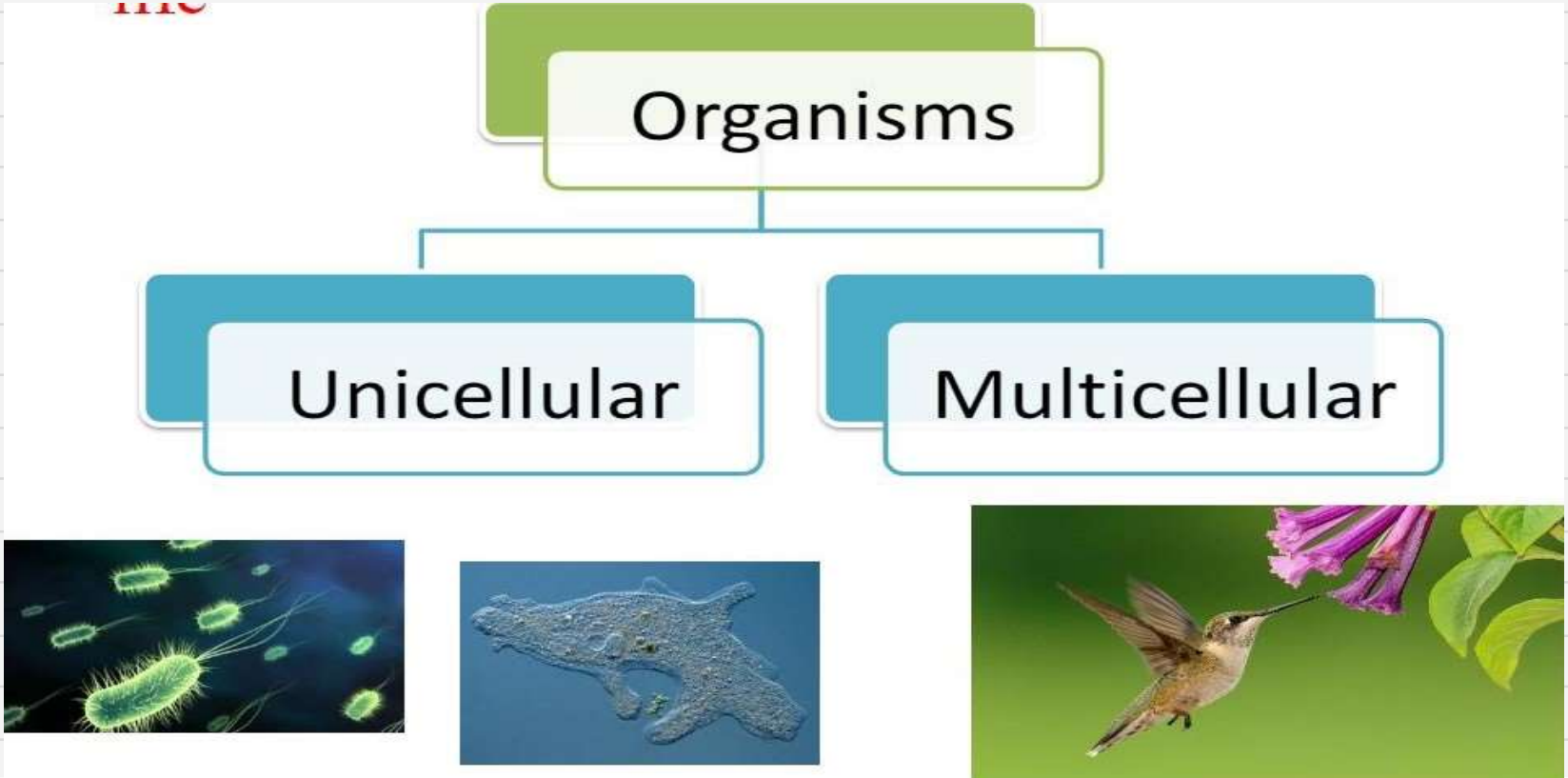
Cellular Communication

Unit- 4C

Cell is the basic structural unit of life

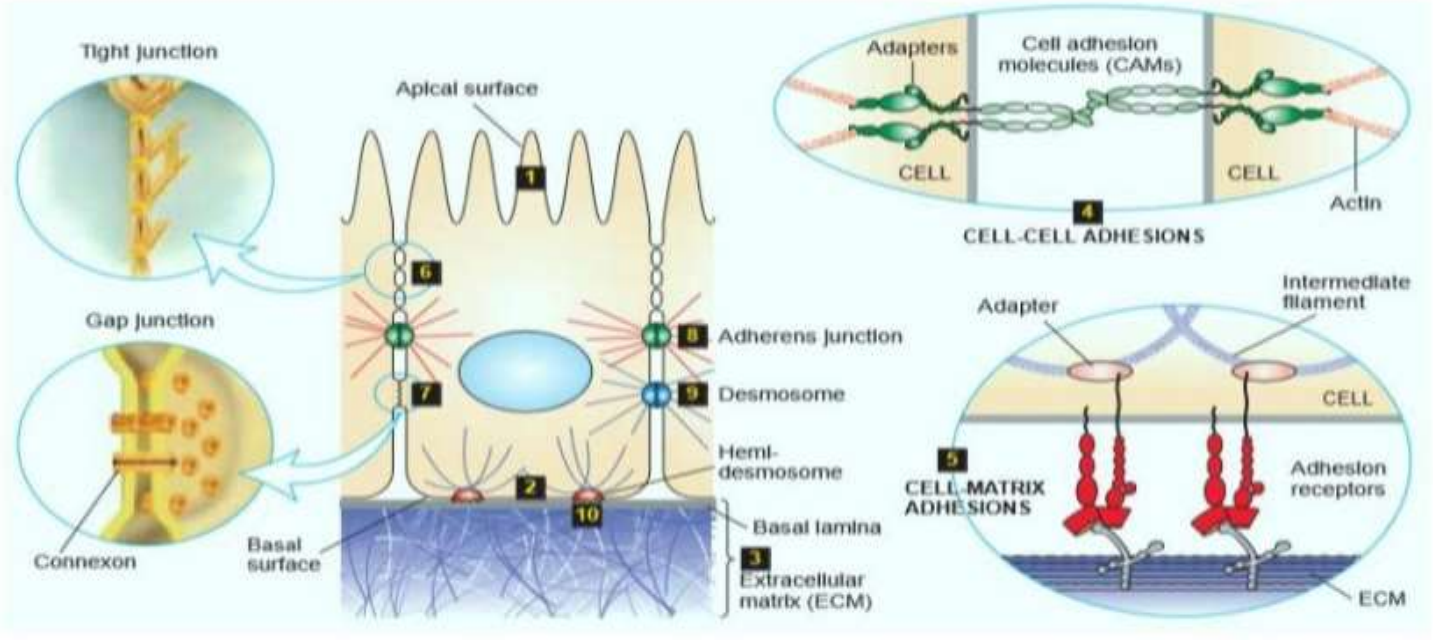


•The assembly of distinct tissues and their organization into organs are determined by molecular interactions at the cellular level

•This is possible due to the temporally and spatially regulated expression of a wide array of adhesive molecules

•Cells in tissues can adhere directly to one another (cell—cell adhesion) through specialized integral membrane proteins called cell-adhesion molecules (CAMs)

•Cells in animal tissues also adhere indirectly (cell matrix adhesion) through the binding of adhesion receptors in the plasma membrane to components of the surrounding extra- cellular matrix (ECM)

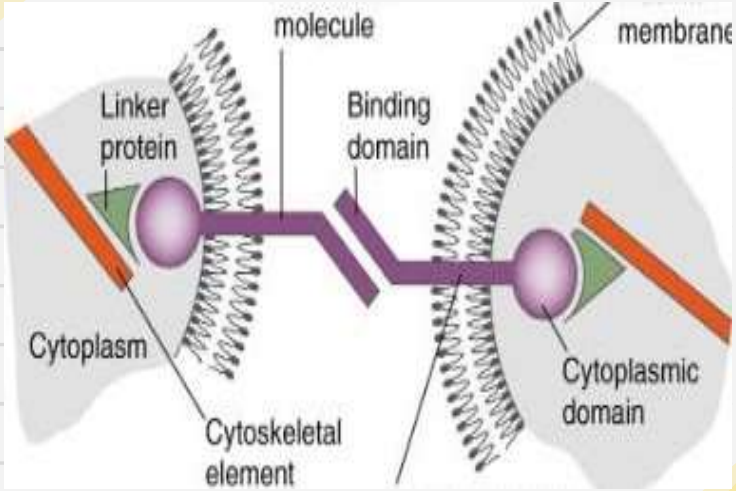

Tight junction
Apical surface
Adapters
Cell adhesion molecules (CAMs)
CELL
CELL
Actin
4
CELL-CELL ADHESIONS
Gap junction
Adherens junction
Desmosome
Hemi-desmosome
Basal lamina
Extracellular matrix (ECM)
Connexon
Basal surface
Adapter
Intermediate filament
CELL
5
CELL-MATRIX ADHESIONS
Adhesion receptors
ECM

cell Adhesion Molecules (CAM)

- Important cell surface proteins molecules promoting cell—cell and cell—matrix interactions.
- Important for many normal biological processes -embryonic cell migration, immune system functions, wound healing.
- Involved in intracellular signalling pathways (primarily for cell death/survival, secretion etc.)
- The major families of cell-surface adhesion molecules are the cadherins, selectins, Ig-superfamily CAMs, and integrins

Three major domains:-

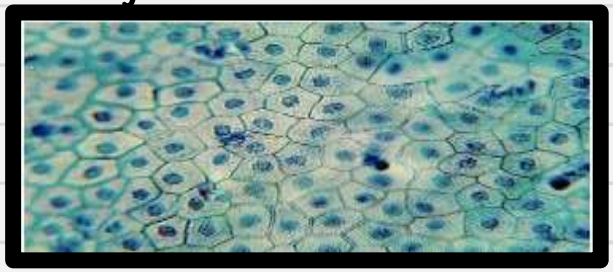
- —The extracellular domain allows one CAM to bind to another on an adjacent cell.
- —The transmembrane domain links the CAM to the plasma membrane through hydrophobic forces
- —The cytoplasmic domain is directly connected to the cytoskeleton by linker proteins.

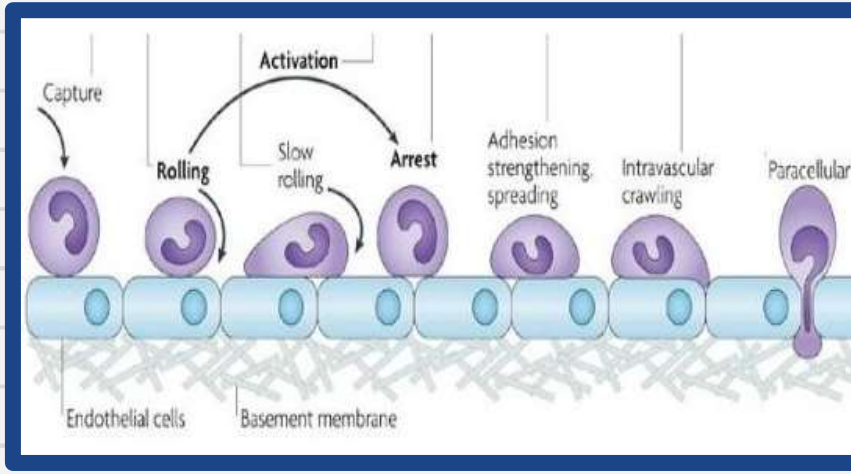


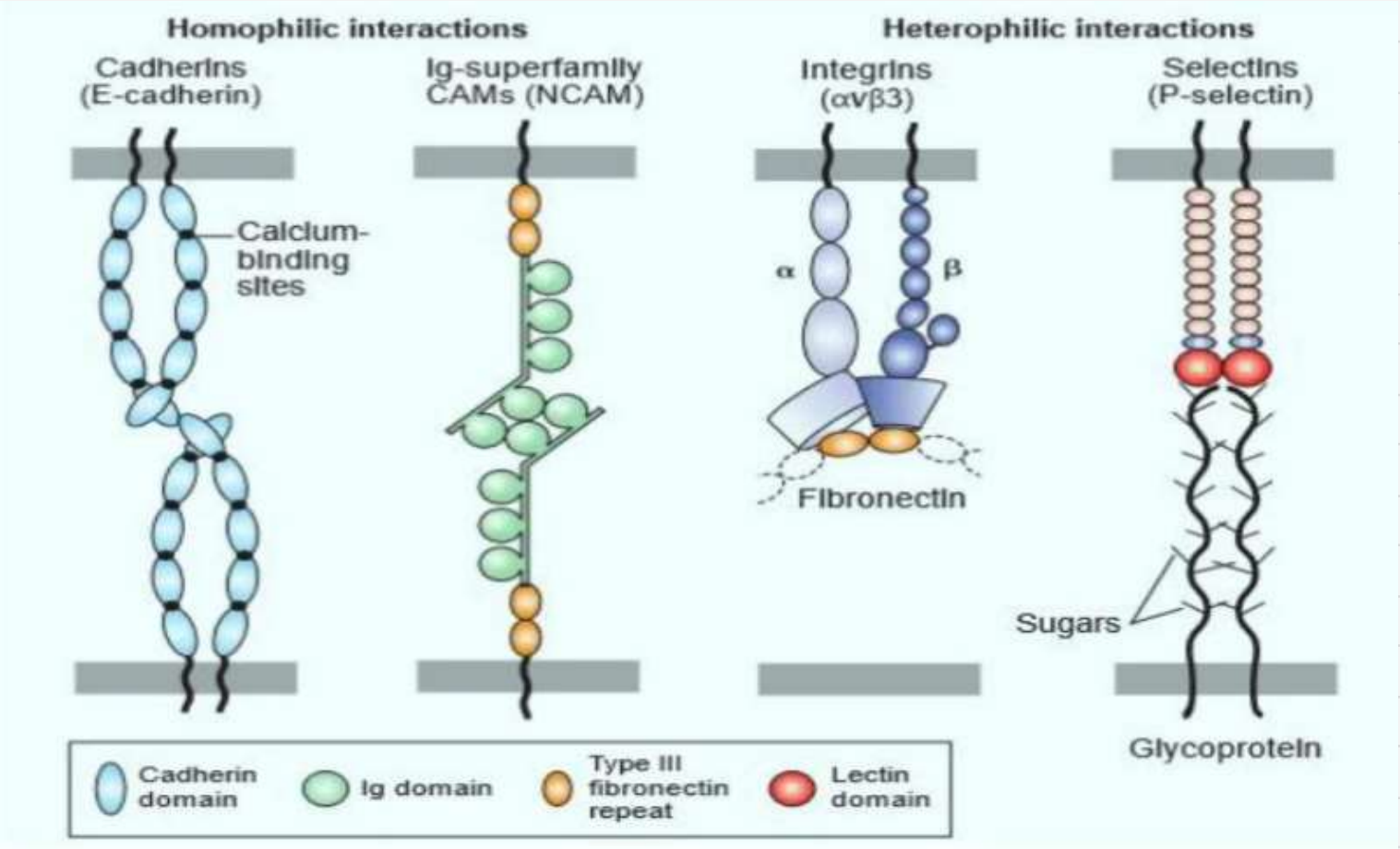
•CAMs mediate, through their extracellular domains, adhesive interactions between cells of the same or different type

•Distribution: broadly distributed along the regions of plasma membranes that contact other cells or clustered in discrete patches or spots called cell junctions

- Cell—cell adhesions can be tight and long lasting or relatively weak and transient

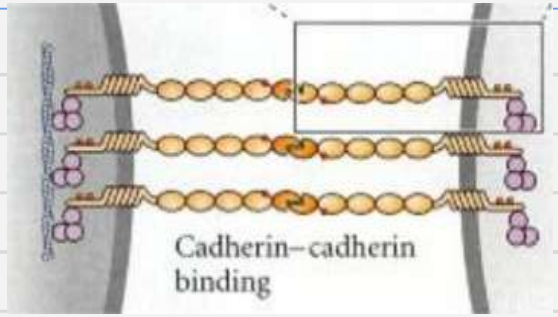





Homophilic interactions
Heterophilic interactions
Cadherins
(E-cadherin)
Ig-superfamily
CAMs (NCAM)
Integrins
(αvβ3)
Selectins
(P-selectin)
Calcium-
binding
sites
α
β
Fibronectin
Sugars
Glycoprotein
Cadherin
domain
Ig domain
Type III
fibronectin
repeat
Lectin
domain

Cadherins

- Family of glycoproteins that mediate Ca^{2}+ dependent cell adhesion
- Cadherins are key molecules in cell—cell adhesion and cell signalling, and they play a critical



•The "classical" E (Epithelial)-, P(P1acenta1)-, and N(Neura1)cadherins are the most widely expressed.

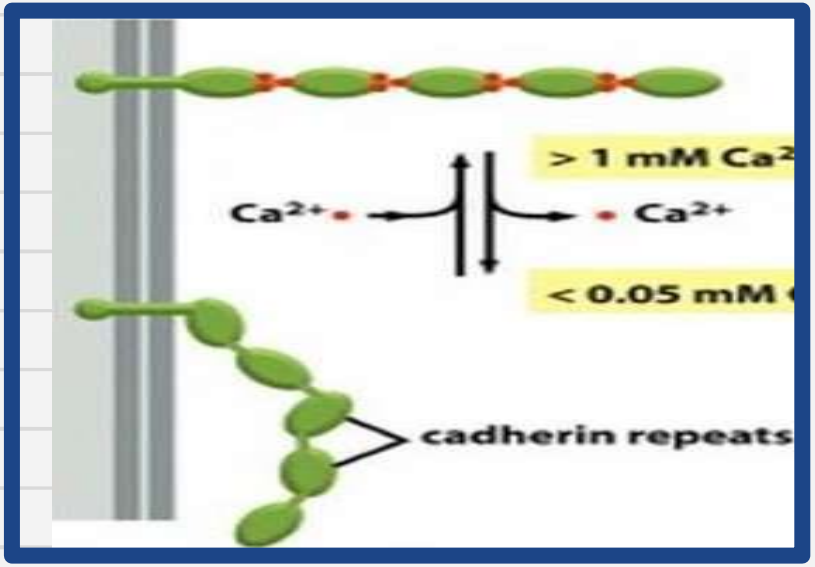
•Cadherins join cells of similar type by binding to same cadherin on the nearby cell surface

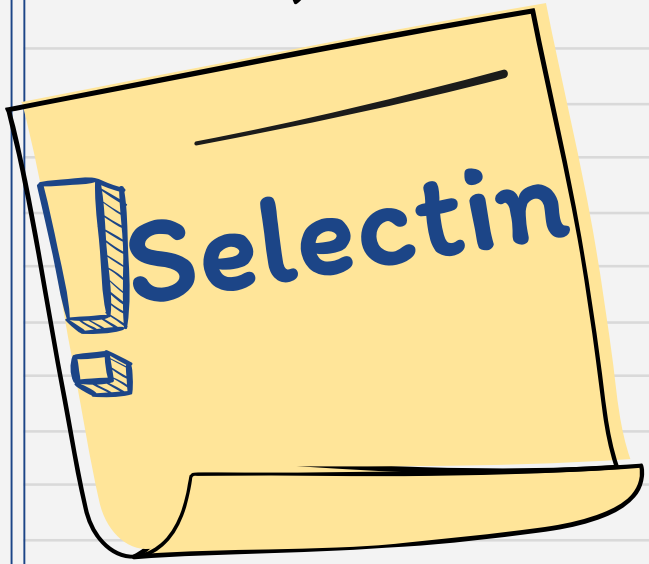
•Cadherin-mediated adhesion entails both lateral (intracellular) and trans (intercellular) molecular interactions

•Each classical cadherin contains a single transmembrane domain, a relatively short C-terminal cytosolic domain, and five "extracellular cadherin" domains.

•The Ca^{2}+ binding sites, located between the cadherin repeats, serve to rigidify the cadherin oligomers.

•The C-terminal cytosolic domain of classical cadherins is linked to the actin cytoskeleton by a number of cytosolic adapter proteins - catenin





•Selectins are family of integral membrane glycoproteins that recognize and bind to a particular arrangement of sugars in the oligosaccharides that project from the surface of other cells

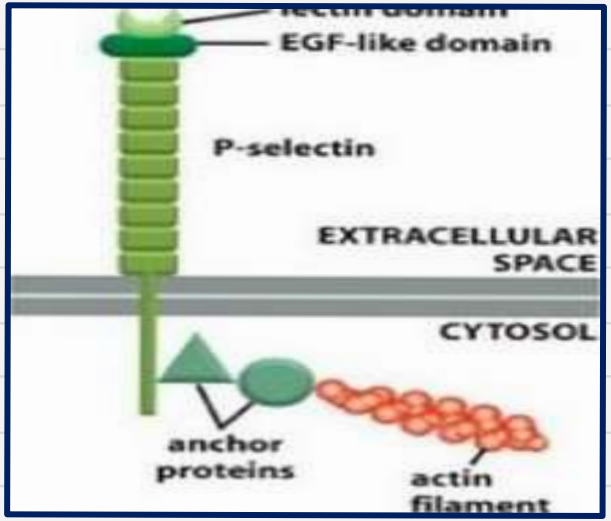
•They posses a small cytoplasmic domain, a single membrane spanning domain and large extracellular segment that contains separate domains

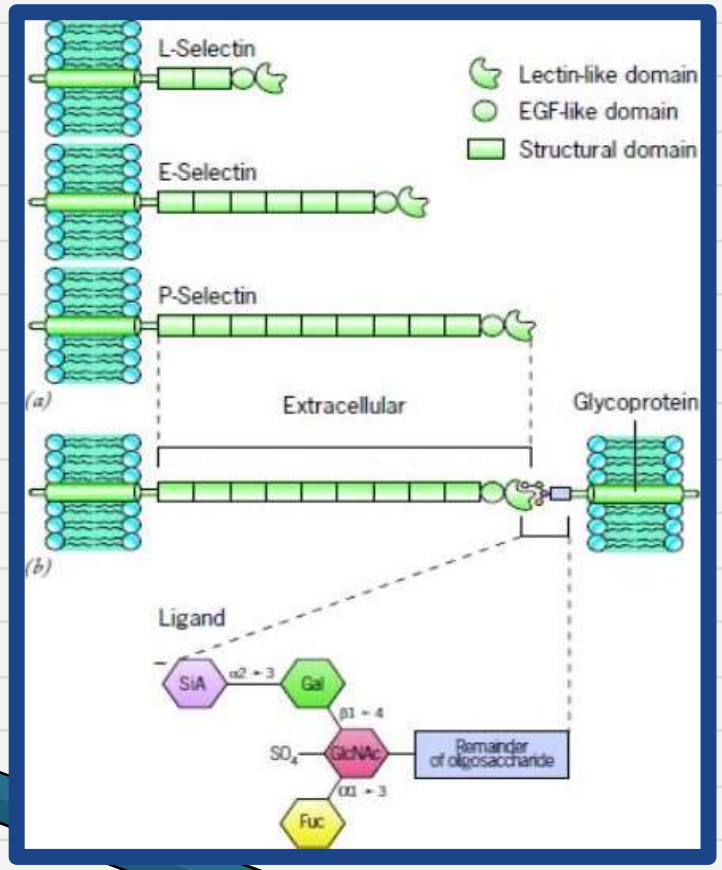
•Binding of selectins to their carbohydrate ligands require calcium

• Terminal fucose, sialic acid moieties are important for selectin binding

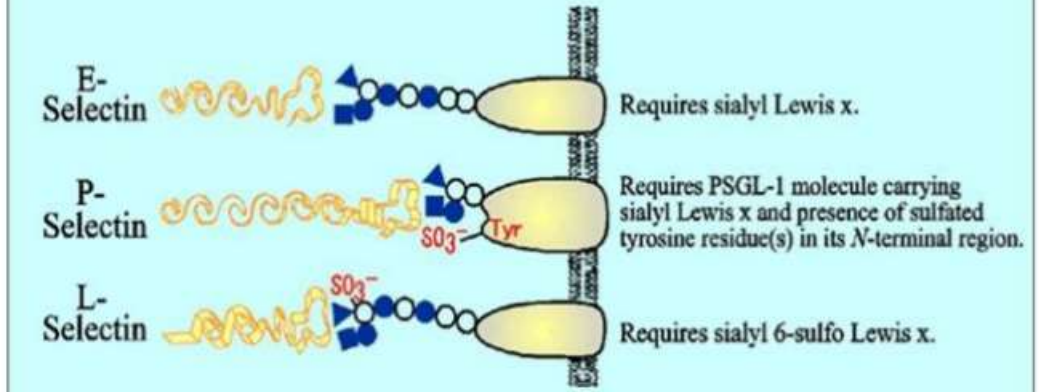
There are three known selectins:

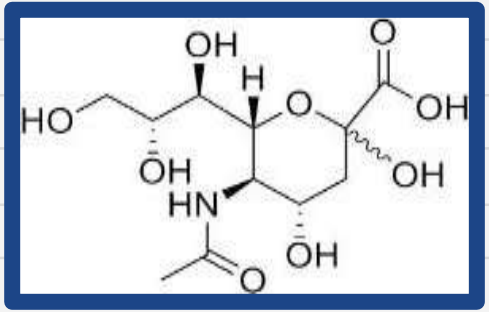
- ❑ E selectin — endothelial cells
- ❑ P selectin — platelets and endothelial cells
- ❑ L selectin - leukocytes

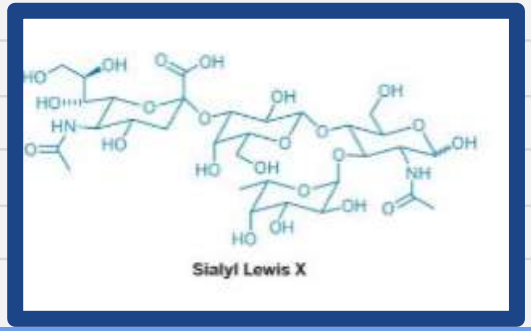


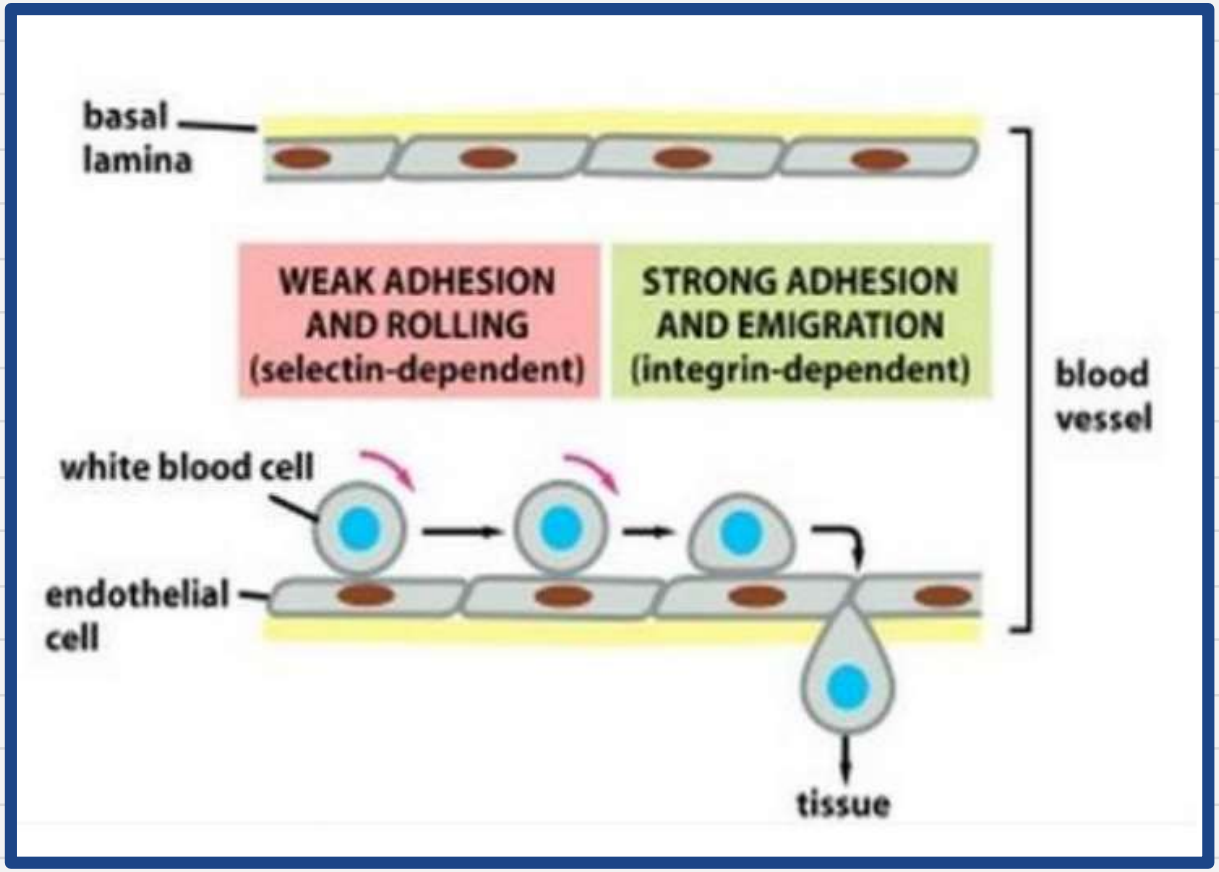


Ligand Specificity of Selectins








basal lamina
WEAK ADHESION AND ROLLING (selectin-dependent)
STRONG ADHESION AND EMIGRATION (integrin-dependent)
blood vessel
white blood cell
endothelial cell
tissue

INTERGRINS

•The integrin family comprises heterodimeric integral membrane proteins that function as adhesion receptors, mediating many cell—matrix interactions

•Vertebrates have at least 24 integrin heterodimers, composed of 18 types of u subunits and 8 types of 13 subunits in various combinations

•Bind epithelial and muscle cells to laminin in the basal lamina

•Allow platelets to stick to exposed collagen in a damaged blood vessel

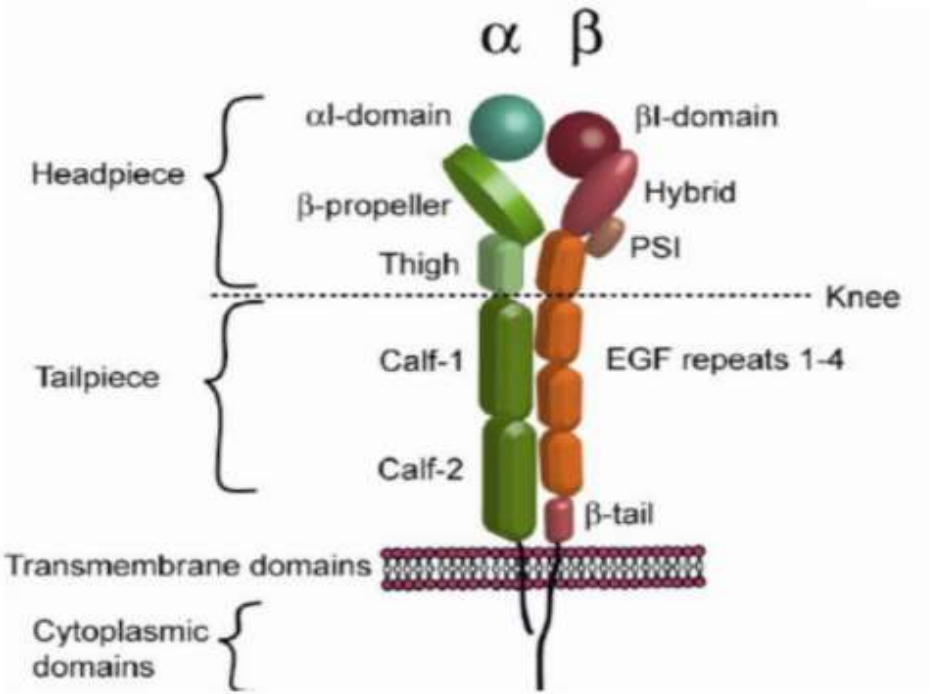
•Allow fibroblasts and white blood cells to adhere to fibronectin and collagen as they mov

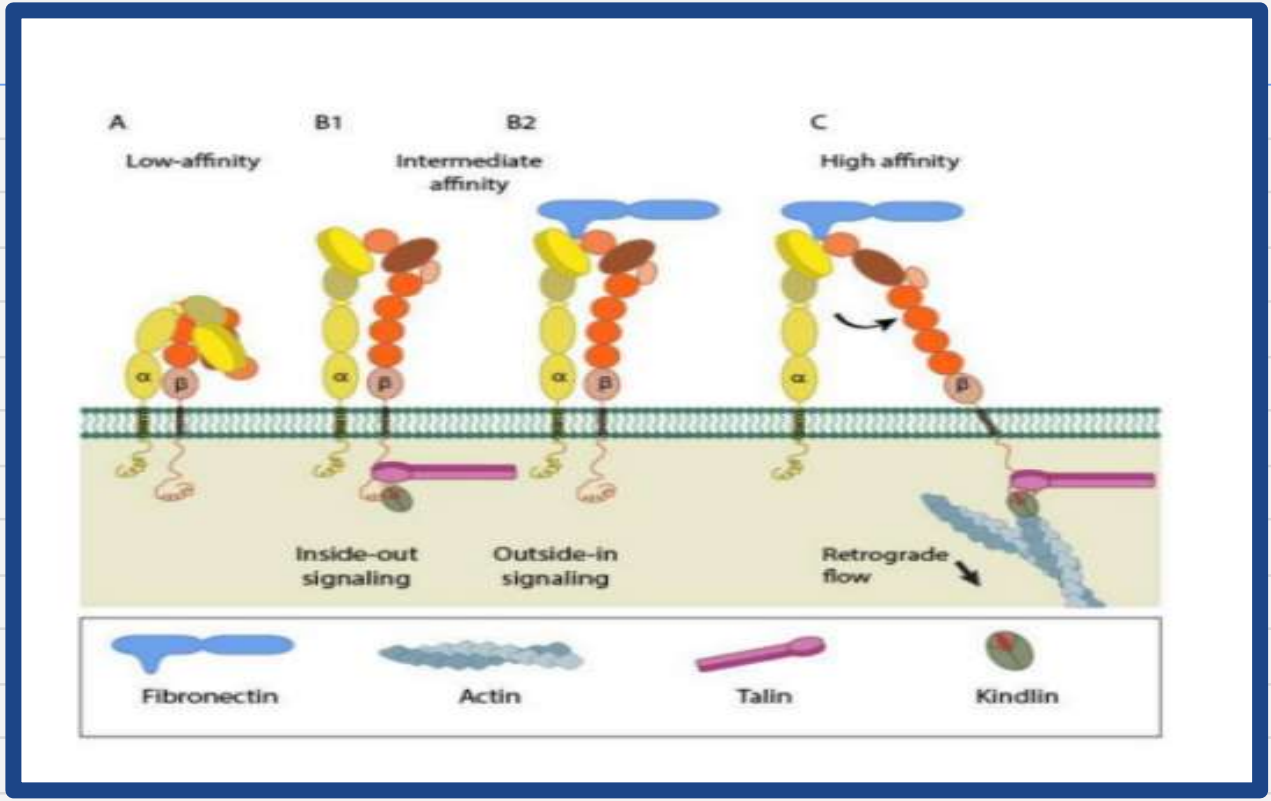
•The alpha subunits N terminal domain extracellular portion consists of 7 repeating modules (approx. 60 aa) folded into a flattened circular single domain called as Seven bladed 1 propeller Three Ca^{2}+ ions are present in part o blade 5, 6, and 7

•Some contain extra module of 200 aa called a I domain on top of 13 propeller

•The ß subunit lacks propeller but has I domai

•Ligand binding site - u subunits is either ß propeller or I domain and ß subunit is I domai


α β
αI-domain
βI-domain
Headpiece
β-propeller
Hybrid
PSI
Thigh
Knee
Tailpiece
Calf-1
EGF repeats 1-4
Calf-2
β-tail
Transmembrane domains
Cytoplasmic domains



Most of the extracellular proteins that bind to integrins like fibronectin, proteoglycans, laminins, collagen etc. contain the amino acid sequence RGD.

Immunoglobulin Superfamily Molecules

- The immunoglobulin superfamily includes the most diverse group of receptors
- Consists of more than 25 molecules
- Contain the immunoglobulin homology domain
- central to both the humoral and cell mediated immune reactions
- IgSF —CAM mediate the specific interactions of lymphocytes with cells required for immune response
- Cell surface receptors responsible for embryonic development

- **Important ones being:**

✓ Intercellular adhesion molecule I (ICAMI; CD54)

✓ **Intercellular adhesion molecule 2 (ICAM2, CDIIO),**

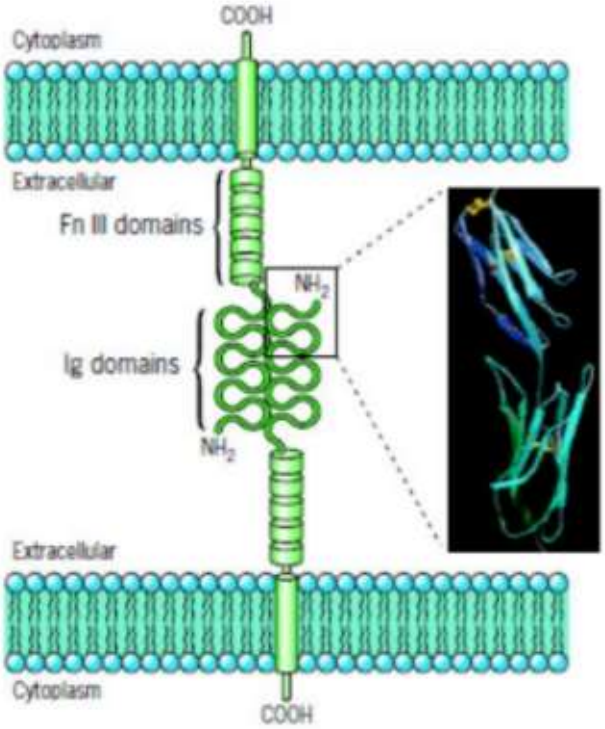
✓ **Vascular cell adhesion molecule 1(VCAMI; CD106),**

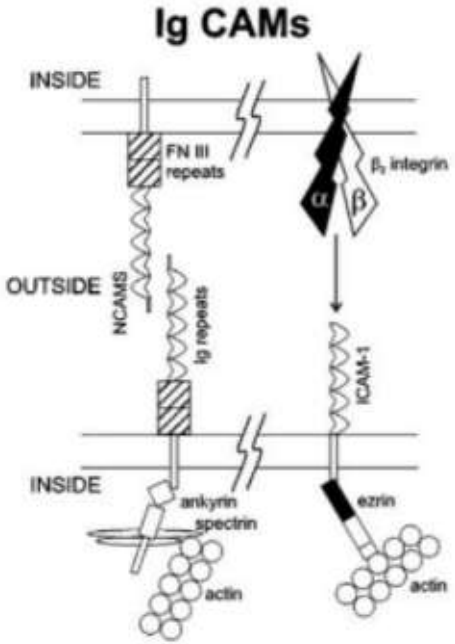
✓ Platelet endothelial cell adhesion molecule I (PECAM l; CD31) and

✓ **the mucosal addressin cell adhesion molecule I (MAdCAM1)** NCAM (neural cell-adhesion molecule)

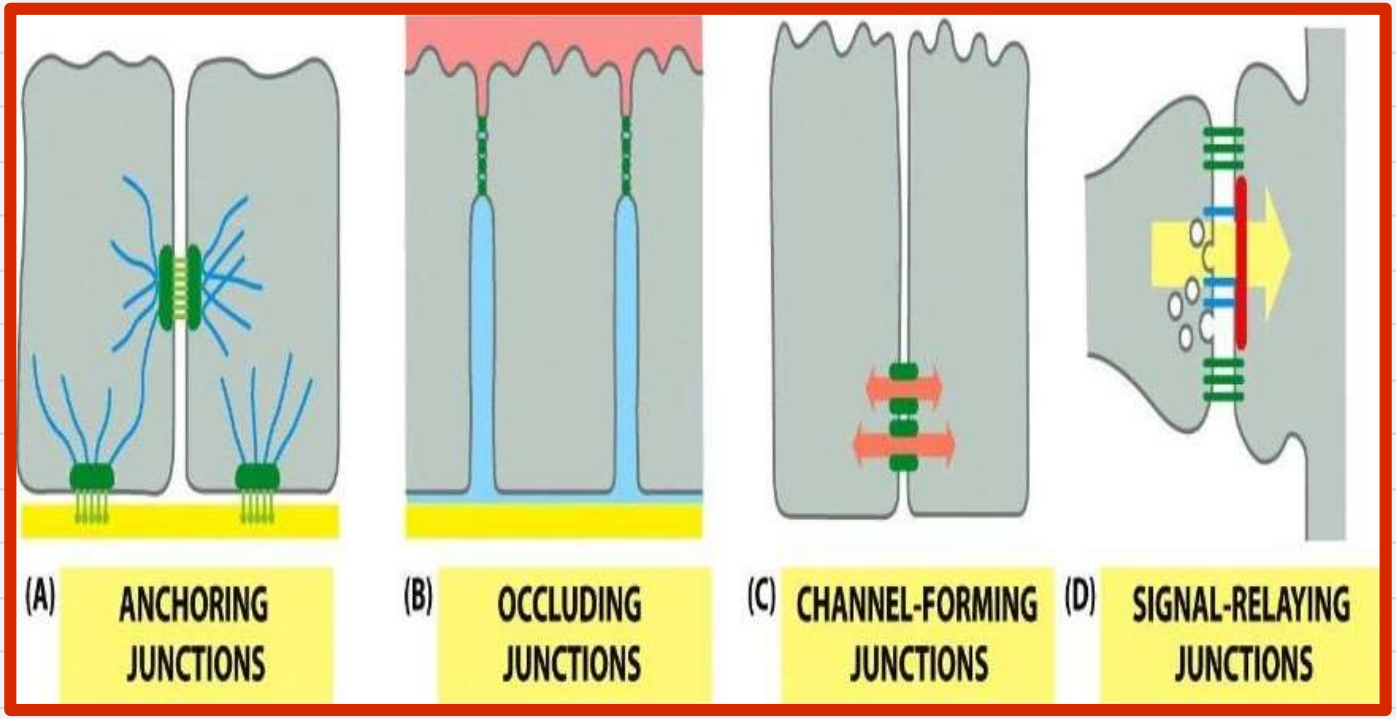
✓ **Upon activation, they elicit intracellular signalling cascades in the tip of the axon, affecting various axonal functions**

✓ **IgSF cell adhesion molecules interact with the components of the cytoskeleton including the actin microfilaments, and microtubules.**


COOH
Cytoplasm
Extracellular
Fn III domains
NH2
Ig domains
NH2
Extracellular
Cytoplasm
COOH

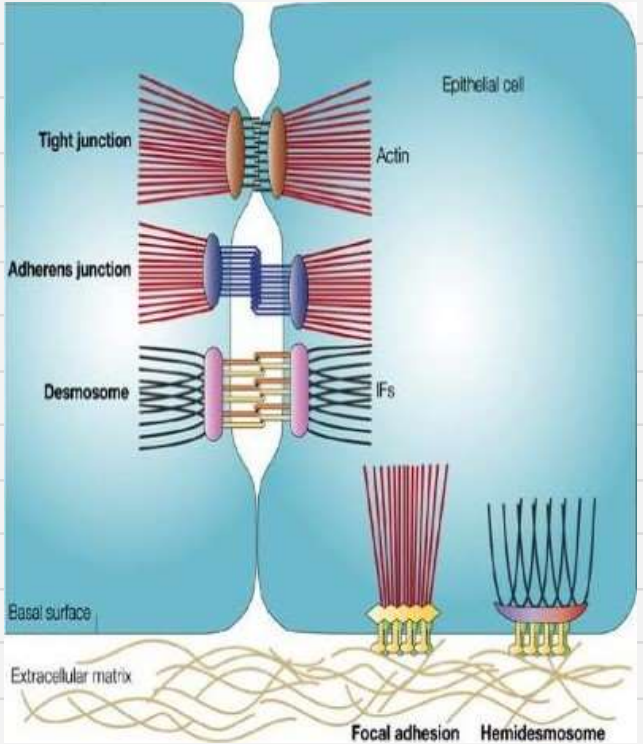

Ig CAMs
INSIDE
FN III repeats
β integrin
α
β
OUTSIDE
NCAMS
Ig repeats
ICAM-1
INSIDE
ankyrin
spectrin
actin
ezrin
actin

Cell junction



Types

- **Between cells**
  - Tight junctions
  - Adherens junctions
  - Desmosomes
  - Gap junctions
- **Between cells and matrix**
  - Hemidesmosomes
  - Focal adhesions



Types

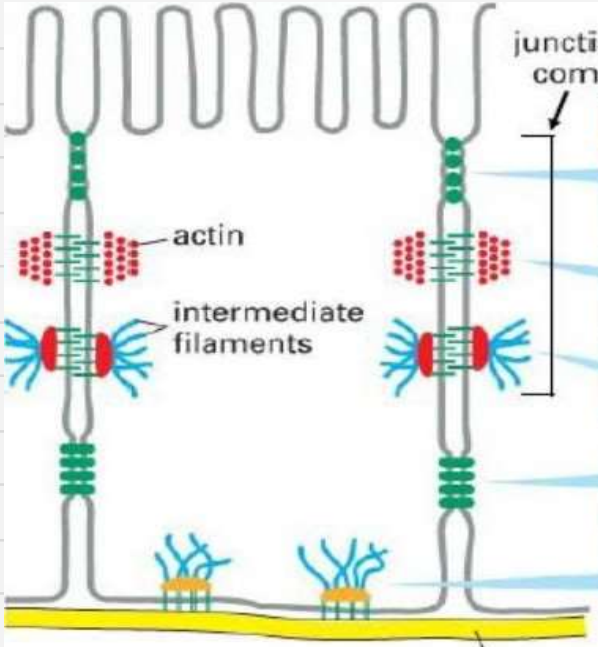
Occluding junctions –

- ✓ Tight junctions
- ✓ Anchoring junctions –
- ✓ Adherens junctions
- ✓ Desmosomes
- ✓ Hemidesmosomes
- ✓ Focal adhesions

Communicating junctions

- ✓ Gap Junctions

Functions Of Cell Junction



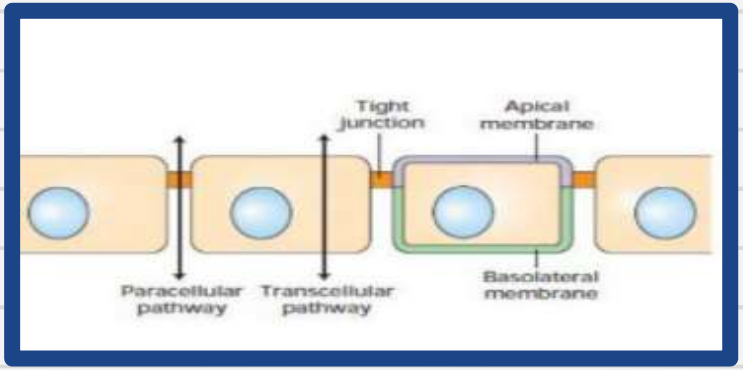
name	function
tight junction	seals neighboring cells together in an epithelial sheet to prevent leakage of molecules between them
adherens junction	joins an actin bundle in one cell to a similar bundle in a neighboring cell
desmosome	joins the intermediate filaments in one cell to those in a neighbor
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 (Zonulae occludens)

-Closely associated areas of two cells whose membranes join together forming a virtually impermeable barrier to fluid

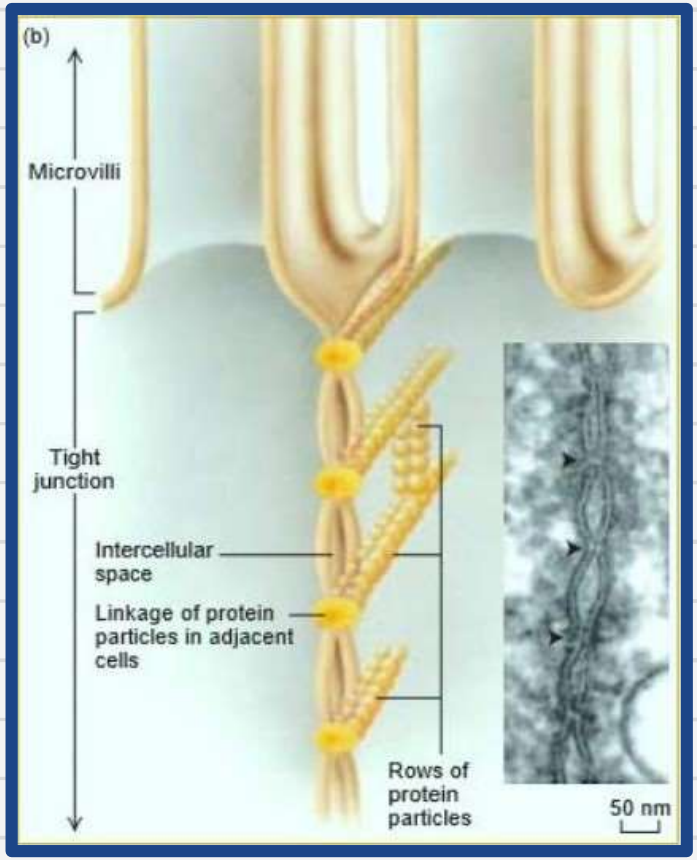
-The tight junctions between adjacent epithelial cells are usually located just below the apical surface and help establish and maintain cell polarity

-These specialized regions of the plasma membrane form a barrier that seals off body cavities such as the intestine, the stomach lumen, the blood etc.



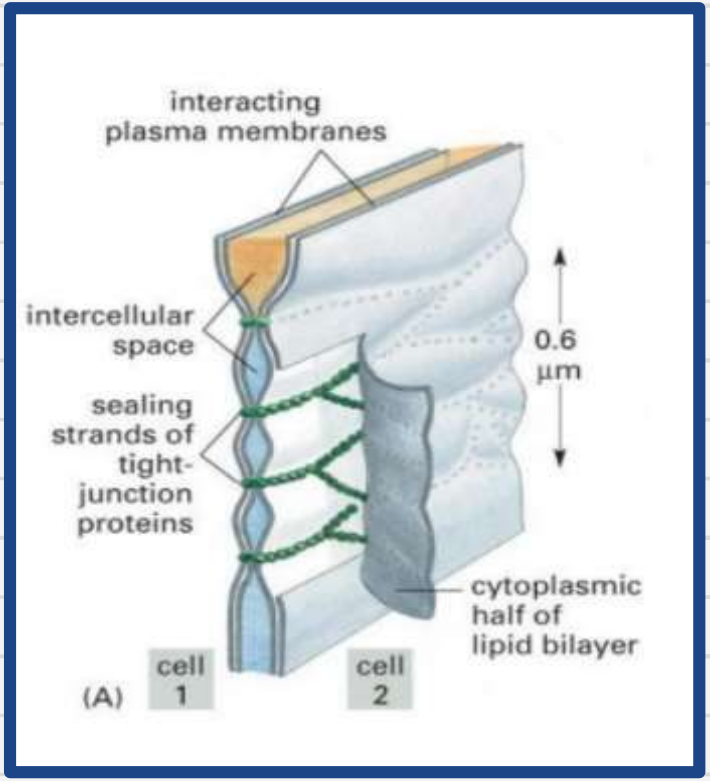
They perform three vital functions:

- They hold cells together, Strength and stability
- They block the movement of integral membrane proteins between the apical and basolateral surfaces of the cell, maintain polarity
- They prevent the passage of molecules and ions through the space between cells. So materials must actually enter the cells in order to pass through the tissue.



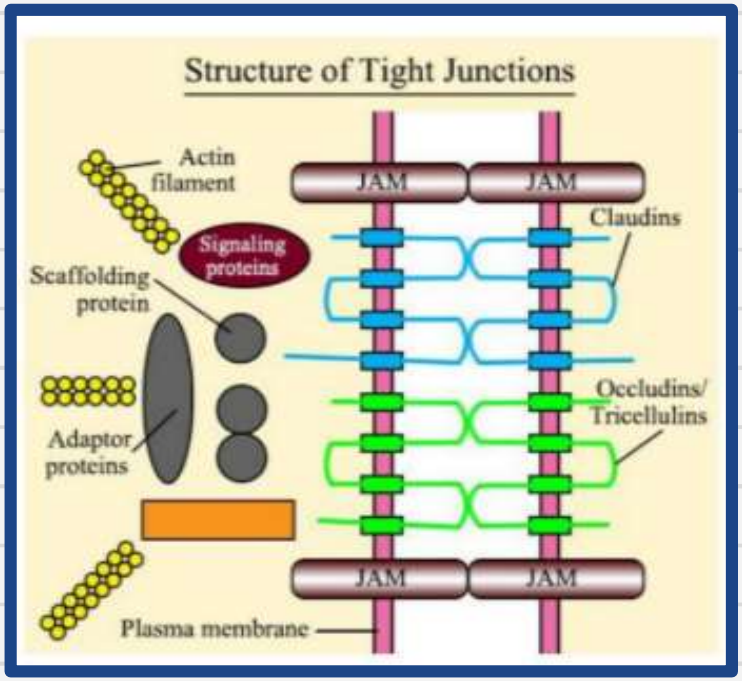
- ✓ Tight Junctions are composed of thin bands interacting plasma membranes of plasma membrane proteins that completely encircle a polarized cell and are in contact with similar thin bands on adjacent cells.

- ✓ The junction membrane proteins are arranged like beads on a thread of the cytoskeletal filaments and are cross-linked to each other.



Structure of Tight Junctions

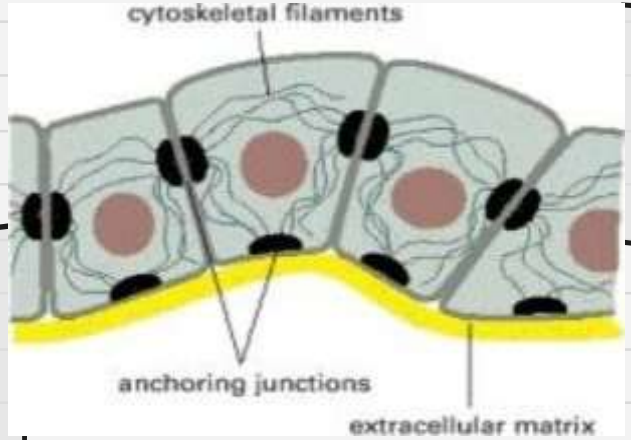
- Tetra span proteins contain four membrane spanning domains, these include proteins like occludins, claudins, and tricellulins.
- Single-span transmembrane proteins include Junctional Adhesion Molecules (JAMs).
- The cytoplasmic plaque is formed by a network of scaffolding and adaptor proteins, that are bound to cell signaling components as well as to the components of the cytoskeleton such as actin filaments.
- The major transmembrane proteins in a tight junction are the claudins, which are essential for tight junction formation and function.



Tight Junctions

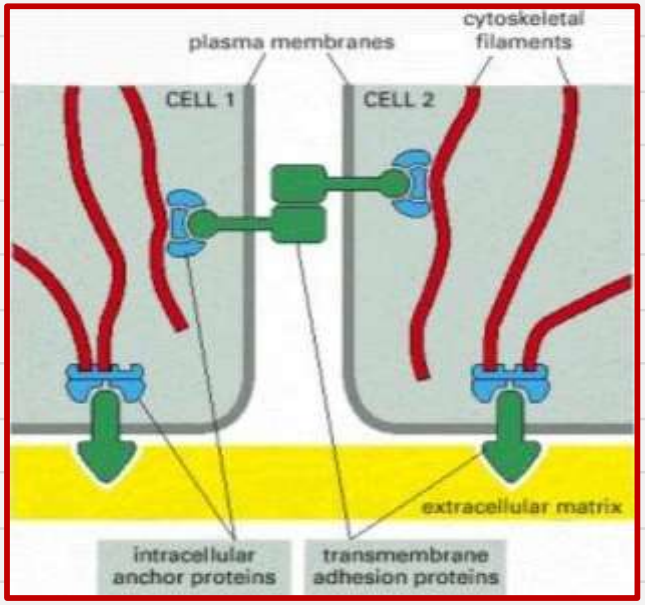
- A specific claudin found in kidney epithelia cells, for example, is required for $Mg^{2}+$ to be resorbed from the urine into the blood.
- A second major transmembrane protein in tight junctions is occludins, the function of which is uncertain.
- Junction adhesion molecules (JAMs) have been found to contribute to homophilic adhesion and other functions of tight junctions.

Anchoring Junction



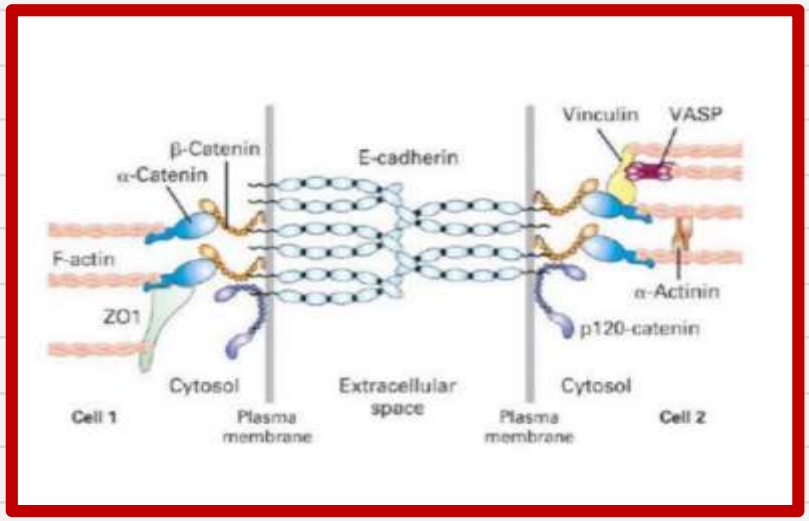
- Anchoring junction are the junction, which provides strength to the cell by acting like mechanical attachment.
- These junction provide firm structural attachment between two cells or between a cell and extracellular matrix
- Anchoring junction are responsible for structural integrity of the tissue.

- They are composed of two main classes of proteins:
  - Intracellular anchor proteins
  - Transmembrane adhesion proteins



- Anchoring junctions occur in two functionally different forms:
- Adherens junctions and desmosomes hold cells together and are formed by transmembrane adhesion proteins that belong to the cadherin family.
- Focal adhesions and hemidesmosomes bind cells to the extracellular matrix and are formed by transmembrane adhesion proteins of the integrin family.
- On the intracellular side of the membrane, Adherens junctions and focal adhesions serve as connection sites for actin filaments, while desmosomes and hemidesmosomes serve as connection sites for intermediate filaments

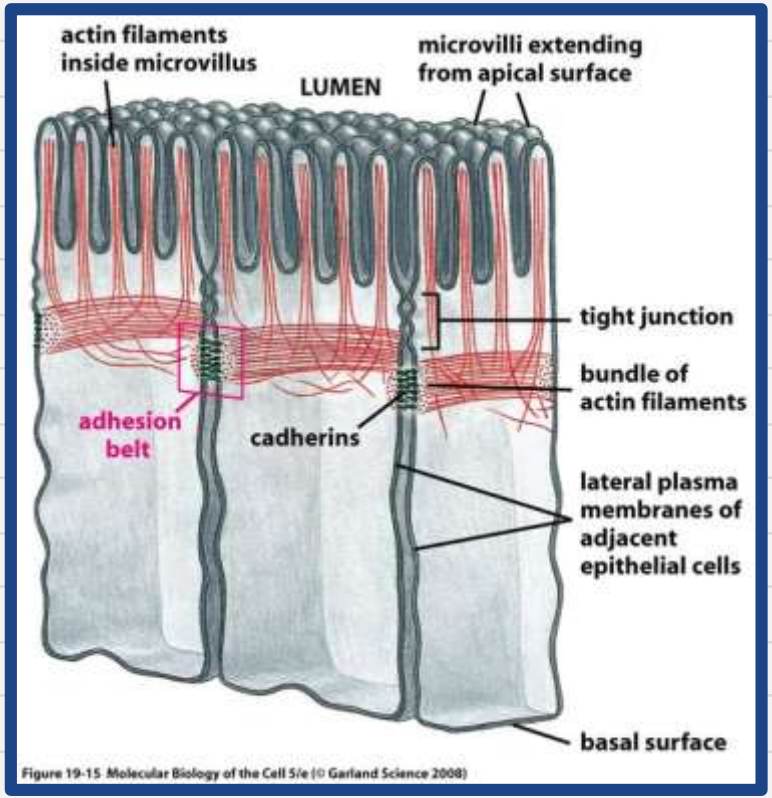
Adherens junctions (Zona Adherens)



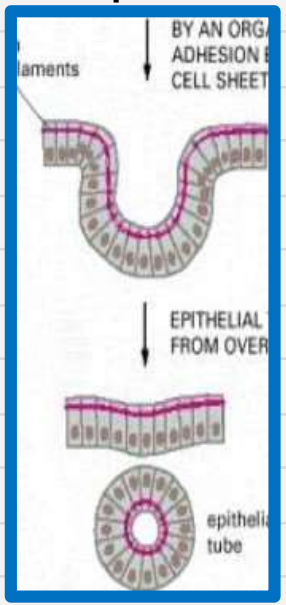
Functions:

Connect the external environment to the actin cytoskeleton and Provide potential pathway for signalling

- They are found in variety of sites within the body.
- The cells at Adherens junction are held together by cadherins molecules which bridge a gap of 30 nm between the neighbouring cells
- Cytoplasmic domains of the cadherins is linked by catenin's to different cytoplasmic protein, actin filaments.

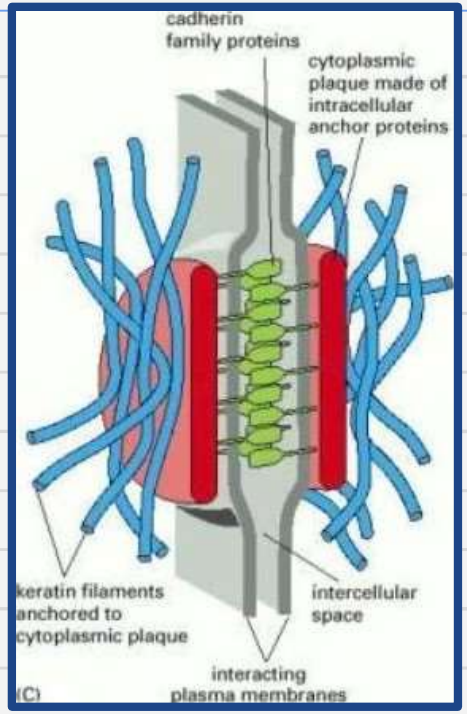


Invagination of epithelial sheet caused



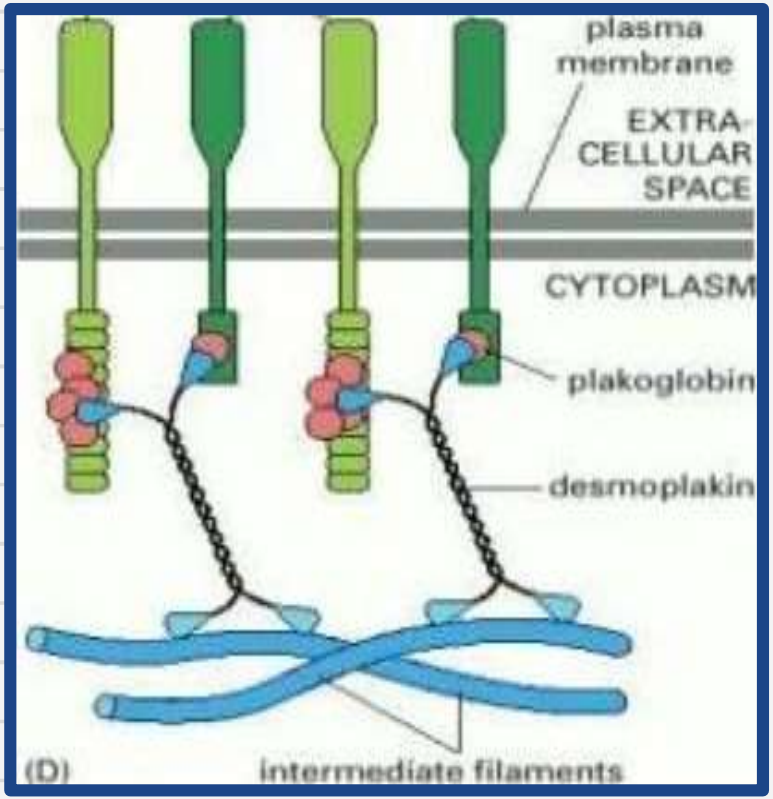
Desmosomes (macula adherens)

- It is a cell structure specialized for cell-to-cell adhesion
- They are button like points of intercellular contact that rivet cells together.
- Are molecular complexes of cell adhesion proteins and linking proteins that attach the cell surface adhesion proteins to intracellular keratin cytoskeletal filaments.

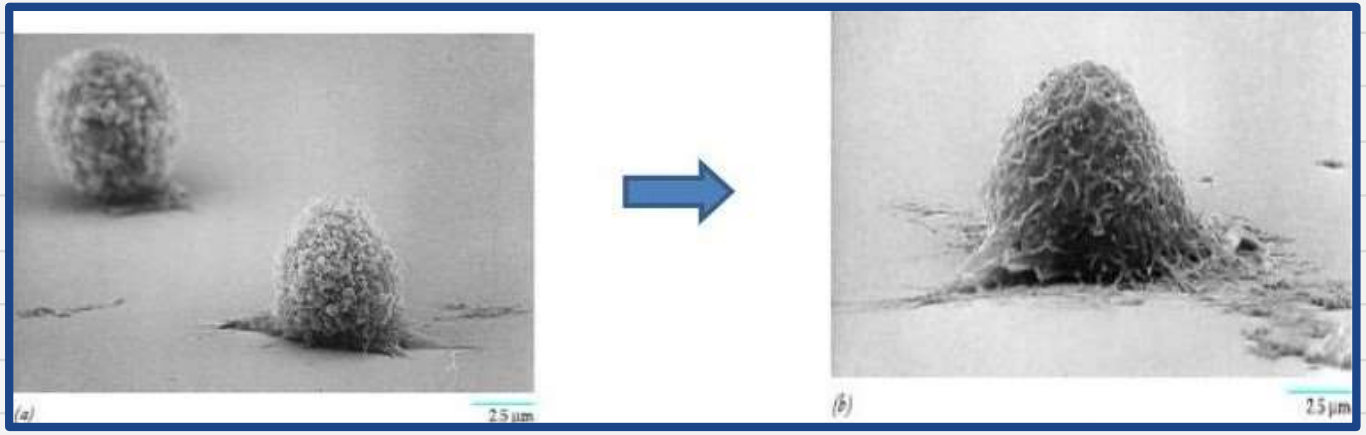


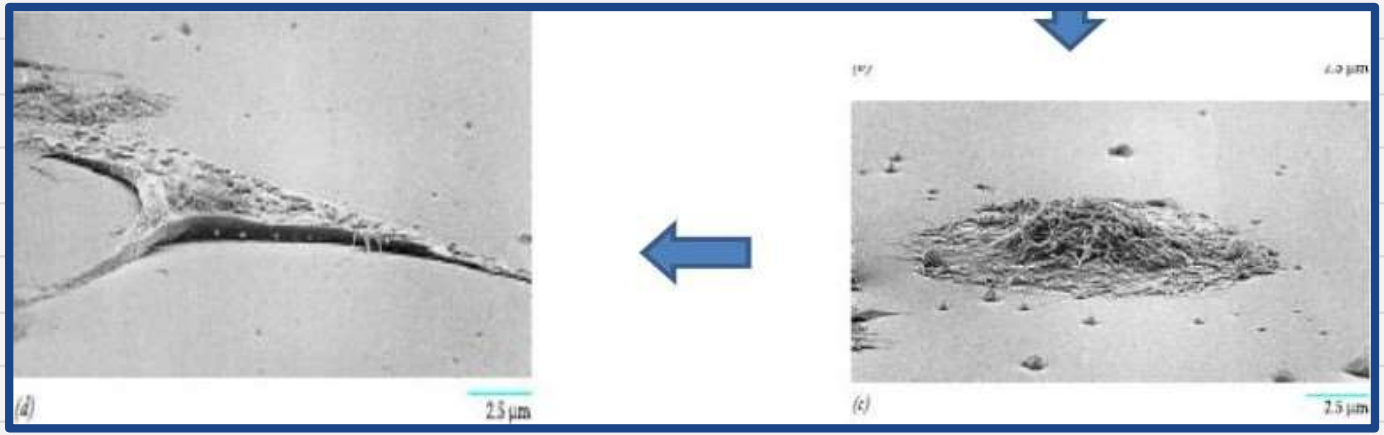
- The junction has a dense cytoplasmic plaque composed of a complex of intracellular anchor proteins (plakoglobin and desmoplakin) that are responsible for connecting the cytoskeleton to the transmembrane adhesion proteins.

- These adhesion proteins (desmoglein and desmocollin), belong to the cadherin family



Focal Adhesion





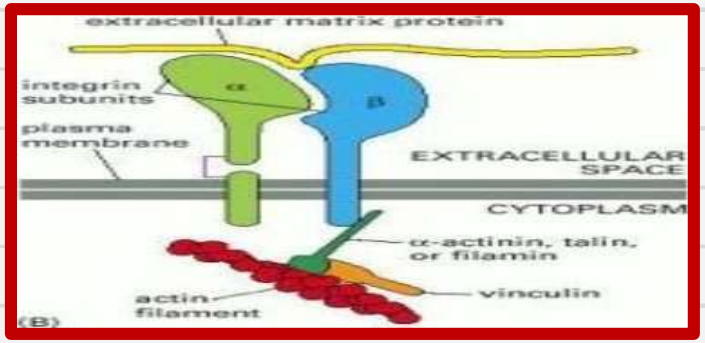
enable cells to get a hold on the extracellular matrix through integrins that link intracellular to actin filaments.

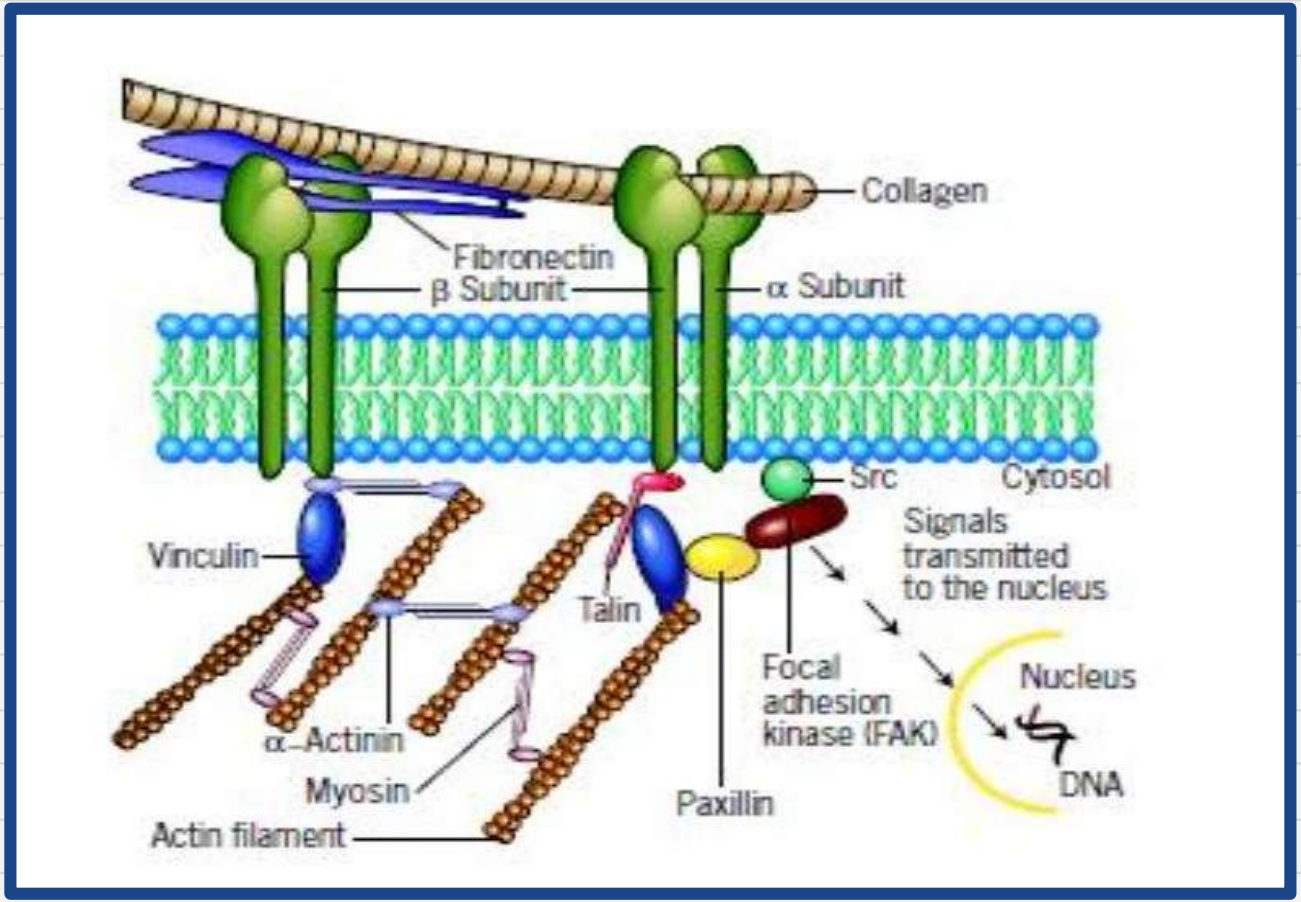
the extracellular domains of transmembrane integrin proteins bind to a protein component of the extracellular matrix, while their intracellular domains bind indirectly to bundles of actin filaments via the intracellular anchor proteins talin, u-actinin, filamin, and vinculin

Focal adhesions are primarily important in in vitro cell culture.

- Binding of extracellular ligands like collagen, fibronectins induces conformational changes in cytoplasmic domain of integrins making to contact with actin filaments

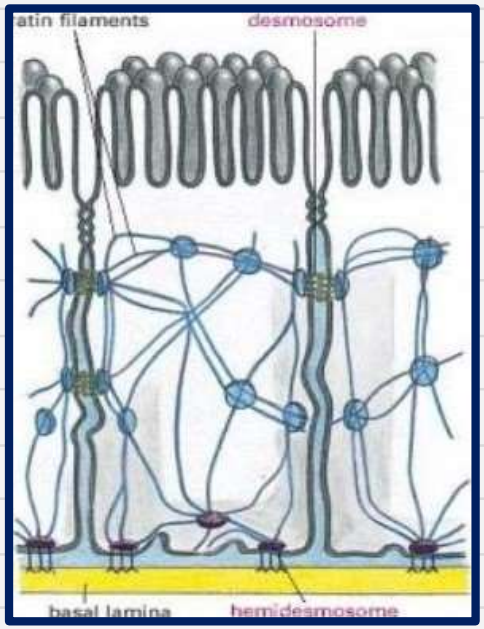
- Cytoplasmic domain also helps in signal transduction by the associated protein kinases such as FAK




Collagen
Fibronectin
β Subunit
α Subunit
Src
Cytosol
Signals transmitted to the nucleus
Vinculin
Talin
Focal adhesion kinase (FAK)
Nucleus
DNA
α–Actinin
Myosin
Actin filament
Paxillin

Hemi desmosomes, or half desmosomes

- Resemble desmosomes morphologically and in connecting to intermediate filaments

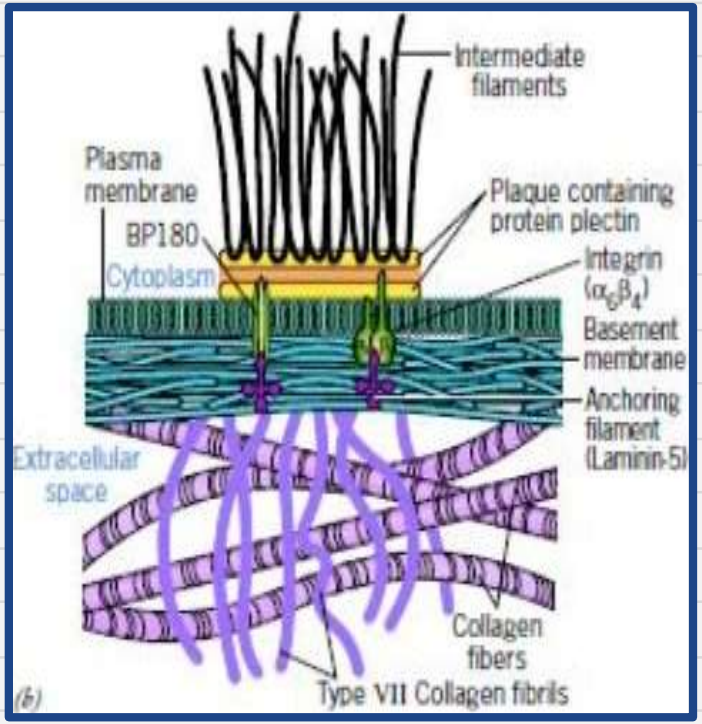


•Similar to desmosomes, they act as rivets to distribute tensile or shearing forces through an epithelium

•hemi desmosomes connect the basal surface of an epithelial cell to the underlying basal lamina

- **The integrin molecule attach to one of many multi-adhesive proteins such as laminins, resident within the extracellular matrix, thereby forming one of many potential adhesions between cell and matrix**

  - an intracellular domain binds via an anchor protein (plectin) to keratin intermediate filaments.



Anchoring Junctions				
Junction	Transmembrane adhesion protein	Extracellular ligand	Intracellular cytoskeletal attachment	Intracellular adaptor proteins
Cell–Cell				
Adherens junction	Classical cadherins	Classical cadherin on neighboring cell	Actin filaments	α-Catenin, β-catenin, plakoglobin (γ-catenin), p120-catenin, vinculin
Desmosome	Nonclassical cadherins (desmoglein, desmocollin)	Desmoglein and desmocollin on neighboring cell	Intermediate filaments	Plakoglobin (γ-catenin), plakophilin, desmoplakin
Cell–Matrix				
Actin-linked cell–matrix junction	Integrin	Extracellular matrix proteins	Actin filaments	Talin, kindlin, vinculin, paxillin, focal adhesion kinase (FAK), numerous others
Hemidesmosome	$\alpha_6\beta_4$ Integrin, type XVII collagen	Extracellular matrix proteins	Intermediate filaments	Plectin, BP230

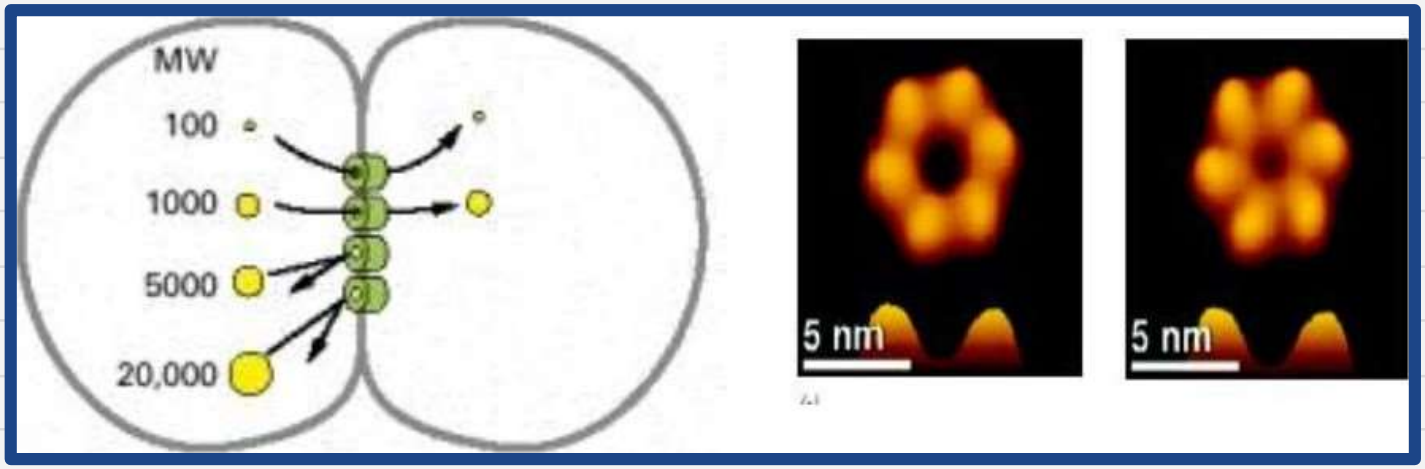
Communicating Junction

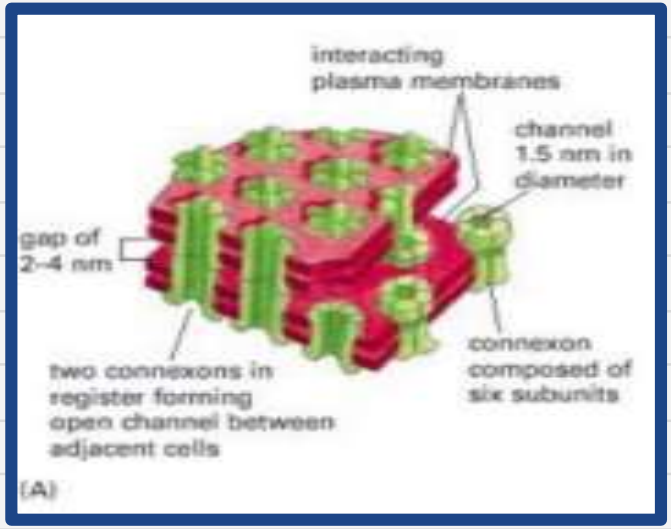
- Cell junction which permit the intercellular exchange of substance are called communicating junction, these junction permit the movement of ions and molecules from one cell to another cell.

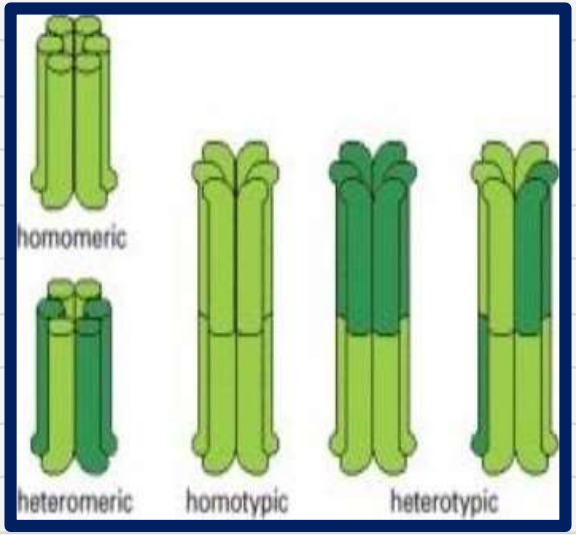
- a- Gap junction
- b- Chemical synapse

Gap junctions

- Gap junctions are clusters of intercellular channels that allow direct diffusion of ions and small molecules between adjacent cells.
- The plasma membrane comes in very close contact to one another (approx 3 nm) but do not make direct contact.
- The gap is spanned by channel(connexons) forming proteins(connexins) — 6
- Gap junctions were first discovered in myocardium because of their properties of electrical transmission between adjacent cells
- Cells share their small molecules (such as inorganic ions, sugars, amino acids, nucleotides, vitamins, and the intracellular mediators cyclic AMP and inositol trisphosphate) but not their macromolecules
- Connexins are four-pass transmembrane proteins, six of which assemble to form a channel, a connexon


MW
100
1000
5000
20,000
5 nm
5 nm


interacting plasma membranes
channel 1.5 nm in diameter
gap of 2–4 nm
two connexons in register forming open channel between adjacent cells
connexon composed of six subunits
(A)

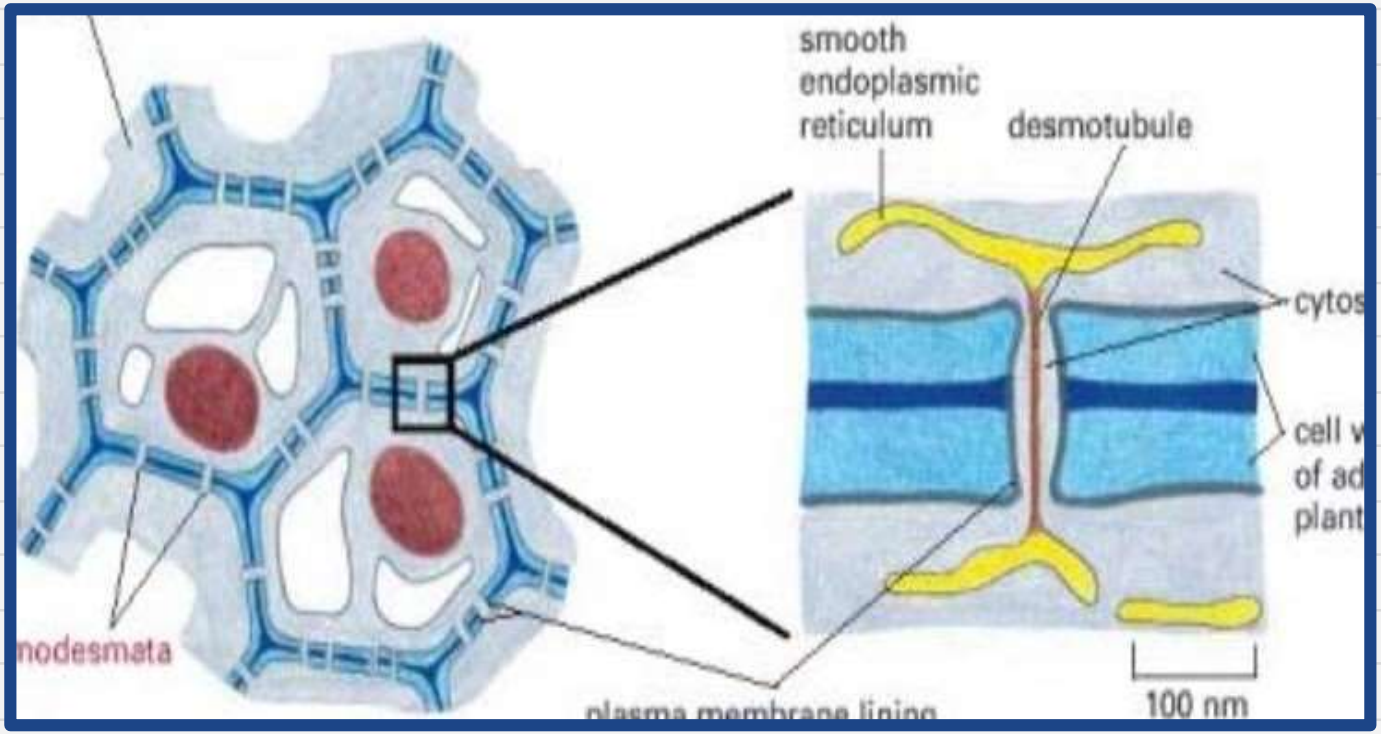

homomeric
heteromeric
homotypic
heterotypic

Functions

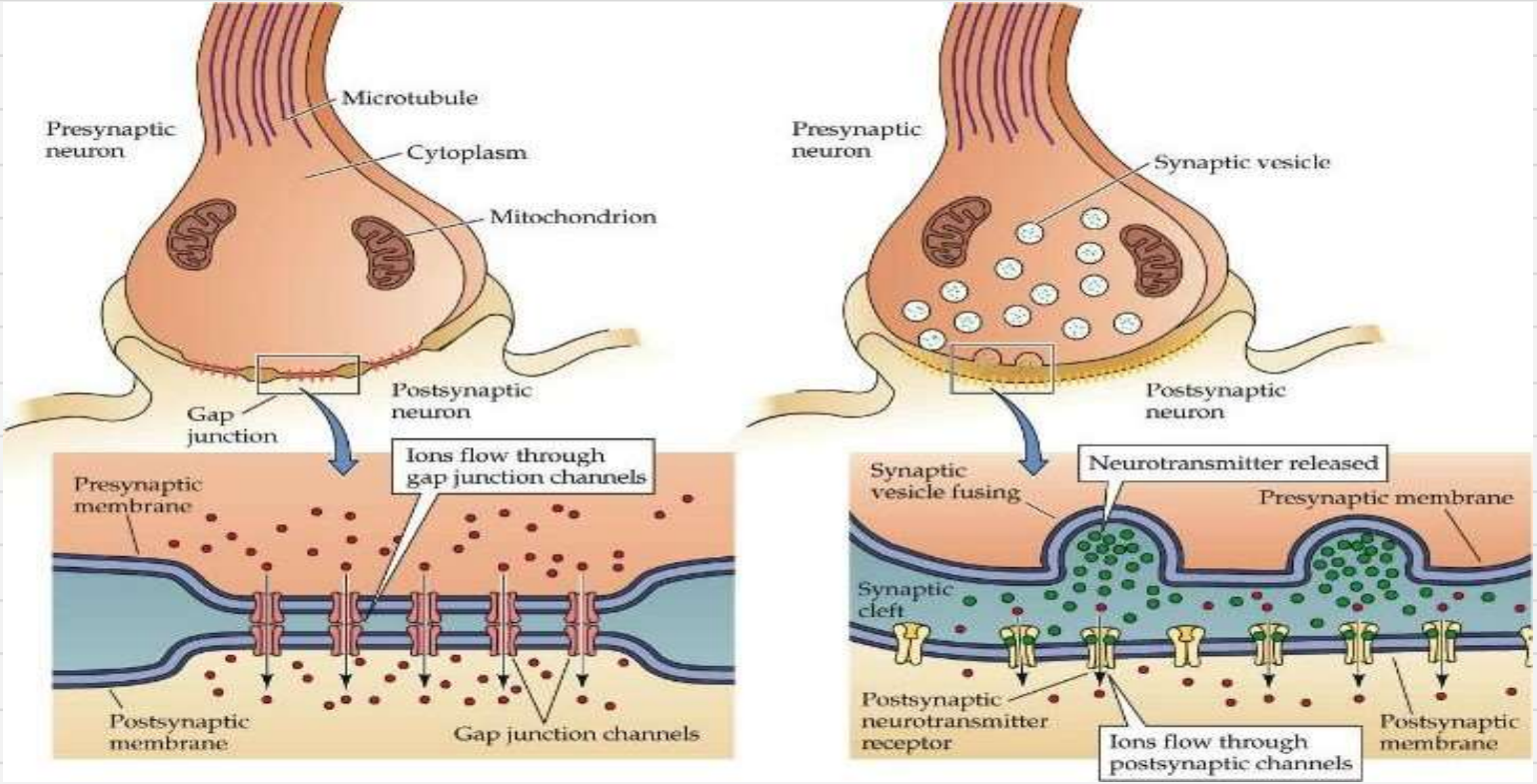
- coupling via gap junctions in electrically excitable cells
- sharing of small metabolites and ions provides a mechanism for coordinating the activities of individual cells in such tissues and for smoothing out random fluctuations in small molecule concentrations in different cells
- normal development of ovarian follicles also depends on gap junction-mediated communication—in this case, between the oocyte and the surrounding granulosa cells

Plasmodesmata

- They are cytoplasmic channels that pass through the cell walls of adjacent cells
- the plasma membrane of one cell is continuous with that of its neighbour at each plasmodesmata, and the cytoplasm of the two cells is connected by a roughly cylindrical channel with a diameter of 20—40 nm
- Running through the centre of the channel in most plasmodesmata is a narrower cylindrical structure, the desmotubule, which is continuous with elements of the smooth endoplasmic reticulum in each of the connected cells
- Between the outside of the desmotubule and the inner face of the cylindrical channel formed by plasma membrane is an annulus of cytosol through which small molecules can pass from cell to cell.
- Unlike gap junctions, whose pipelines have a fixed opening, the plasmodesmatal pore is capable of dilation


smooth
endoplasmic
reticulum
desmotubule
cytos
cell w
of ad
plant
nodesmata
plasma membrane lining
100 nm

Two Principal Kinds Of Synapses: Electrical And Chemical



Electrical Synapse

Chemical Synapse

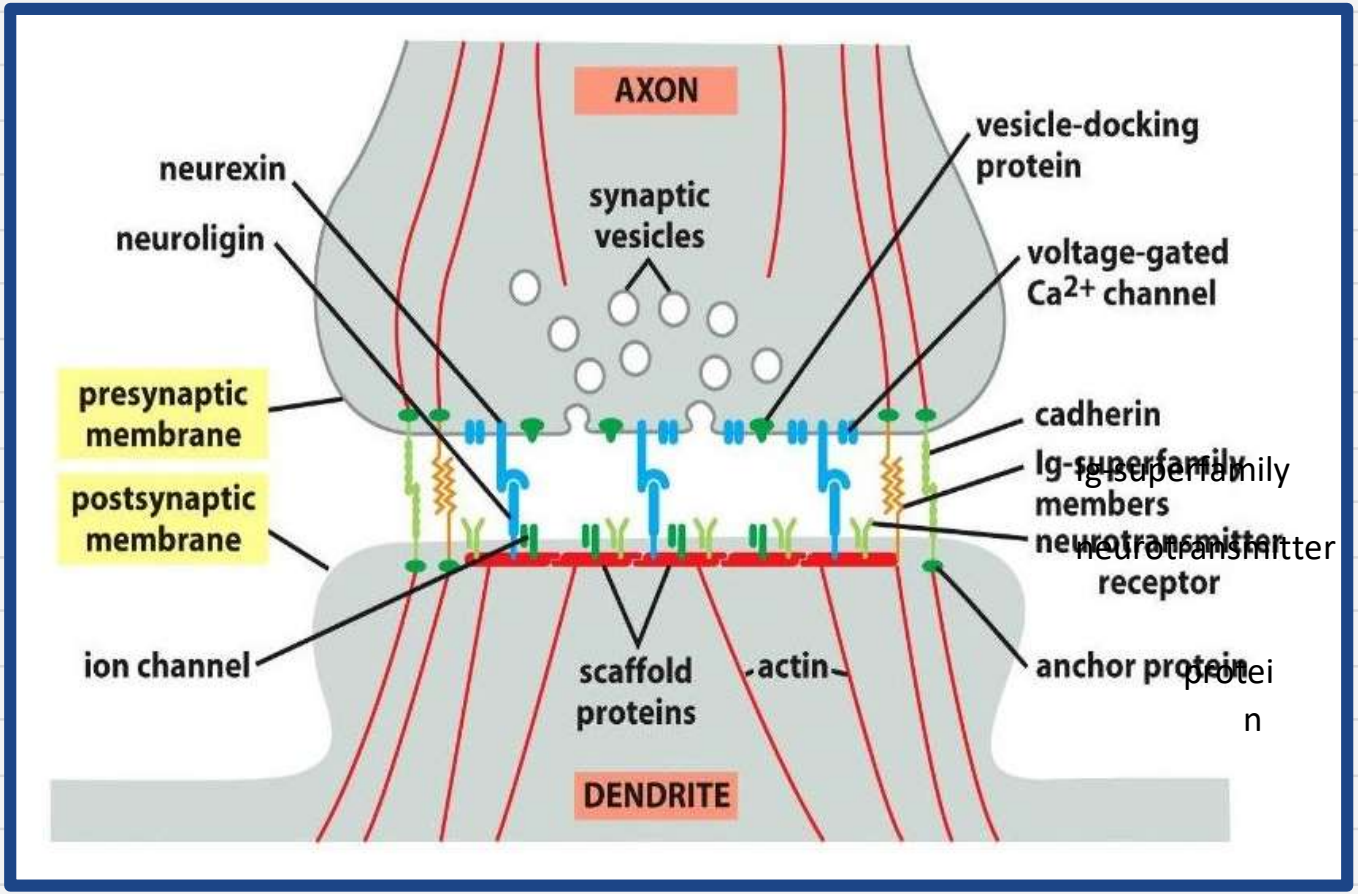
Chemical Synapse

- Chemical synapse is the junction between a nerve fibre and a muscle fiber or between two nerve fibre ,through which signals transmitted by the release of chemical transmitter.

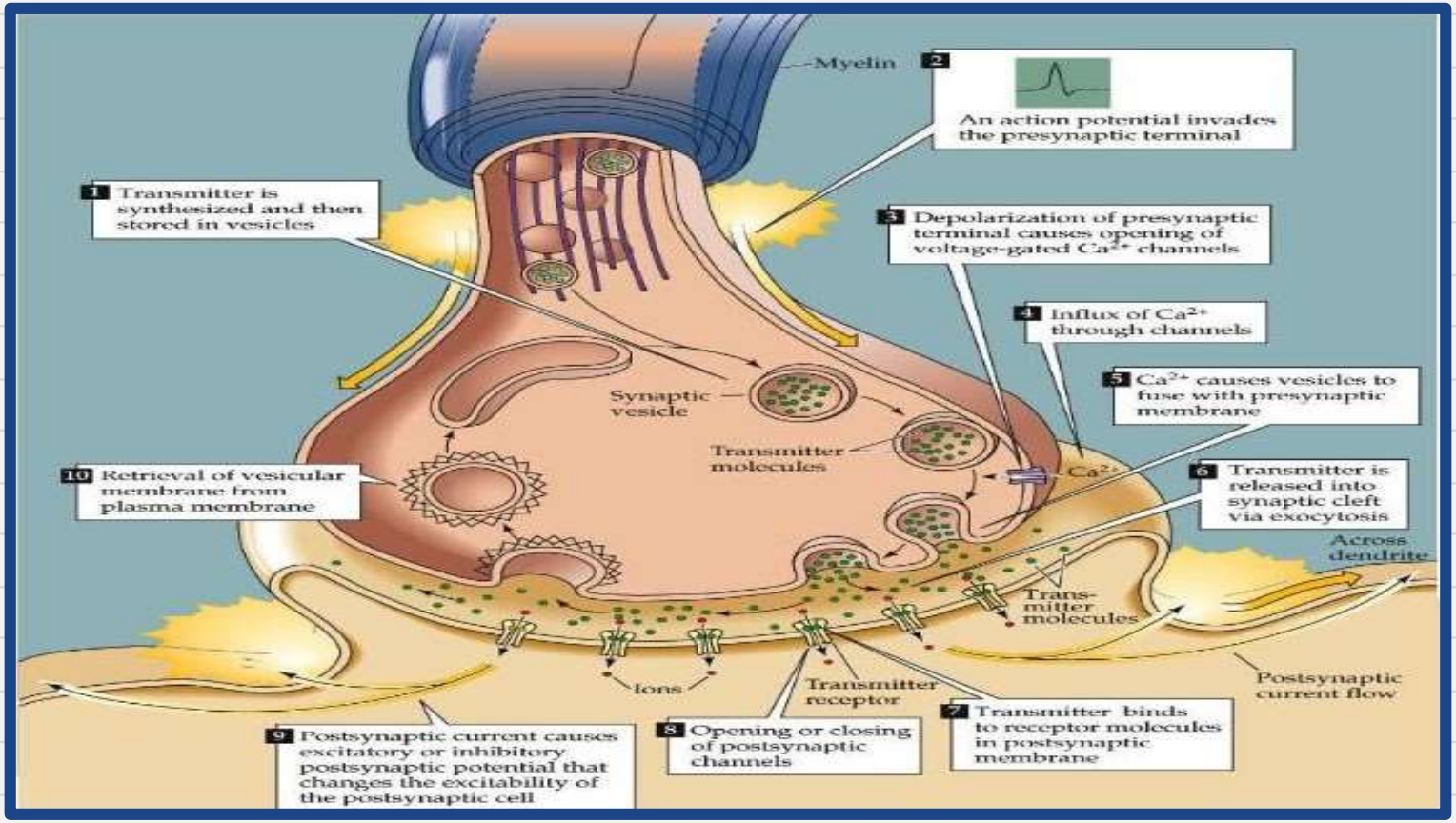
- Neurexin (NRXN) is a presynaptic protein that helps to connect neurons at the synapse. They are located mostly on the presynaptic membrane and contain a single transmembrane domain.

- Neuroligin (NLGN), a type I membrane protein, is a cell adhesion protein on the postsynaptic membrane that mediates the formation and maintenance of synapses between neurons.

- Neuroligins act as ligands for 13-Neurexins, which are cell adhesion proteins located presynaptically.

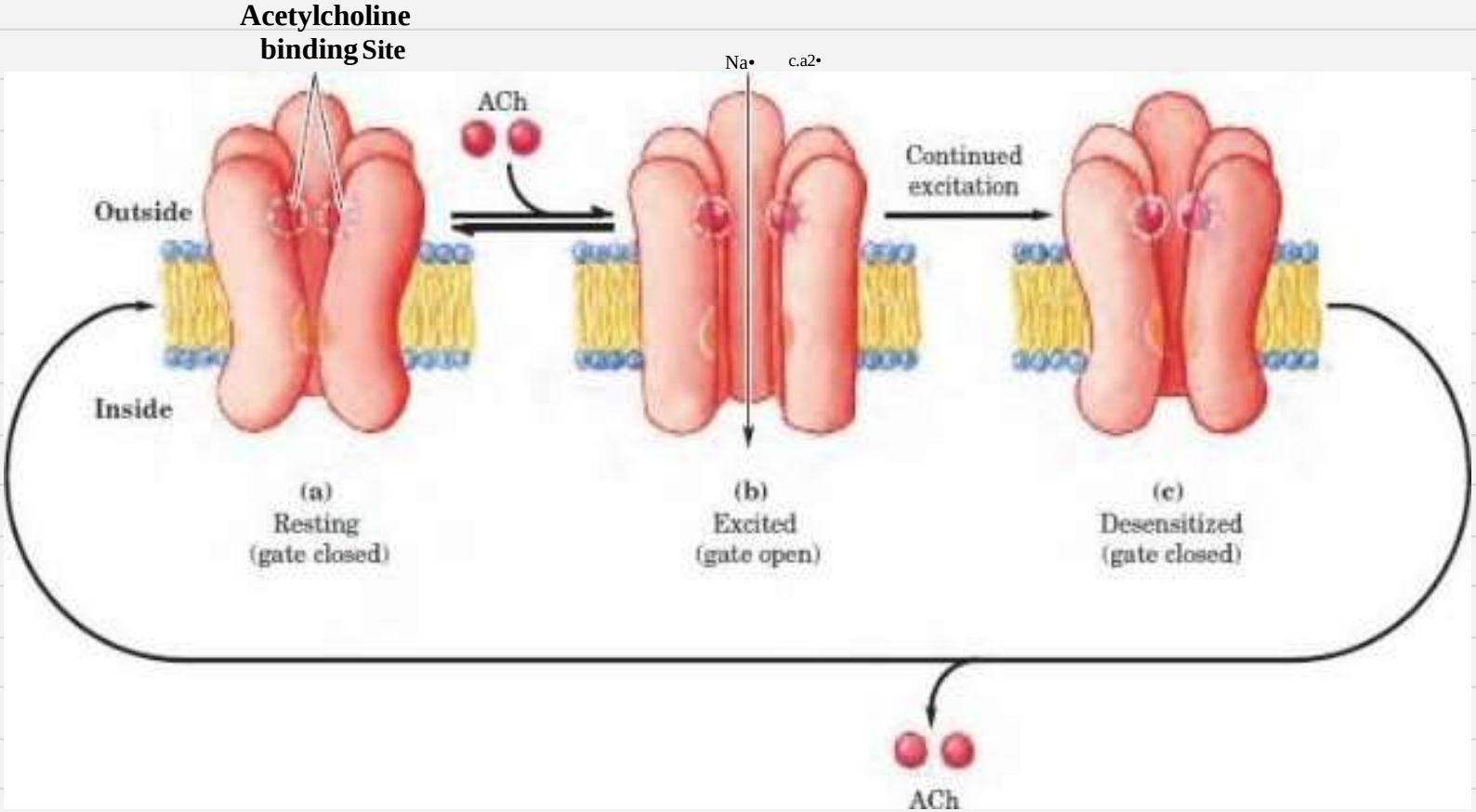

AXON
neurexin
neuroligin
synaptic vesicles
vesicle-docking protein
voltage-gated Ca^{2+} channel
presynaptic membrane
postsynaptic membrane
cadherin
Ig-superfamily members
neurotransmitter receptor
ion channel
scaffold proteins
actin
anchor protein
DENDRITE

Chemical synapses: the predominant means of communication between neurons



Gated Ion Channels

- The excitability of sensory cells, neurons, and myocytes depends on ion channels that provide a regulated path for the movement of inorganic ions such as Na, K, $Ca^{2}+$, and Cl-
- They may be open or closed, depending on whether the associated receptor has been activated by the binding of its specific ligand (a neurotransmitter) or by a change in the transmembrane electrical potential
- Example of a ligand-gated receptor channel is the nicotinic acetylcholine receptor.The receptor channel opens in response to the neurotransmitter acetylcholine
- This receptor is found in the postsynaptic membrane of neurons at certain synapses and in muscle fibres (myocytes) at neuromuscular junctions.


Acetylcholine binding Site
Na•
c.a2•
ACh
Outside
Inside
Continued excitation
(a) Resting (gate closed)
(b) Excited (gate open)
(c) Desensitized (gate closed)
ACh

- The binding of acetylcholine causes a change from the closed to the open conformation. The process is positively cooperative: binding of acetylcholine to the first site increases the acetylcholine-binding affmity of the second site.

- Normally, the acetylcholine concentration in the synaptic cleft is quickly lowered by the enzyme acetylcholinesterase, present in the cleft

- When acetylcholine levels remain high for more than a few milliseconds, the receptor is desensitized

- The receptor channel is converted to a third conformation in which the channel is closed, and the acetylcholine is very tightly bound

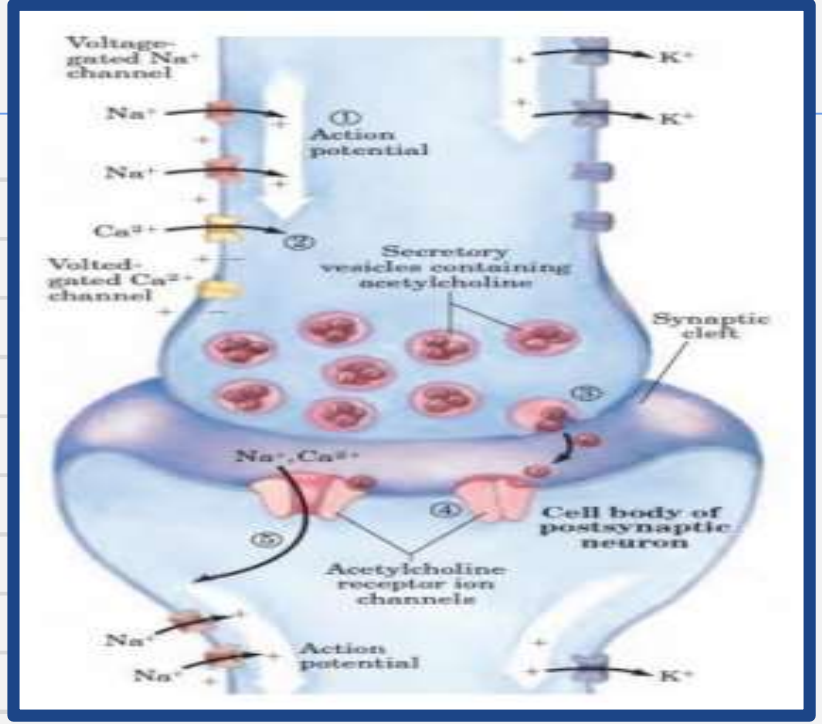
- The slow release (in tens of milliseconds) of acetylcholine from its binding sites eventually allows the receptor to return to its resting state—closed

Voltage-Gated Ion Channels

Three types of voltage-gated ion channels are essential to this signaling mechanism

•Along the entire length of the axon are voltage-gated Na channels which are closed when the membrane is at rest (Vm - 70 mV) but open briefly when the membrane is depolarized locally in response to acetylcholine

•The depolarization induced by the opening of Na + channels causes voltage gated K + channels to open, and the resulting efflux of K + repolarizes the membrane locally



- At the distal tip of the axon are voltage-gated Ca^2 + channels. When the wave of depolarization reaches these channels, they open, and Ca^2 + enters from the extracellular space

Extracellular Matrix

- In animals, the extracellular matrix helps organize cells into tissues and coordinates their cellular functions by activating intracellular signalling pathways that control cell growth, proliferation, and gene expression
- It acts like a packing material.The principal class of adhesion receptors that mediate cell matrix adhesion are integrins
- Three types of molecules are abundant in the extracellular matrix of all tissues.
- Highly viscous proteoglycans, a group of glycoproteins that cushion cells and bind a wide variety of extracellular molecules
- Collagen fibres, which provide mechanical strength and resilience
- Soluble multi adhesive matrix proteins, which bind to and cross-link cells

Basal lamina

In animals, epithelia and most organized groups of cells are underlain or surrounded by the basal lamina, a sheet like meshwork of ECM components usually no more than 60 120 nm thick

Surrounds muscle and fat cells

Underlies the basal surface of epithelial tissues

Underlies the inner endothelial lining of blood vessels

- Most of the ECM components in the basal lamina are synthesized by the cells that rest on it Basement membranes.
- provide mechanical support for the attached cells generate signals that maintain cell survival
- serve as a substratum for cell migration,separate adjacent tissues within an organ
- act as a barrier to the passage of macromolecules

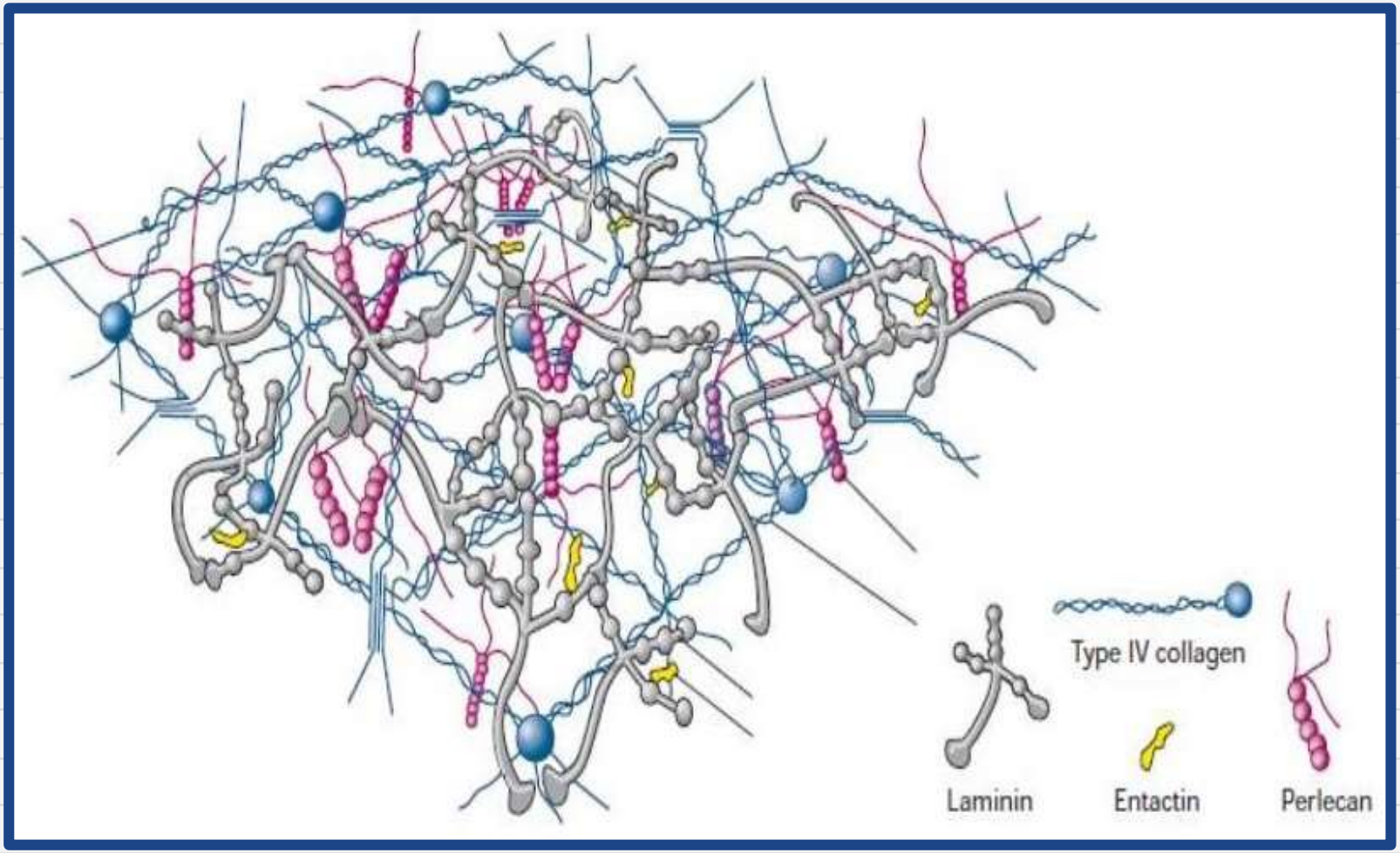
Four ubiquitous protein components are found in basal laminae:

1) Type IV collagen, trimeric molecules with both rod like and globular domains that form a two-dimensional network

2) Laminins, a family of multi adhesive proteins that form a fibrous two-dimensional network with type IV collagen and that also bind to integrins

3) Entactin (also called nidogen), a rod like molecule that crosslinks type IV collagen and laminin and helps incorporate other components into the ECM

4) Perlecan, a large multi domain proteoglycan that binds to and cross-links many ECM components and cell-surface molecules


Type IV collagen
Laminin
Entactin
Perlecan

Collagen

- Comprise a family of fibrous glycoproteins that are present in extracellular matrix
- Primarily produced by fibroblasts and by smooth muscle cells and epithelial cells
- More than 20 types of collagen that participate in the formation of the extracellular matrix in various tissues Additional complexity is provided by mixing of different collagen types in the same fibre
- **Common features of collagen:**
  - Collagen moleucles are trimer consisting of three polypeptide chains (u chains)
  - Three polypeptides of collagen wound around each other to form unique, rod like triple helix

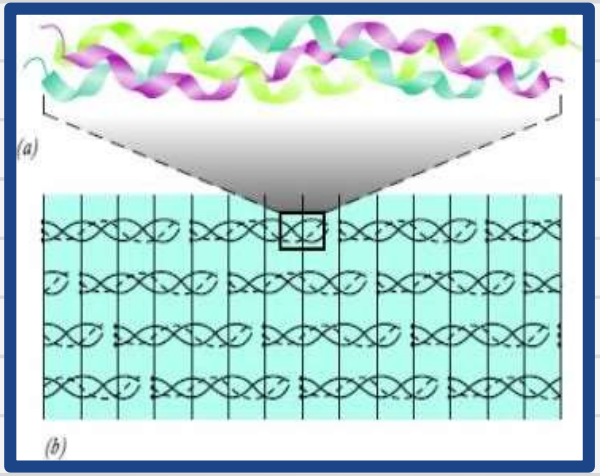
The major ones are:

Type I, II, III are fibrillar collagen as assemble into rigid cable like fibrils

Type I. The chief component of tendons, ligaments, and bones.

Type II. Represents more than 50% of the protein in cartilage. It is also used to build the notochord of vertebrate embryos.

Type III. Strengthens the walls of hollow structures like arteries, the intestine, and the uterus.

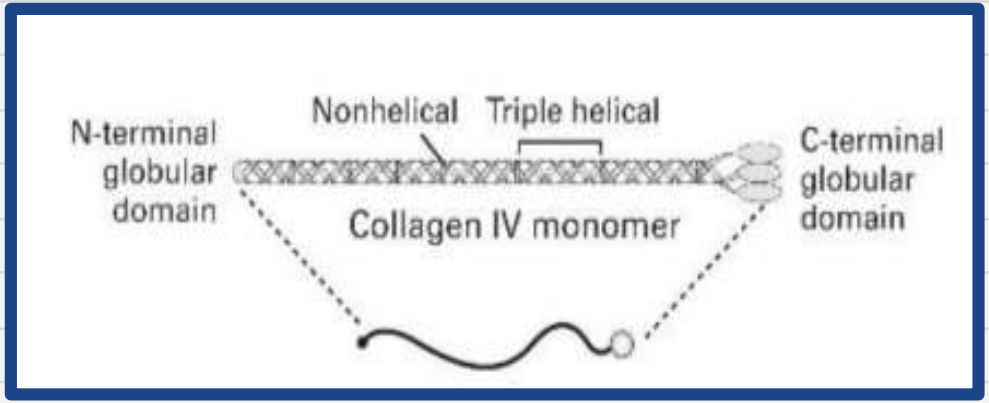


Type IV. Forms the basal lamina of epithelia. A meshwork of Type IV collagens provides the filter for the blood capillaries and the glomeruli of the kidneys.

- These fibrils form thicker fibres, which are held strongly by covalent crosslinks between lysine and hydroxylysine residues on adjacent collagen

- It provides an insoluble framework to ECM

- Type IV is non-fibrillar collagen, contains nonhelical segments interspersed along with molecule and globular domains at the ends



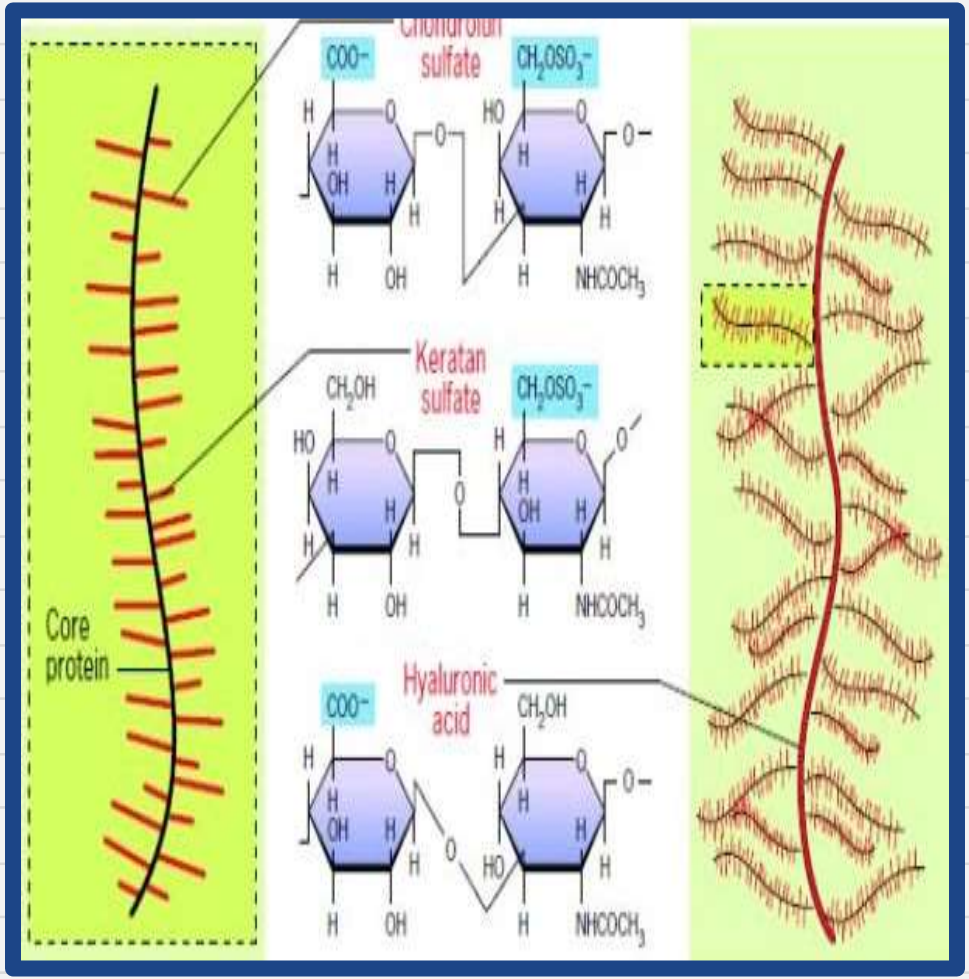
Proteoglycans

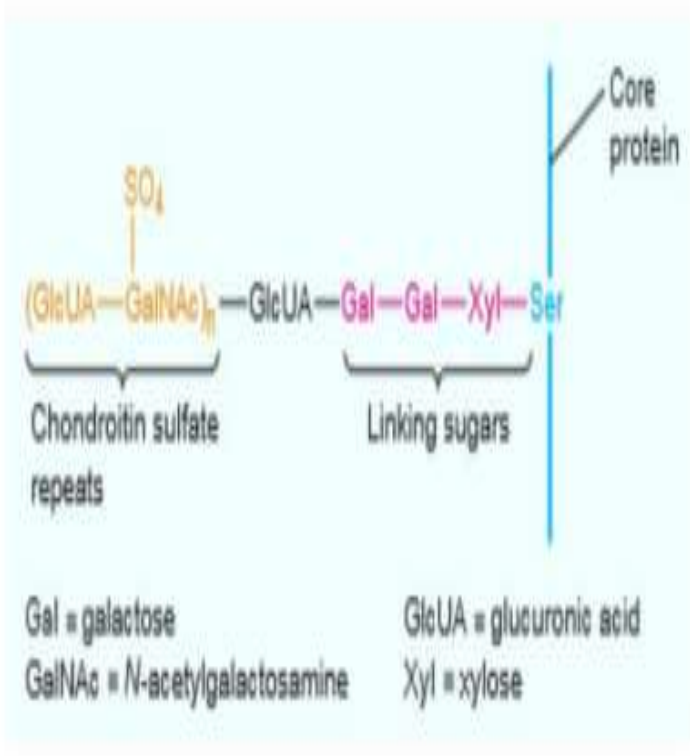
- ECM contains distinctive protein-polysaccharide complex called as proteoglycans

- They have a core protein covalently linked to specialized polysaccharide chains called glycosaminoglycans (GAGs), which are long linear polymers of specific repeating disaccharides

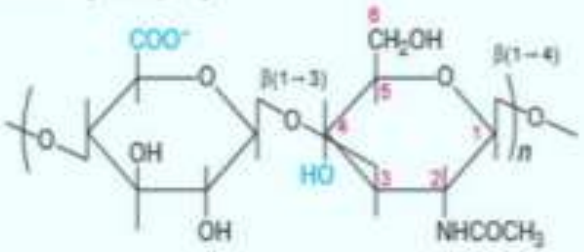
- Usually one sugar is either a uronic acid (D-glucuronicacid or L-iduronic acid) or D galactose; the other sugar is Nacetylglucosamine or Nacetylgalactosamine

- **each GAG chain bears many negative charges**


Chondroitin sulfate
Keratan sulfate
Hyaluronic acid
Core protein

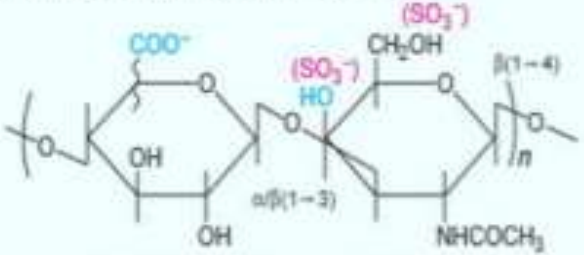

Core protein
SO4
(GlcUA—GalNAc)n
GlcUA
Gal—Gal—Xyl—Ser
Chondroitin sulfate repeats
Linking sugars
Gal = galactose
GalNAc = N-acetylgalactosamine
GlcUA = glucuronic acid
Xyl = xylose

(a) Hyaluronan ($n \leq 25{,}000$)



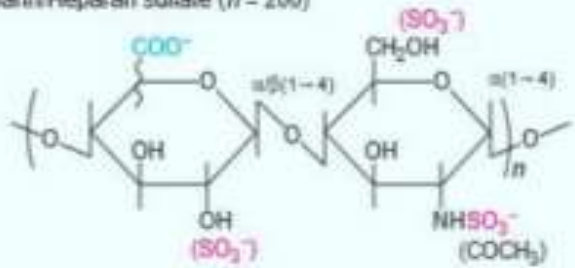
D-Glucuronic acid — *N*-Acetyl-D-glucosamine

(b) Chondroitin (or dermatan) sulfate ($n \leq 250$)



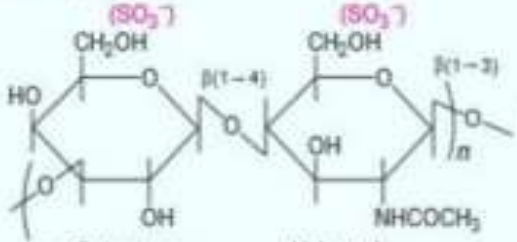
D-Glucuronic acid (or L-iduronic acid) — *N*-Acetyl-D-galactosamine

(c) Heparin/Heparan sulfate ($n = 200$)



D-Glucuronic or L-iduronic acid — *N*-Acetyl- or *N*-sulfo-D-glucosamine

(d) Keratan sulfate ($n = 20$–40)



D-Galactose — *N*-Acetyl-D-glucosamine

- Because of the negative charges, proteoglycans bind a huge numbers of cations
- This in turn binds large number of water molecules
- As a result proteoglycans form porous, hydrated gel that fills the extracellular space like packing material
- Also resists crushing forces, this property complements adjacent collagen molecules

GAG	Localization	Comments
Hyaluronate	synovial fluid, vitreous humor, ECM of loose connective tissue	large polymers, shock absorbing
Chondroitin sulfate	cartilage, bone, heart valves	most abundant GAG
Heparan sulfate	basement membranes, components of cell surfaces	contains higher acetylated glucosamine than heparin
Heparin	component of intracellular granules of mast cells lining the arteries of the lungs, liver and skin	more sulfated than heparan sulfates
Dermatan sulfate	skin, blood vessels, heart valves	
Keratan sulfate	cornea, bone, cartilage aggregated with chondroitin sulfates	

Laminins

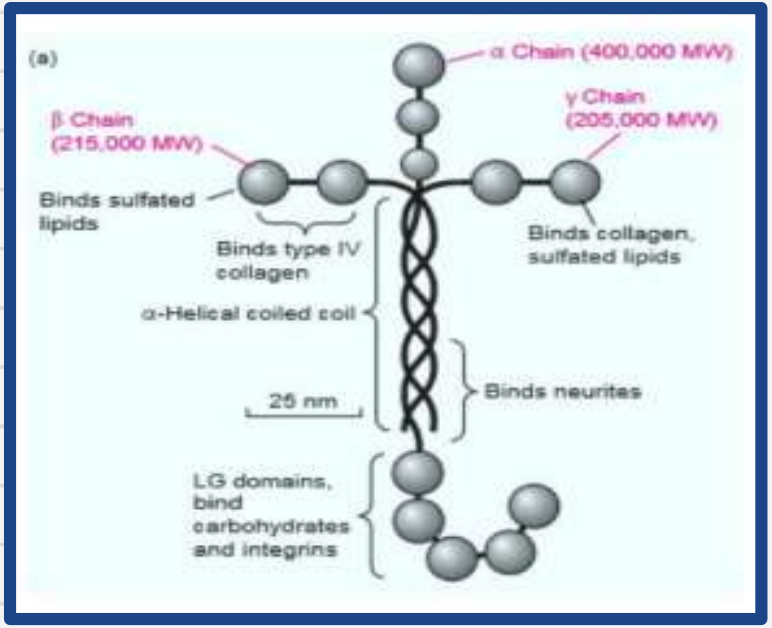
Multi adhesive matrix proteins are long, flexible molecules that contain multiple domains responsible for binding various types of collagen, other matrix proteins, polysaccharides, cell-surface adhesion receptors, and extracellular signalling molecules

Laminin, the principal multi adhesive matrix protein in basal laminae, is a hetero trimeric, cross-shaped protein with a total molecular weight of 820,000

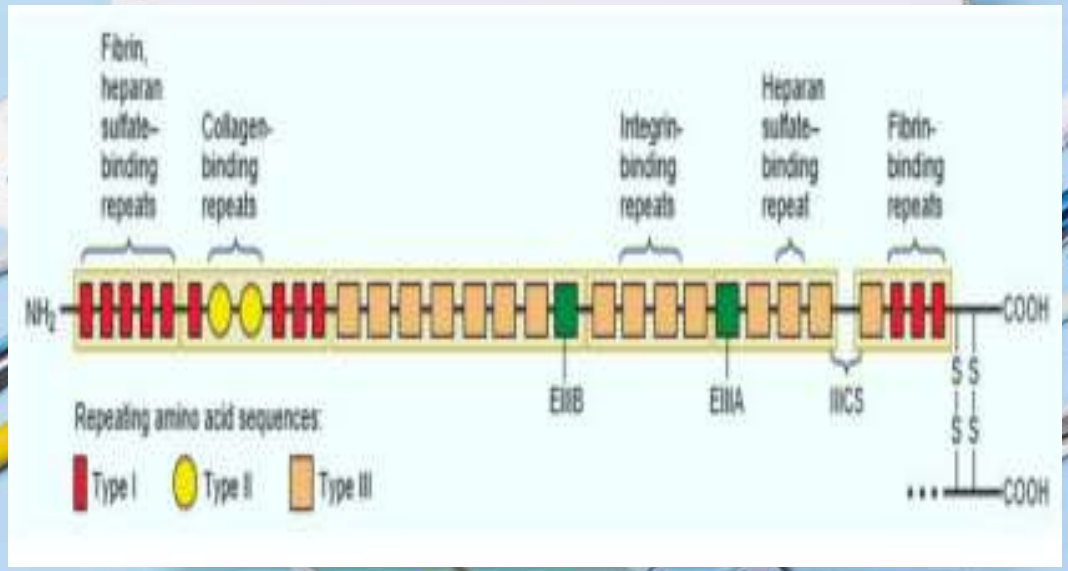
Laminins influence cells potential to migrate, grow and differentiate E.g. play a critical role in migration of primordial germ cells

The principal function of laminins are:-

- To provide an adhesive substrate for cell
- To resist tensile forces in tissue

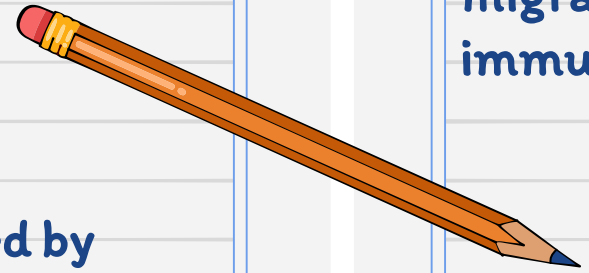


Fibronectins



Many different cell types synthesize fibronectins, an abundant multi adhesive matrix protein found in all vertebrates

The 20 or so isoforms of fibronectins are generated by alternative splicing of the RNA transcript produced from a single gene



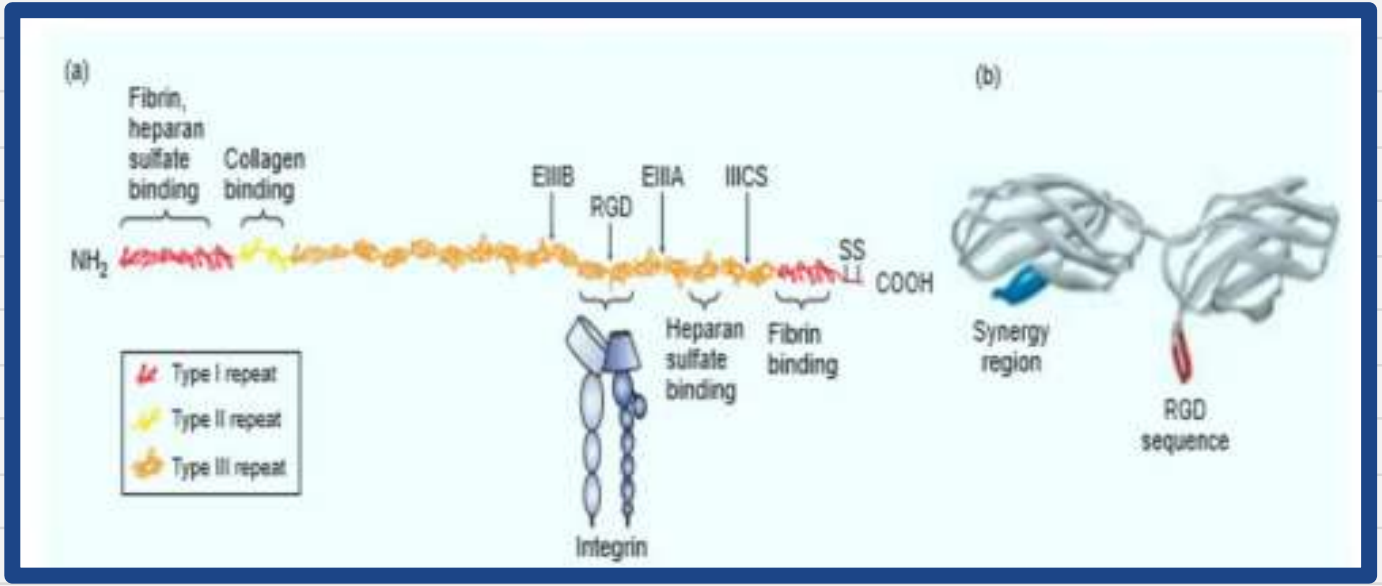
- Fibronectins are essential for the migration and differentiation of man cell types in embryogenesis, promote blood clotting and facilitate the migration of macrophages and other immune cells into the affected area.

- Fibronectins help attach cells to the extracellular matrix by binding to oth ECM components, particularly fibrou collagens and heparan sulphate proteoglycans, and to cell surface adhesion receptors such as integrins.

- Through their interactions with adhesion receptors, fibronectins influence the shape and movement of cells and the organization of the cytoskeleton.

- Each fibronectins polypeptide is constructed from a sequence of approx. 30 independently folding Fn domain.

- These domains combine to form 5 or 6 larger functional units



PROTEASES

Cells must routinely degrade and replace their extracellular matrix as a normal pan of

- development
- wound healing

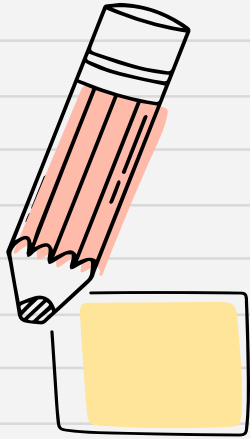
Extracellular matrix proteins are degraded by specific proteases, which cells secrete in an inactive form.

These proteases are only activated in the tissues where they are needed.

- Activation usually occurs by proteolytic cleavage of a pro peptide on the protease
- The matrix metalloproteinase (MMP) family is one of the most abundant classes of these proteas
- They are Zn containing enzymes either secreted into the extra cellular space or bound to the external surface of the plasma membrane

Protease

- It can degrade all of the major classes of extracellular matrix proteins.
- Cells secrete inhibitors of these proteases to protect themselves from unnecessary degradation
- Mutations in the MMP gene give rise to numerous skeletal abnormalities in humans



THANK YOU