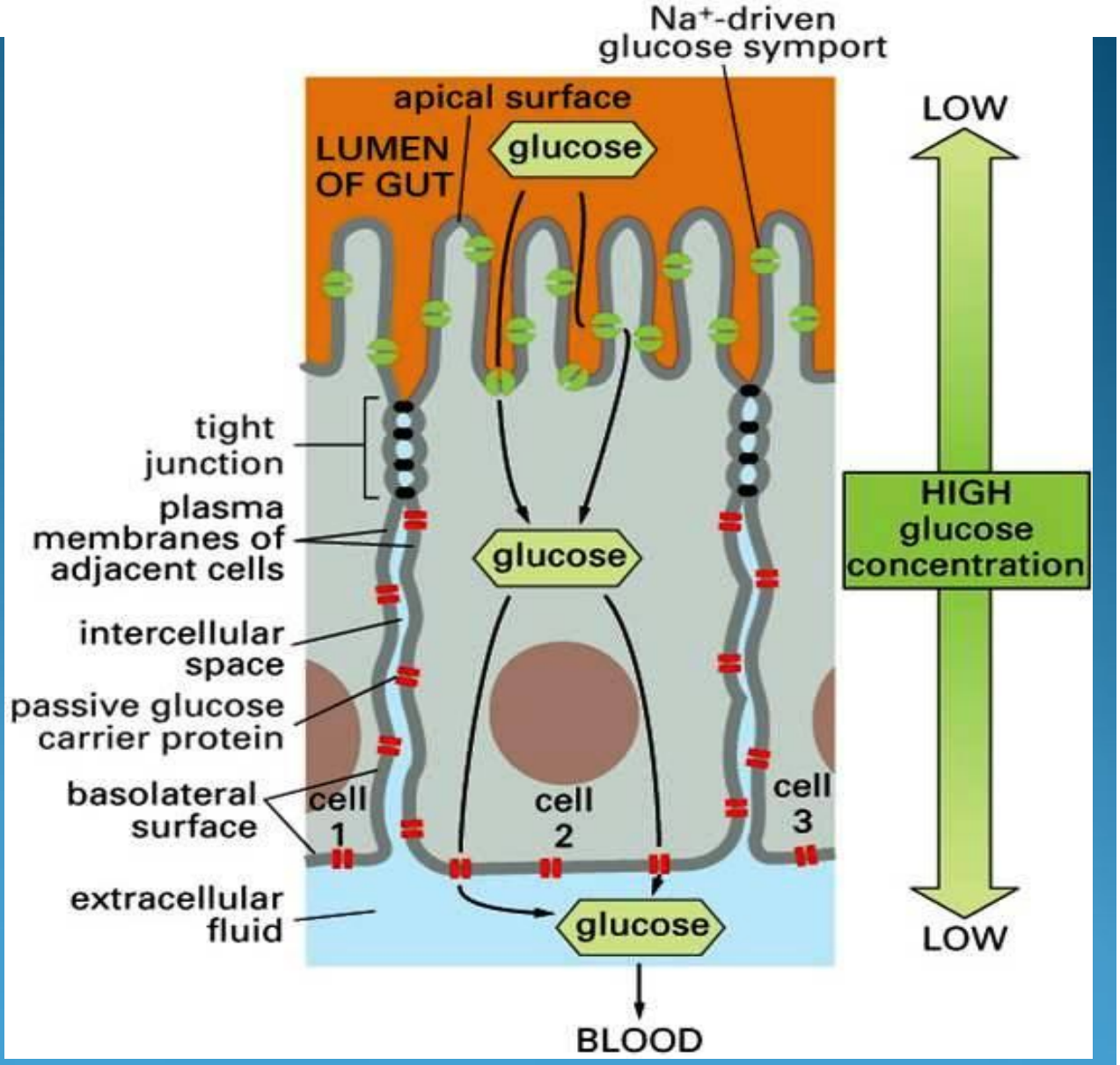
1. **Occluding junctions**: seal cells together into sheets (forming an impermeable barrier)

2. **Anchoring junctions**: attach cells (and their cytoskeleton) to other cells or extracellular matrix (providing mechanical support)

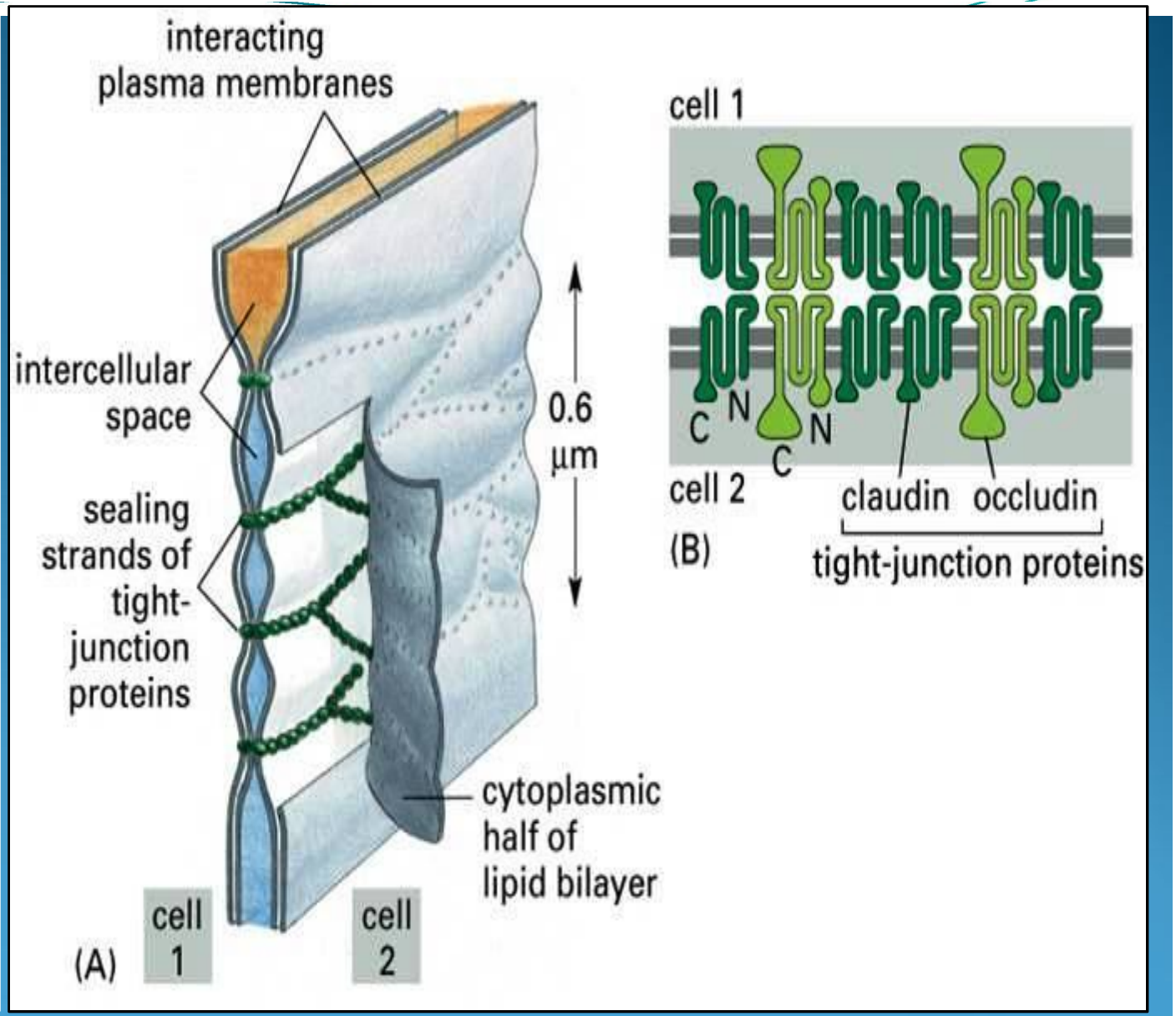
3. **Communicating junctions**: allow exchange of chemical/electrical information between cells

Ex:

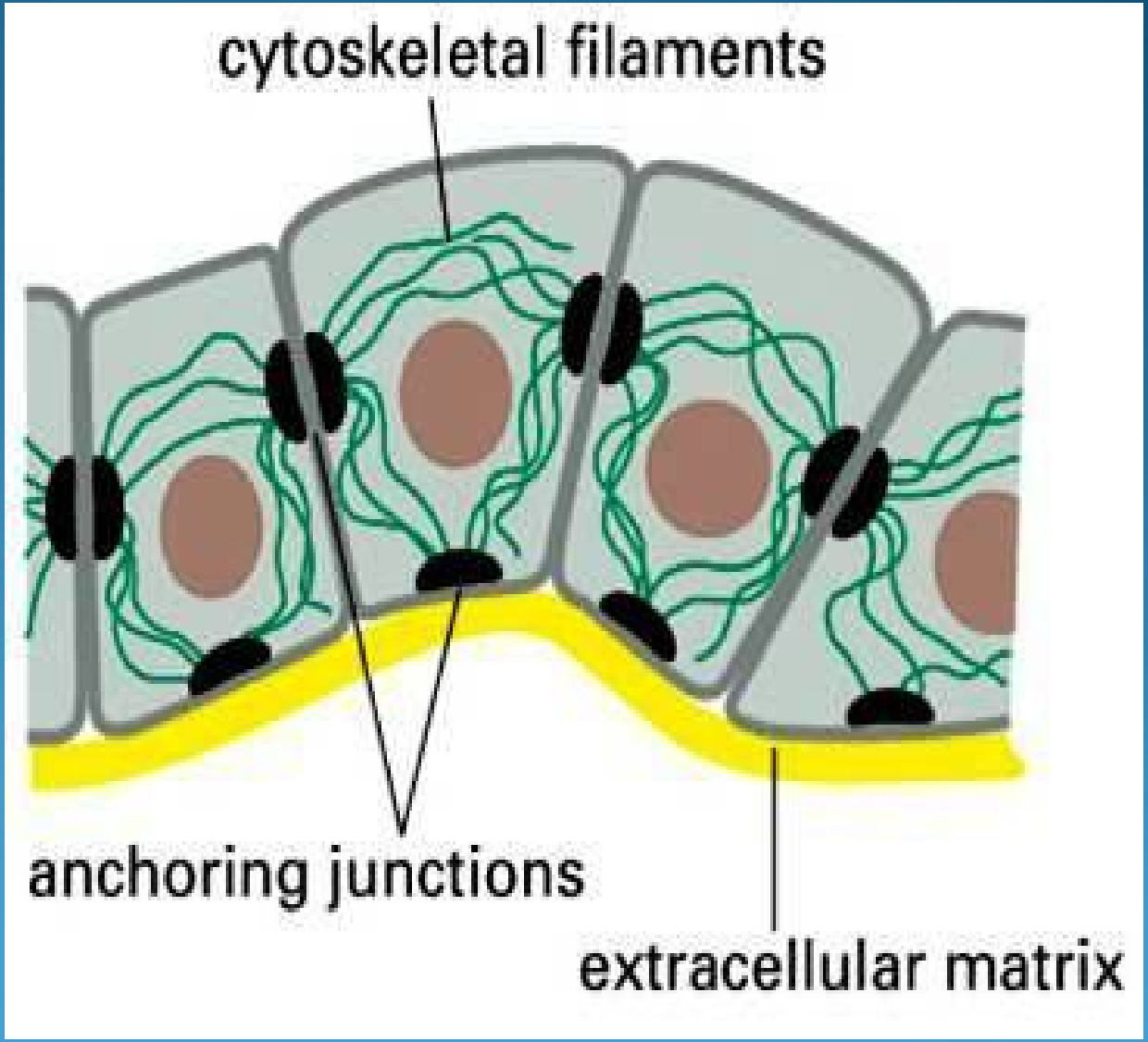
Tight junctions of intestinal epithelium



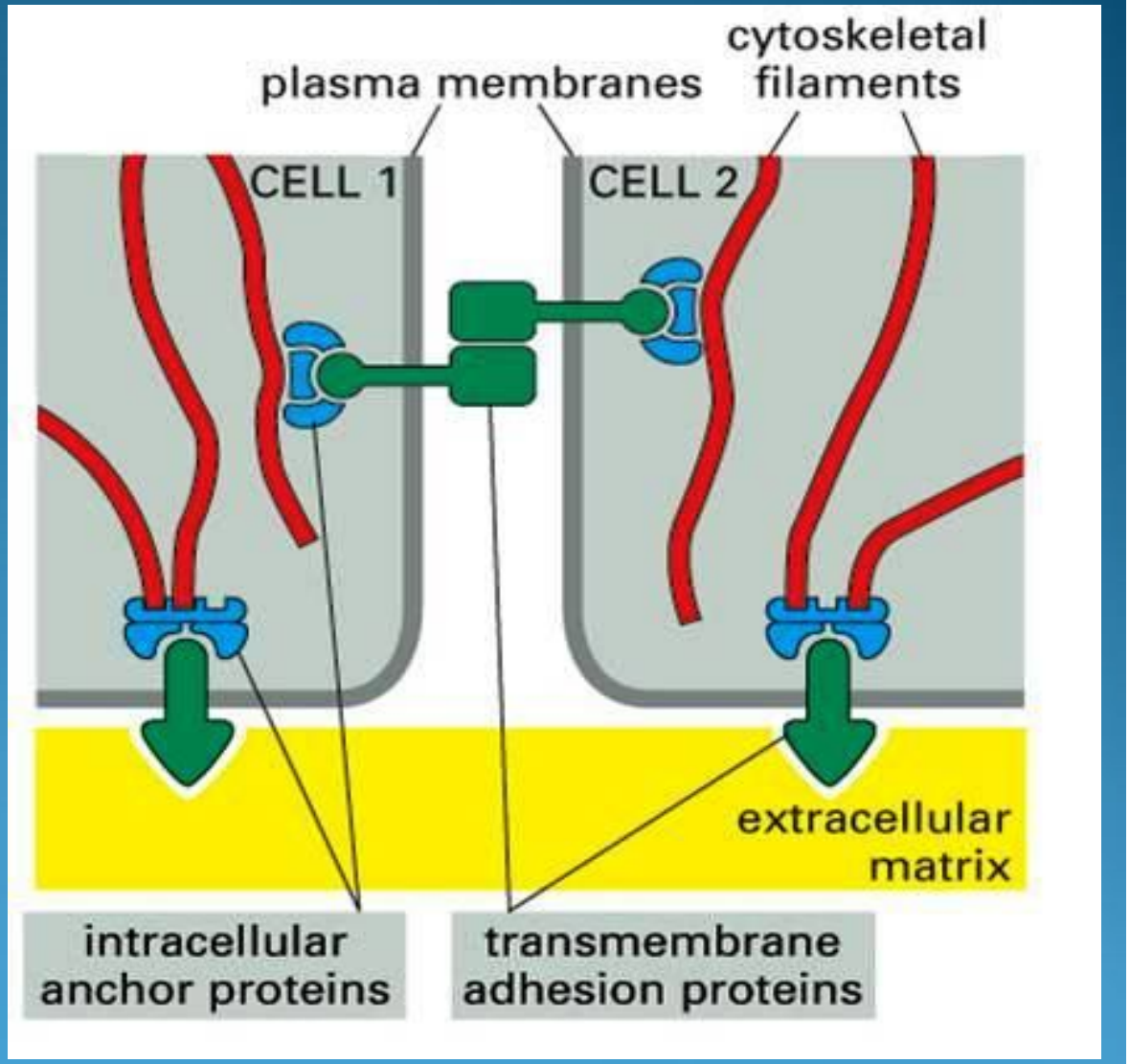
Each cell possesses integral membrane proteins that bind to similar proteins in the adjacent, forming a continuous "weld"



Integral membrane proteins connect a cell's cytoskeleton to another cell or extracellular matrix

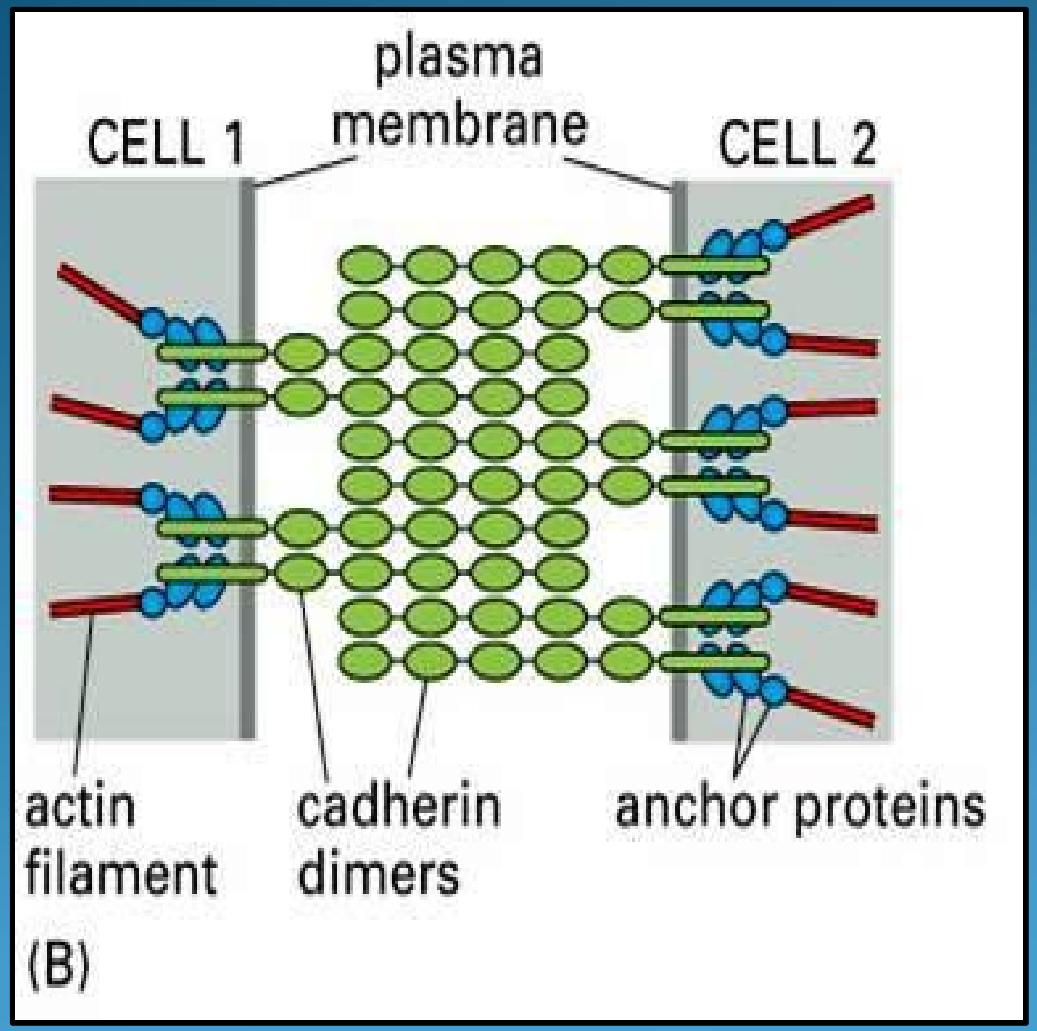


Integral membrane proteins connect a cell's cytoskeleton to another cell or extracellular matrix



Cytoskeletal fibers (MF, intermediate filaments) connect to a Membrane protein receptor

which attaches to another protein in either:
-the extracellular matrix or
-another cell membrane

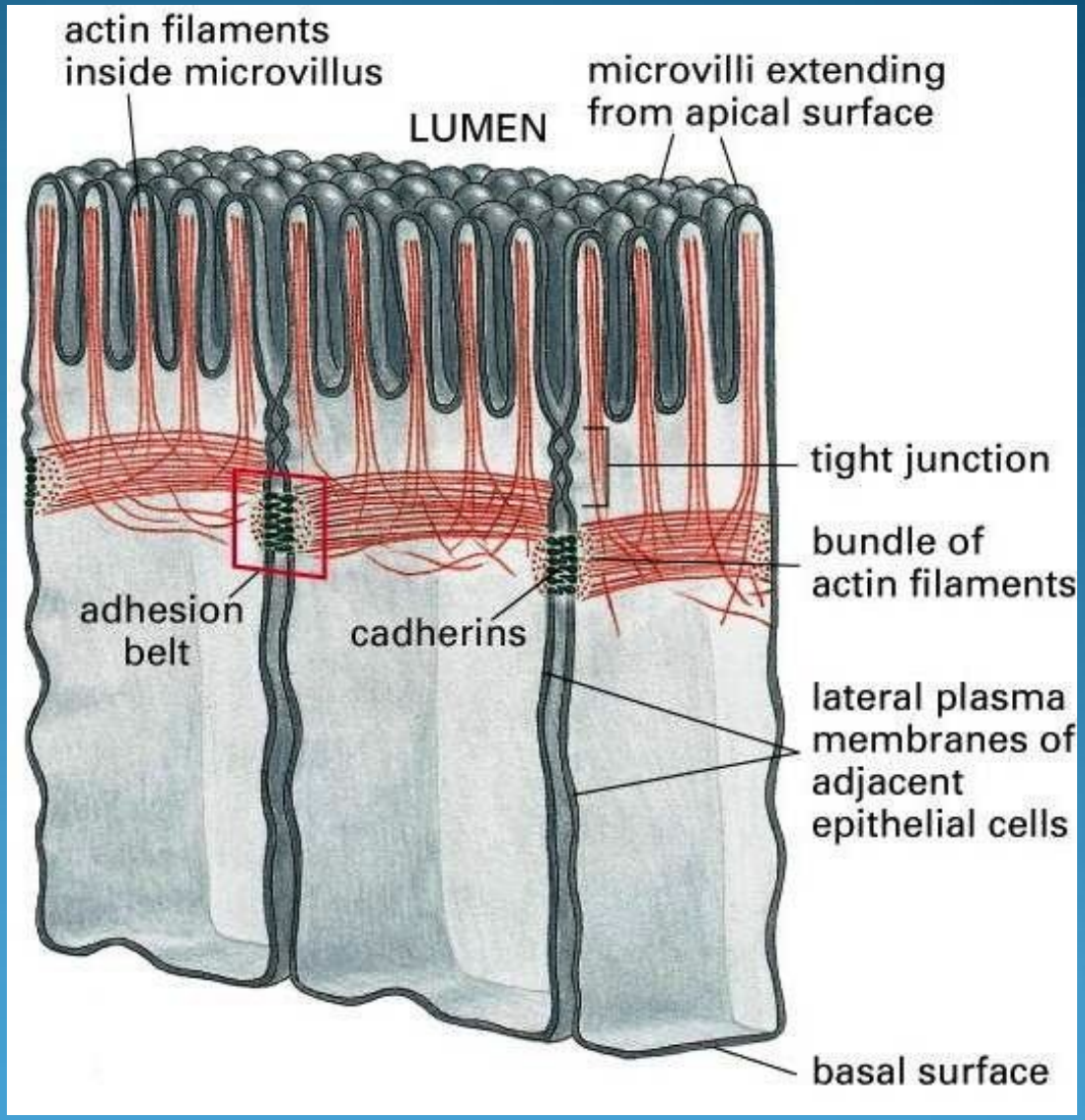


Cell to cell connections are mediated by cadherins.

These receptors extend out from the cell, binding to other cadherens

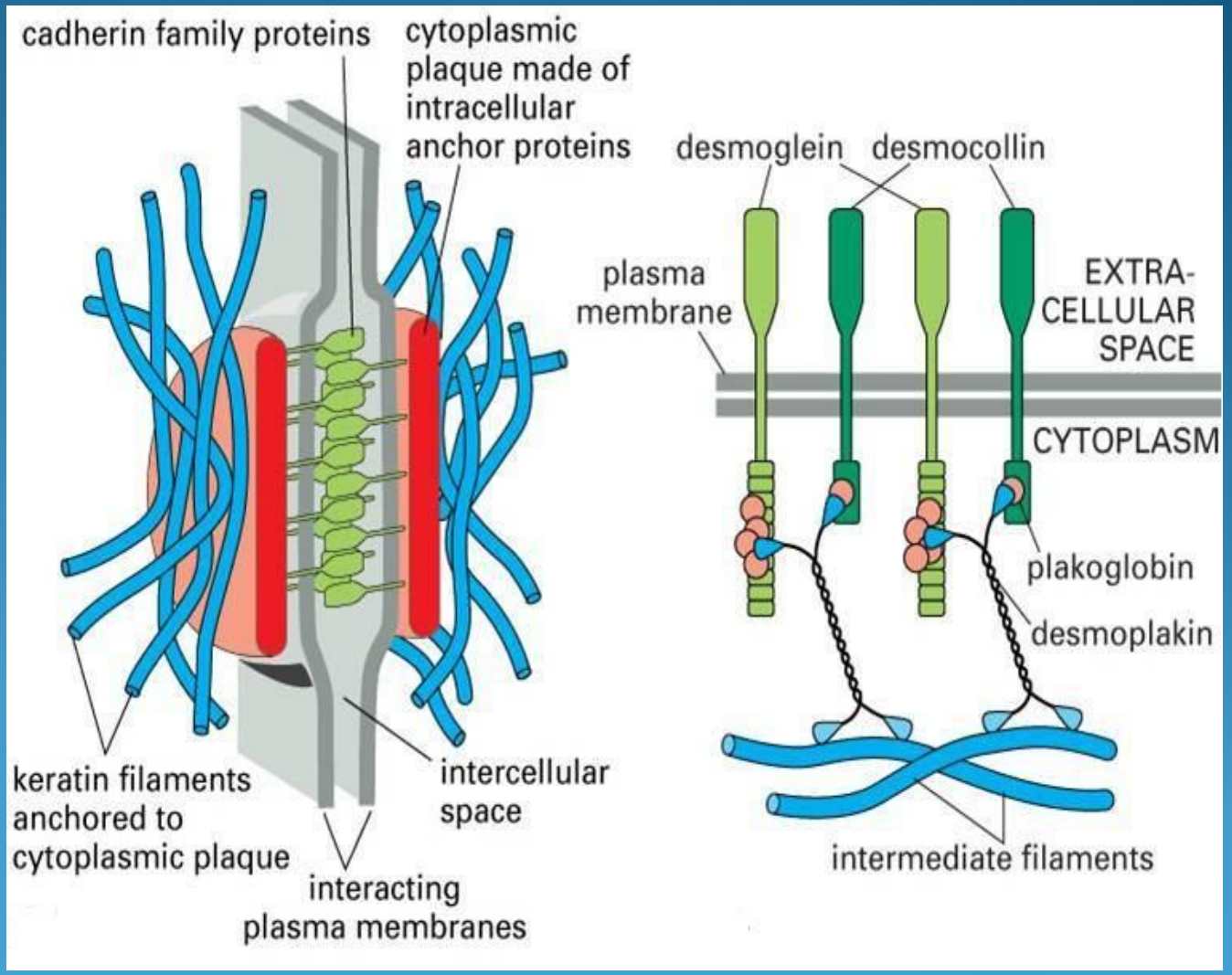
Under the cell membrane, contractile fibers of microfilaments connect to cell membrane proteins called cadherins

They surround the cell, forming a belt



Cadherins can also form localized spot connections

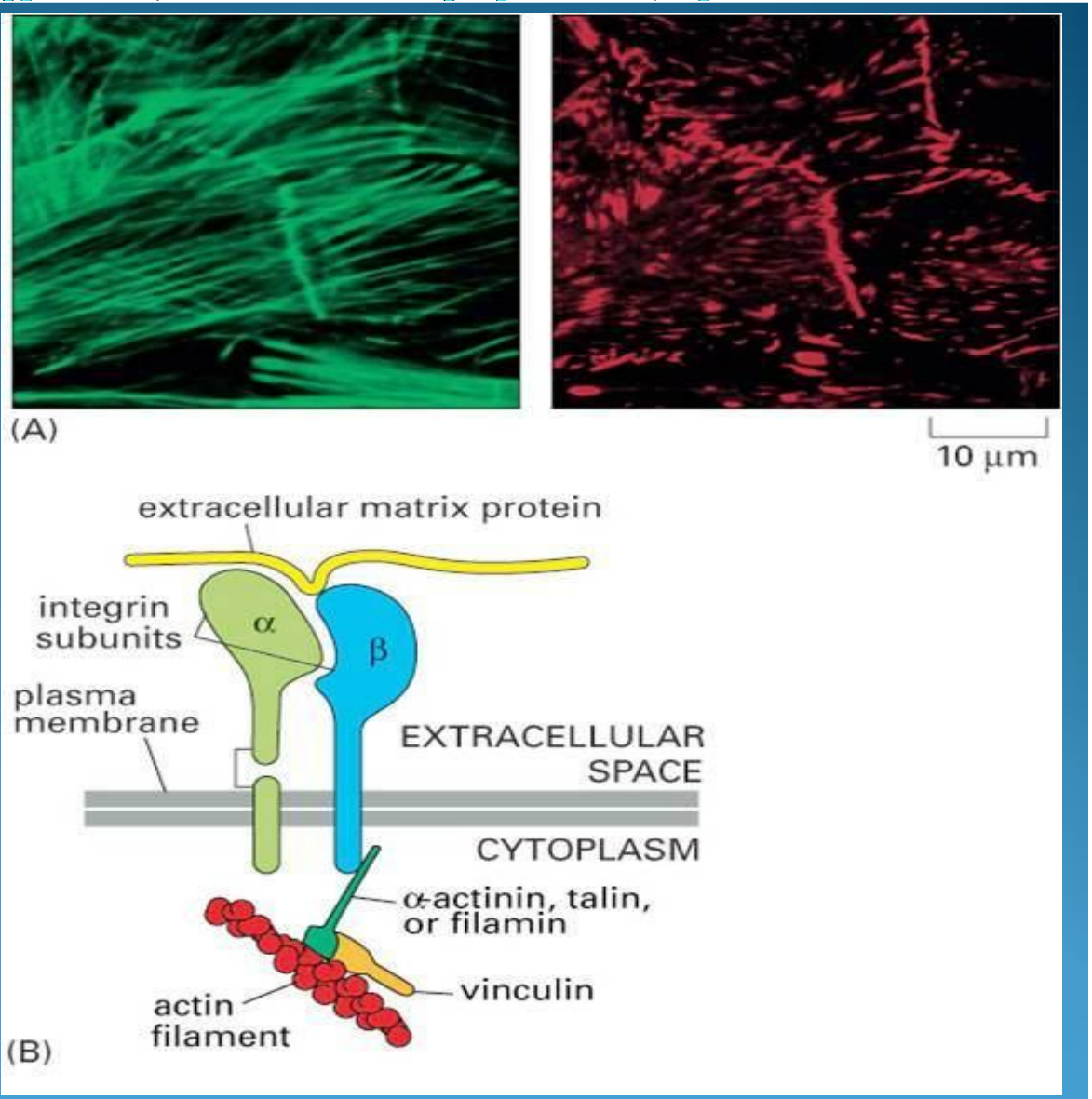
Cadherins attach to intermediate filaments via anchoring proteins: a desmosome



Cells-to-ECM attachments:

Cytoskeletal fibers attach to transmembrane receptors (integrins) that are attached to extracellular matrix components

- Focal adhesions use MF
- Hemidesmosomes use IF



Gap junctions allow cells to exchange electrical and/or chemical signals

Composed of proteins that form channels that allow small molecules to pass.

Subunits of these channels are connexins that are assembled together to make connexons. The connexons from 2 cells join together to make a gap junction.

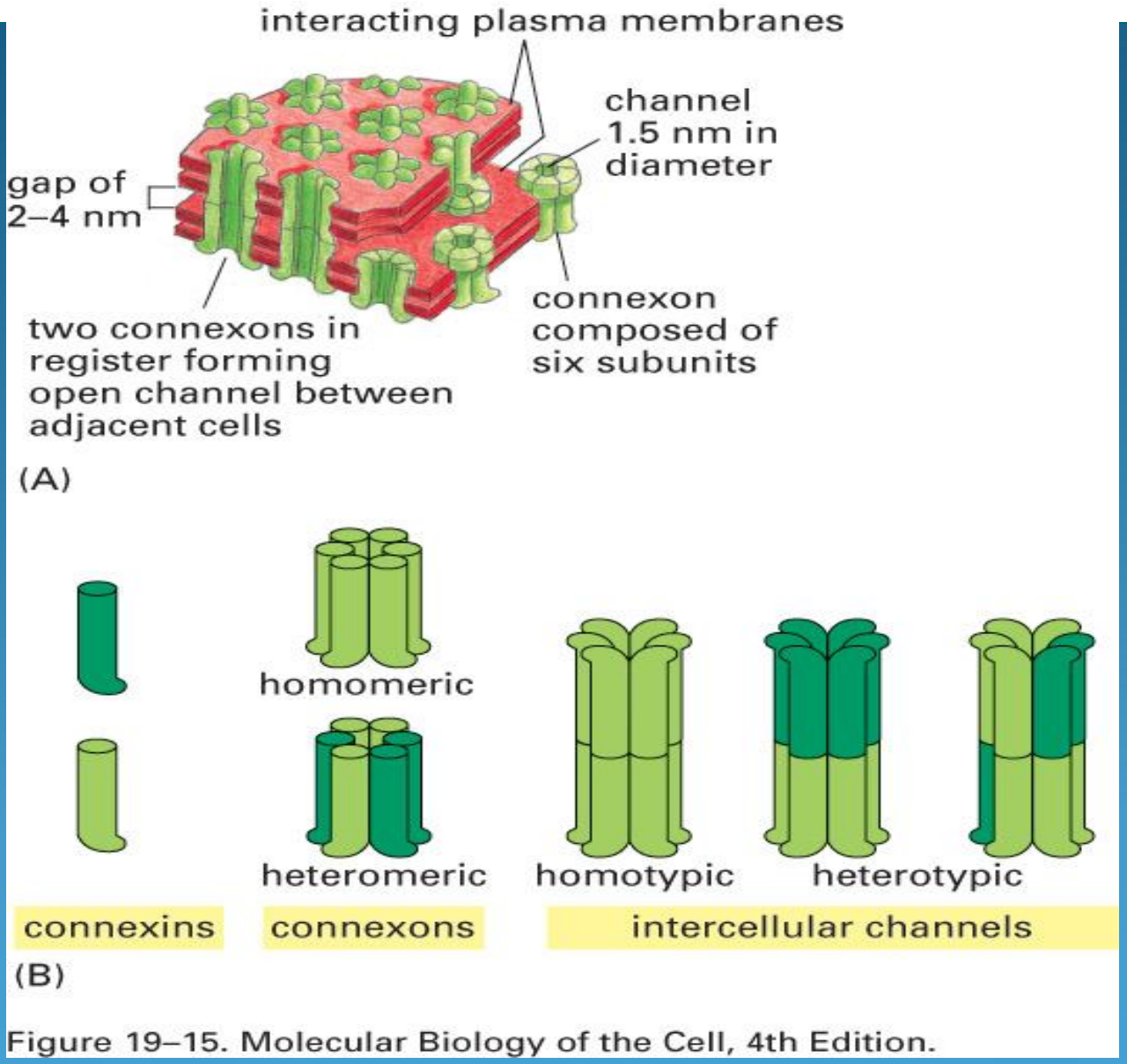


Figure 19–15. Molecular Biology of the Cell, 4th Edition.

When might a cell want to alter its connections to other cells?

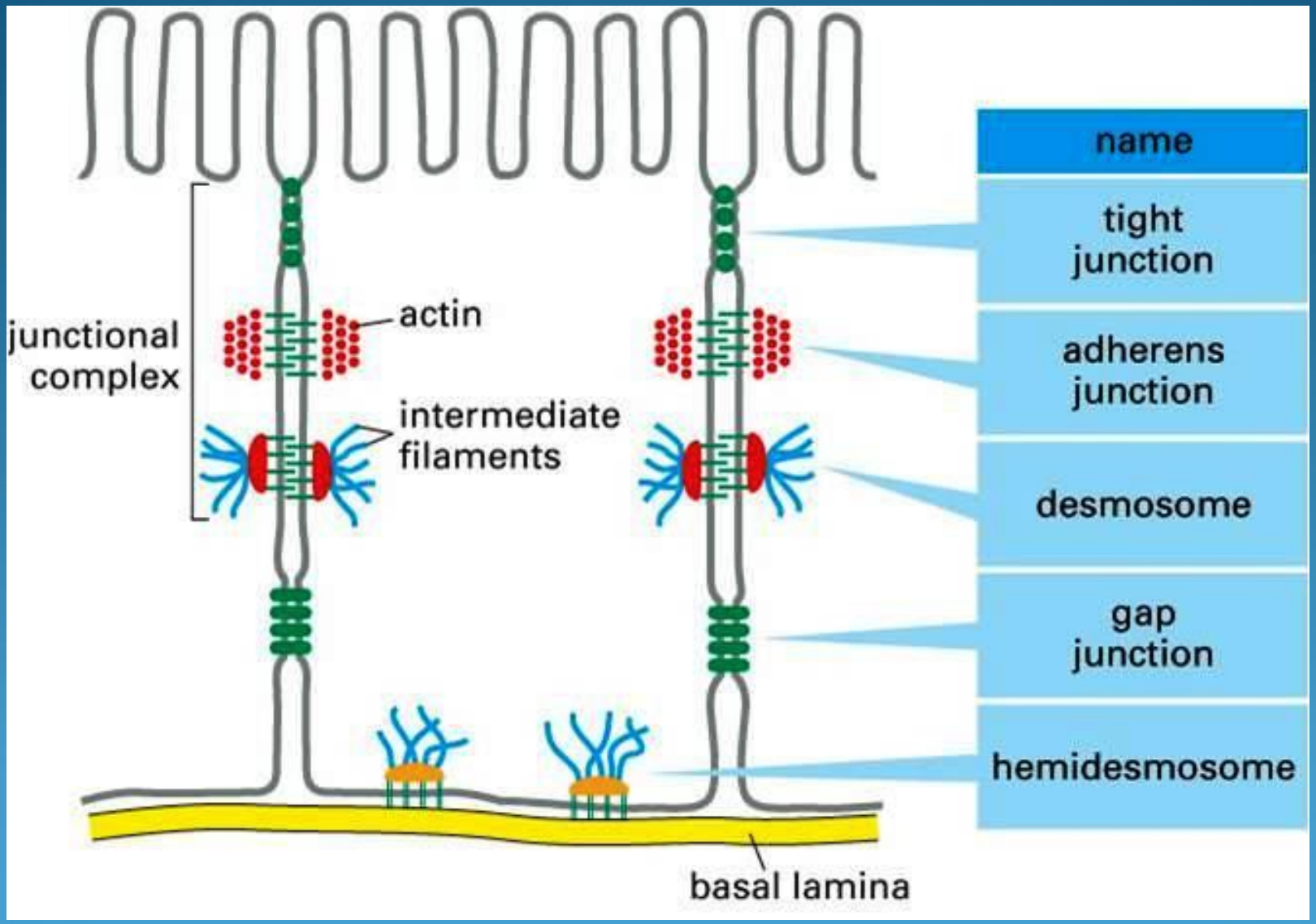
How do cells alter these connections?

-alter the profile of cytoskeletal connections, receptors, and extracellular matrix

-alter the binding affinity of receptors

-many are Ca^{2+} dependent

-many are affected by protein kinases


junctional complex
actin
intermediate filaments
basal lamina
name
tight junction
adherens junction
desmosome
gap junction
hemidesmosome

name	function
tight junction	seals neighboring cells together in an epithelial sheet to prevent leakage of molecules between them
adherens junction	joins an actin bundle in one cell to a similar bundle in a neighboring cell
desmosome	joins the intermediate filaments in one cell to those in a neighbor
gap junction	allows the passage of small water-soluble ions and molecules
hemidesmosome	anchors intermediate filaments in a cell to the basal lamina

- A network of proteins, glycosoaminoglycans (GAGs) and combinations of the two (proteoglycan) found in the extracellular space
- All ECM components are secreted by cells
- Most cells can secrete elements of the ECM but many ECMs are built by fibroblasts

Examples of ECM:

-connective tissue, basal lamina, cartilage, bone, plant/fungi cell walls, myelin sheath,

References

- *TORTORA-Essentials of anatomy & physiology 11th edition*
- *P.K Gupta Cell & molecular biology 2nd edition*
- *Geoffrey M.cooper The Cell-A molecular approach*
- *Stephen.l.wolfe Introduction to cell biology*
- *MARTINI, BARTHOLONEW Essentials of anatomy & physiology – 2nd Edn*
- *Robert B. Genns Biomembranes-molecular structure & function*
- *K. & P. Sembulingam Essentials of Medical Physiology-5th edition*
- *J. M. Anderson, 2005. Mol. Str. of tight junctions. J.Memb.Biol. 207, 55-68*
- *www.google.com.*
- *www.wikipedia.org*

conclusion

- Many cells in tissues are linked to one another and to the extracellular matrix at specialized contact sites called cell junctions.
- Tight junctions are occluding junctions that are crucial in maintaining the concentration differences of small hydrophilic molecules across epithelial cell sheets.
- Gap junctions are important in coordinating the activities of electrically active cells, and they have a coordinating role in other groups of cells as well. Cells connected by gap junctions share many of their inorganic ions and other small molecules .
- Anchoring junctions hold cells tightly together & confer mechanical strength to tissues that are subjected to severe stress.

Thank You

for your attention.....