# From cell to higher structures I

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# Content of the present lecture

## 1) Basic concept

## 2) Adhesion molecules

- **A)** Integrins
- **B)** Kadherins
- **C)** Catenins
- **D)** Other adhesion molecules

## 3) Intercellular junctions

- **A) Anchoring junctions**
- **B) Occluding junctions**
- **C) Channel-forming junctions**
- **D) Signal-relaying junctions**

# *Basic concept*

**Of all the social interactions between cells in a multicellular organism, the most fundamental are those that hold the cells together**

- **Cells may cling to one another through direct cell-cell junctions or**
- **They may be bound together by extracellular materials that they secrete (cell-matrix junction), but**
- **They must cohere if they are to form an organized multicellular structure**

Equally important for the tissues are blood vessels, nerves, and other specialized cells (macrophages,...) that allow cells to coordinate with each other, maintain cells and replace them with new cells of the same type

# The organization of cells in animal tissues and in the tissues of plants differs because of their different ways of life

The strength of plant tissues is determined by the cell walls of individual cells

The cell wall → **is the type of extracellular matrix, because of** it is produced by the cell

The cell wall can vary according to the type of cell it surrounds (thin, waxy, wooden,...)

## The organization of cells in animal tissues and in the tissues of plants differs because of their different ways of life

Animal tissues are also composed of cells and extracellular matrix

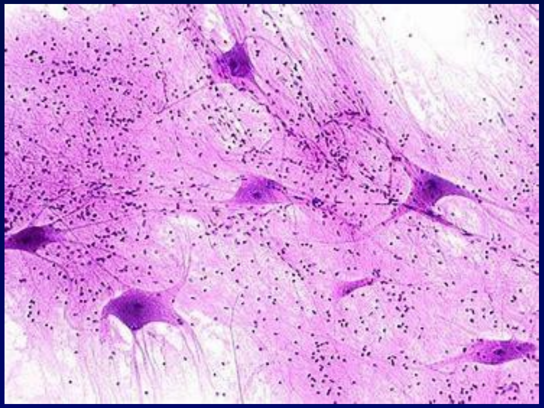
In connective tissues (bones, tendons,...) the extracellular matrix bears the main load

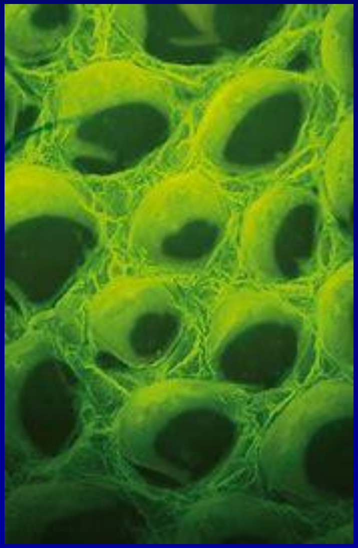
In other types of tissues (mainly epithelial), the mechanical support is mainly the cytoskeleton of the cell - the interconnectedness of the cells and therefore the interconnectedness of the cytoskeleton is important

The structure of animal tissues is much more diverse than that of plant tissues

# *Plant versus animal tissues*

**In plants, the extracellular matrix is all-important; plant tissues owe their strength to the cell walls that surround each cell**





**In animals, both architectural strategies are used, but to different extents in different tissues**

# *Functions of the cell junctions*

**The junctions between cells create pathways for communication, allowing the cells to exchange the signals that**

- **coordinate their behaviour and**
- **regulate their pattern of gene expression**

# *The cell attachments*

**Attachments to other cells and to extracellular matrix <u>control the orientation</u> of each cell's internal structure**

**The making and breaking of the attachments and the modelling of the matrix <u>govern the way cells move</u> within the organism, guiding them as the body grows, develops, and repairs itself**

# *Junction apparatus*

**The apparatus of cell junctions, cell adhesion mechanism, and extracellular matrix is critical for every aspect of the organization, function, and dynamics of multicellular structures**

**Defects in this apparatus underlie an enormous variety of diseases**

# *Large multicellular organisms*

They all consist of small objects with flimsy plasma membrane and form massive, strong and stable structures

**How is this possible ?**

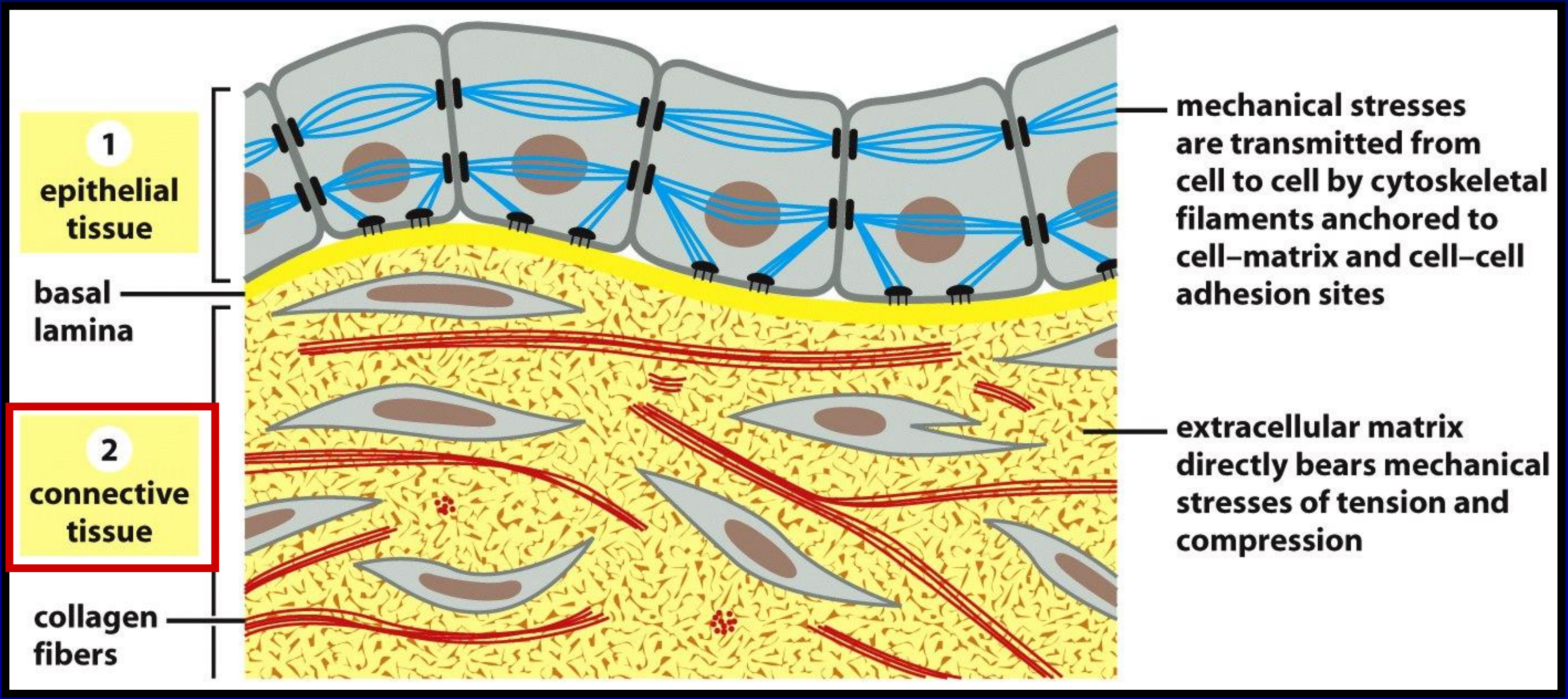
**The two strategies which depend on**

- **The strength of the extracellular matrix**
- **The strength of the cytoskeleton inside the cell and on cell-cell adhesion that tie the cytoskeleton of neighbouring cells together**

# Two main ways for animal cells

**In connective tissue**

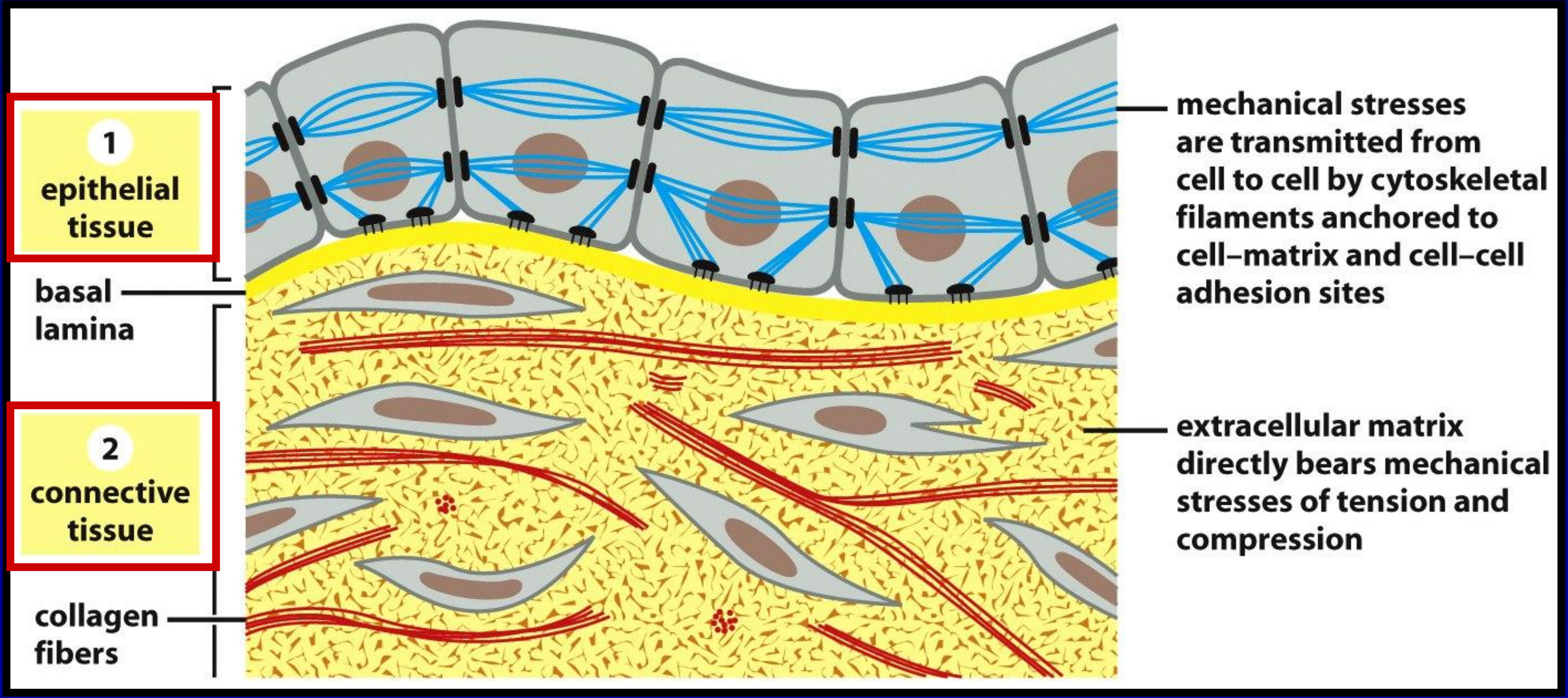
**The main-stress-bearing component is the extracellular matrix**



# Two main ways for animal cells

**In epithelial tissue**

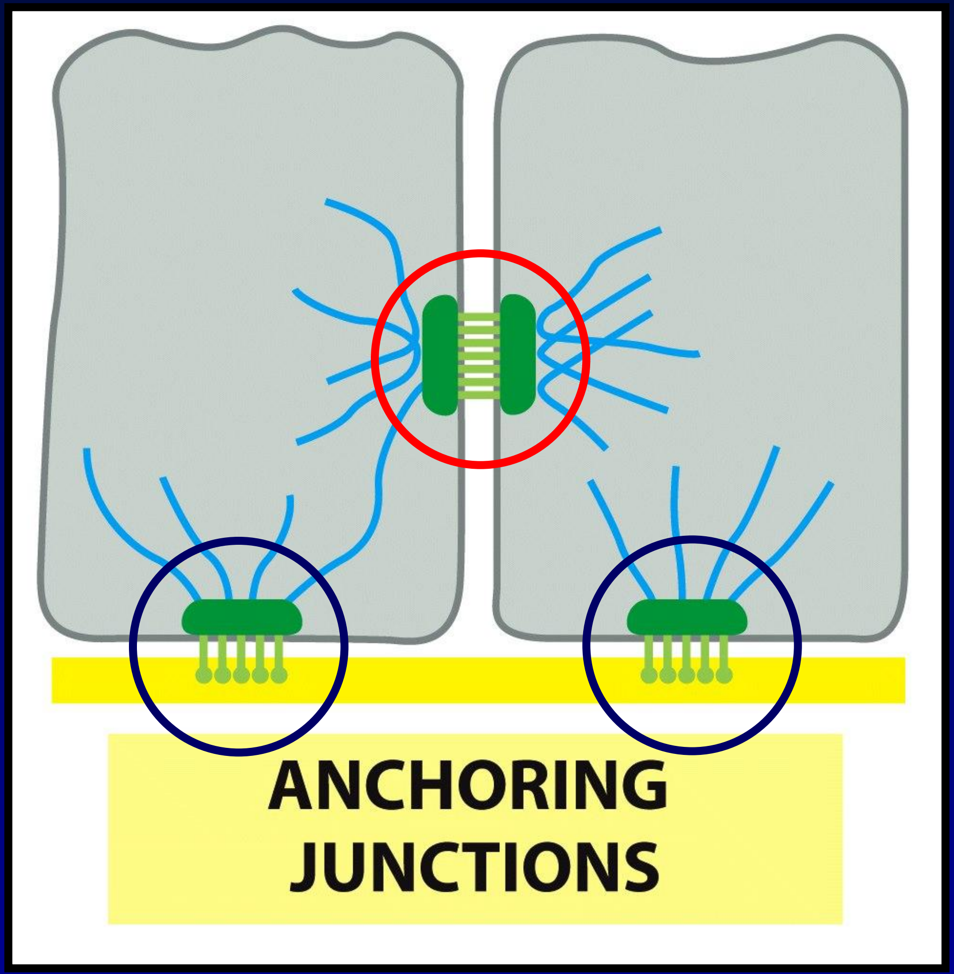
**It is the cytoskeletons of the cells themselves, linked from cell to cell by anchoring junctions**



# *Four main junctions*

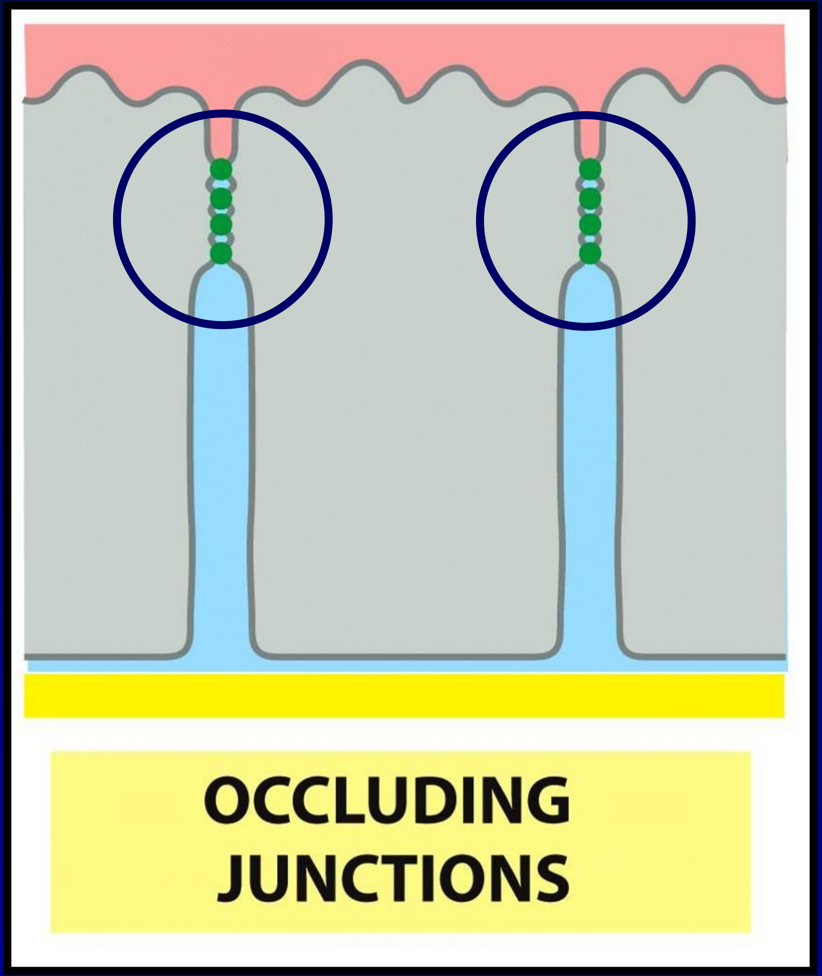
1) Anchoring junctions
2) Occluding junctions
3) Channel-forming junctions
4) Signal-relaying junctions

# *Anchoring junction*



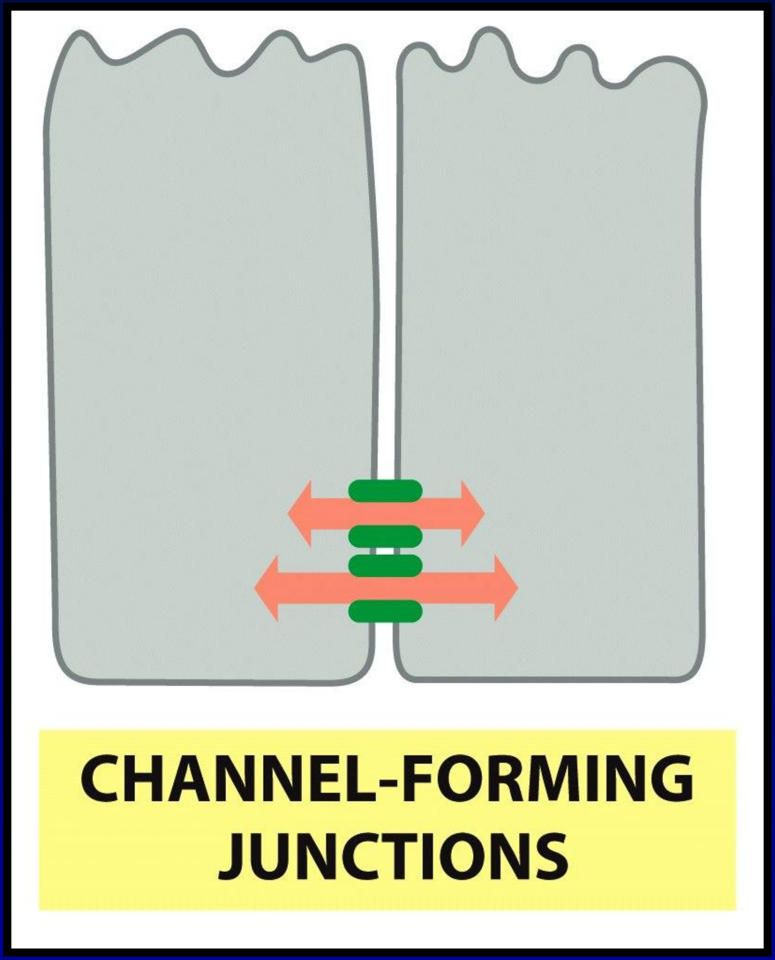

- Include both cell-cell adhesions and cell-matrix adhesion
- Transmit stresses, and are tethered to cytoskeletal filaments inside the cell
- The cell to cell link is performed by transmembrane <u>cadherin</u> proteins
- Cell to matrix via transmembrane <u>integrin</u> proteins

# *Occluding junction*



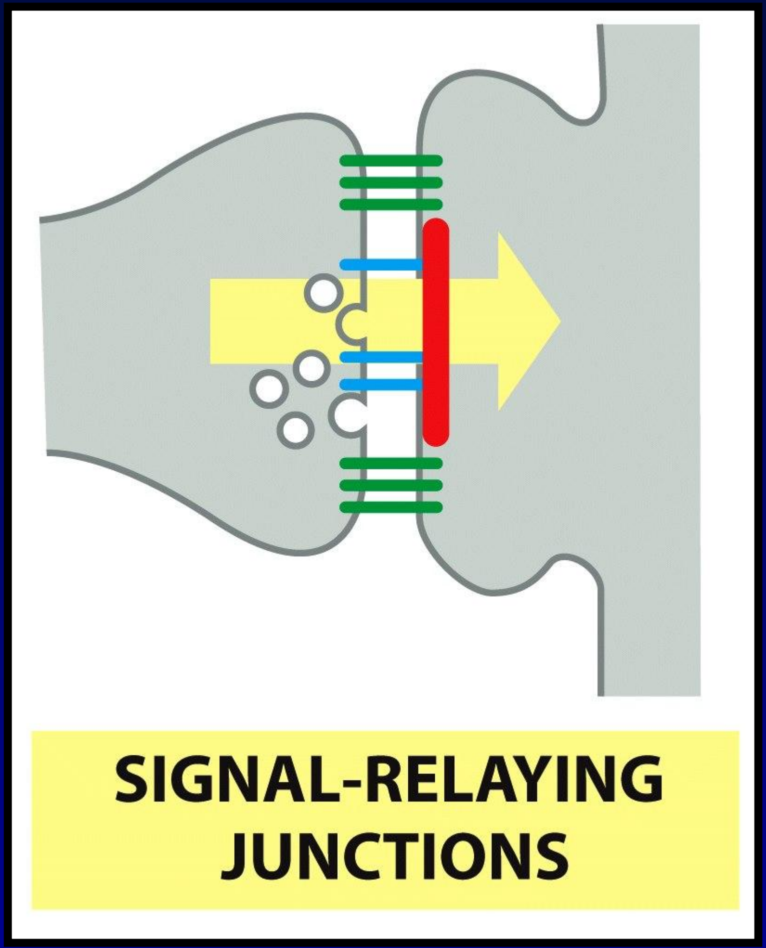

- Seal the gaps between cells in epithelia so as to make the cell sheet into an impermeable (or selectively permeable) barrier
- Involve claudin proteins

# *Channel-forming junction*




- **Create passageways linking the cytoplasms of adjacent cells**
- **Composed of <u>connexin</u> or <u>innexin</u> proteins**

# *Signal-relaying junctions*

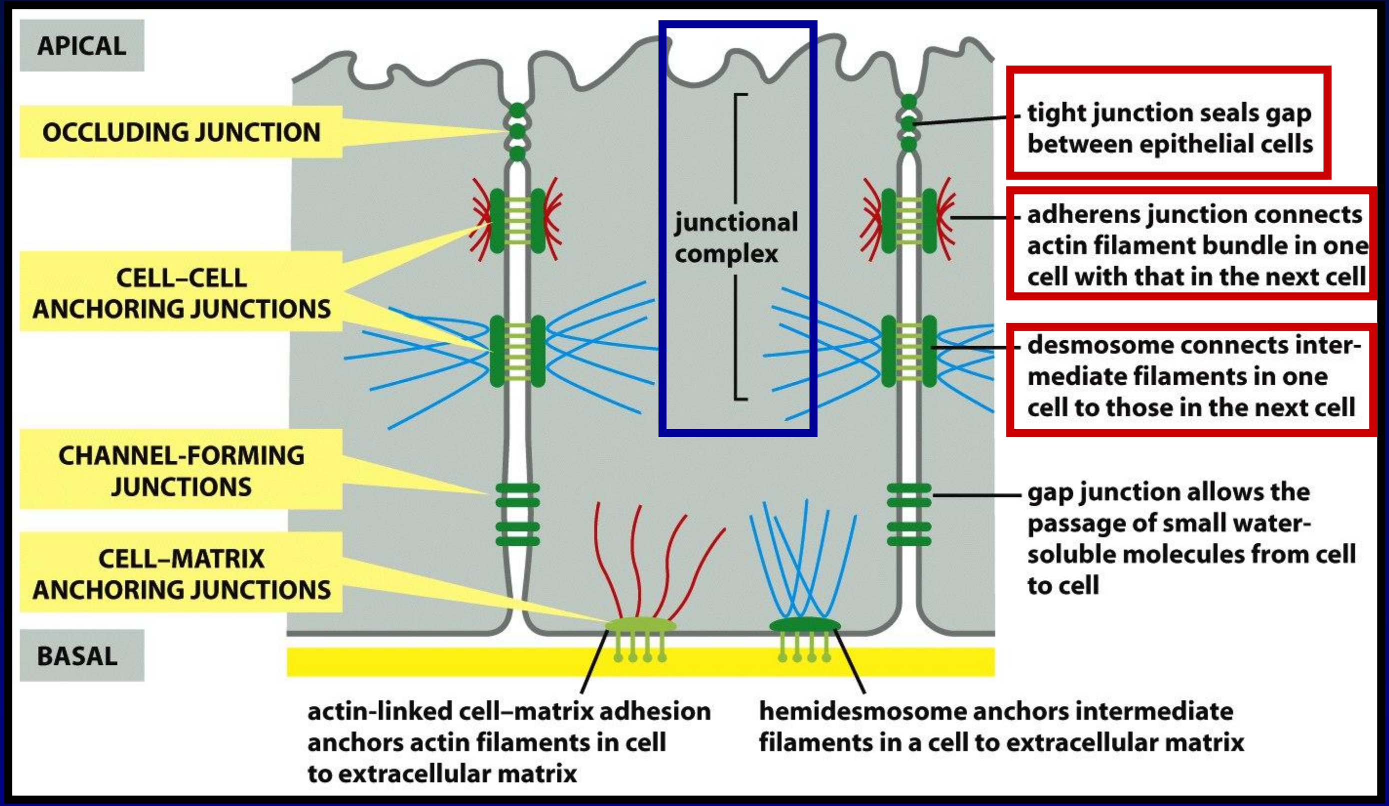



- **Allow signals to be relayed from cell to cell across their plasma membranes at sites of cell-to-cell contact**
- **Complex structures typically involving anchorage proteins alongside proteins mediating signal transduction**

# Functional classification

| ANCHORING JUNCTIONS | |
|---|---|
| ***Actin filament attachment sites*** | |
| 1. | cell–cell junctions (adherens junctions) |
| 2. | cell–matrix junctions (actin-linked cell–matrix adhesions) |
| ***Intermediate filament attachment sites*** | |
| 1. | cell–cell junctions (desmosomes) |
| 2. | cell–matrix junctions (hemidesmosomes) |
| **OCCLUDING JUNCTIONS** | |
| 1. | tight junctions (in vertebrates) |
| 2. | septate junctions (in invertebrates) |
| **CHANNEL-FORMING JUNCTIONS** | |
| 1. | gap junctions (in animals) |
| 2. | plasmodesmata (in plants) |
| **SIGNAL-RELAYING JUNCTIONS** | |
| 1. | chemical synapses (in the nervous system) |
| 2. | immunological synapses (in the immune system) |
| 3. | transmembrane ligand–receptor cell–cell signaling contacts (Delta-Notch, ephrin-Eph, etc.). Anchoring, occluding, and channel-forming junctions can all have signaling functions in addition to their structural roles |

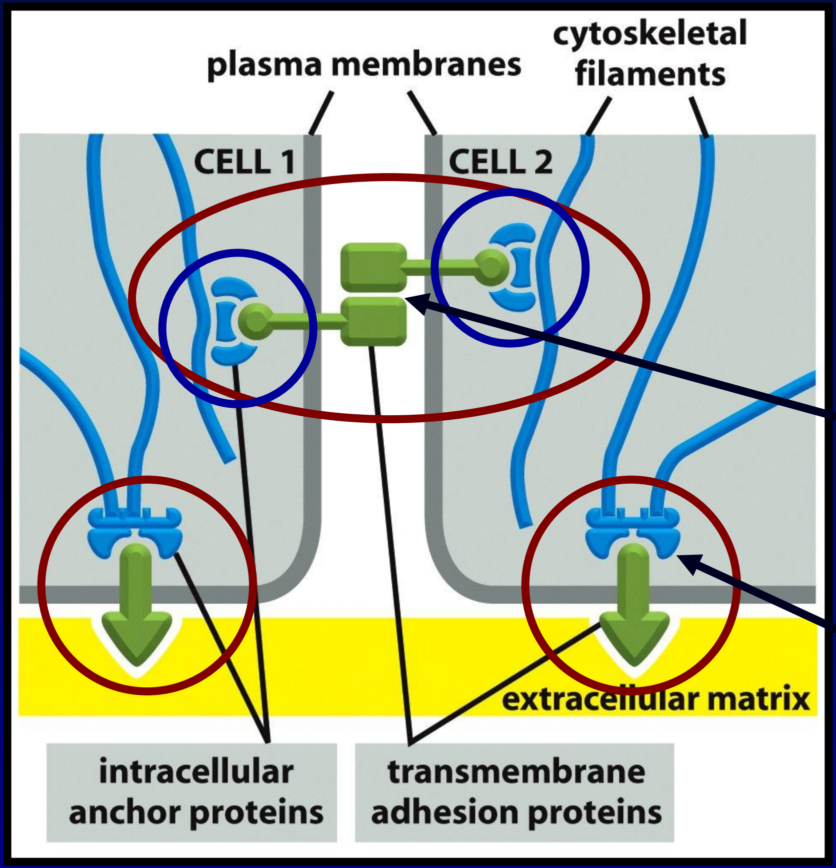
# Various cell junctions in vertebrate




- The tight junction occupies the most apical position
- Adherens junction follows
- Then a special parallel row of desmosomes continues

# *Anchoring junctions*

# Transmembrane adhesion proteins




- Play the central role at each of the four types of anchoring junctions
- External linkage may be either to parts of other cells (cell-cell anchorage) mediated by cadherins
- Or to extracellular matrix (cell-matrix anchorage) mediated by integrins

- The internal linkage to the cytoskeleton is generally indirect, via intracellular anchor proteins

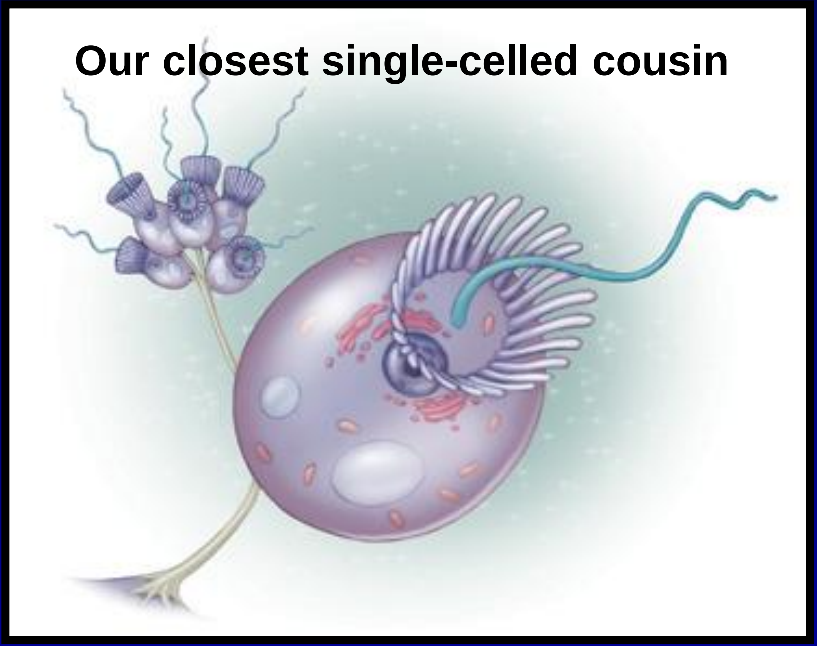
# Anchoring junctions

| JUNCTION | TRANSMEMBRANE ADHESION PROTEIN | EXTRACELLULAR LIGAND | INTRACELLULAR CYTOSKELETAL ATTACHMENT | INTRACELLULAR ANCHOR PROTEINS |
|---|---|---|---|---|
| *Cell–Cell* | | | | |
| adherens junction | cadherin (classical cadherin) | cadherin in neighboring cell | actin filaments | α-catenin, β-catenin, plakoglobin (γ-catenin), p120-catenin, vinculin, α-actinin |
| desmosome | cadherin (desmoglein, desmocollin) | desmoglein and desmocollin in neighboring cell | intermediate filaments | plakoglobin (γ-catenin), plakophilin, desmoplakin |
| *Cell–Matrix* | | | | |
| actin-linked cell–matrix adhesion | integrin | extracellular matrix proteins | actin filaments | talin, vinculin, α-actinin, filamin, paxillin, focal adhesion kinase (FAK) |
| hemidesmosome | integrin α6β4, type XVII collagen (BP180) | extracellular matrix proteins | intermediate filaments | plectin, dystonin (BP230) |

- **Cytoskeleton-linked transmembrane molecules fall nearly into two superfamilies corresponding to the two basic kinds of external attachments – cadherin and integrin superfamily**

# *Cadherins*

Cadherins are present in all multicellular animals and *choanoflagellates*, representatives of the group of protists from which all animals evolved




- Other eukaryotes, including fungi and plants, lack cadherins, and they are absent from bacteria and archae also
- Cadherins therefore seem to be part of the essence of what it is to be an animal

# *Cadherins mediate $Ca^{2+}$ dependent cell-cell adhesion*

**Cadherins take their name from their dependence on $Ca^{2+}$ ions: removing $Ca^{2+}$ from the extracellular medium causes adhesions mediated by cadherins to come adrift**

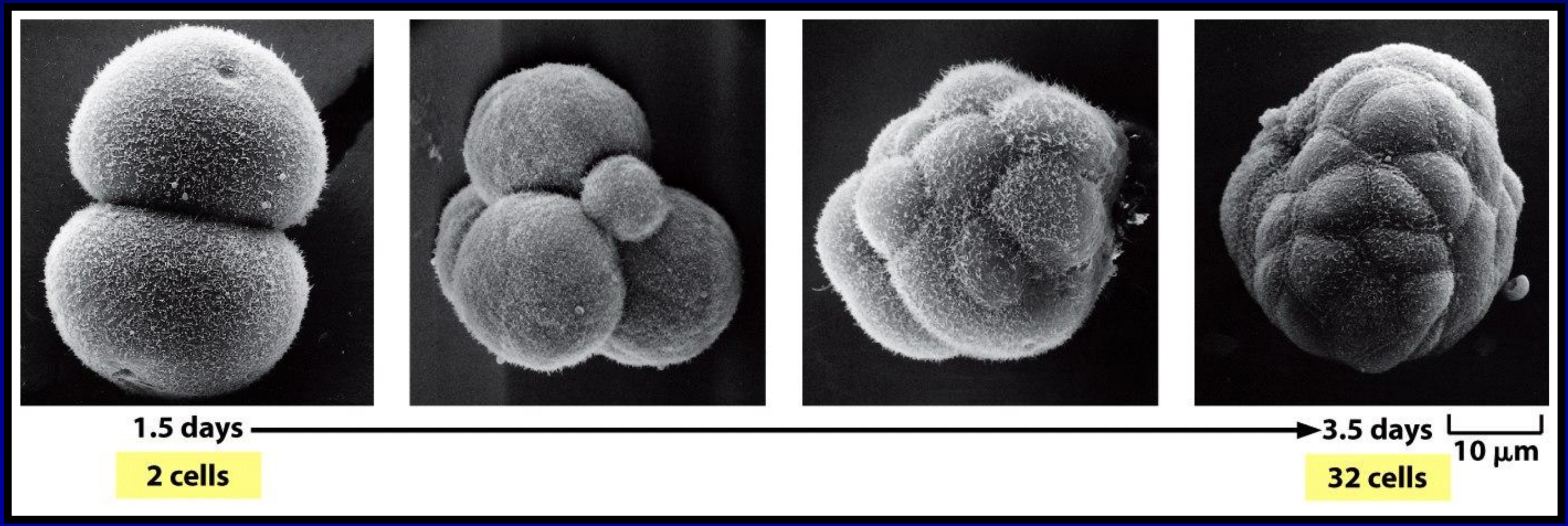
**Embryonic tissues in culture disintegrate when treated with anti-cadherin antibodies**

# Some cadherins

| NAME | MAIN LOCATION | JUNCTION ASSOCIATION | PHENOTYPE WHEN INACTIVATED IN MICE |
|---|---|---|---|
| *Classical cadherins* | | | |
| E-cadherin | many epithelia | adherens junctions | death at blastocyst stage; embryos fail to undergo compaction |
| N-cadherin | neurons, heart, skeletal muscle, lens, and fibroblasts | adherens junctions and chemical synapses | embryos die from heart defects |
| P-cadherin | placenta, epidermis, breast epithelium | adherens junctions | abnormal mammary gland development |
| VE-cadherin | endothelial cells | adherens junctions | abnormal vascular development (apoptosis of endothelial cells) |
| *Nonclassical cadherins* | | | |
| Desmocollin | skin | desmosomes | blistering of skin |
| Desmoglein | skin | desmosomes | blistering skin disease due to loss of keratinocyte cell–cell adhesion |
| T-cadherin | neurons, muscle, heart | none | unknown |
| Cadherin 23 | inner ear, other epithelia | links between stereocilia in sensory hair cells | deafness |
| Fat (in *Drosophila*) | epithelia and central nervous system | signal-relaying junction (planar cell polarity) | enlarged imaginal discs and tumors; disrupted planar cell polarity |
| Fat1 (in mammals) | various epithelia and central nervous system | slit diaphragm in kidney glomerulus and other cell junctions | loss of slit diaphragm; malformation of forebrain and eye |
| α, β, and γ-Protocadherins | neurons | chemical synapses and nonsynaptic membranes | neuronal degeneration |
| Flamingo | sensory and some other epithelia | cell–cell junctions | disrupted planar cell polarity; neural tube defects |

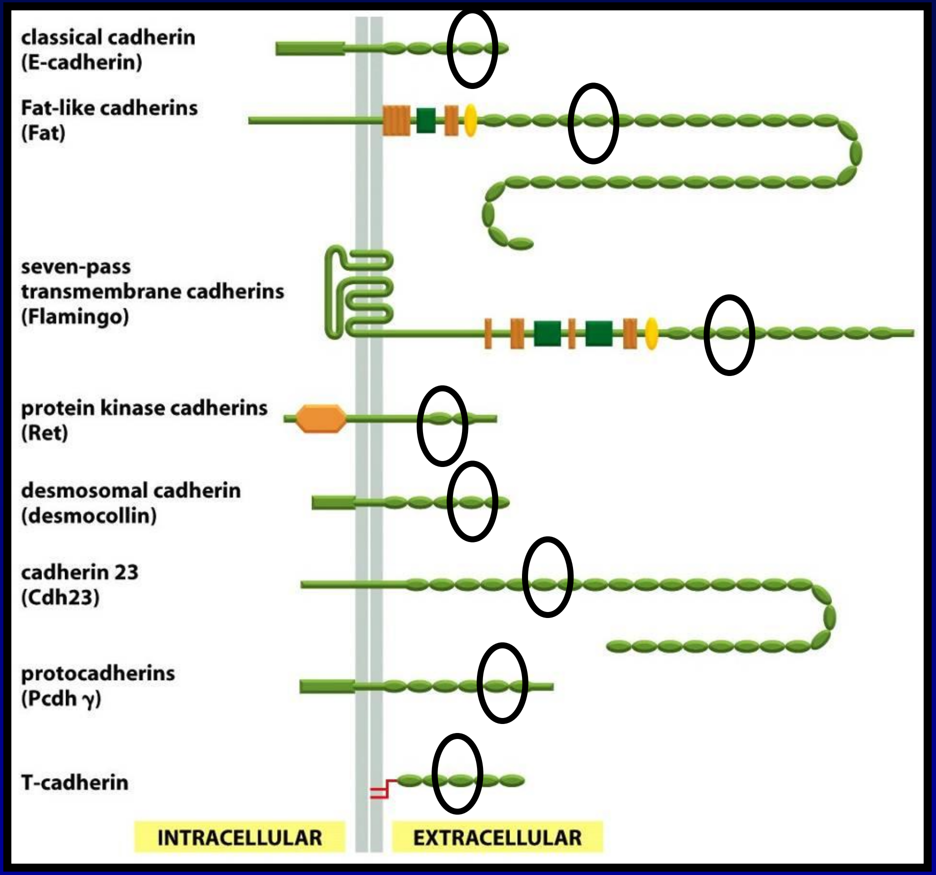
# Compaction of an early embryo

- The cells of the early embryo at first stick together only weakly
- At about the eight-cell stage, they begin to express E-cadherin and as a result becomes strongly and closely adherent to one another
- The outer surface of the embryo becomes smoother



# The cadherin superfamily

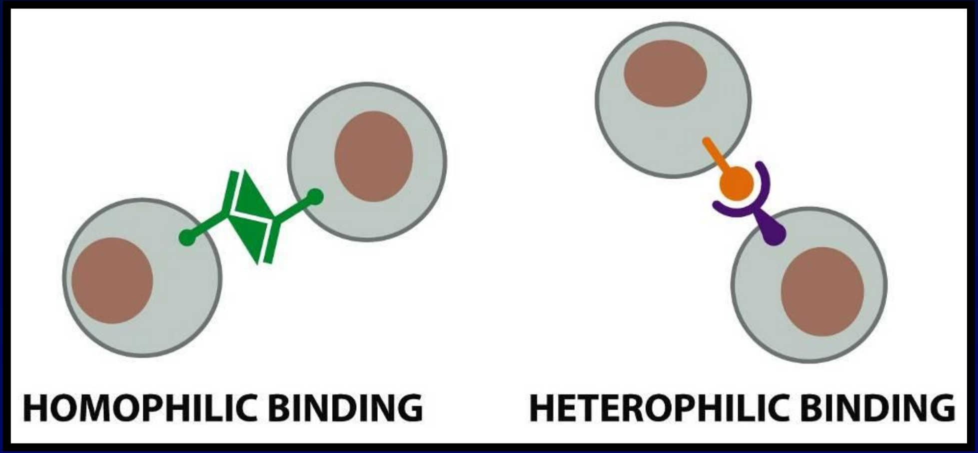
**All cells seem to express one or more proteins of the cadherin family according to the cell type**

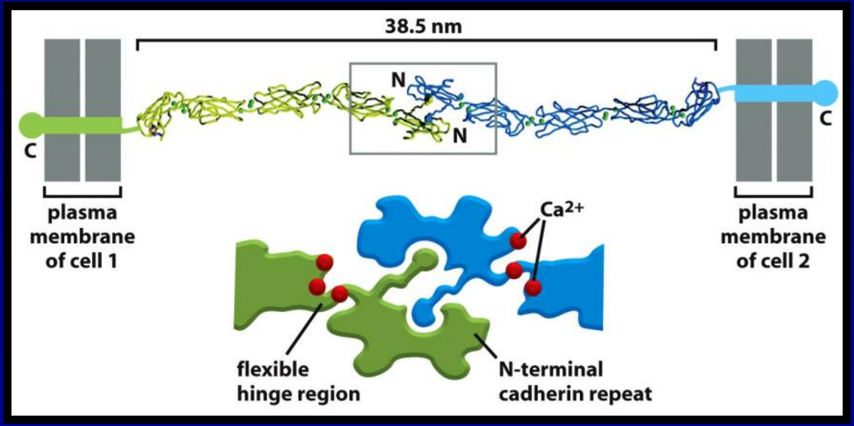



- **All have extracellular portion containing multiple copies of the cadherin domain motif**
- **Their intracellular portions are more varied**

# Homophilic adhesion

Cadherins form specific homophilic attachments

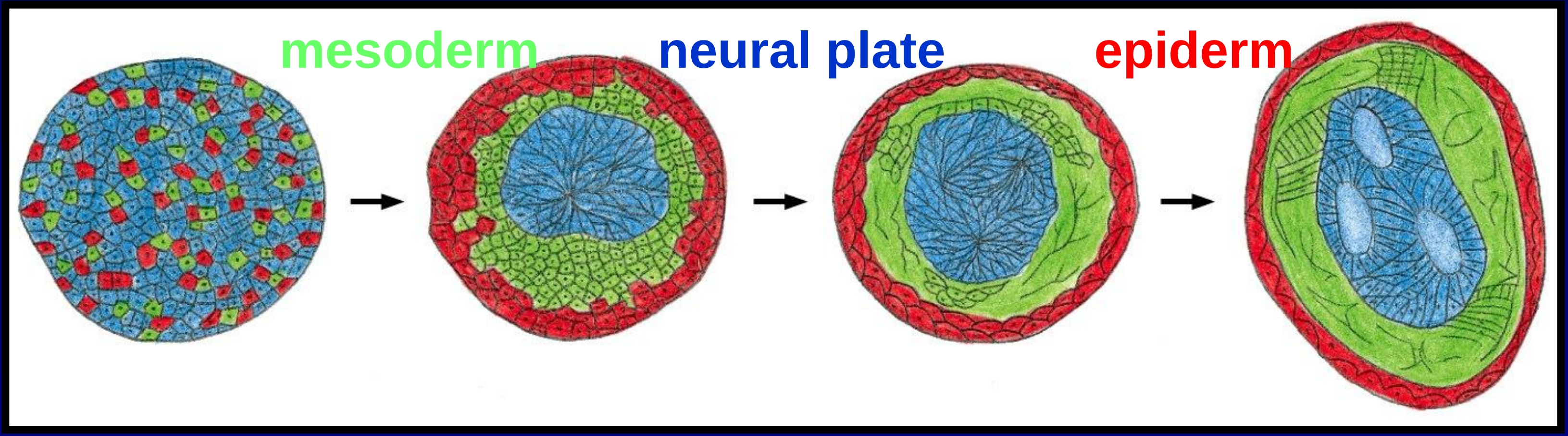



- C-cadherin shown here illustrating how two such molecules on opposite cells are thought to bind homophilically, end-to-end

# *Selective cell-cell adhesion*

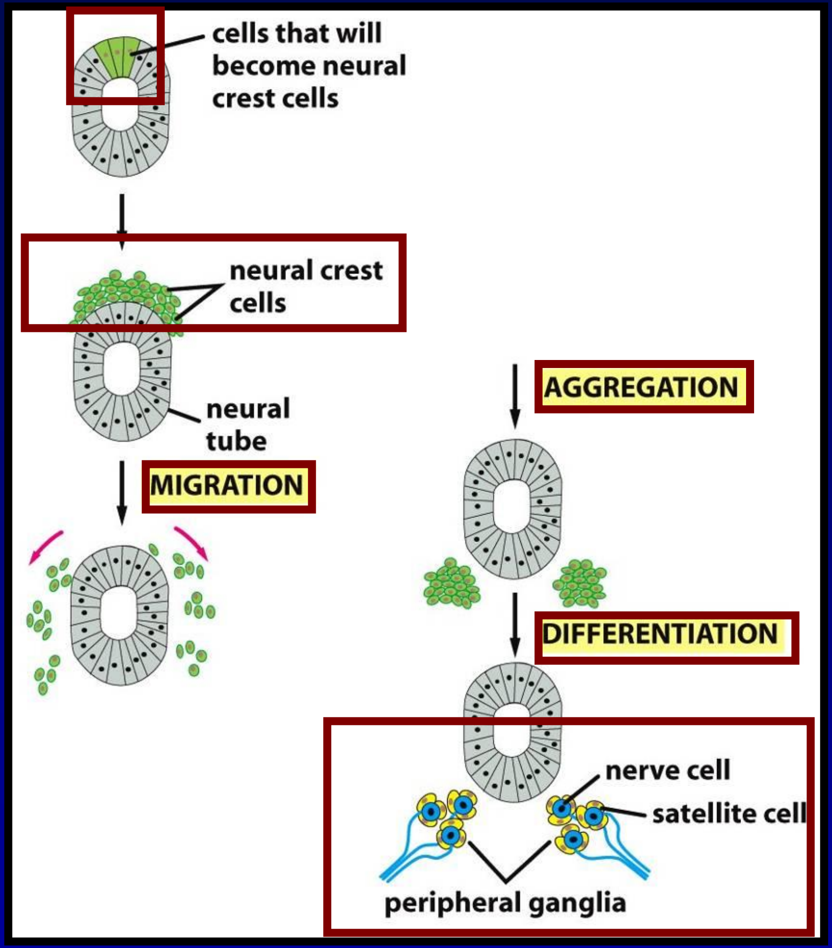
**Homophilic attachments mediate highly <u>selective recognition</u>, enabling cell of a similar type to stick together and to stay segregated from other types of cells**




**Cells from different parts of an early embryo will sort out according to their origin**

# Tissue forming in embryo

Some cells that are initially part of the epithelial neural tube alter their adhesive properties and disengage …

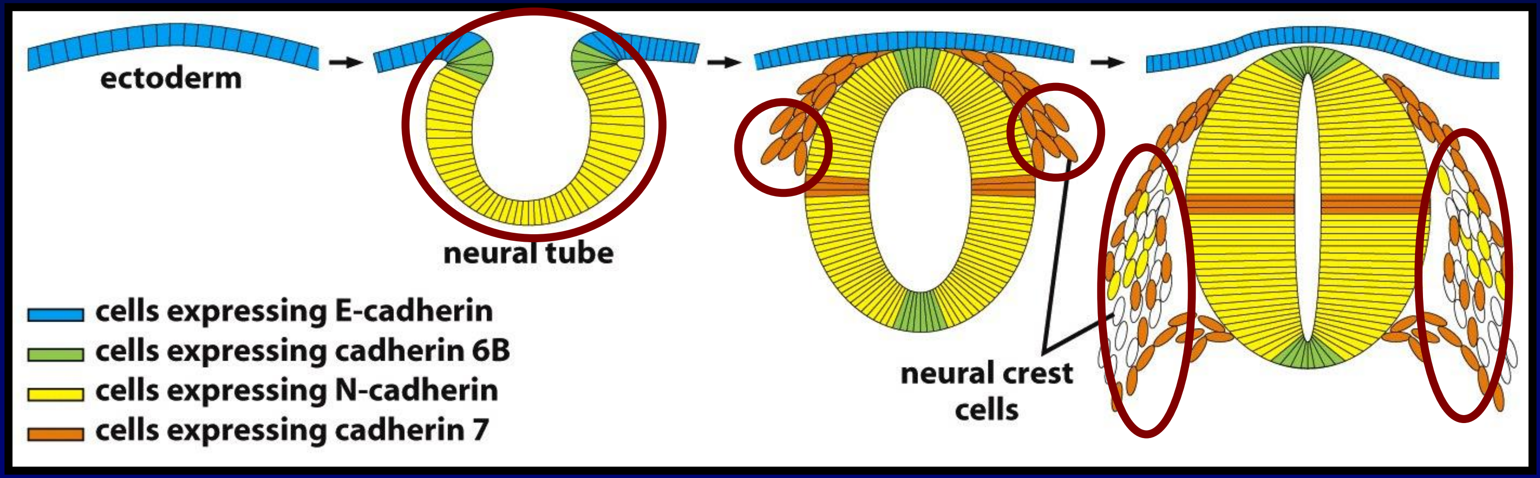



… from the epithelium to form the neural crest

… the cells then migrate away and form a variety of cell types and tissues

# Cadherin expression

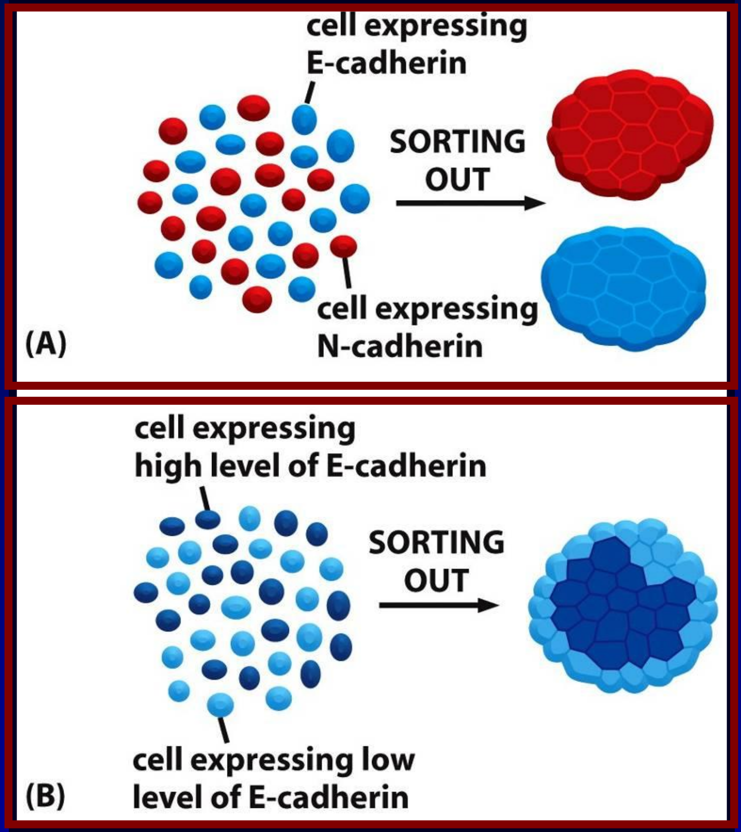
Steps in embryonic development correlate with appearance and disappearance of specific cadherins




- As the neural tube forms and pinches off from the overlying ectoderm, neural tube cells lose E-cadherin and acquire other cadherins, including N-cadherin
- Then the neural crest cells migrate away another cadherin (cadherin 7) appears helps hold the migrating cells together and aggregate to ganglion

# Sorting out

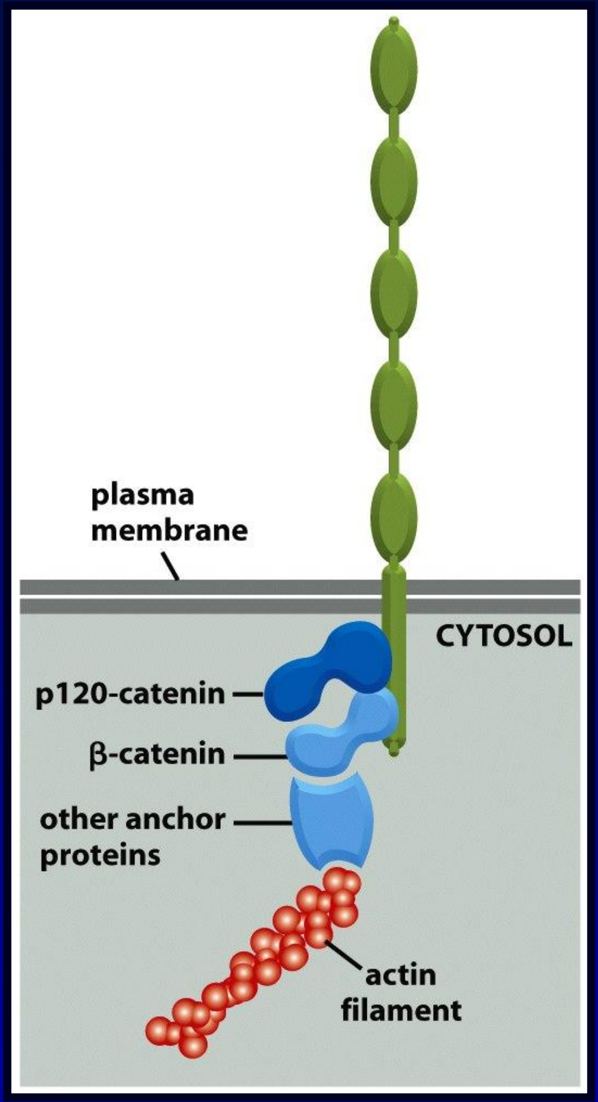
**If cells expressing different cadherins are mixed together, they sort out and aggregate separately**




- **different cadherins preferentially bind to their own type**
- **cells expressing E-cadherin sort out from cells expressing N-cadherin**
- **cells expressing high levels of E-cadherin sort out from cells expressing low levels**

**! QUALITATIVE and QUANTITATIVE expression !**

# Catenins link cadherins …




… to the actin cytoskeleton

- several different proteins are included to form anchor
- general parts is β-catenin

# *Types of junctions*

## Adherent junction

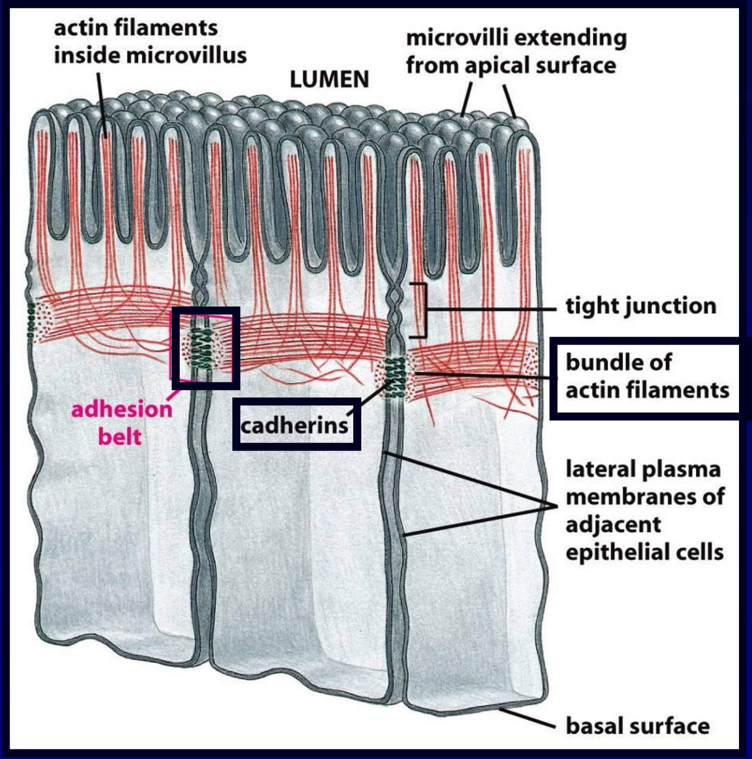
- Essential part for modelling shape of multicellular structures

## Desmosome junction

- Similar to adherent junctions, but link to intermediate filaments instead of actin

# Adhesion belt

## Prototypal example of adherent junctions




- Adhesion belt encircles each of the interacting cells
- Its most obvious feature is a contractile bundle of actin filaments running along the cytoplasmic surface of membrane
- Cadherins span the plasma membrane
- Cadherins extracellular domains bind to cadherins on the adjacent cell, adjacent cells are tied together

# *Other cell-cell adhesion proteins*

**Integrins**

- **For binding most extracellular matrix proteins**

**Selectins**

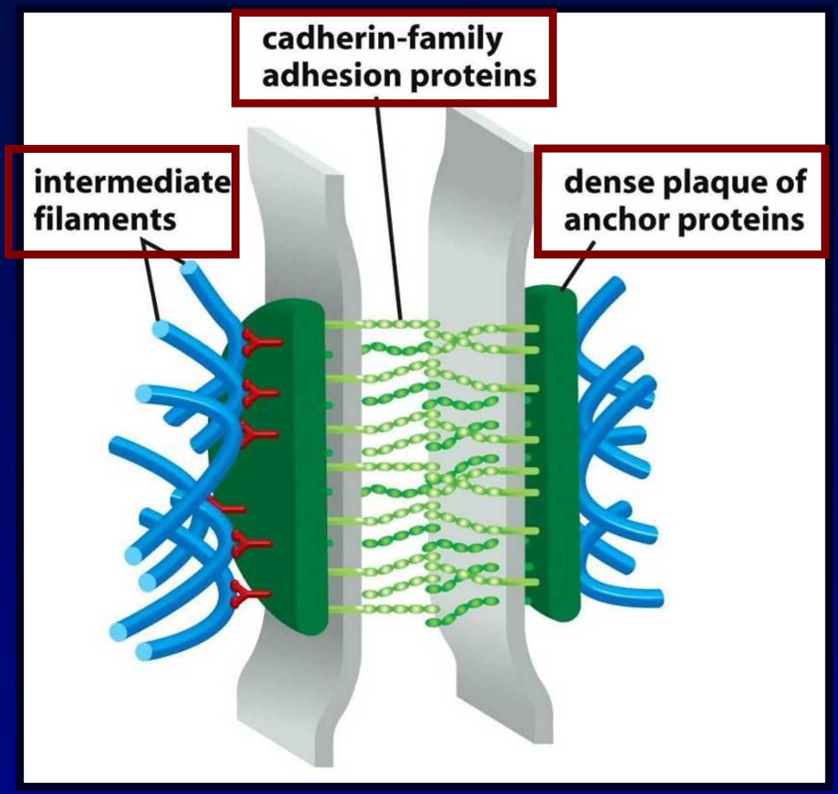
- **Cell surface carbohydrate binding proteins (lectins) that mediate adhesion interactions in bloodstream**

**Immunoglobulins**

- **Mediate $Ca^{2+}$ independent cell-cell adhesion**

# *Desmosomes and hemidesmosomes*

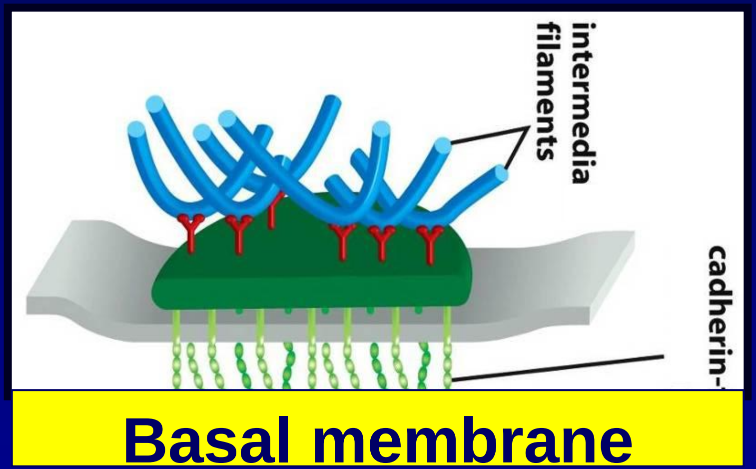
# General structure of desmosome




- On the cytoplasmic surface of each interacting plasma membrane is a dense plaque composed of a mixture of intracellular anchor proteins
- A bundle of keratin intermediate filaments is attached to the surface of each plaque
- Transmembrane adhesion proteins (cadherins) bind to the plaques and interact through their extracellular domains to hold the adjacent membranes altogether

# *Hemidesmosomes*

- The connection between the cell and the extracellular matrix
- Bind to the basement membrane
- Integrin-mediated junctions
- They look like half of a desmosome




Where even hemidesmosomes are no longer enough!

**Why do people get blisters?**

**This is a reminder that it is not enough for epithelial cells to be connected to each other, but they must also be connected to the underlying tissues**

# *Tight junctions and the organization of epithelia*

# Introduction

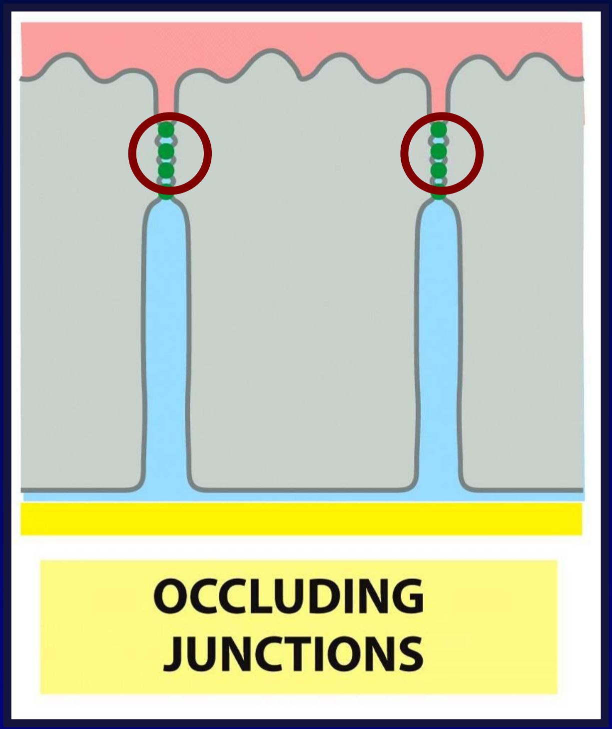
More than 60% of the cell types in vertebrate body are epithelial

- Essentially all epithelia are anchored to other tissue on one side – the basal side, and
- Free of such attachments on their opposite side – the apical side

A basal lamina lies at the interface with the underlying tissue, mediating the attachment, while the apical surface of the epithelium is generally bathed by extracellular fluid

! Epithelia are structurally polarized !

# *Occluding junctions*

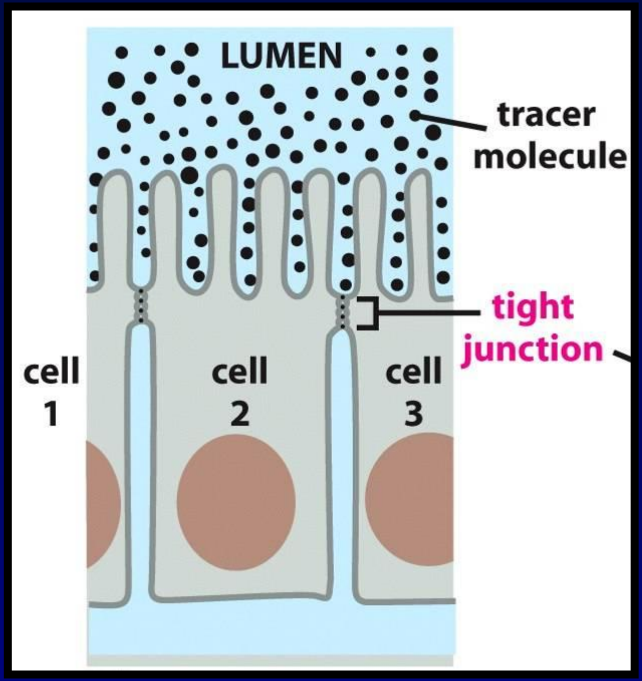



They form a seal between cells and a fence between membrane domains

- Transport proteins are confined to different regions of the plasma membrane in epithelial cell of the small intestine

- This segregation permits a vectorial transfer of nutrients across the epithelium from the gut lumen to the blood

# Occluding junction in vertebrate

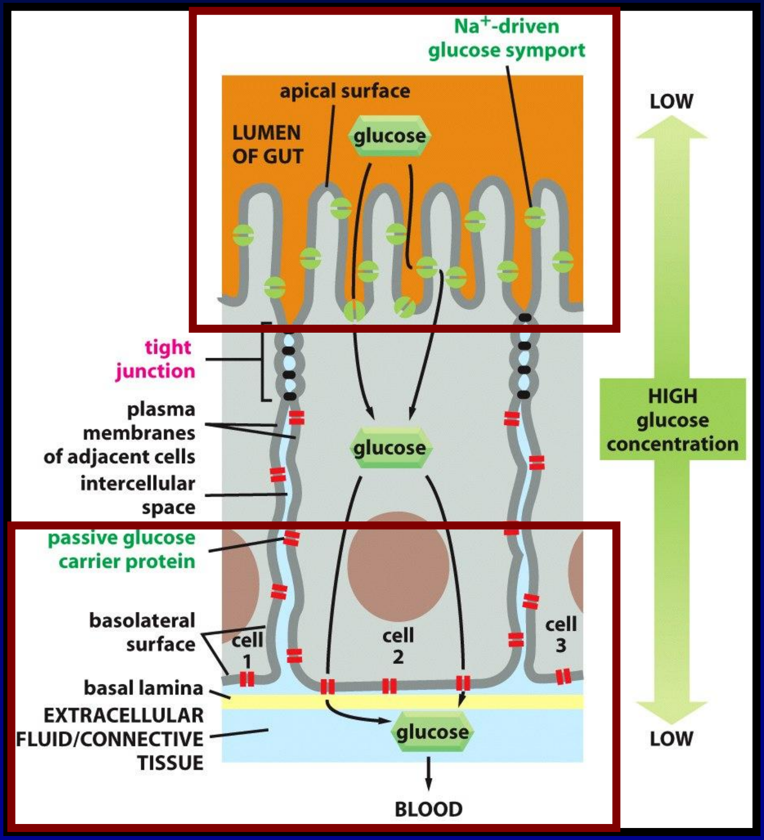



## = Tight junctions

Epithelia serve as selective permeability barriers, separating the fluid that permeates the tissue from their basal side from fluid with a different chemical composition on their apical side

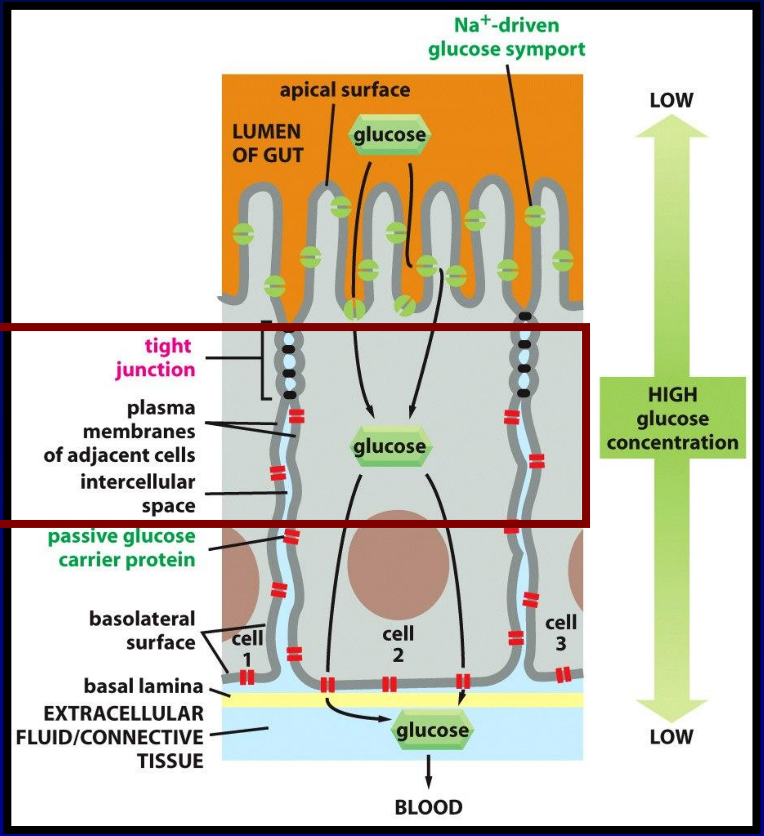
- This barrier function requires that the adjacent cells be sealed together by tight junctions
- So that molecules cannot leak freely across the cell sheet

# Tight junctions in transcellular transport




- Glc is actively transported into cell by $Na^+$ driven glc symport at its apical surface
- Glc diffuses out of the cell by facilitated diffusion mediated by glucose carriers in its basolateral membrane

# Tight junctions in transcellular transport




- Tight junctions are thought to confine transport proteins to their appropriate membrane domains by acting as diffusion barriers within the lipid bilayer of the plasma membrane
- These junctions also block the backflow of glucose from the basal side of the epithelium into the gut lumen

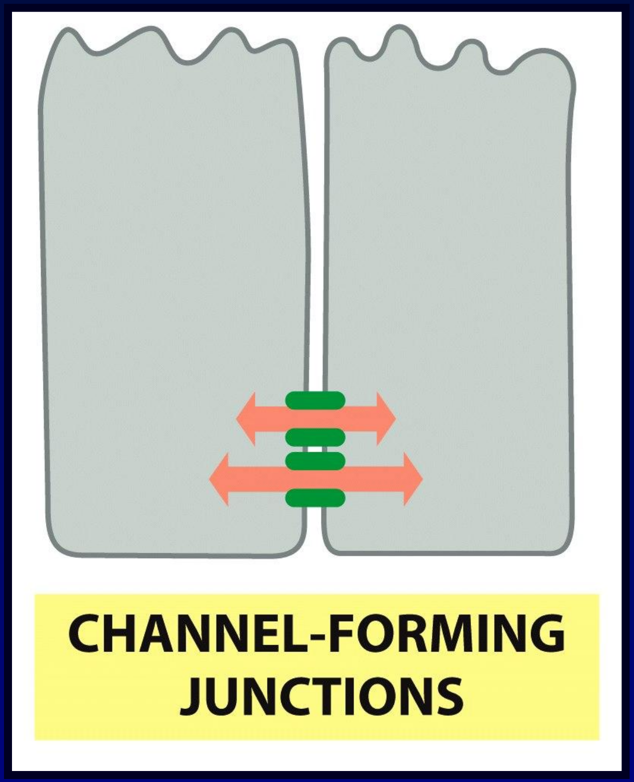
# *Gap junctions and plasmodesmata - passageways from cell to cell*

# *Types of passageways*

- **Gap junctions in animals**
- **Plasmodesmata in plants**

- **Quite different forms**
- **Similar function**

# *Channel-forming junctions*




They bridge gaps between adjacent cells so as to create direct passageways from the cytoplasm of one into that of the other

The connections allow neighbouring cells to exchange small molecules but no macromolecules

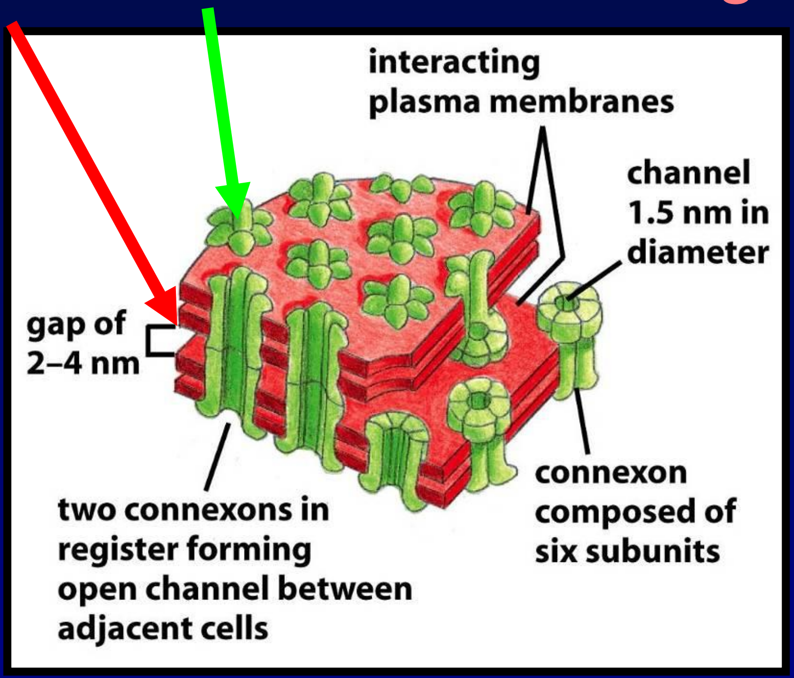
- gap-junction (in animals)
- plasmodesmata (only type of inter-cell in plant)

This junction enables communications between cells

**Junctions are performer by conexin and inexin**

# Gap junctions (animals)

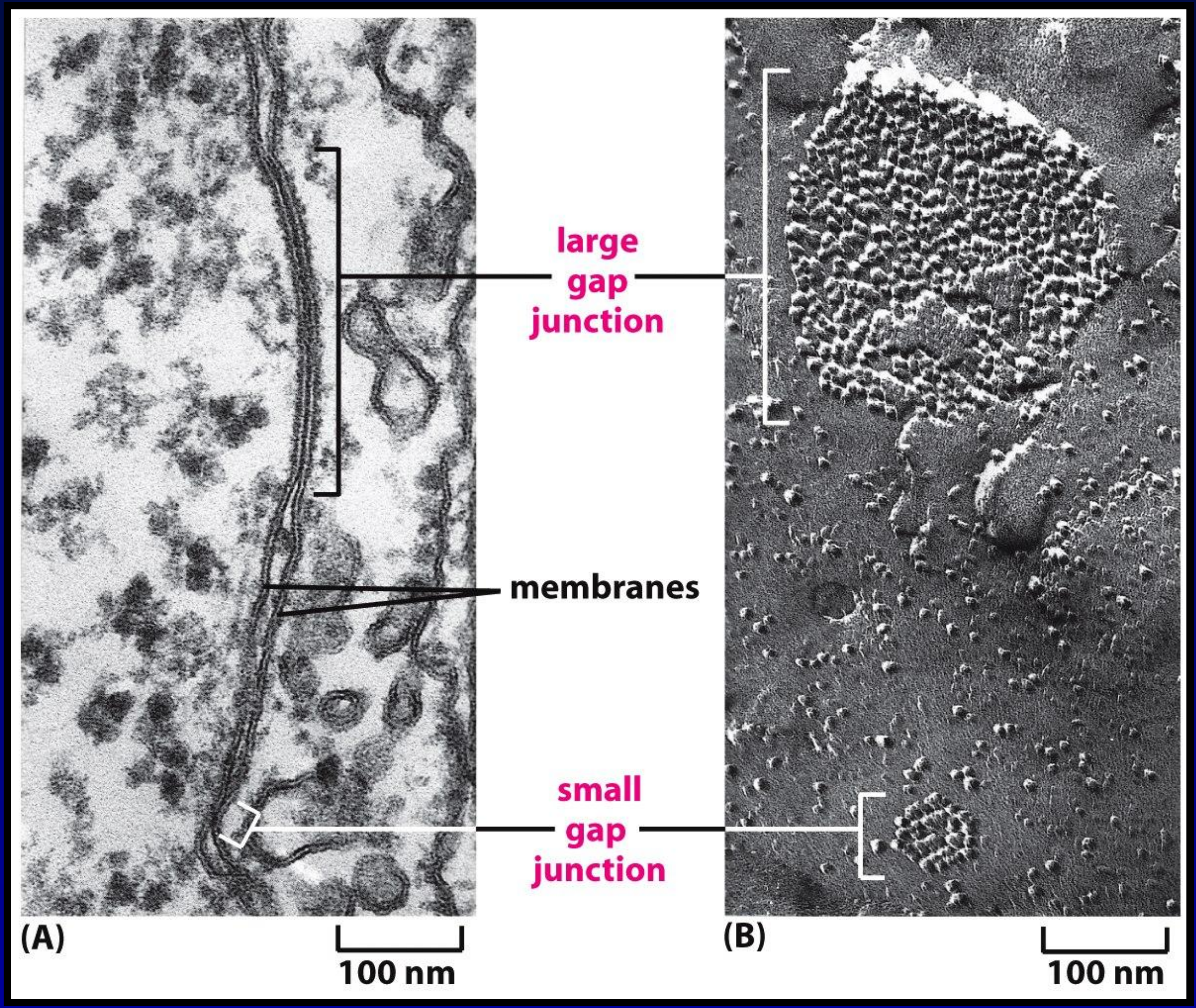
Plasma membranes of two adjacent cells connected by gap junctions




- Each lipid bilayer is shown as a pair of red sheets
- Protein assemblies called connexons, each is formed by six connexin subunits

- Connexin subunits penetrate the opposed lipid bilayer
- Two connexons join across the intracellular gap to form a continuous aqueous channel connecting the two cells

# Gap junctions in electron microscope



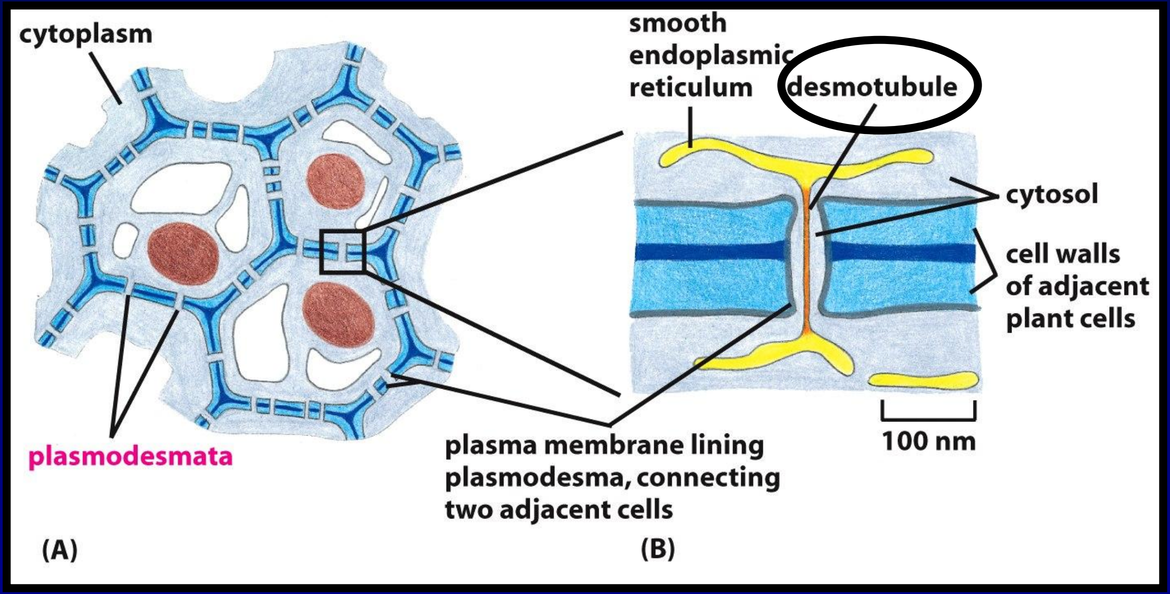
# *Functions of gap junctions*

- **Spreading action potential in tissues containing electrically excitable cells**
- **Synchronization the contracting of heart muscle cells as well as smooth muscle cells responsible for the peristaltic movements of the intestine**
- **In liver to coordinate the response of the liver cells to signals from nerve terminals that contact only a part of the cell population**
- **Normal development of ovarian follicles also depends on gap junction between the oocyte and the surrounding granulosa cells**

# Plasmodesmata (plant)

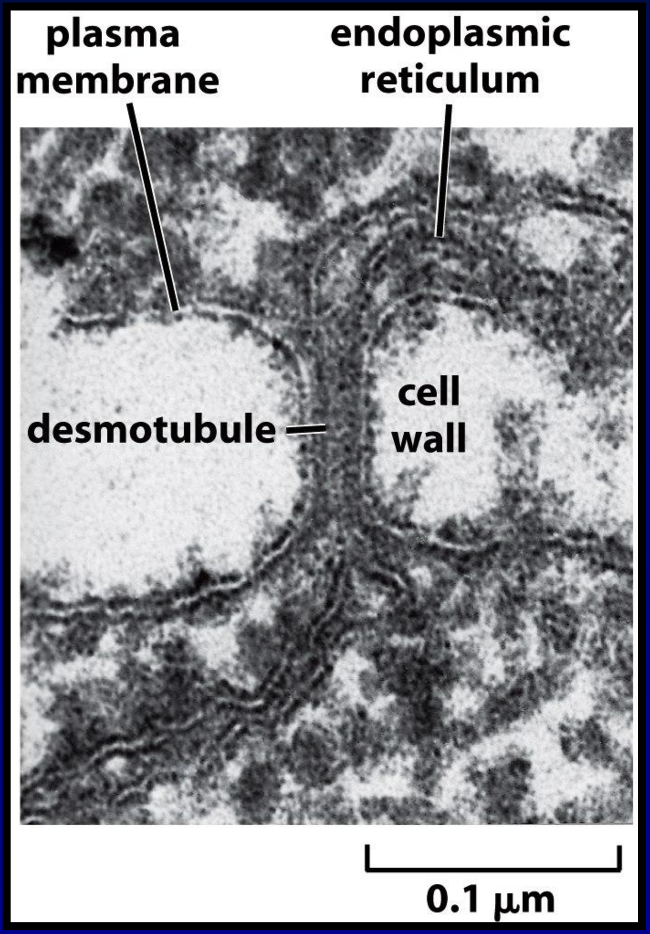
Pierce the plant cell wall and connect all cells in a plant together

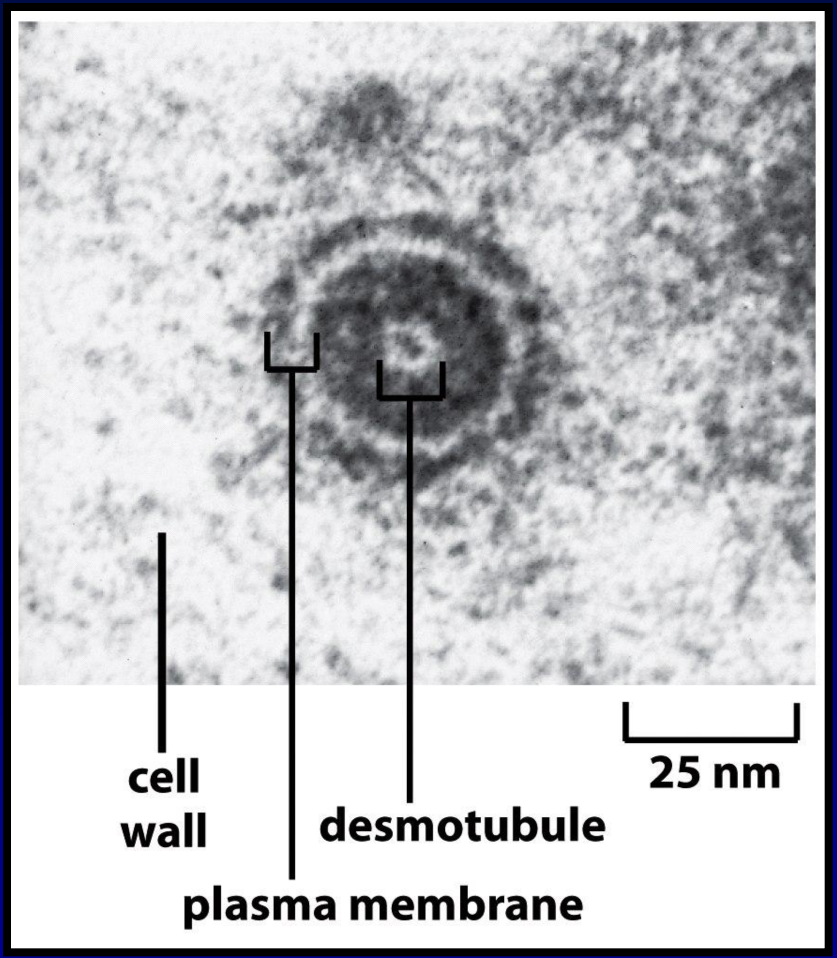
Each plasmodesma is lined with plasma membrane that is common to two connected cells




It usually also contains a fine tubular structure, the desmotubule, derived from smooth ER

# Plasmodesma in electron microscope



# *The basal lamina*

# *Tissues are not made up solely of cells*

- **A part of the tissue volume is formed by <u>extracellular space</u>**
- **Extracellular space is occupied by an intricate network of macromolecules constituting the <u>extracellular matrix</u>**
- **This matrix is composed of various proteins and polysaccharides**

# *Basal lamina*

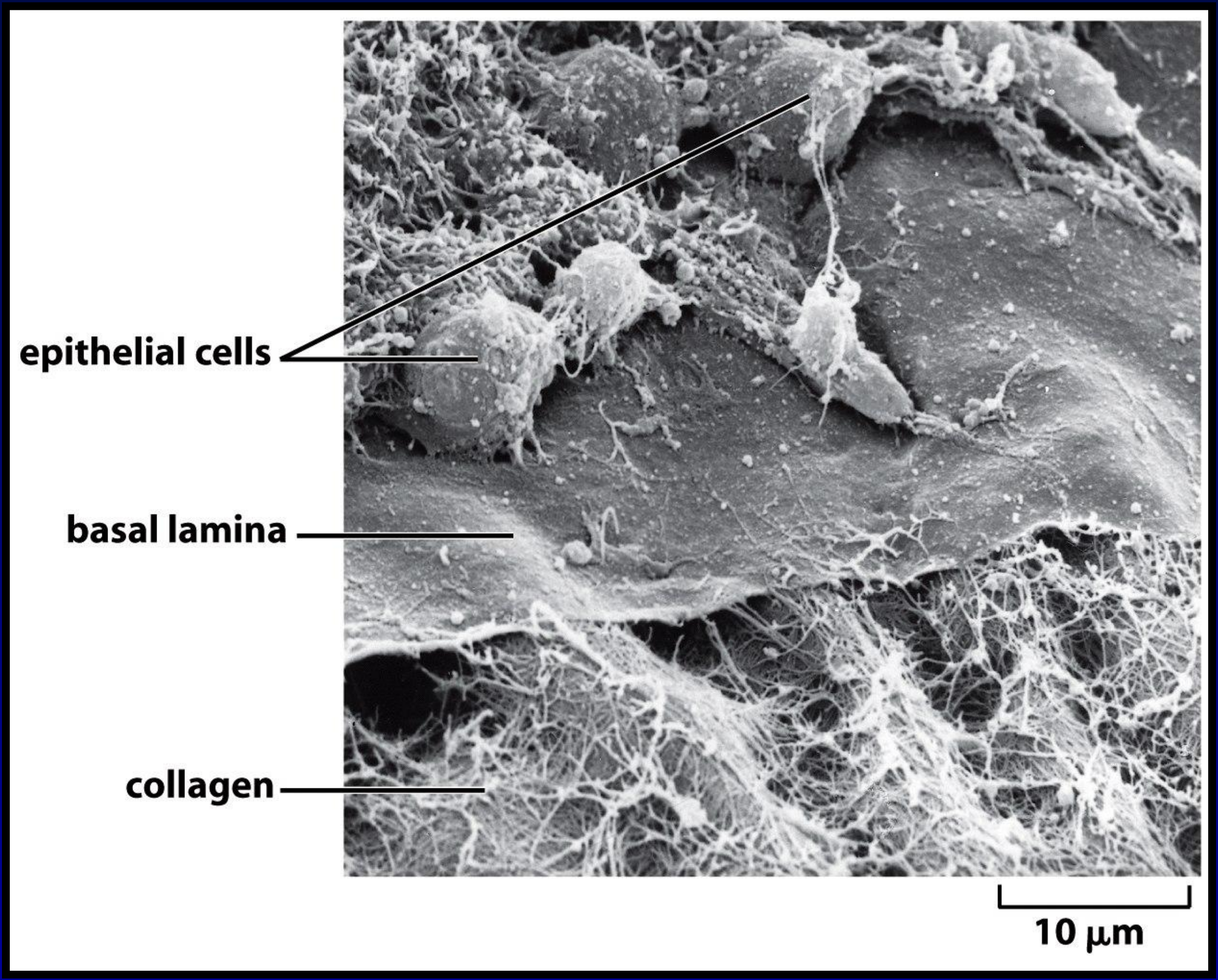
## Extracellular matrix in our bodies

- Thin, though, flexible sheet of matrix molecules which is essential underpinning of all epithelia
- Small as it is in volume, it has a critical role in the architecture of the body

**Like the cadherins it seems to be one of the defining features common to all multicellular animals**

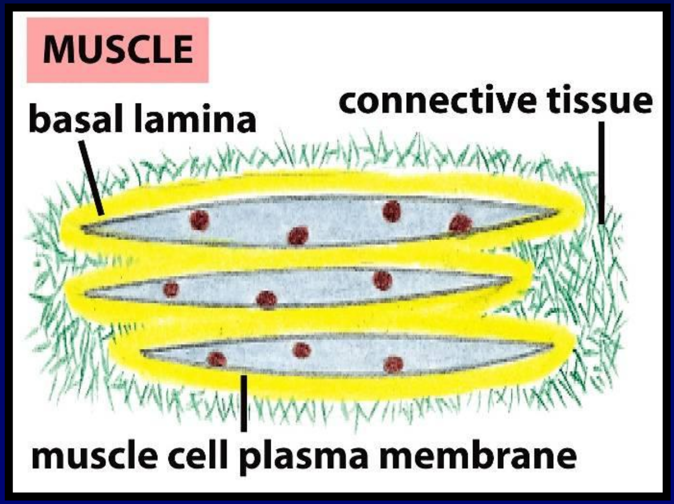
# Basal lamina

## Cornea of a chicken embryo

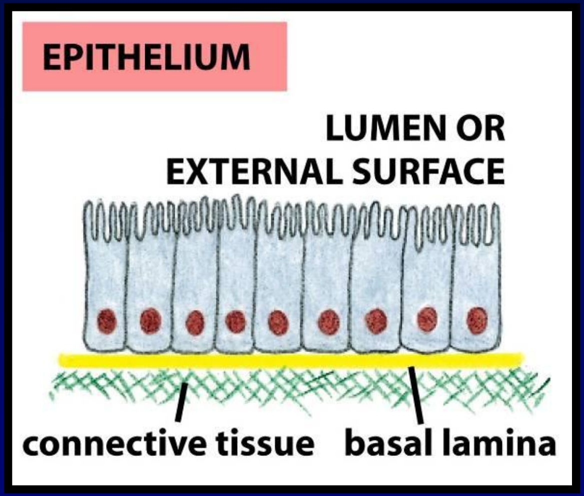


# Organization of basal lamina

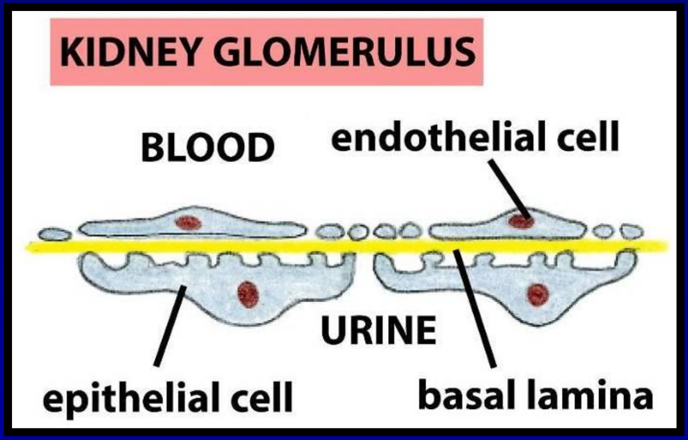
Surround certain cells



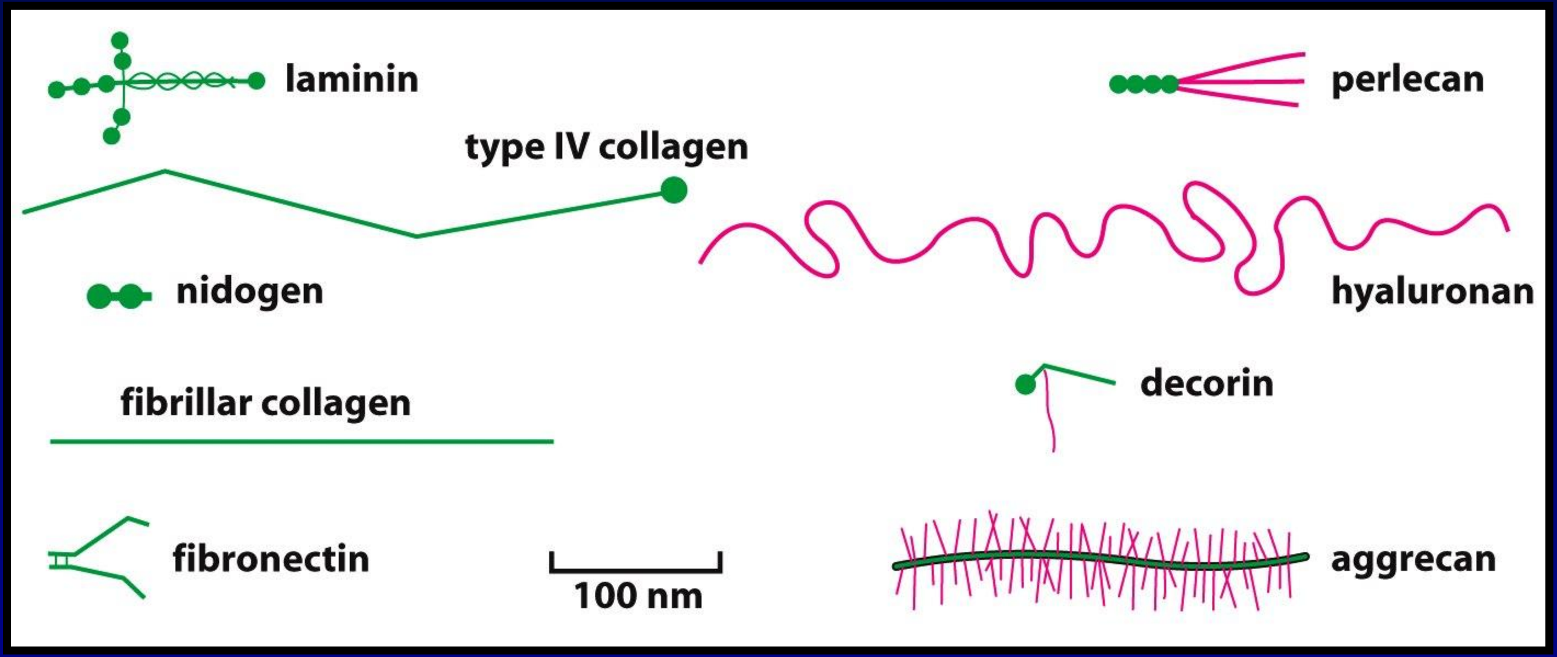

Underlie epithelia




Are interposed between two cell sheets



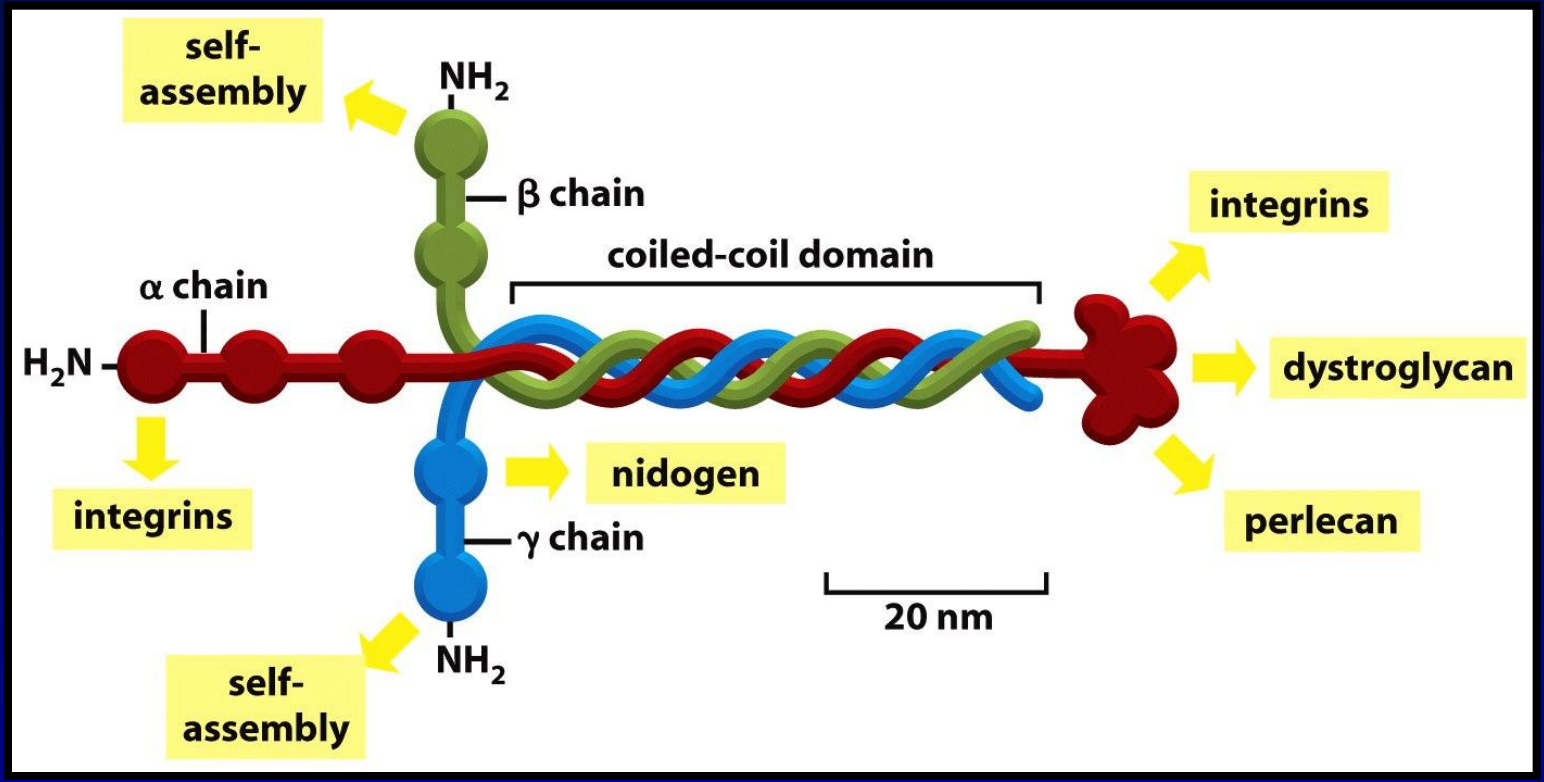
# Shapes and sizes of matrix macromolecules




**Proteins are shown in green**
**Glycosaminoglycan is red**

# Laminin

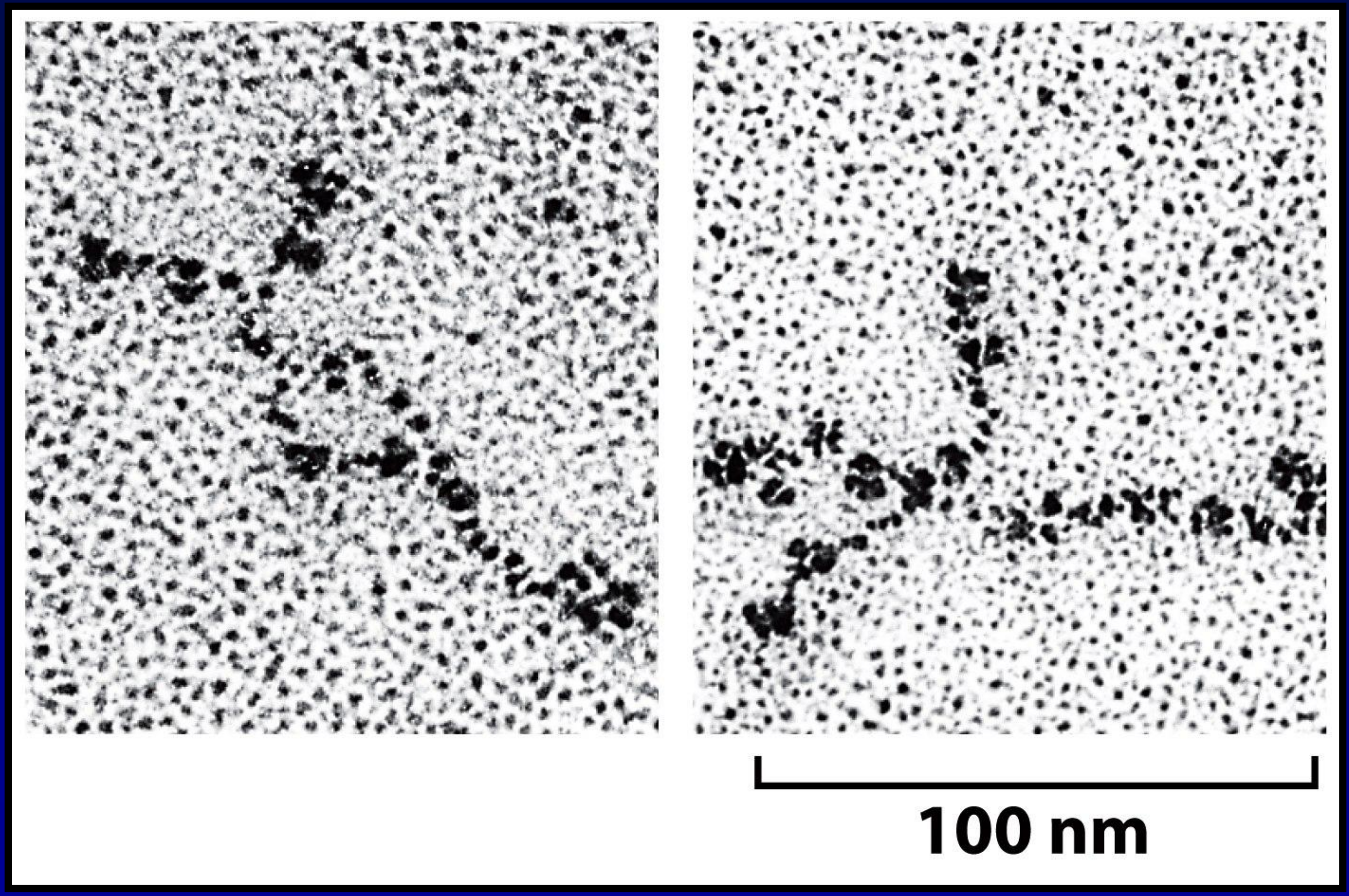
## The primary organizer of the sheet structure




**Large, flexible protein composed of three very long polypeptide chains (α, β, and γ) held together by disulfide bonds**

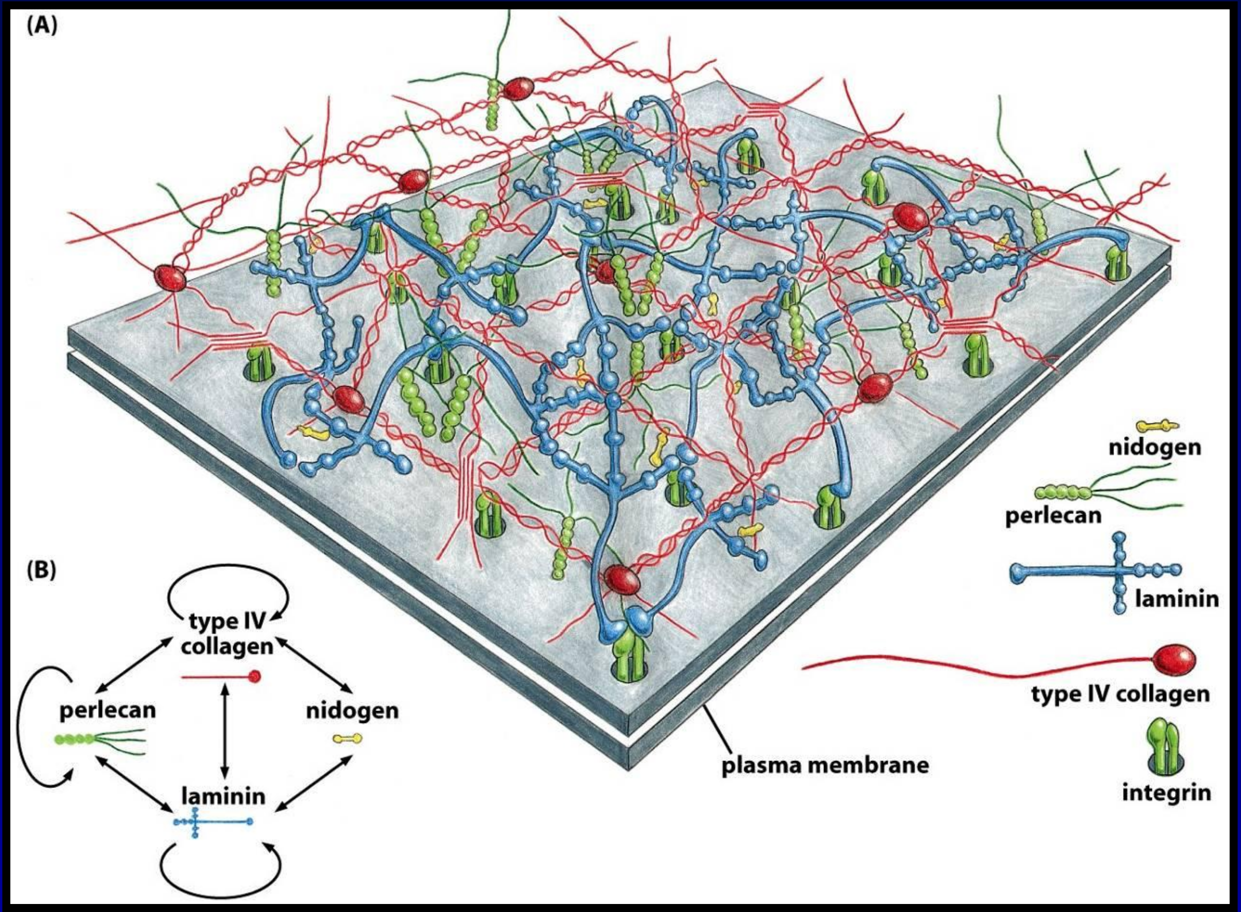
# EM of laminin molecules

## Shadowed by platinum



# Model of the molecular structure

**The basal lamina is formed by specific interactions between the proteins - laminin, type IV collagen, and nidogen, and the proteoglycan perlecan**

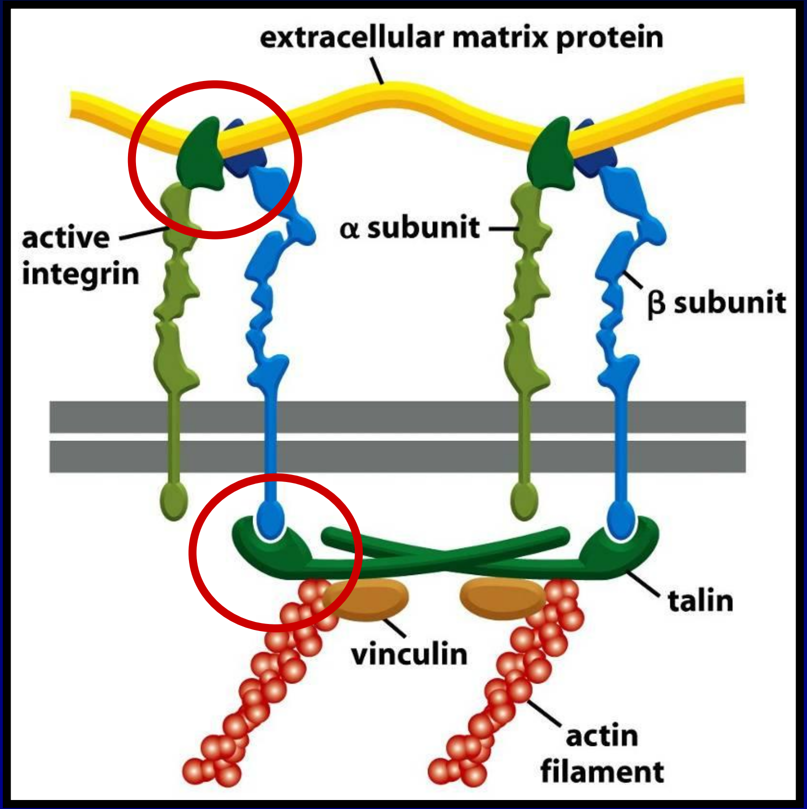


# *Basal lamina functions*

1) Molecular filter (unusually thick basal lamina in the kidney glomerulus)
2) A selective barrier to the movement of cells
3) Beneath an epithelium, for example usually prevents fibroblast in the underlying connective tissue from making contact with the epithelial cells
4) Tissue regeneration after injury – muscles, nerves, and epithelia

# *Integrins*

## Proteins that function as matrix receptors on animal cells




- Head of the integrin molecule attaches directly to extracellular protein such as fibronectin
- Intracellular tail of the integrin binds to talin, which in turn binds to filamentous actin

- A set of other intracellular anchor proteins, α-actinin, filamin, and vinculin, help to reinforce the linkage