

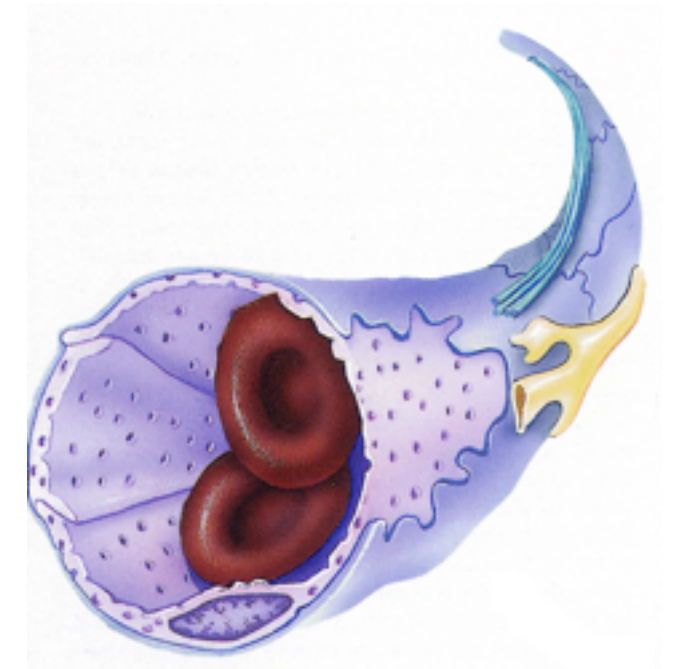
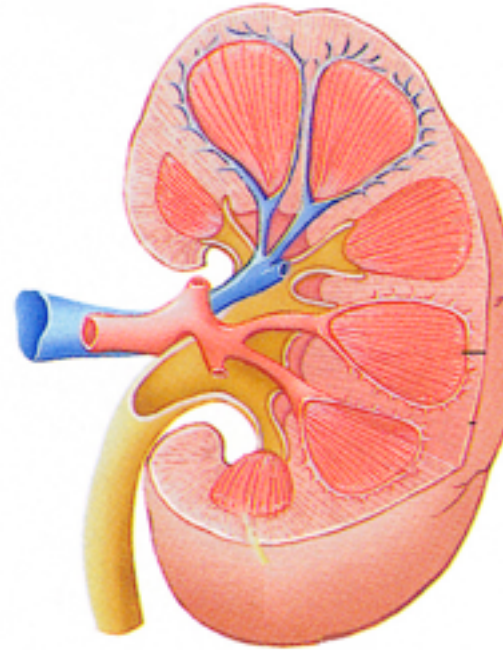
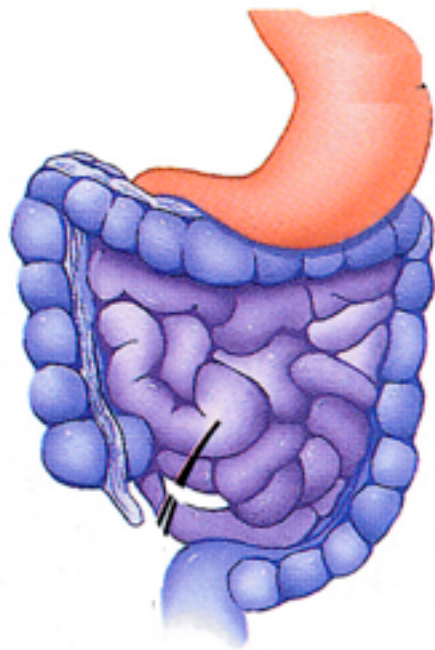
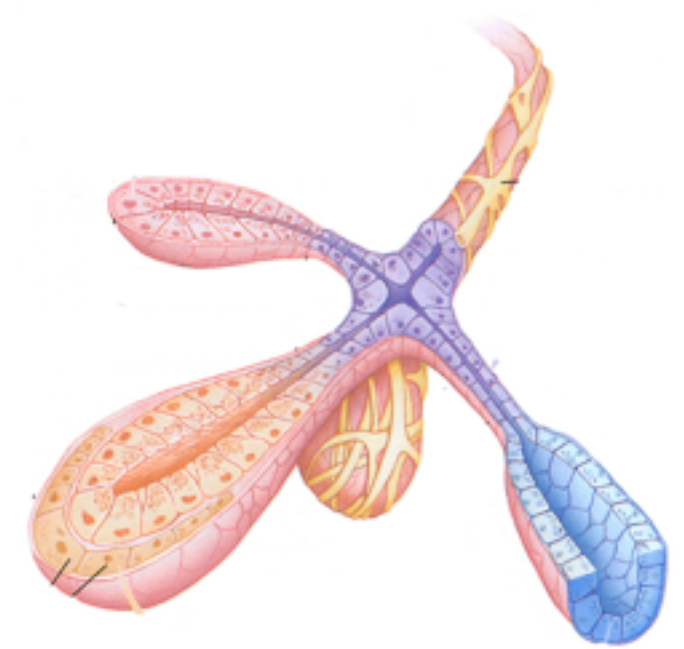
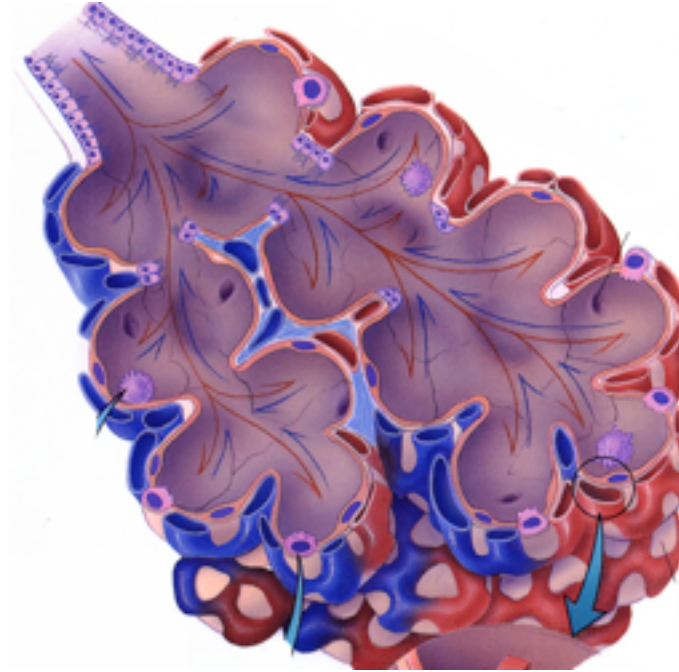
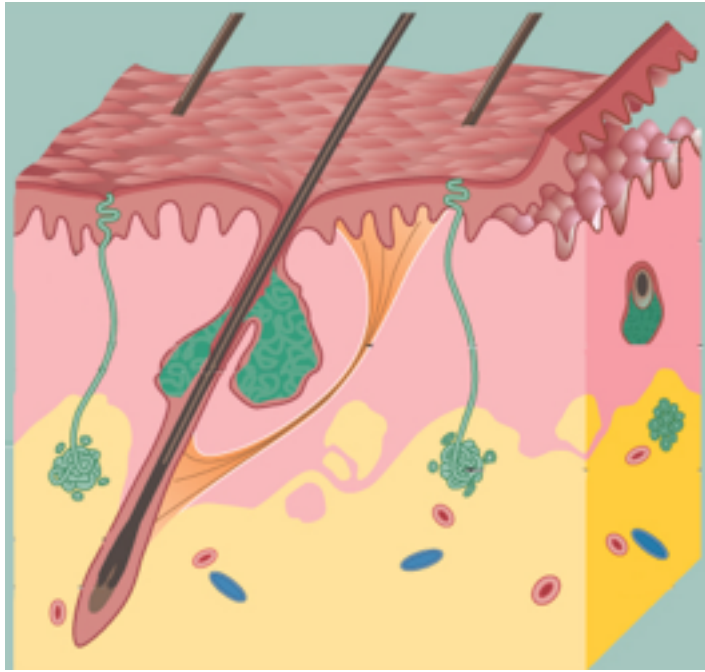
Epithelial Structure

Peter Takizawa

Department of Cell Biology

- Type of epithelia
- Adhesion between epithelial cells
- Basement membrane
- Epithelial cell polarity
- Cell renewal

All organs contain epithelia in some form.

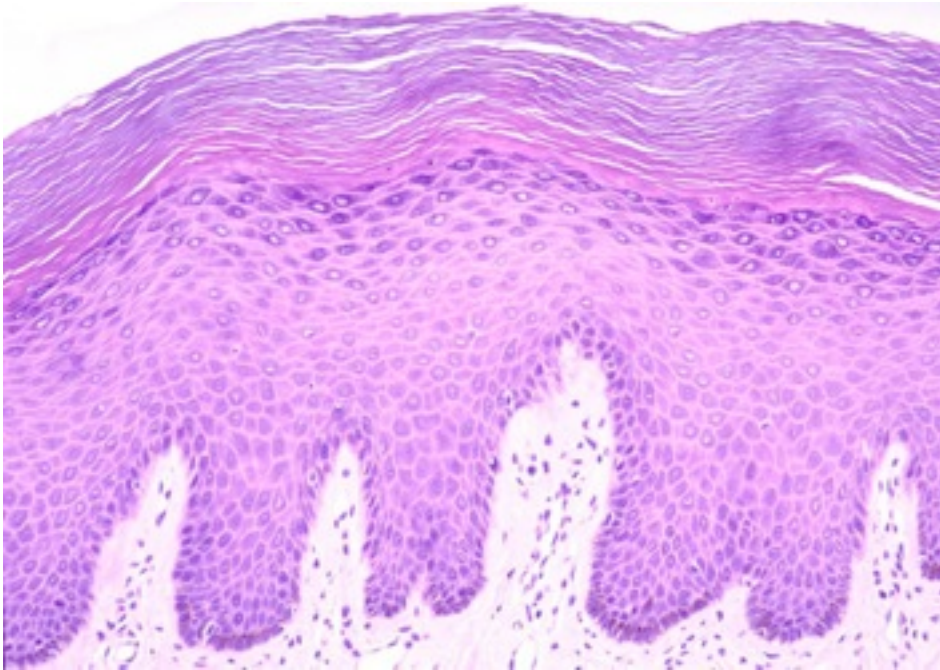


Epithelia are a collection of cells that form functional unit. Most epithelia form a sheet of cells. Epithelia line most body surfaces, including the skin digestive tract, respiratory tract and all body cavities. They form the functional unit and ducts of secretory glands. Epithelia are also the inner lining of all blood vessels and lymphatics.

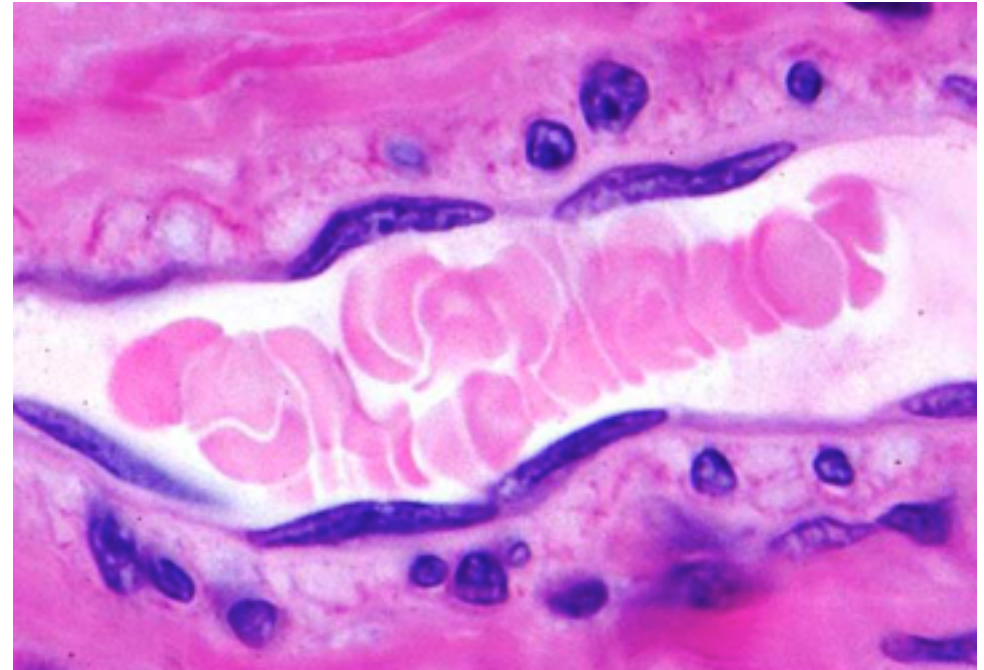
~85% of cancers derive from epithelia.

Epithelia perform a variety of functions.

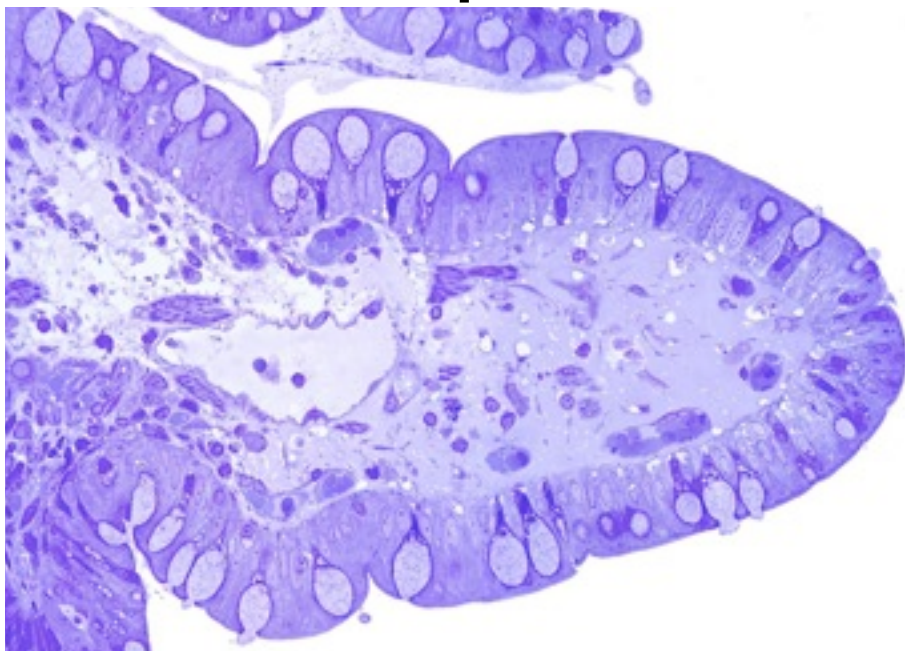
Protection



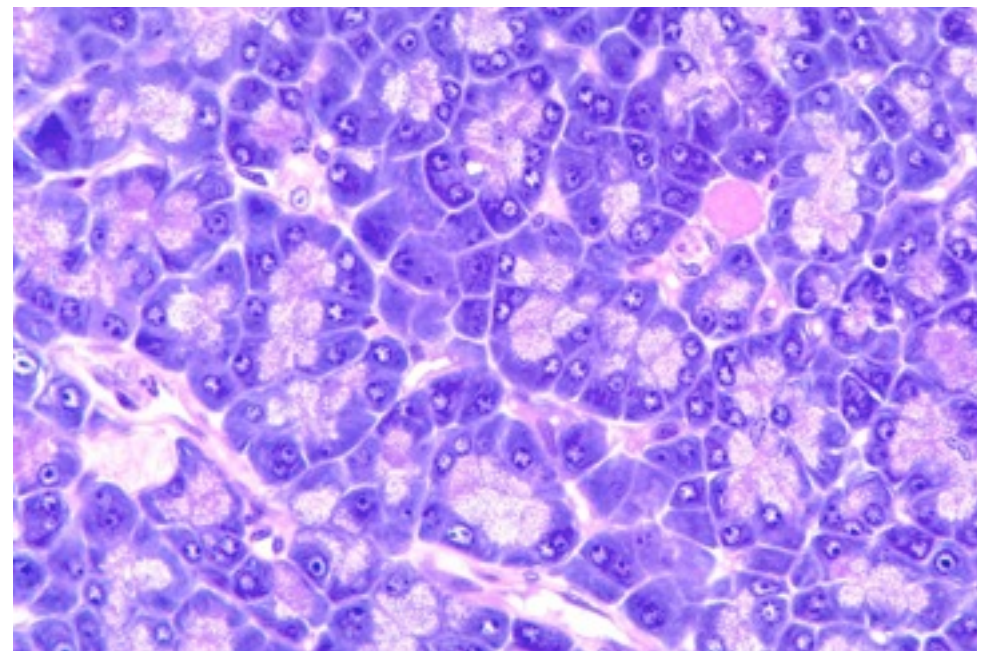
Diffusion



Absorption

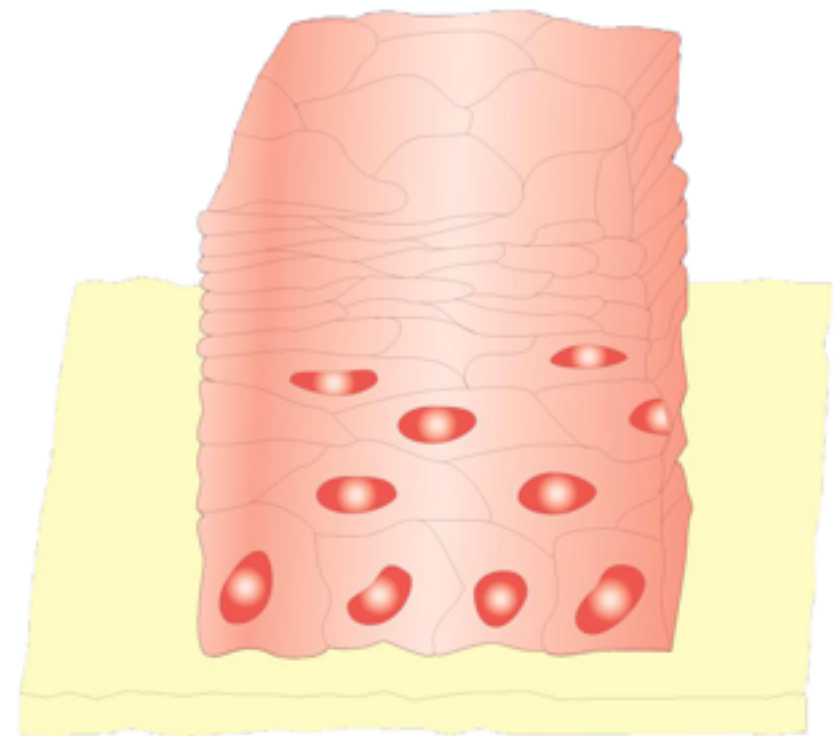
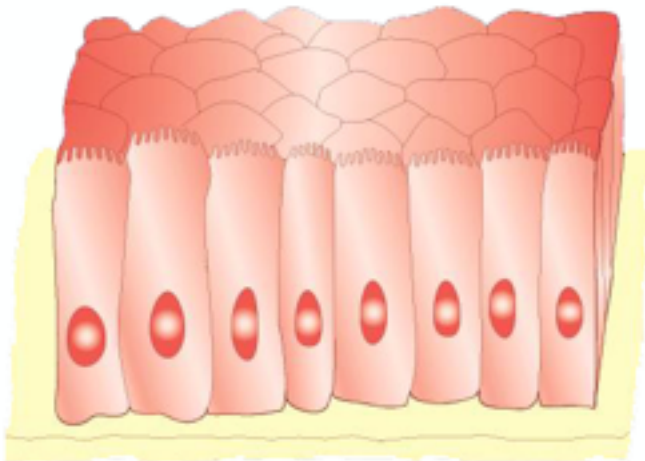
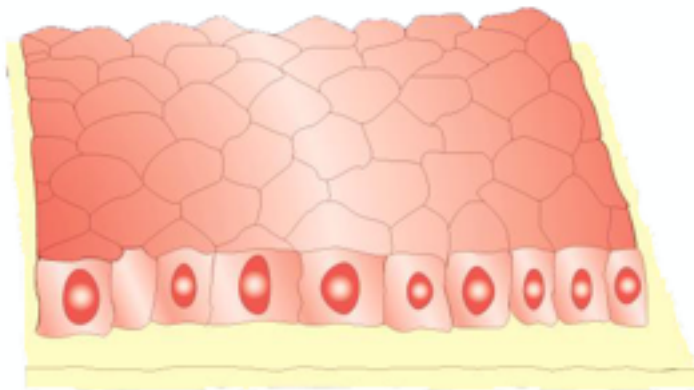
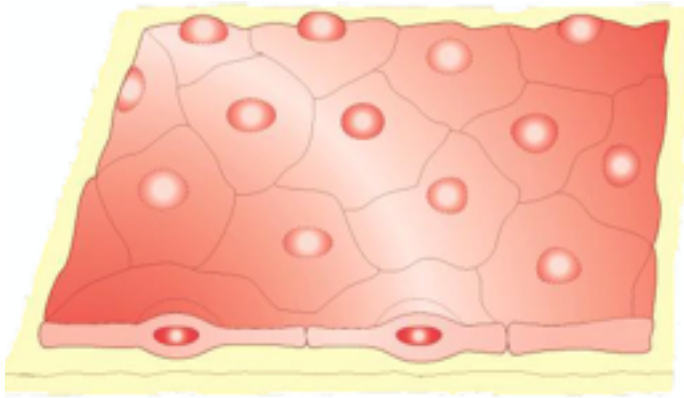


Secretion



Epithelia serve a number of functions. They offer protection to organs such as the skin. They absorb material in the intestine. They secrete material in glands. And they allow for passive diffusion of gases in the lung and blood vessels.

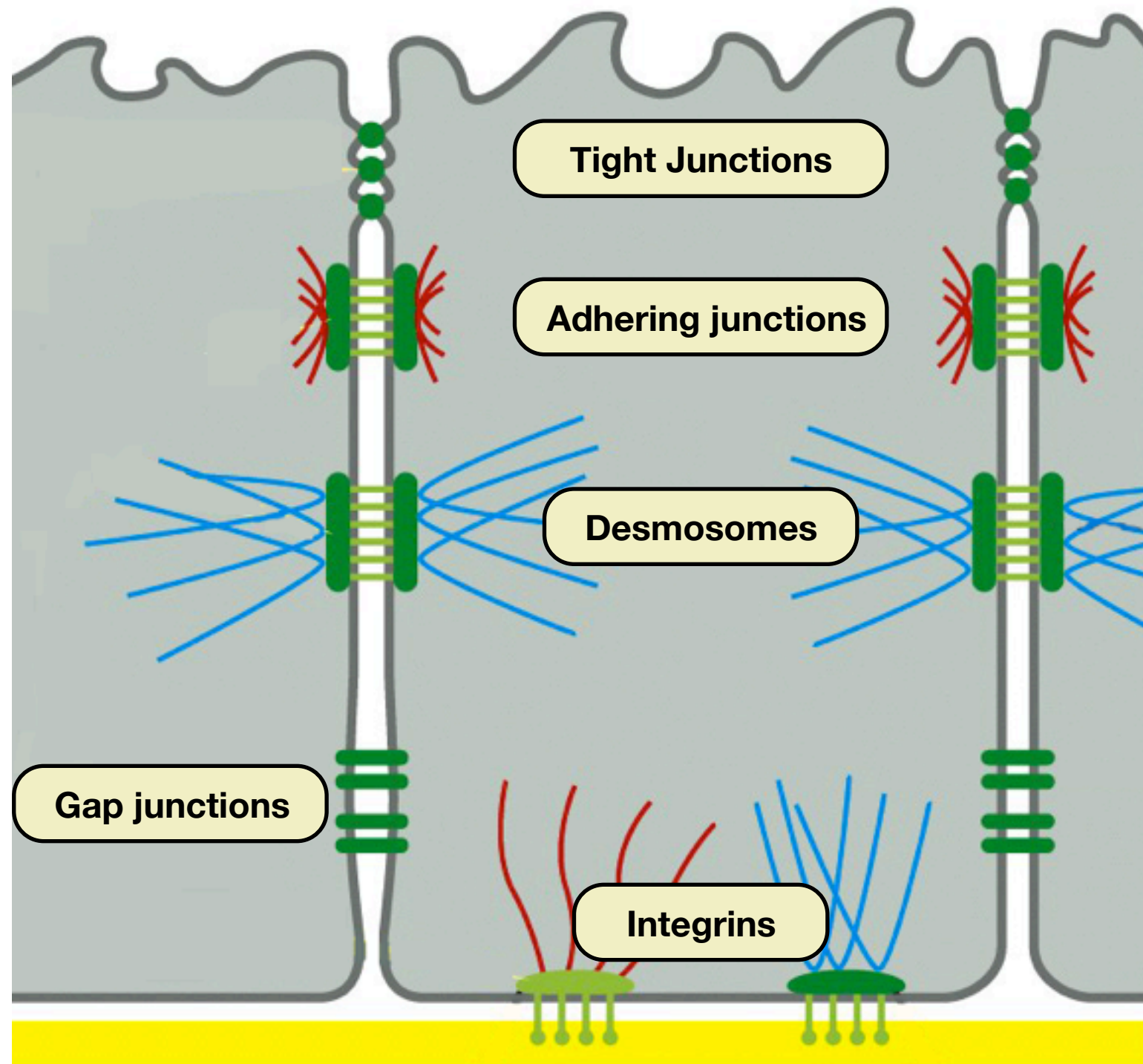
Layers and shape of cells in epithelium facilitate its functions.



To accomplish these different functions, epithelia come in a variety of structures. Most epithelia are classified based on two criteria: shape and layers of cells. A single layer of cells is called simple whereas a epithelium with two or more layers of cells is called stratified. If the most superficial layer of cells is flat, the epithelium is referred to as squamous. Squamous epithelia facilitate diffusion of gases and other small molecules. Epithelia where the cells are about as tall as they are wide are called cuboidal. If the cells are taller than they are wide, then they are called columnar. Cuboidal and columnar cells are usually involved in secretion and/or absorption and need more cytoplasmic volume to accommodate the organelles needed for these activities. Two special types of epithelia are pseudostratified and transitional.

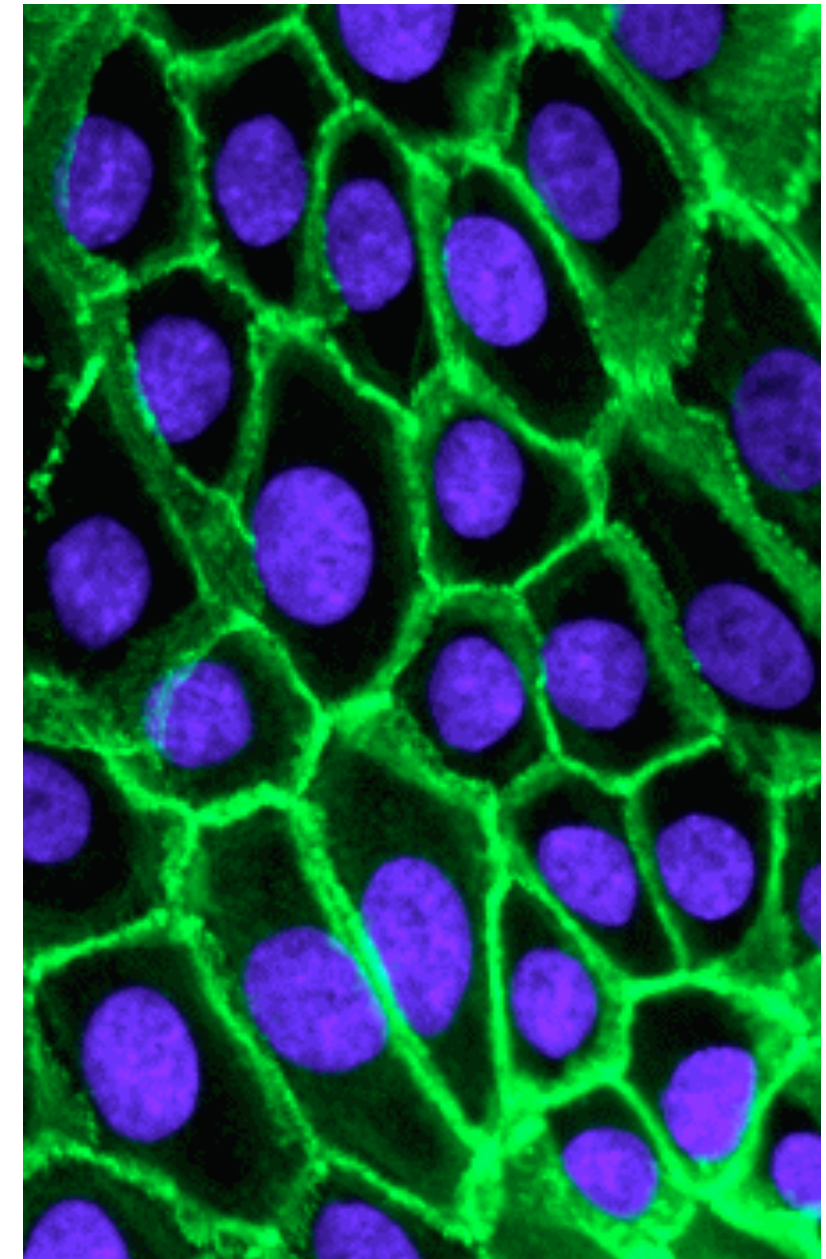
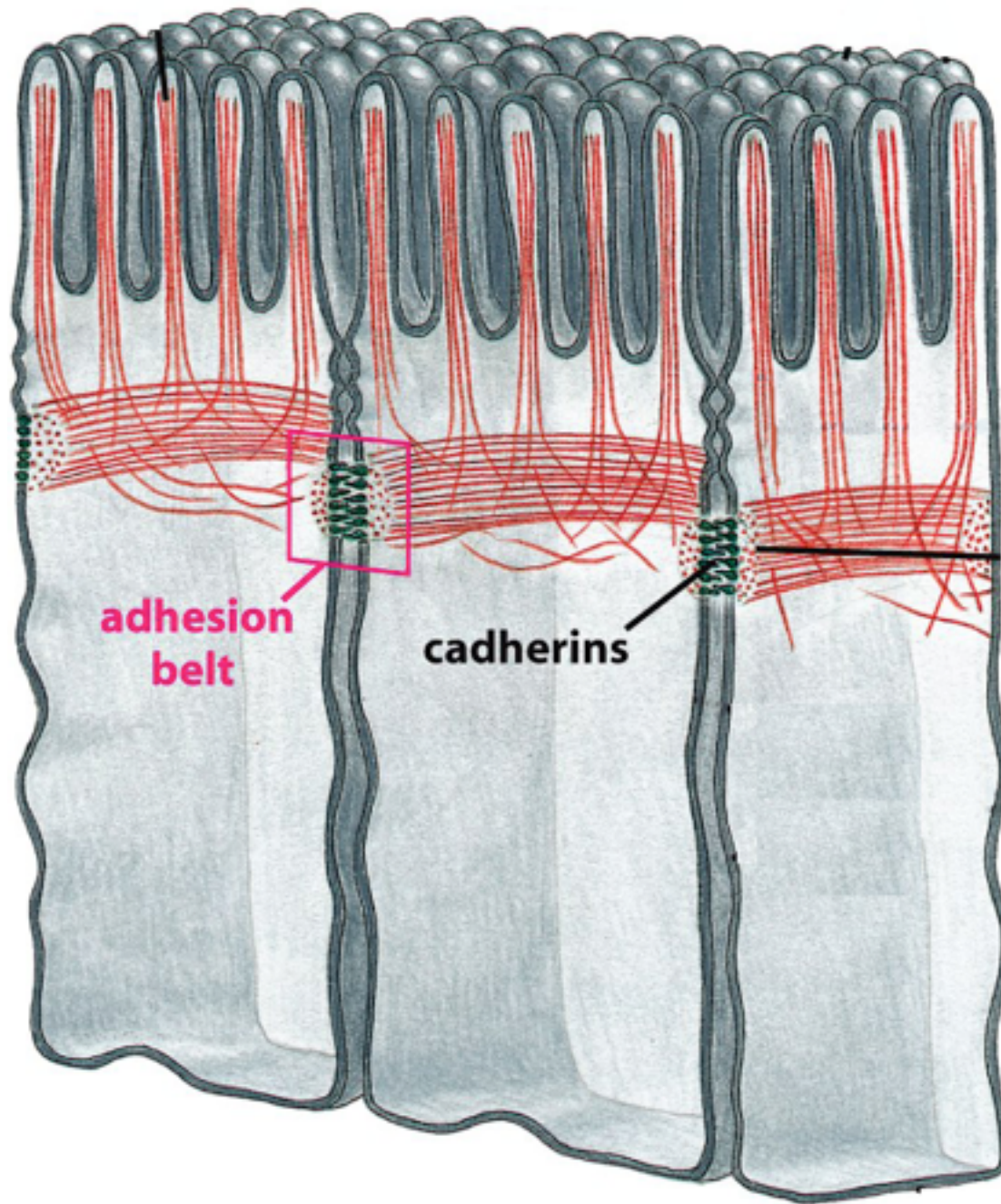
Adhesion between epithelial cells.

Epithelial cells are held together by three junctional complexes.



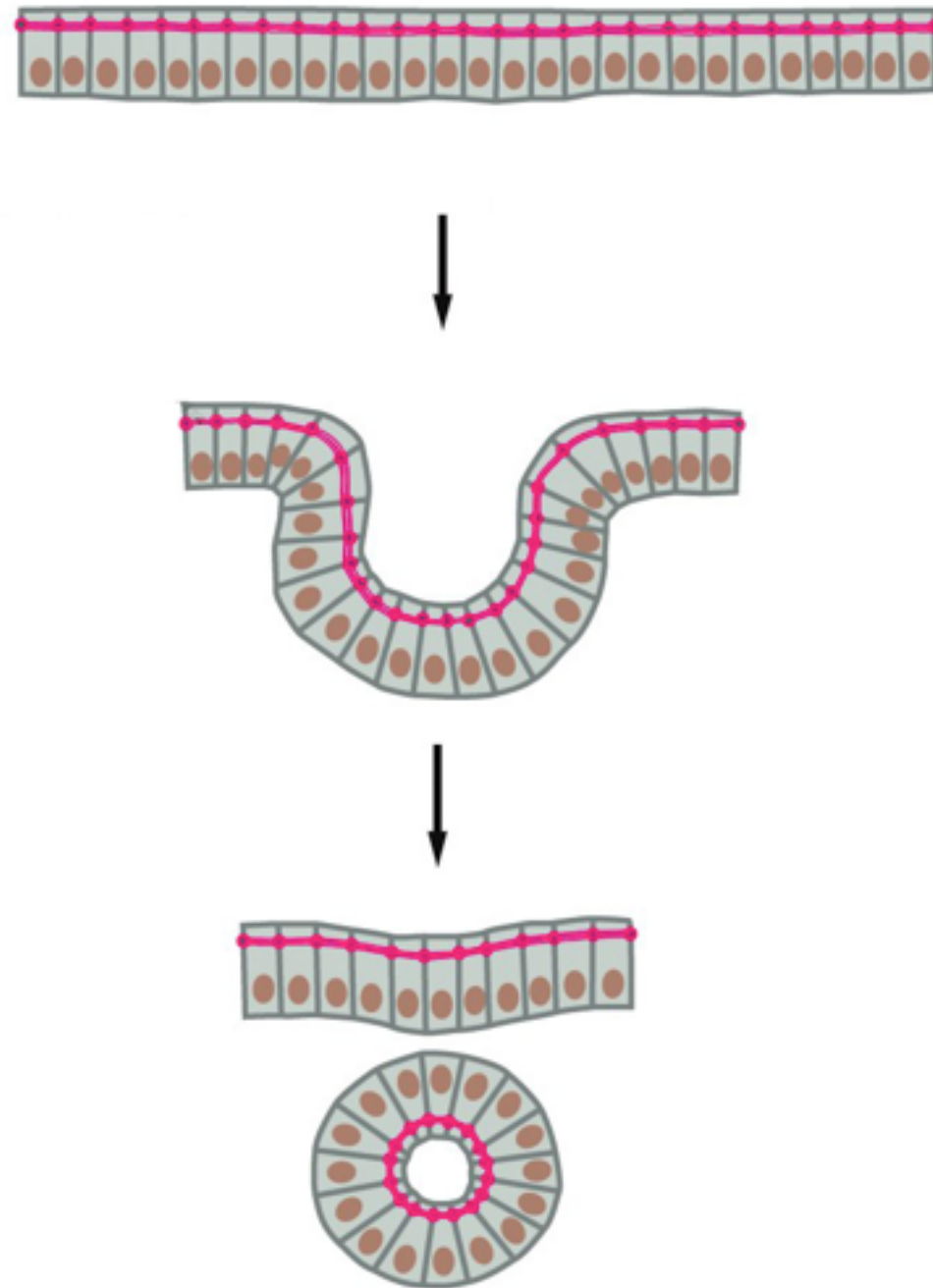
Epithelial cells are held together by three junctional complexes. All epithelia will have adhering junctions, but only some will have desmosomes. Epithelia also contain tight junctions which control the diffusion of material between epithelia cells.

Adhering junctions form a belt-like adhesion zone around epithelial cells.



Adhering junctions have characteristic arrangement in epithelial cells. They form continuous belt around the circumference of epithelial cells. The adherens junctions are linked to bundles of actin filaments that also wrap around the cell. Myosin filaments can pull on the actin filaments to contract the cell. Because the adherens junctions are located closer to the apical surface, contraction causes the apical surface to shrink. This allows epithelia to form a tube from a sheet of cells.

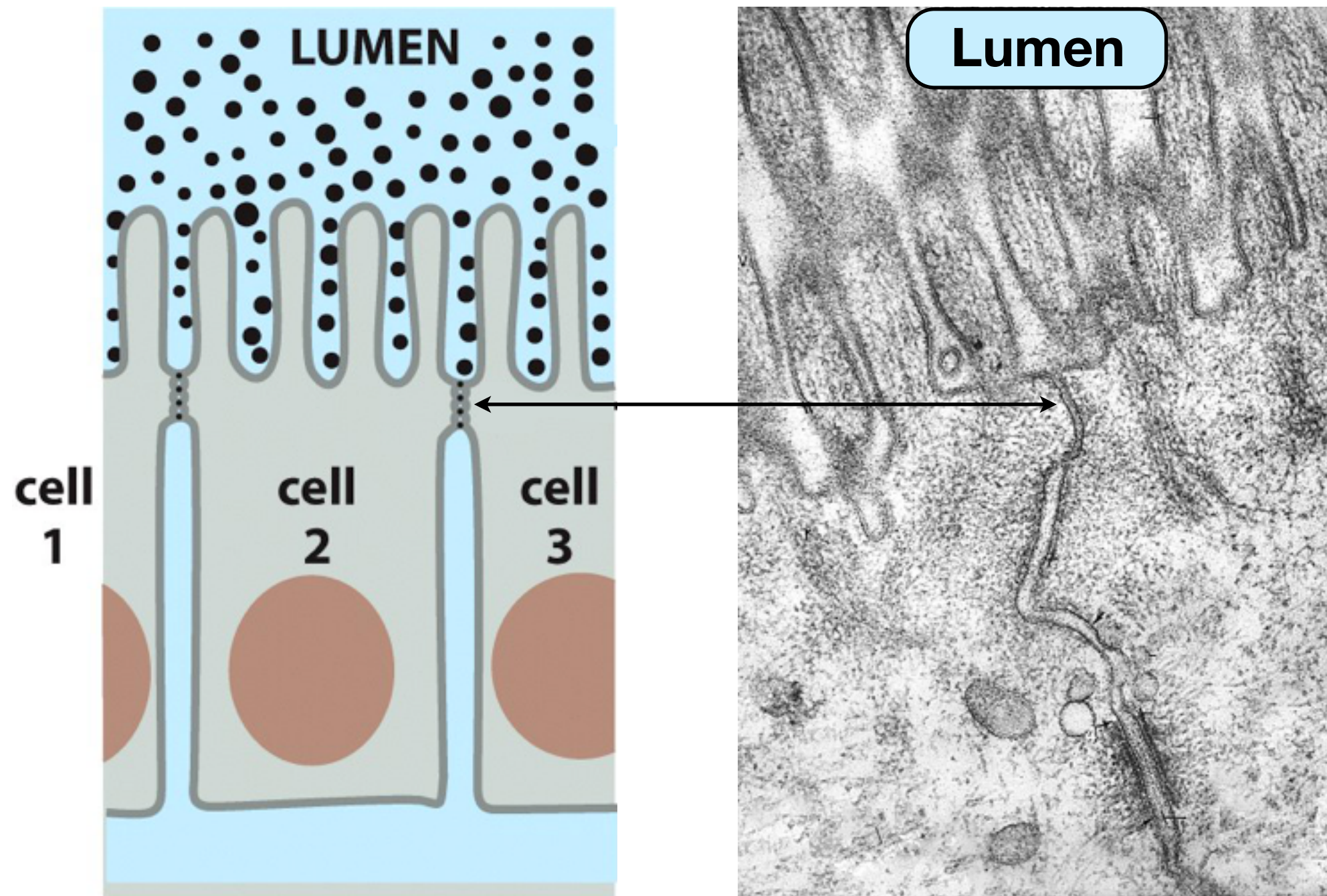
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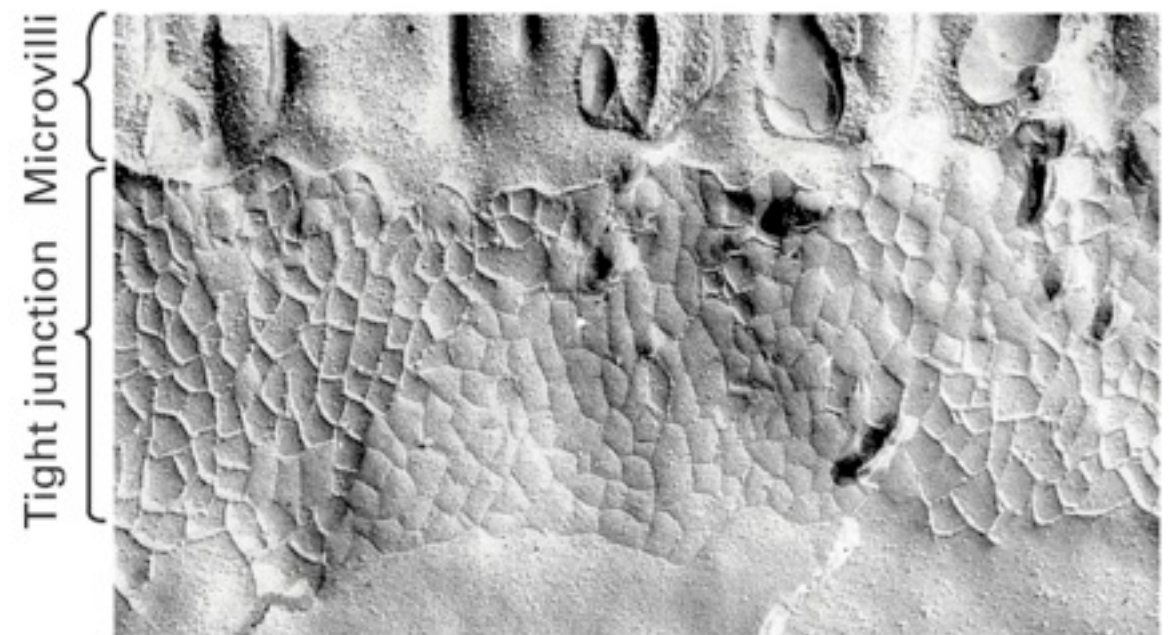
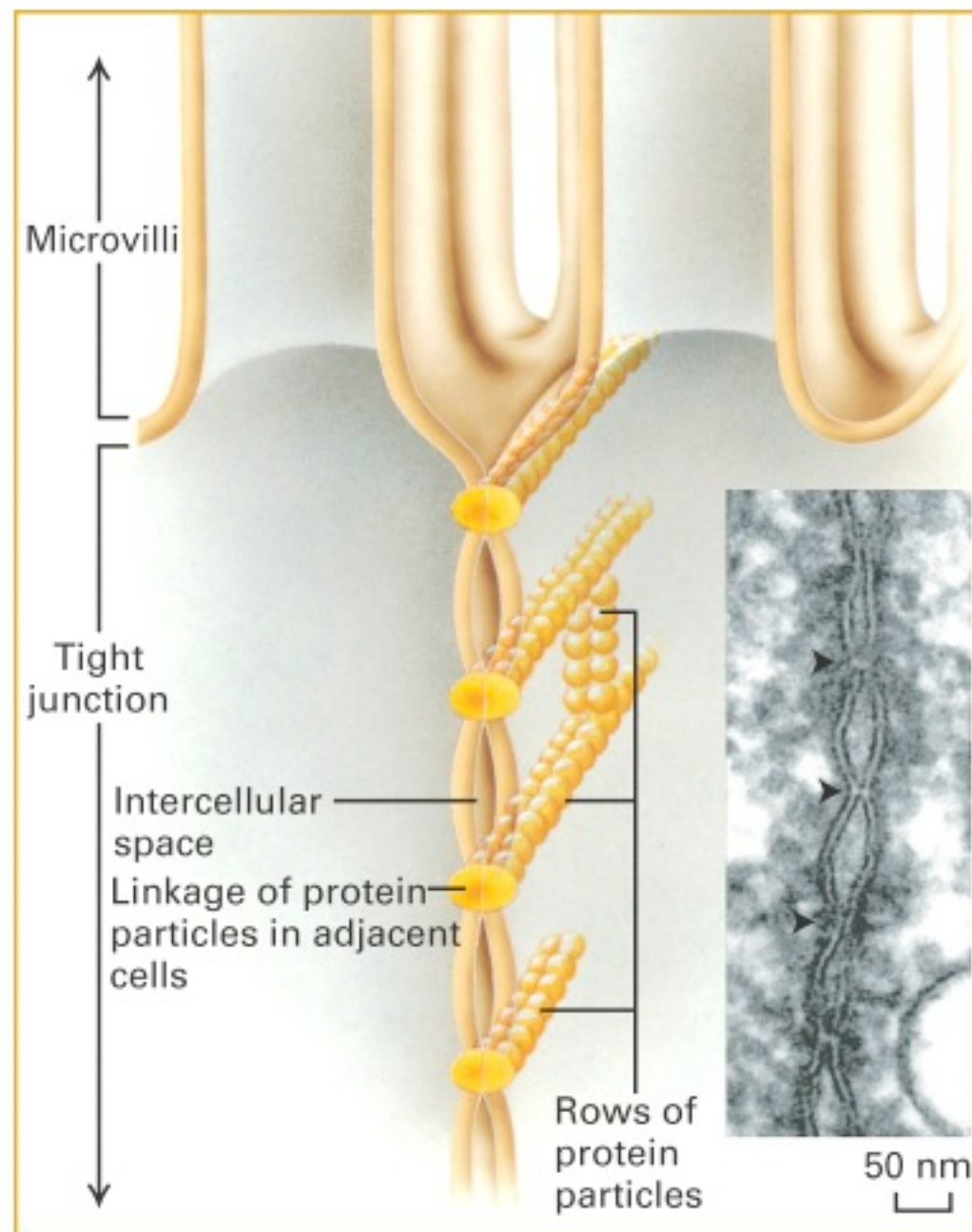
Tight junctions: controlling paracellular diffusion

Tight junctions prevent diffusion of molecules between epithelial cells.



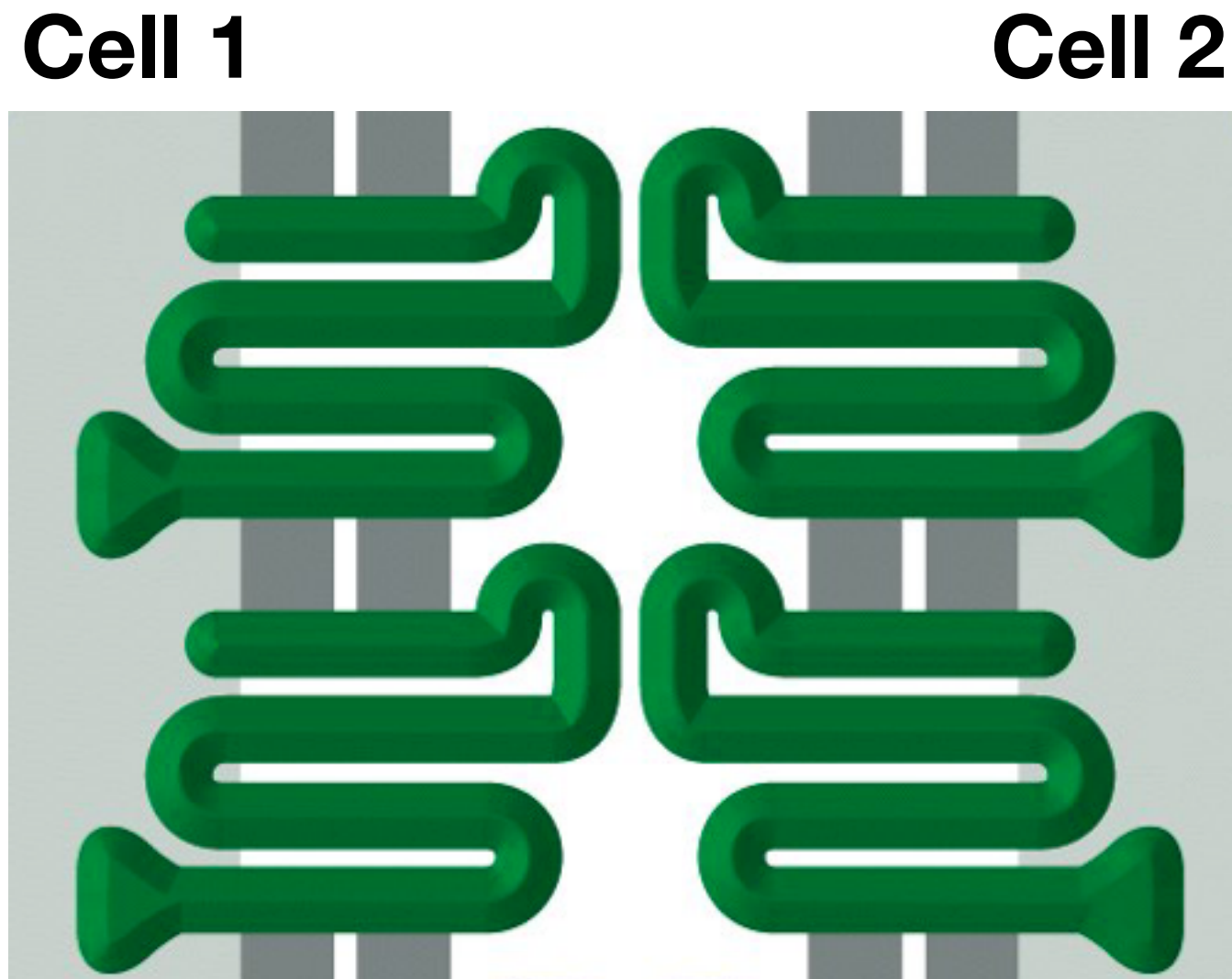
Epithelia usually separate two compartments. Often one compartment is an external space or lumen of a tube and the other is the rest of a tissue or organ. The apical side of the epithelial cells faces the external space or lumen and the basal side faces the rest of the organ. One role for epithelia is to control the mixing of material between the two compartments. To accomplish this, epithelia must control the ability of small molecules and ions to diffuse between cells or paracellular diffusion. Tight junctions that link adjacent epithelial cells determine how permeable an epithelia is to ions and small molecules. Some epithelia are very permeable (e.g. intestine) whereas others are restrictive (e.g. bladder).

Tight junctions form a network of sealing strands that encircle epithelial cells.



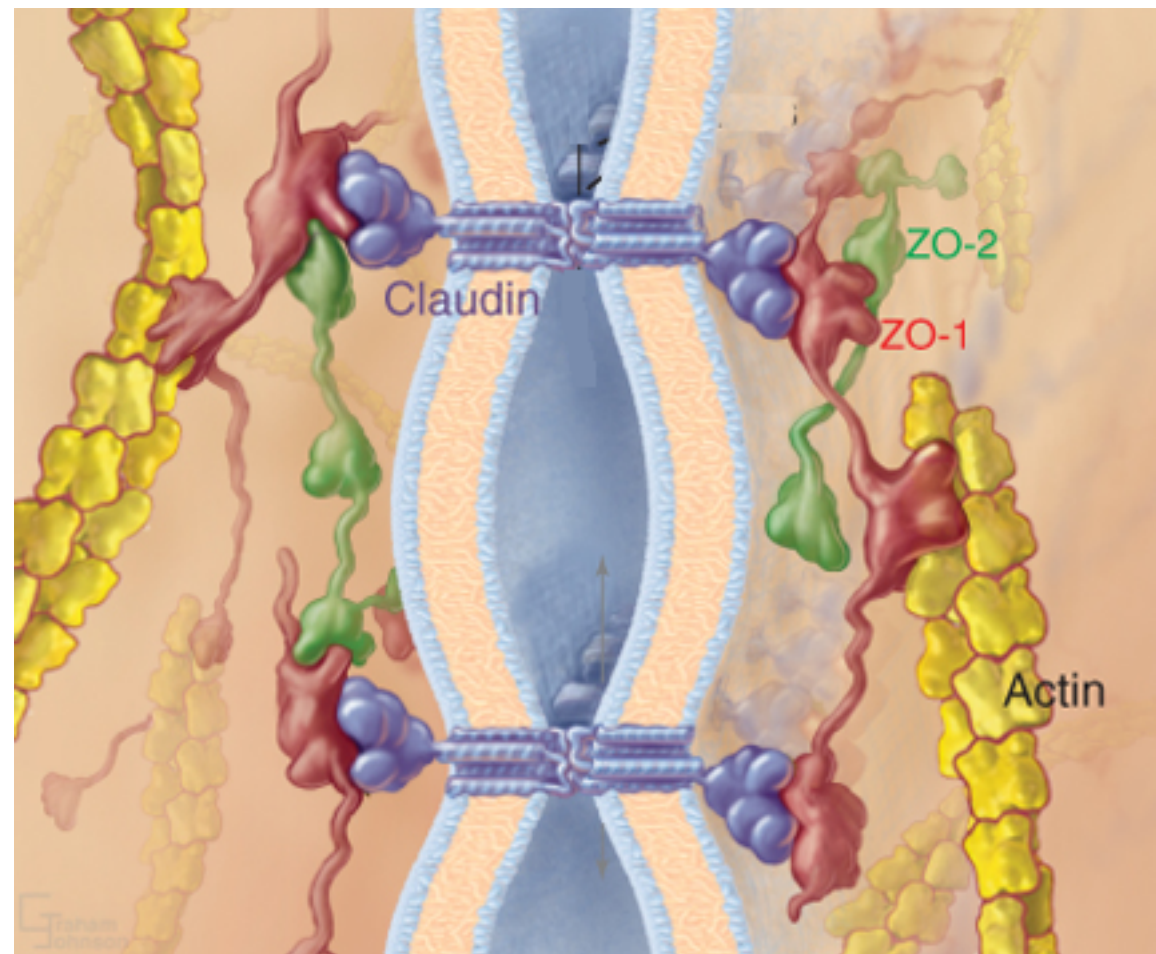
Tight junctions are similar to adhering junctions in that they encircle the entire circumference of cell. They bring together the cell membranes of adjacent cells. Tight junctions consist of set of strands that are defined by protein-protein interactions between adjacent cells.

Claudins are the primary functional component of tight junctions.



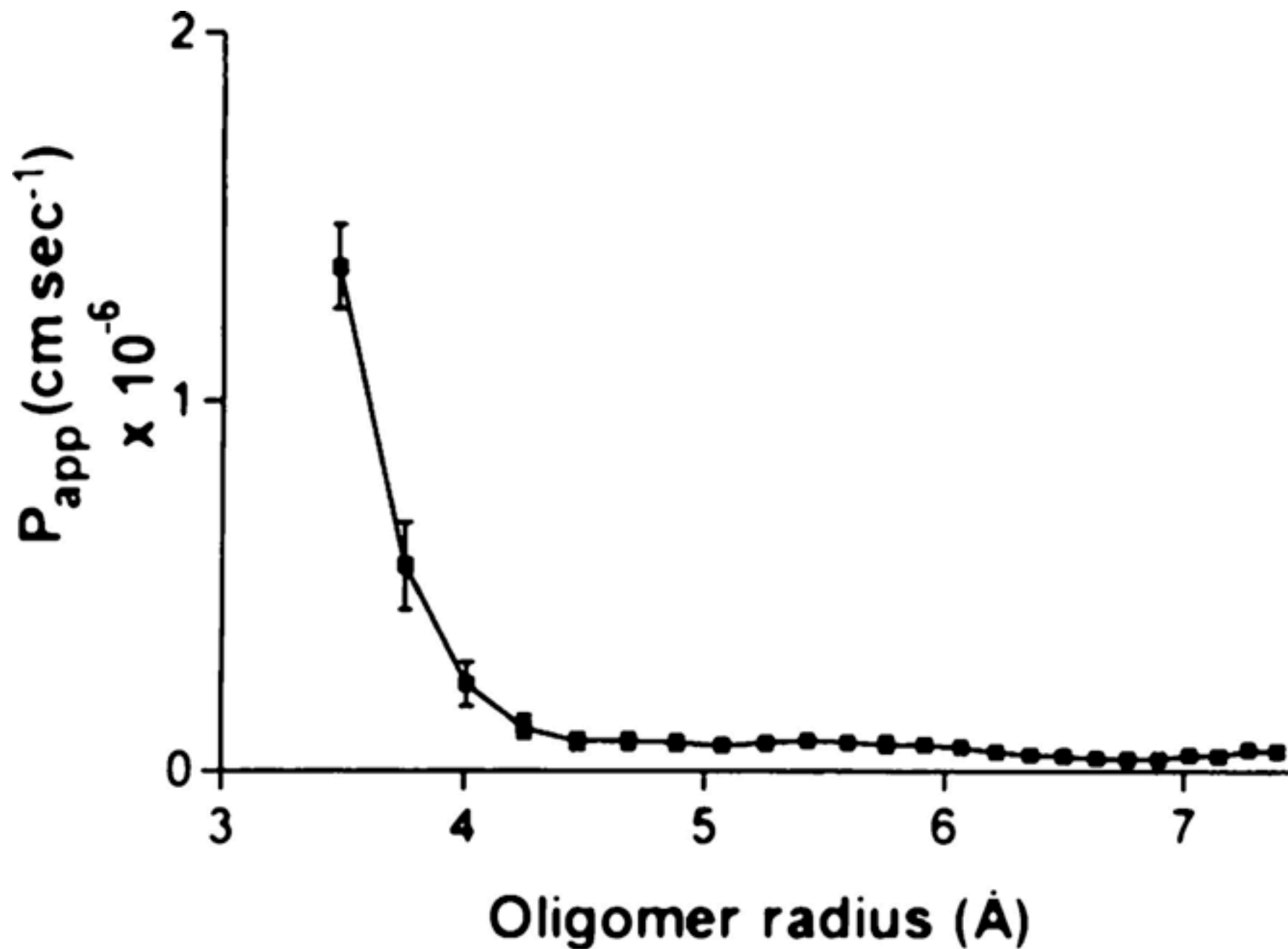
Tight junctions contain more than 50 different types of proteins. Claudins are the proteins that primarily determine the permeability of the tight junction. Claudins contain four transmembrane domains and interact with claudins in adjacent cells. The intracellular domains of claudins are linked indirectly to actin filaments by a set of proteins called ZO proteins. The interaction with actin filaments help stabilize the claudins in the cell membrane. Also, myosin filaments can generate tension on the actin filaments to loosen the tight junctions.

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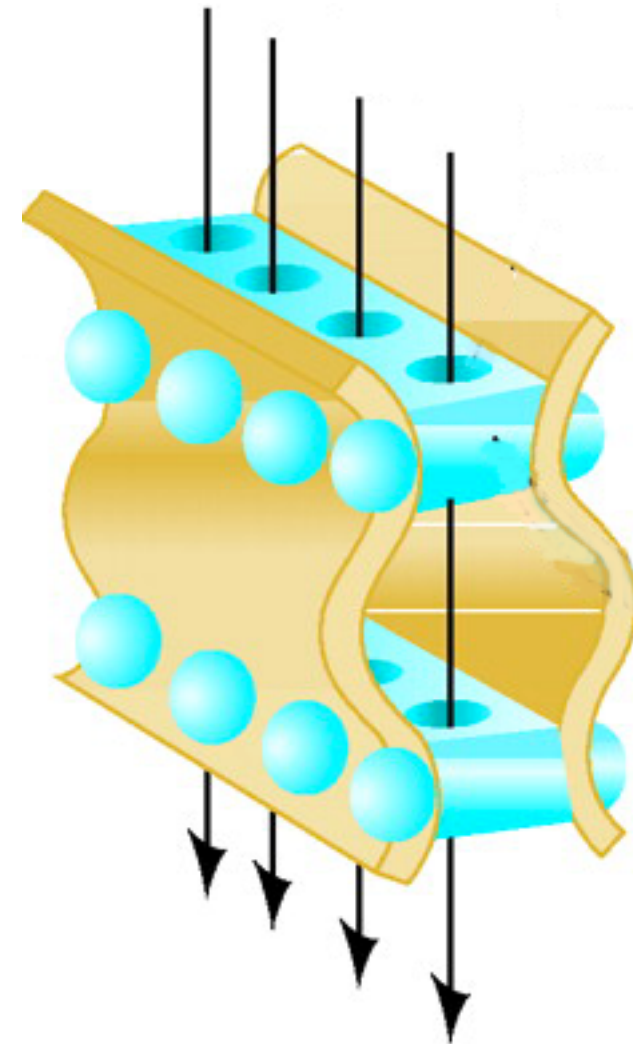
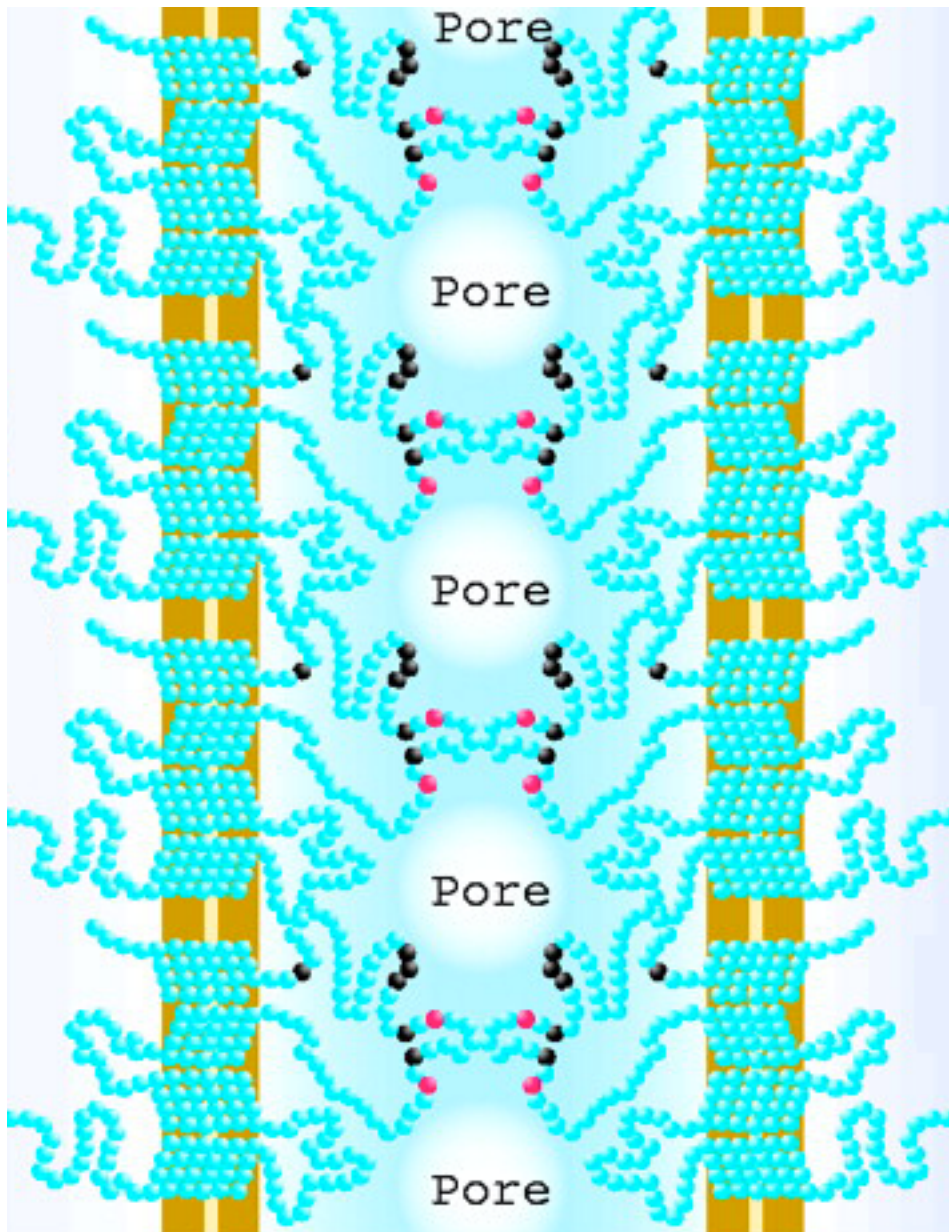
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Interactions between claudins generates size restrictive pores.



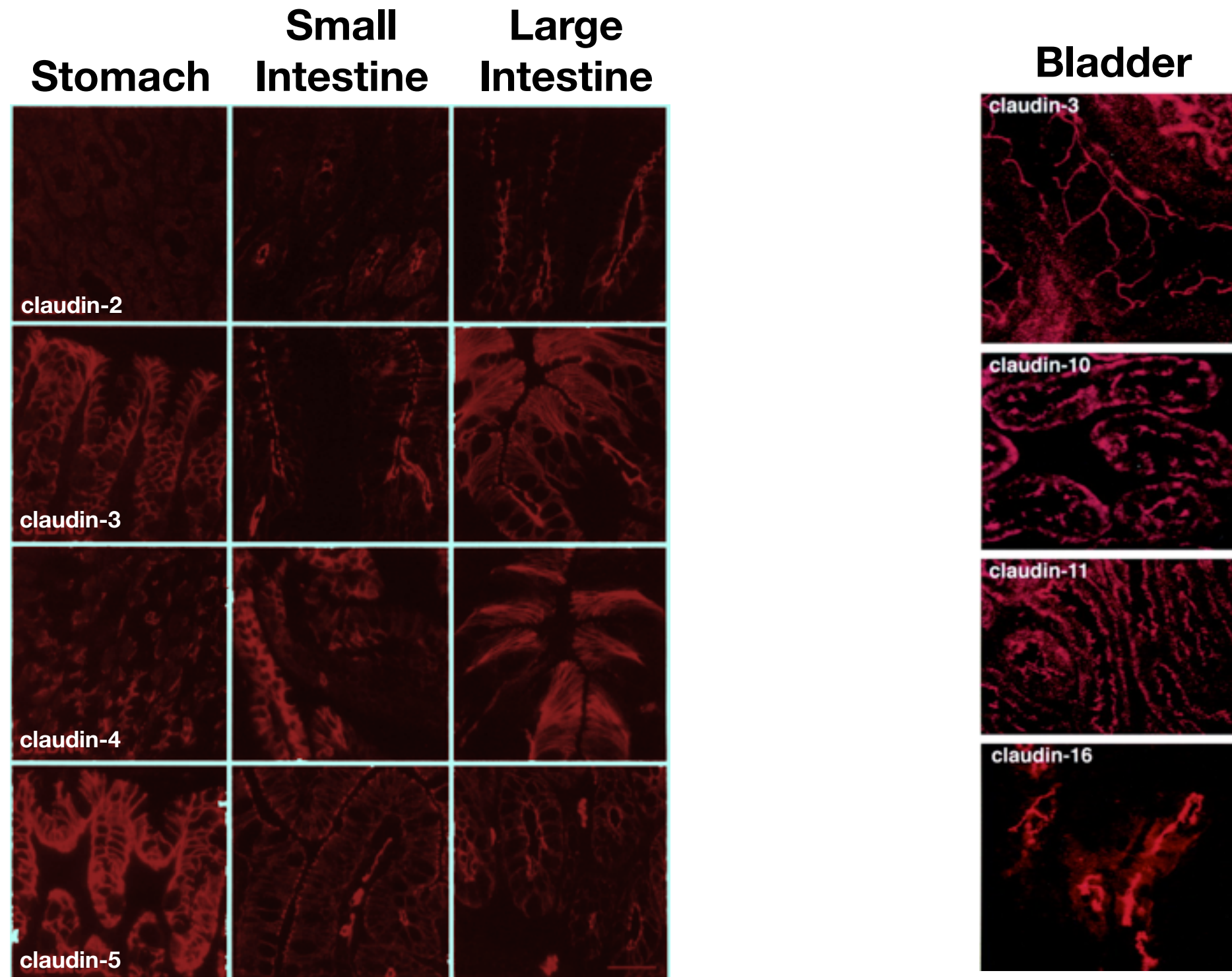
The extracellular domains of claudins interact to form size-restrictive pores. The permeability of an ion or molecule is inversely related to size.

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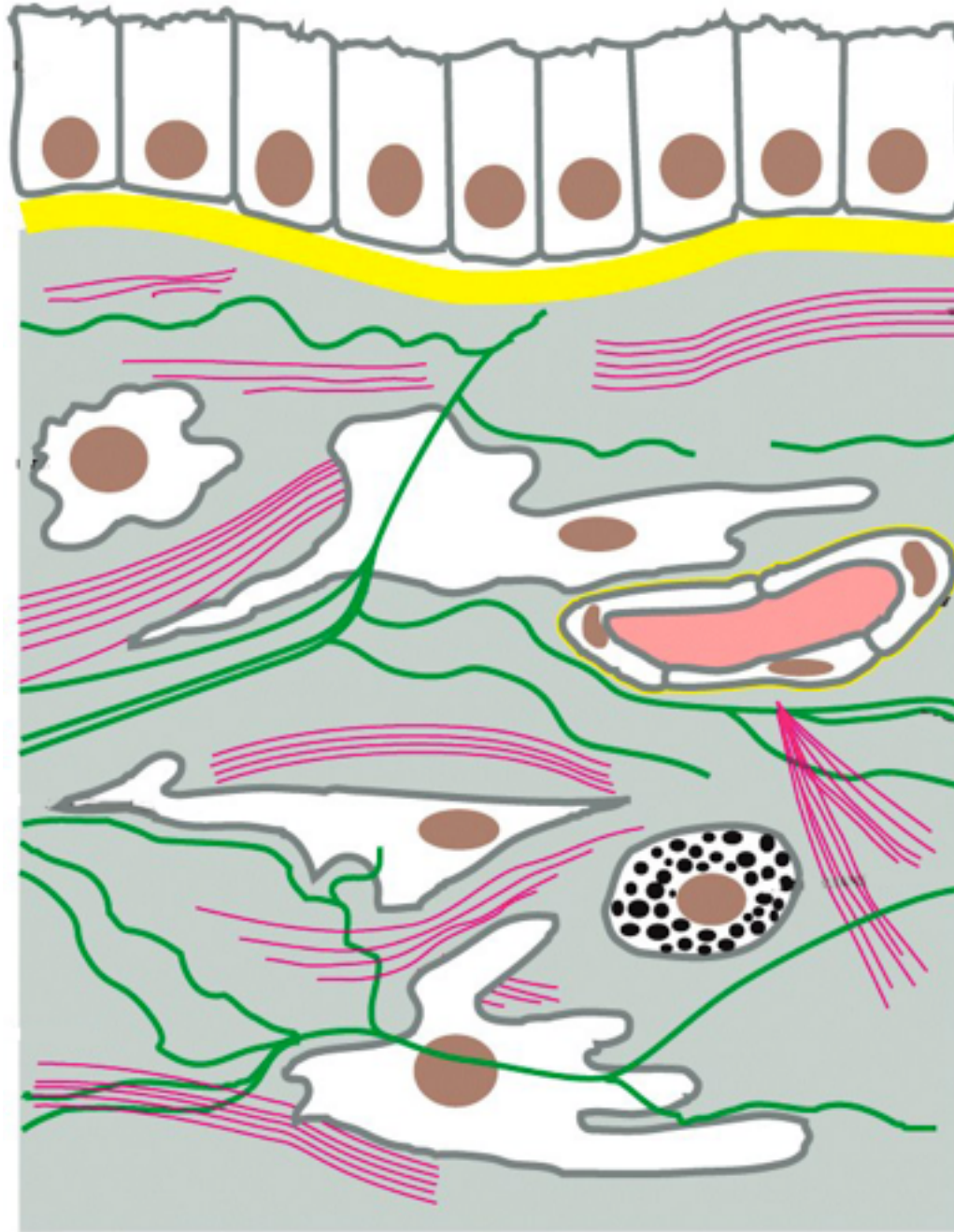
Leakiness of tight junctions varies by type claudin expressed in cells.



The permeability of epithelia varies between organs up to 10,000 fold difference. The epithelia of the small intestine is more permeable than the epithelia of the bladder. There are 24 different claudin genes and each encodes a protein with different permeability properties. Some claudins are selective for certain ions. For example, mutations in claudin 16 lead to magnesium wasting because the kidney epithelia becomes permeable to magnesium. Epithelia generate different degrees of permeability by expressing different combinations of claudin genes.

Basement membrane

All epithelia rest on a basement membrane.

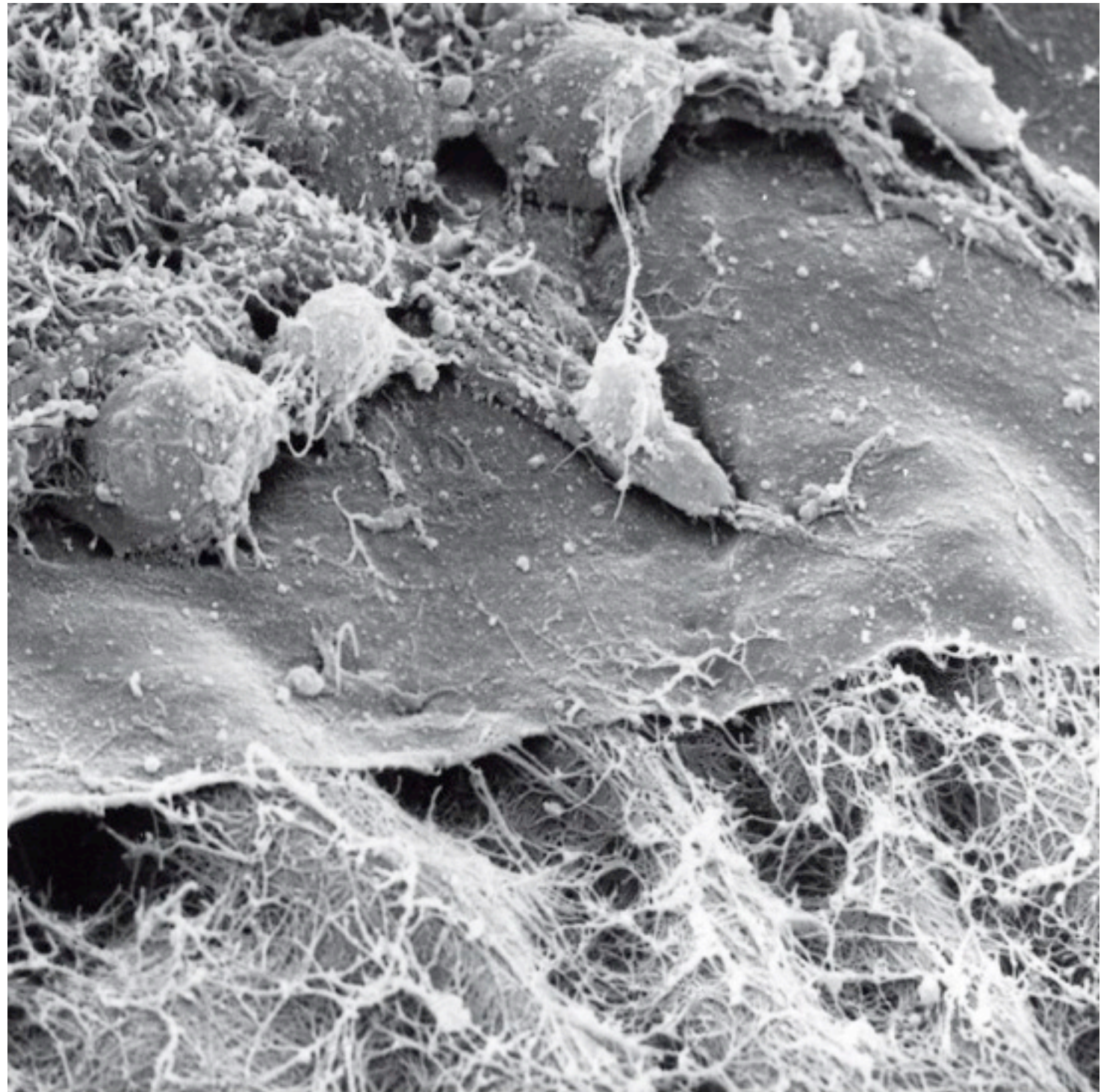


All epithelial cells are attached on their basal surface to a basement membrane. The basement membrane provides some mechanical support as it tethers together a sheet of epithelial cells. It also supports the growth and survival of the epithelia as it controls the access of epithelia to nutrients, ions, proteins and oxygen. Epithelia lack their own blood supply and rely on the capillaries in the underlying tissues. All the nutrients from the blood must cross the basement membrane to reach the epithelial cells. The basement membrane also regulates the growth and division of epithelial cells.

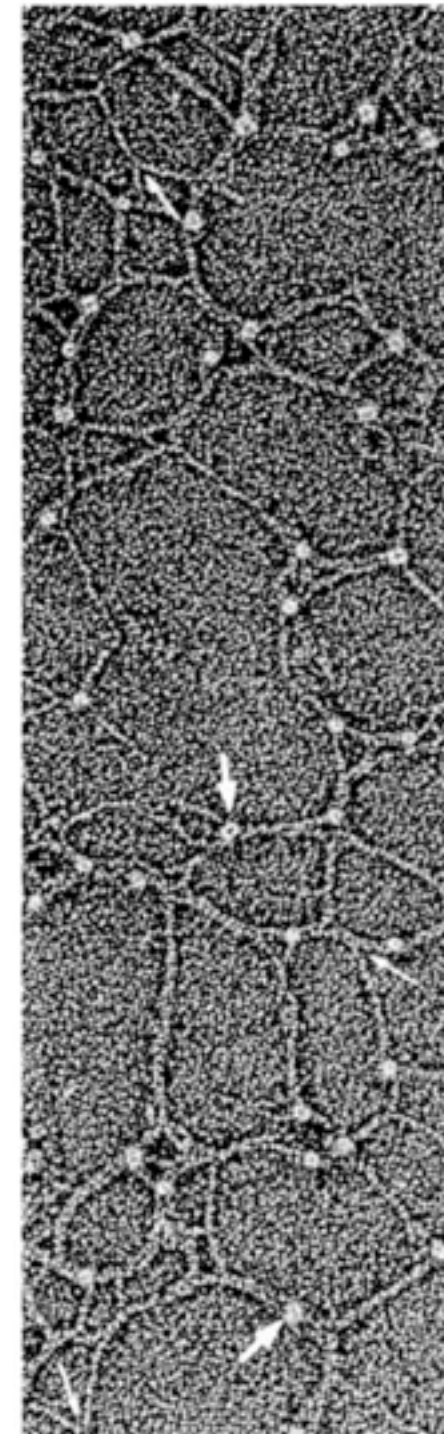
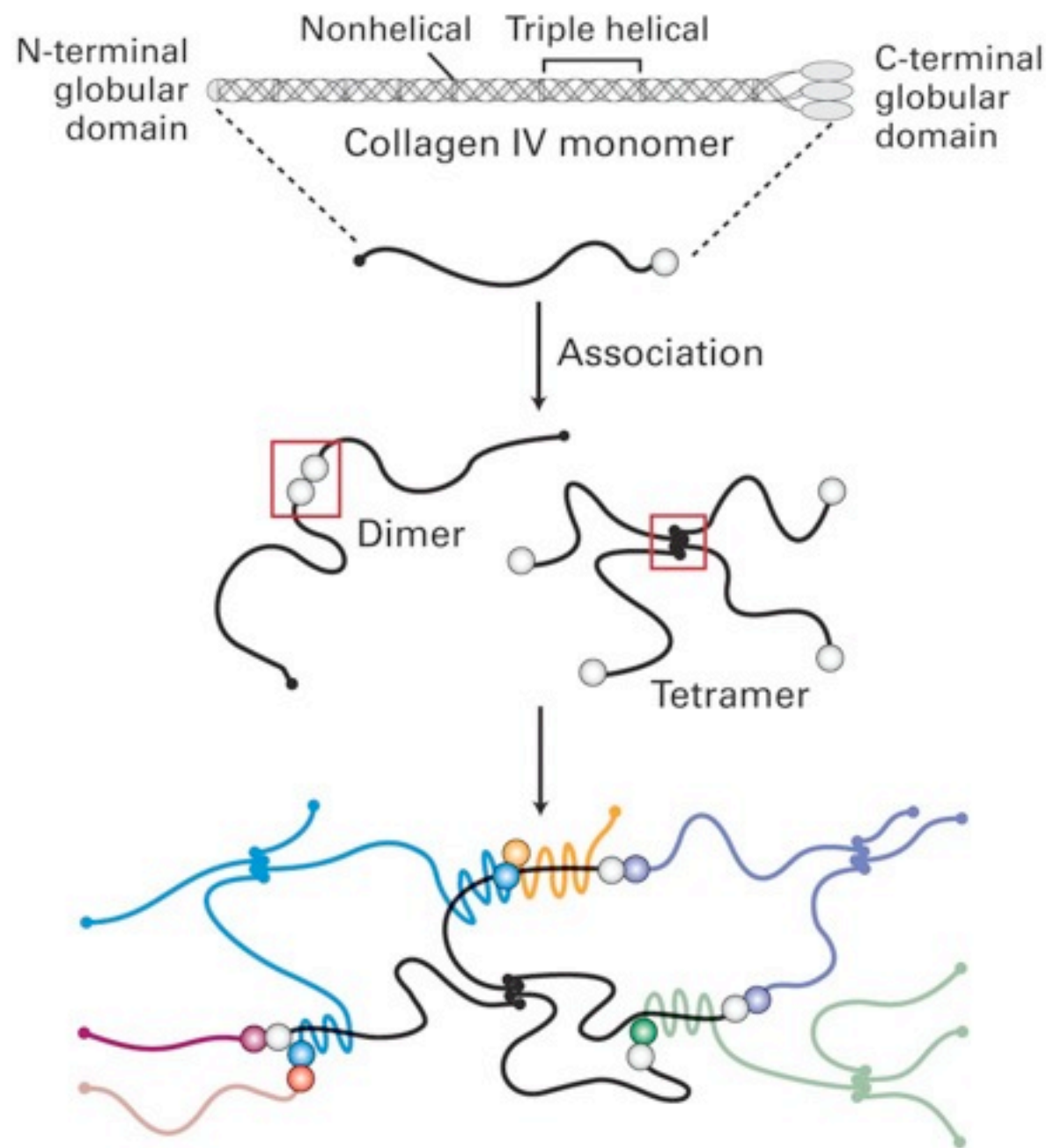
Basement membrane separates epithelial cells from surrounding tissue.

Epithelial Cells

Basement membrane

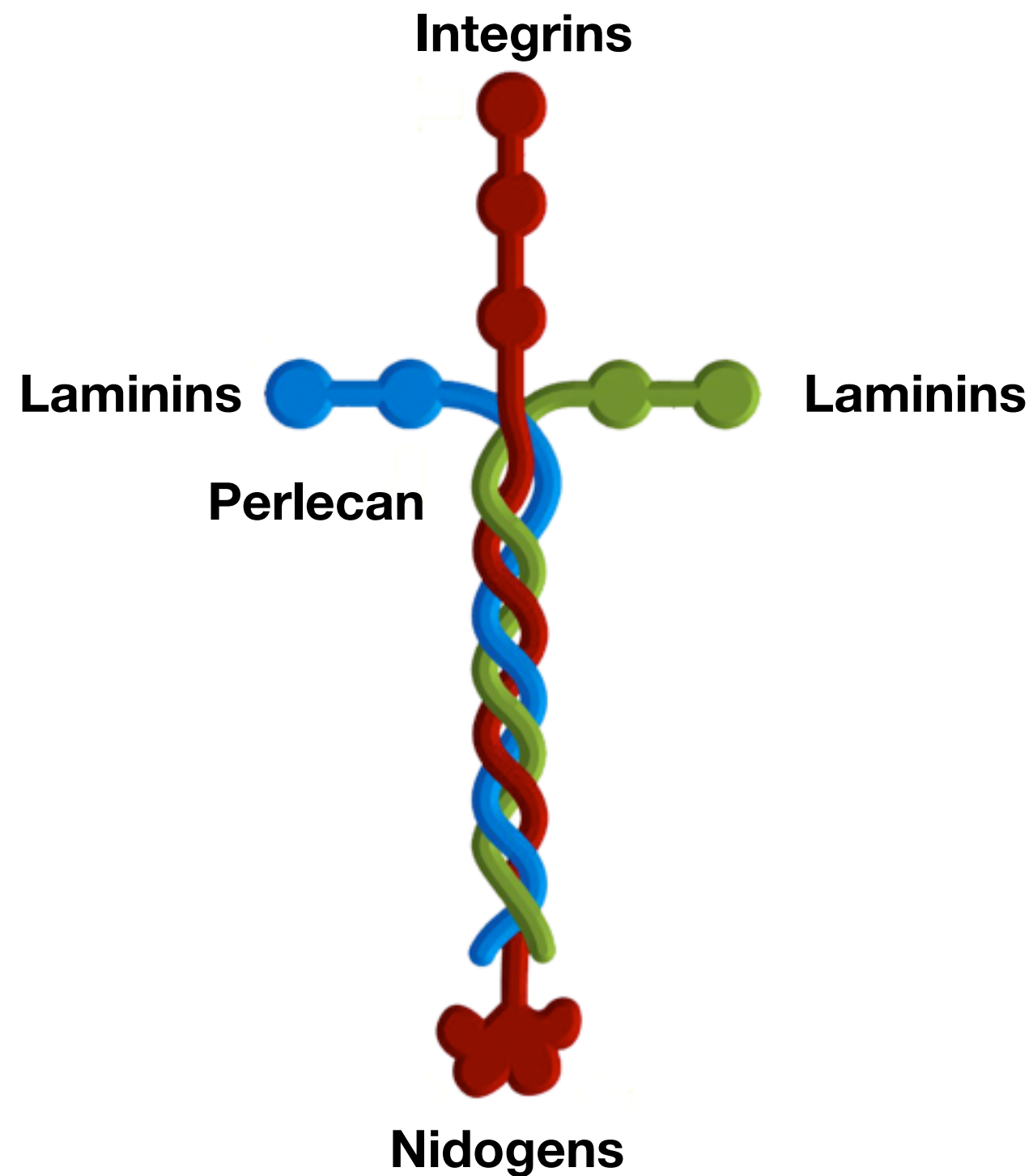


Type IV collagen is the main structural component of the basement membrane.



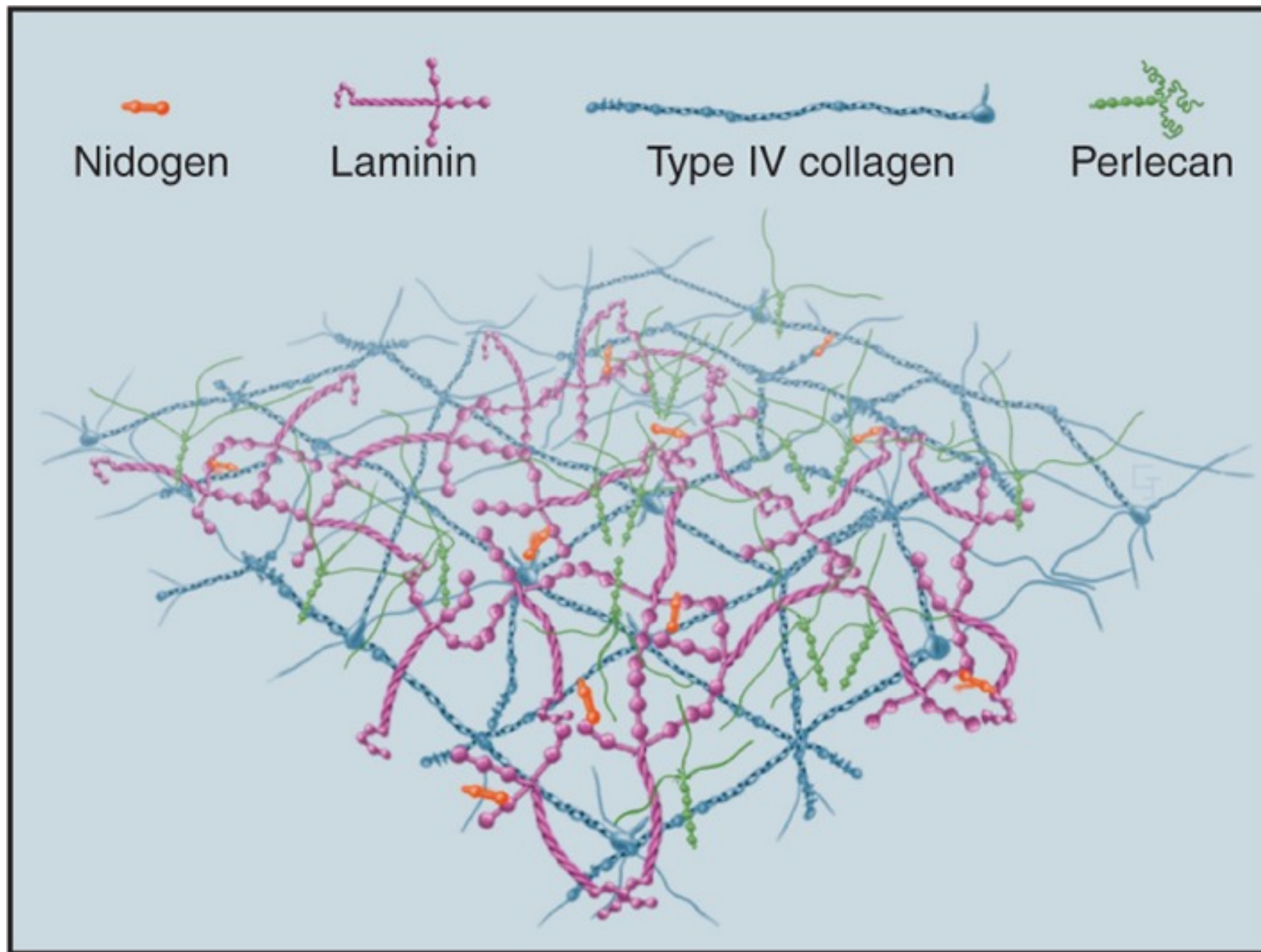
Type IV collagen is similar in structure to its fiber-forming family members in that it contains trimers that wrap around one another into a helical structure. However, these trimers do not assemble into parallel, crosslinked arrays to form fibrils. Instead, type IV collagen retains domains at its N and C-termini (remember that these are removed in fibril-forming collagens). These domains interact to assemble type IV collagen into branching networks as seen in this EM image of type IV collagen. These branching networks of collagen are what give the basal lamina its sheet-like structure.

Laminin organizes components of the basement membrane.



Laminin is primary organizer of those components as it contains domains that allow it to form a network, bind to cells and interact indirectly with the collagen network. Laminin consists of a trimer of alpha, beta and gamma subunits.

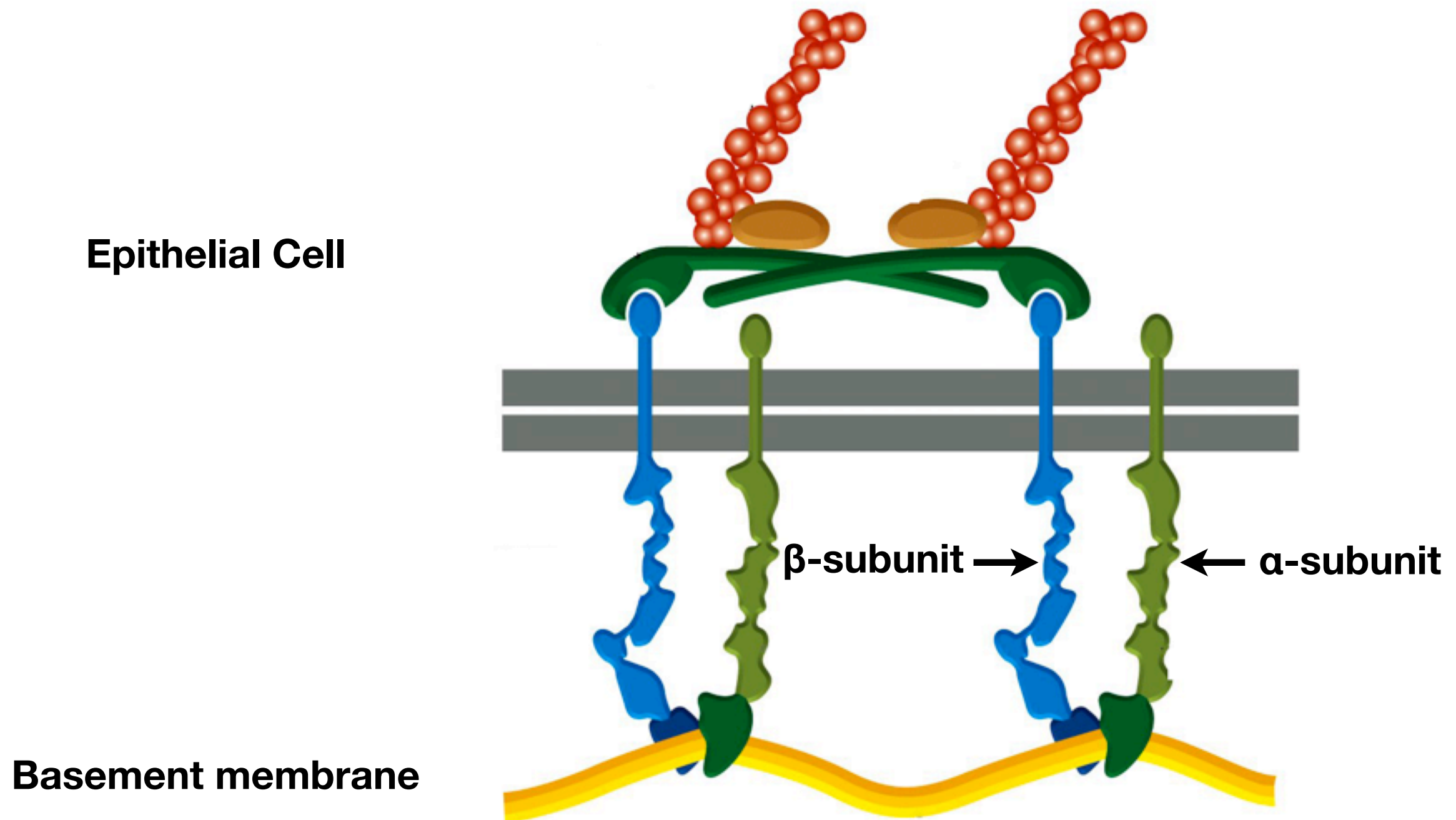
Perlecan and nidogen link laminin network to collagen network.



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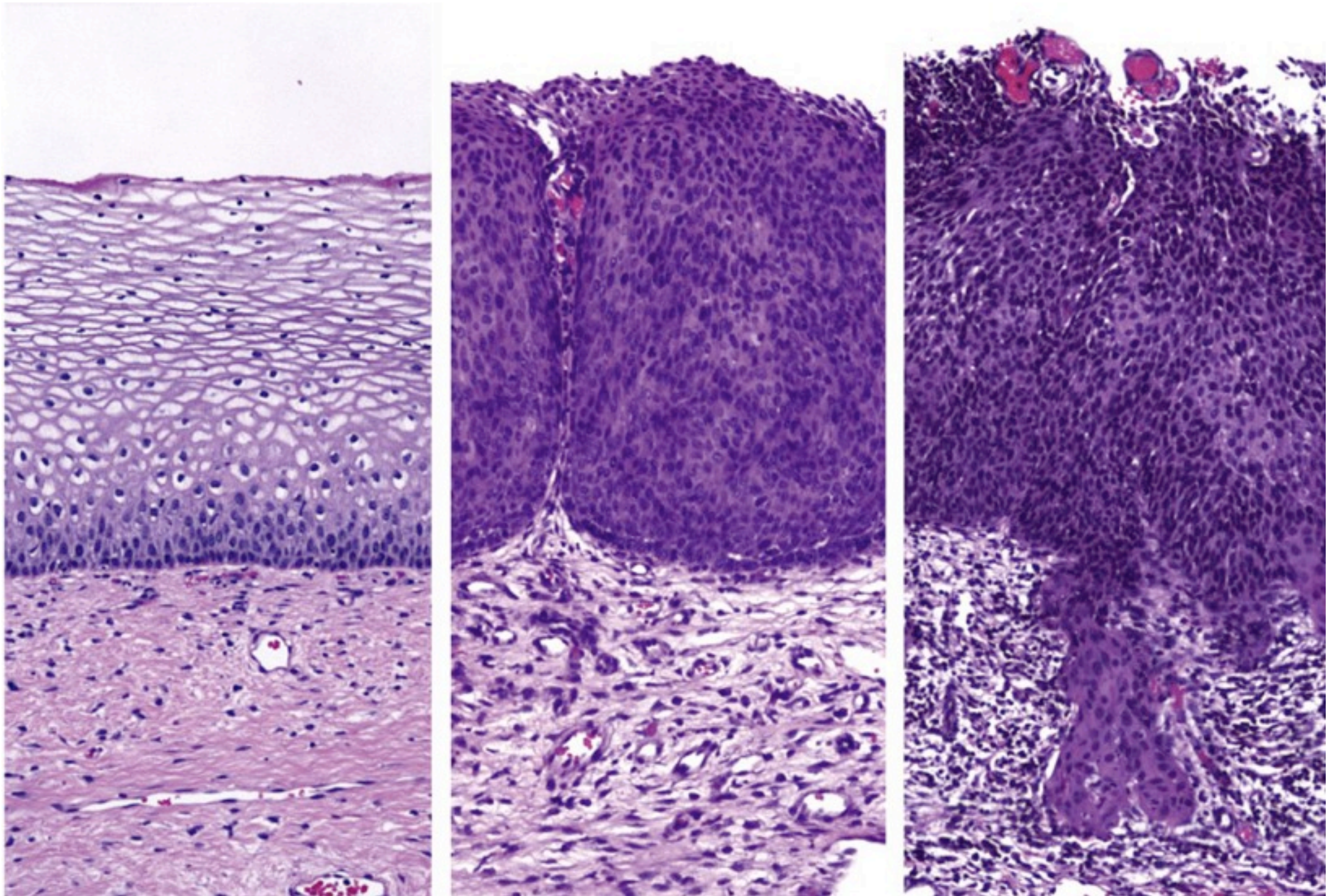
The collagen and laminin networks are linked via two proteins: nidogen and perlecan. The space within the two networks is filled in with proteoglycans and fibronectin.

Integrins in epithelial cells bind laminin and fibronectin in basement membrane.



Epithelial cells attach to their basement membrane via integrins. Integrins in the plasma membrane associate with components of the basement membrane, mostly laminin and fibronectin.

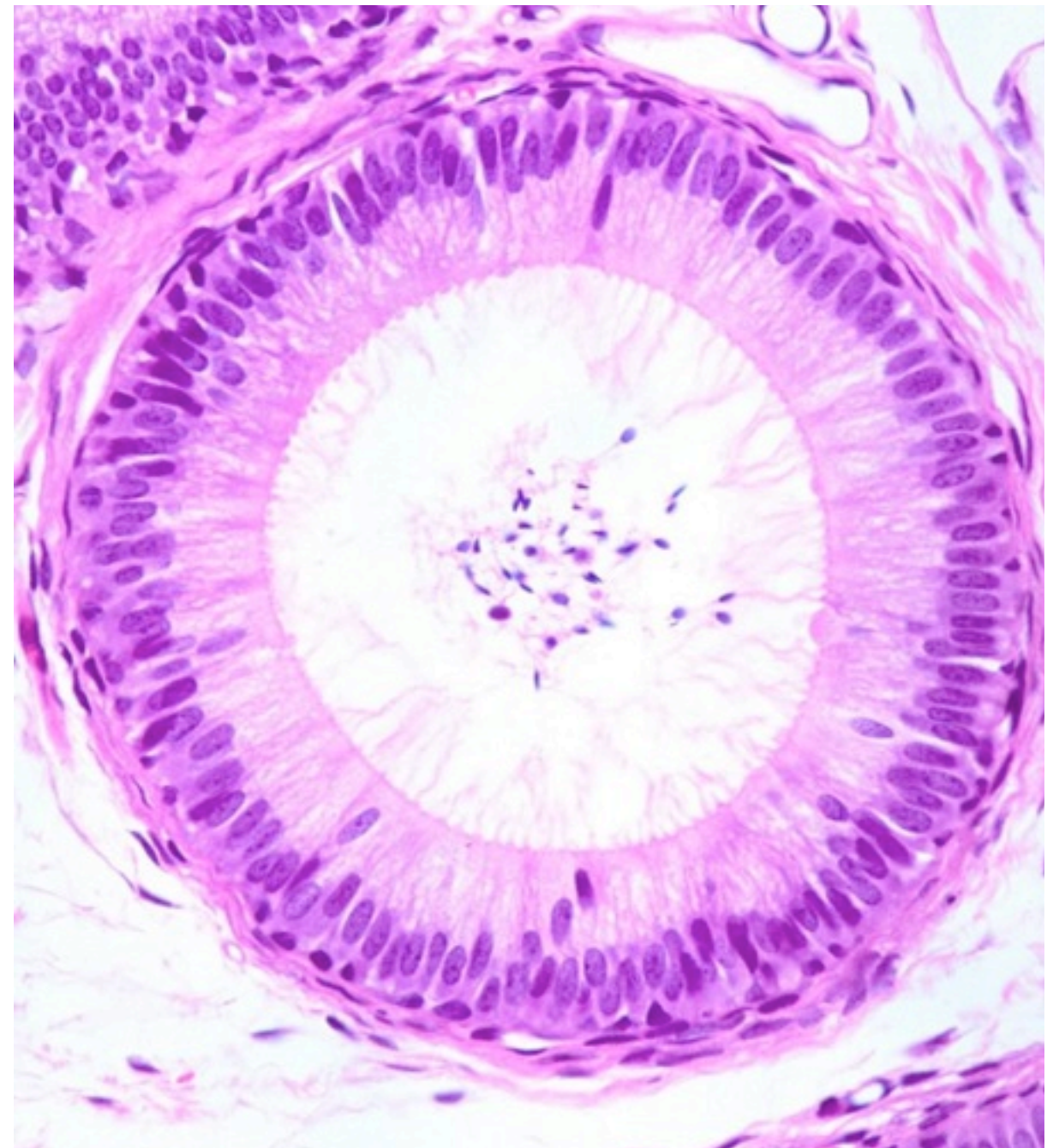
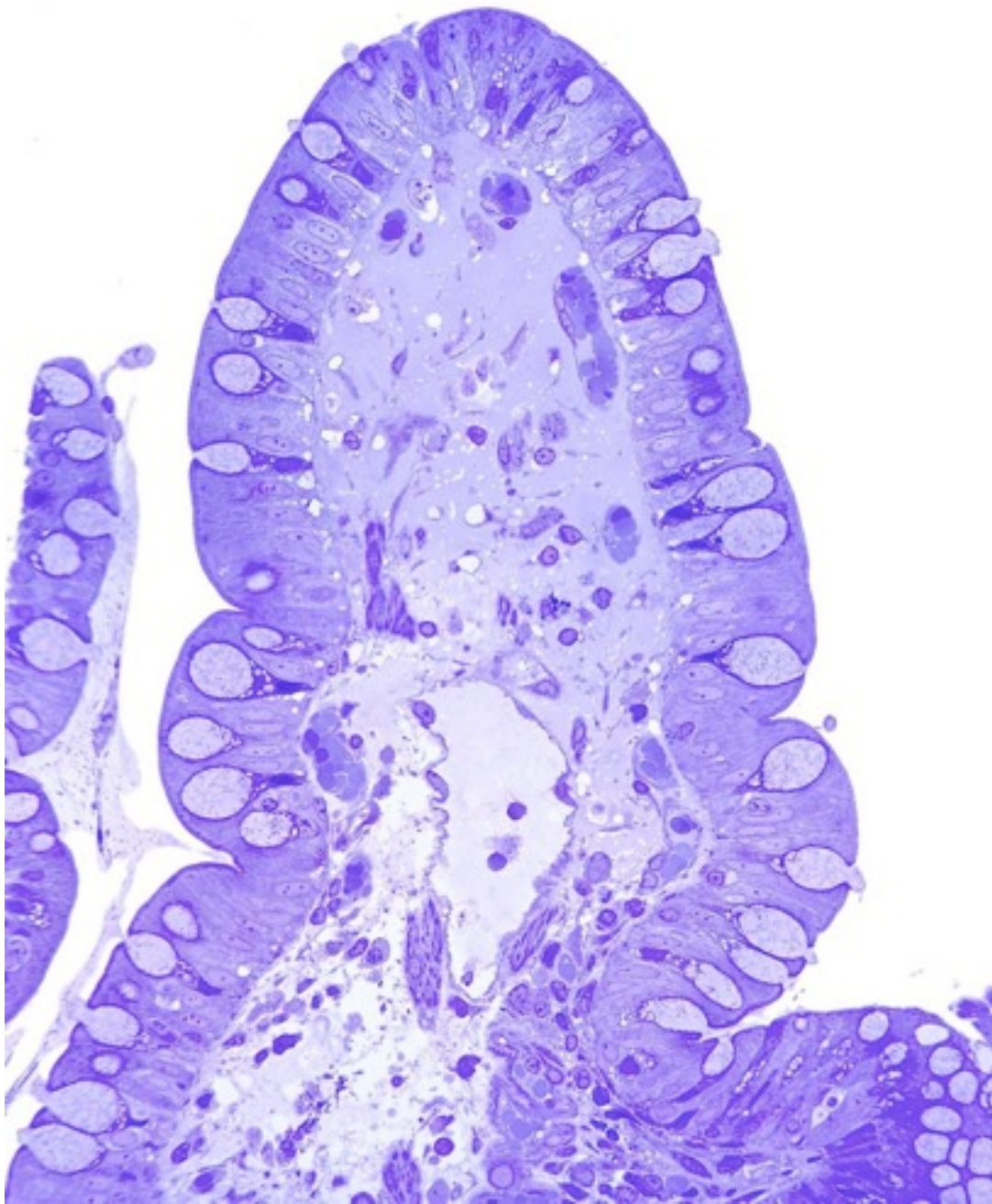
Basement membrane restricts migration of metastatic cells.



One medically important function of the basement membrane is that it keeps carcinomas (cancers of epithelial origin) from gaining access to the lymph and blood vessels and spreading to other parts of the body. Because epithelia lack blood vessels and lymph vessels, cancerous cells must cross the basement membrane into the underlying tissue to enter the blood or lymph system. Carcinomas that have not crossed the basement membrane are often referred to as carcinomas in situ. Carcinomas that have crossed the basement membrane have a high probability of becoming metastatic.

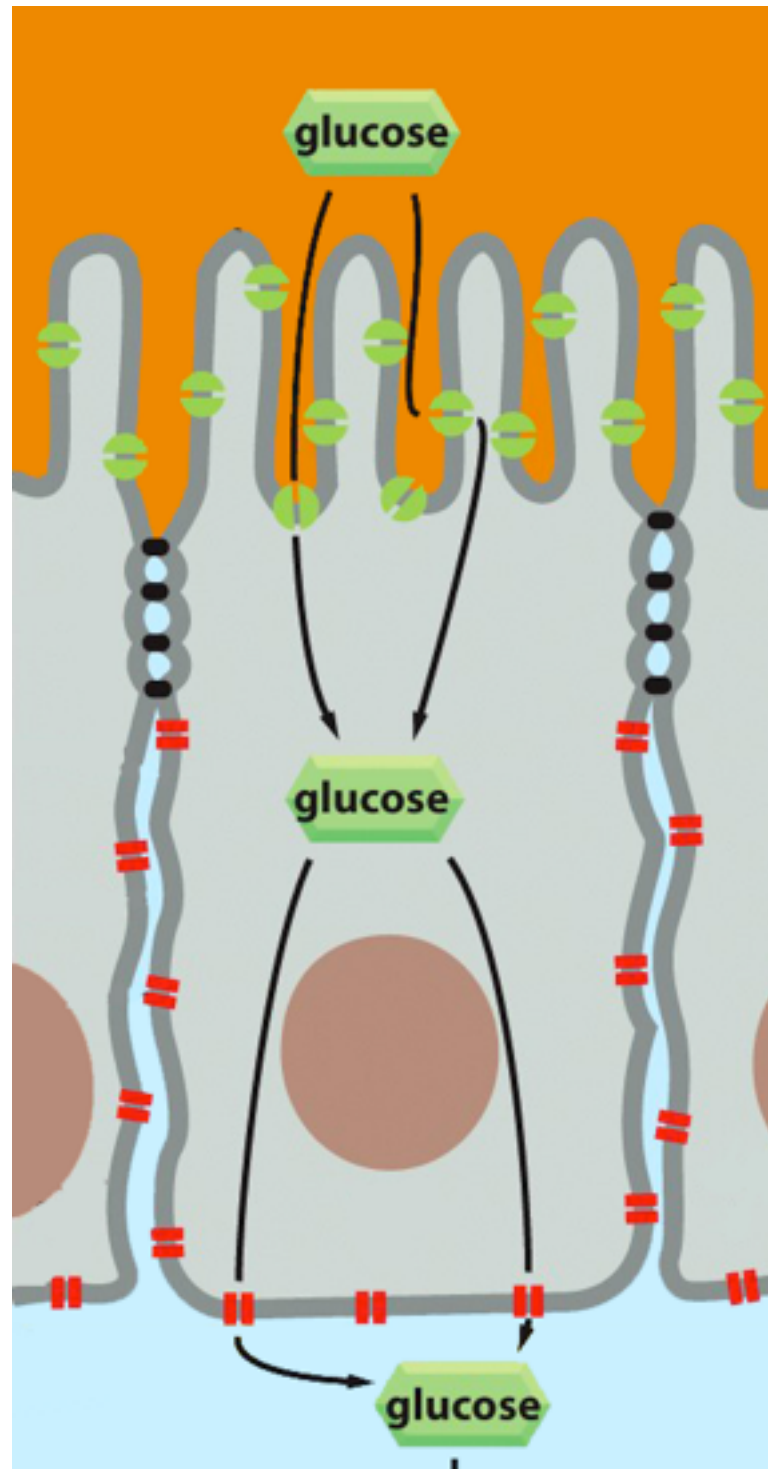
Epithelial cell polarity

Epithelia are polarized with apical and basal surfaces.



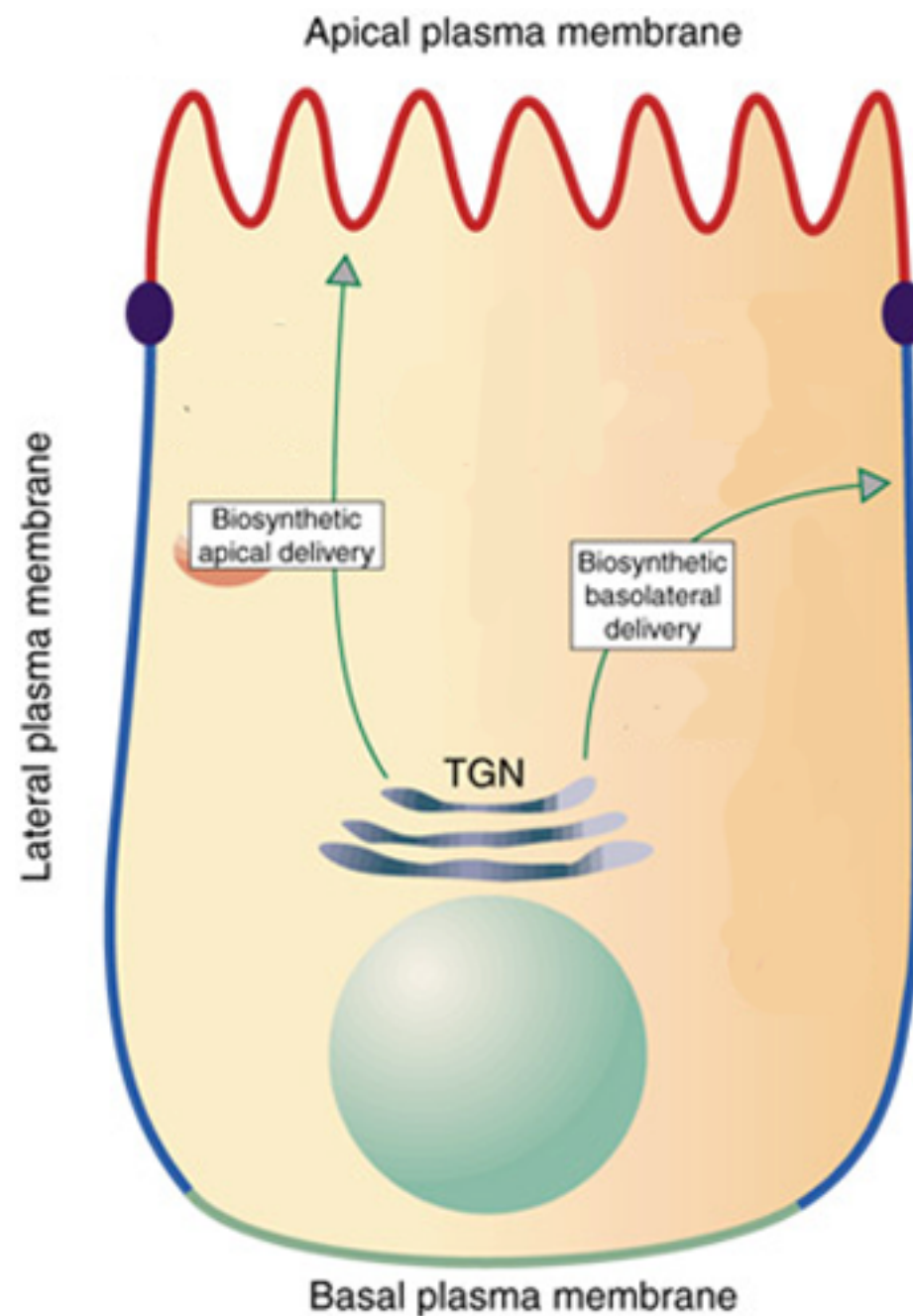
Epithelial cells have two functionally and biochemically different surfaces. The apical faces external environment or lumen of a tube where it is often involved in absorption or secretion. The basal mediates attachment to underlying tissue or surface via integrins. Because the apical and basal sides of the cells have different biochemical activities, cells need to deliver certain proteins to one side or the other.

Polarity of epithelial cells is critical for their function.



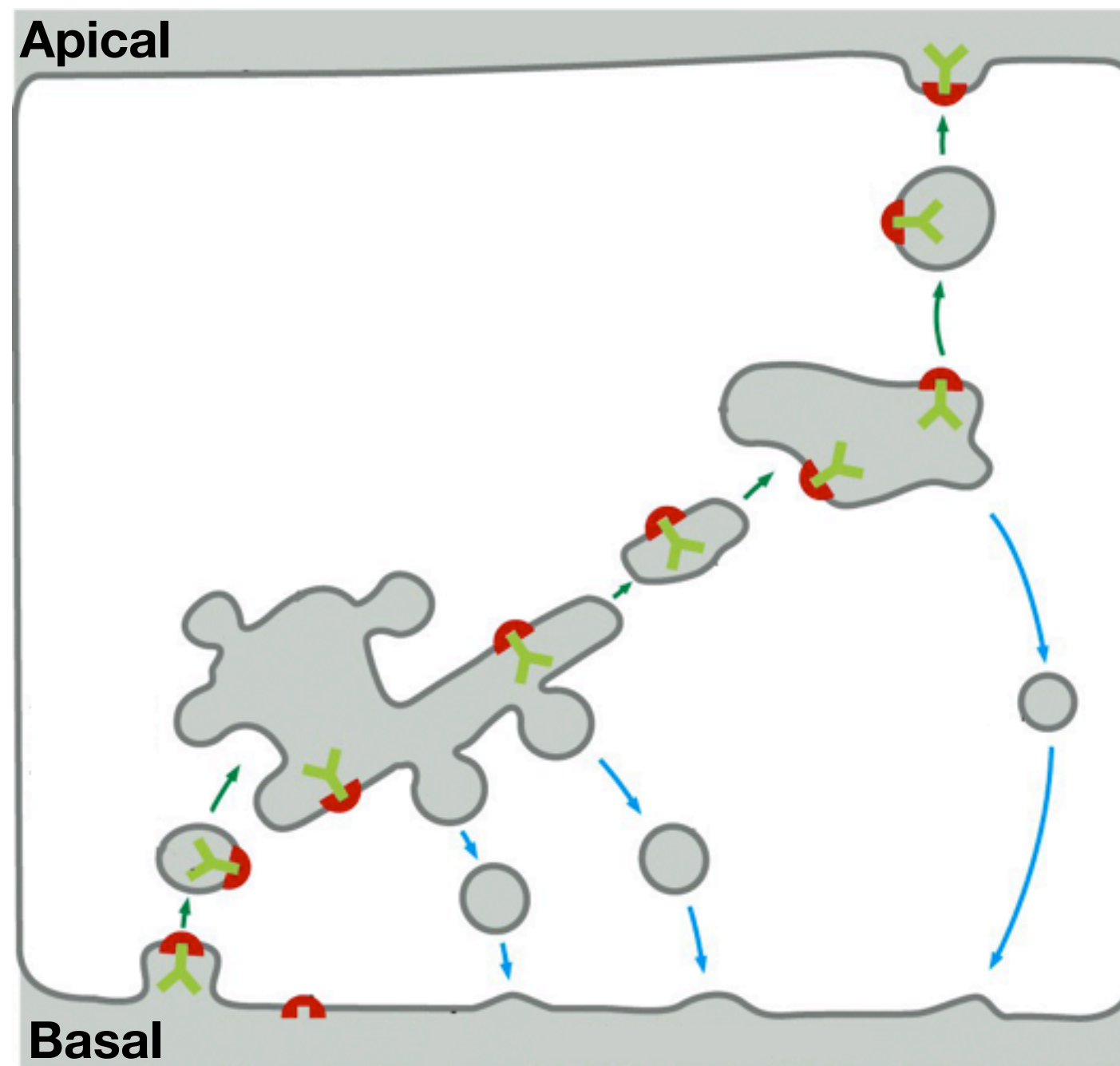
An example of the importance of proper sorting of proteins to the apical and basal surfaces is the intestinal epithelial cell. One function of these cells is to transport glucose from lumen of intestine to into blood stream. Na symport channels help the cells move glucose against a concentration gradient from the lumen of the intestine into the cell. The basal surface of the cells contains passive glucose channels that allow glucose to leave the cell and enter capillaries beneath the basement membrane. This system only works if the two different types of glucose channels are localized to the correct surface of the cell.

Proteins are sorted in trans-Golgi network before delivery to plasma membrane.



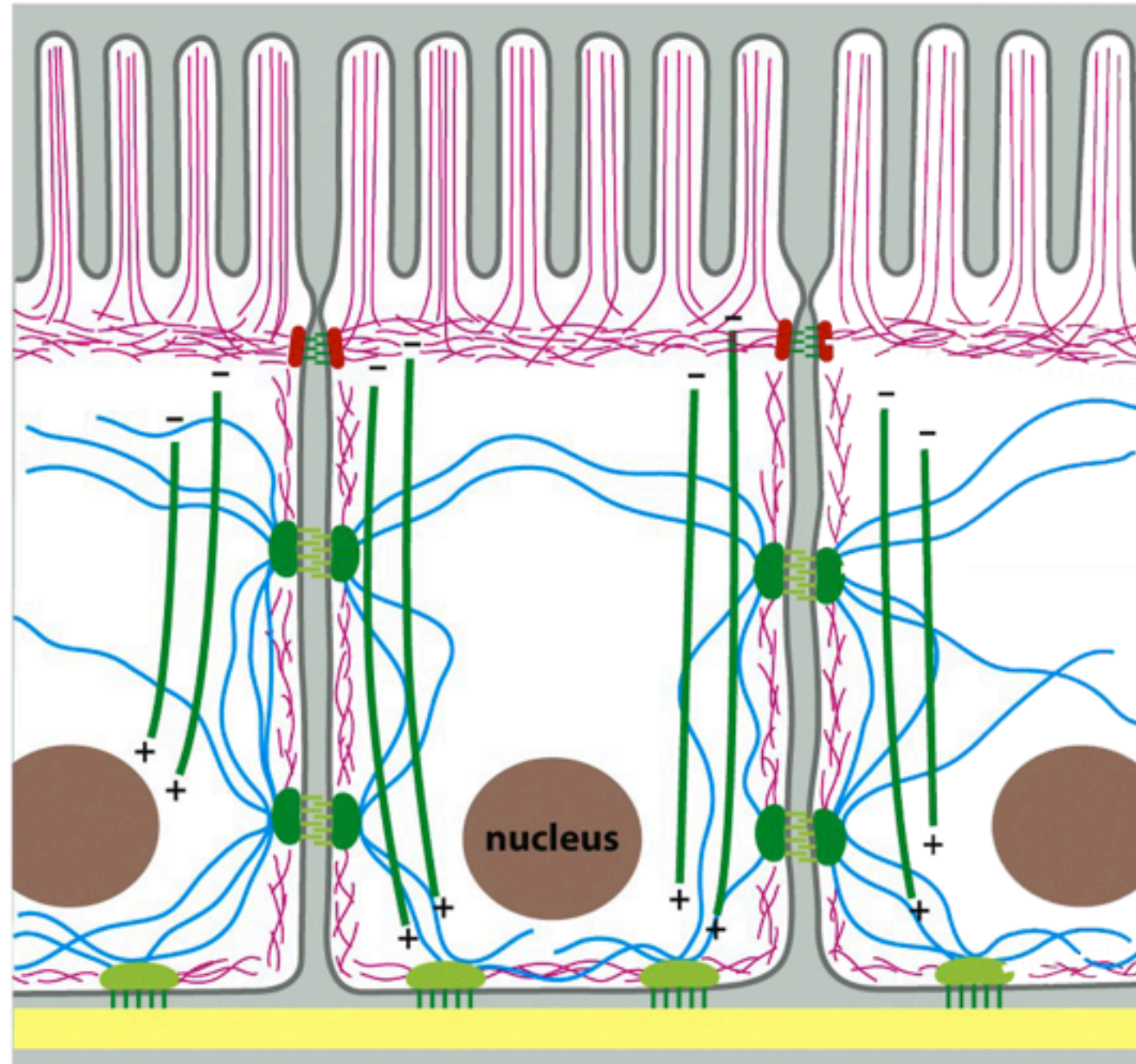
Proteins that are destined for apical or basal surface have signal sequences. These proteins are sorted in the trans-Golgi network and then delivered via vesicles to the apical or basal cell membrane. The signal sequence to deliver a protein to the basal surface is often found in the cytoplasmic tail of the protein. The signal sequence for apical proteins is less clear.

Transcytosis mediates transfer of protein across epithelial cells.



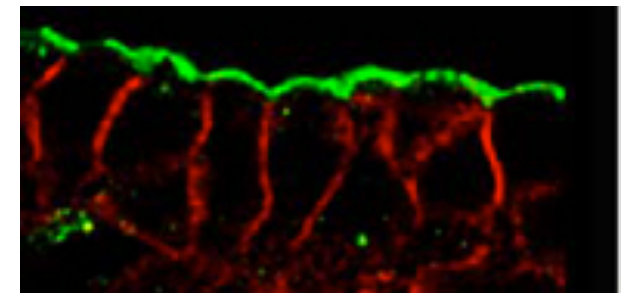
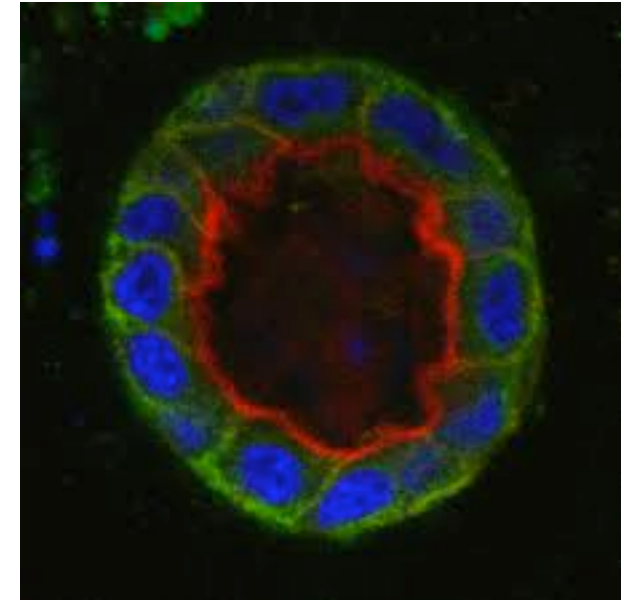
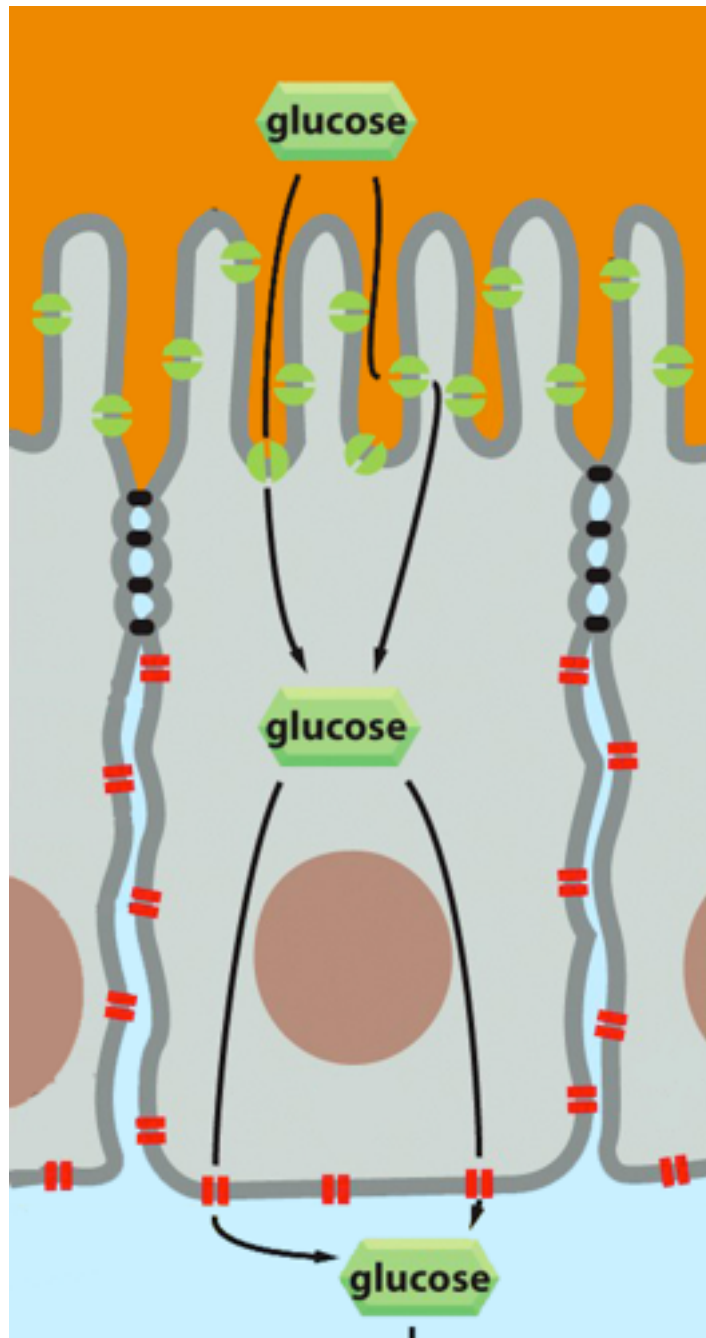
Epithelial cells can also move protein and lipid from one side of the cell to the other by transcytosis. Transcytosis consists of endocytosis from one side of the cell, transport of the vesicles to the other side of the cell and then fusion of the vesicle with the cell membrane. Transcytosis allows cells to capture and deliver misdirected protein to their correct location. Also, cells can transfer extracellular proteins from one side to the other. An example is the delivery of antibodies into the lumen of the intestine. B-cells, which produce antibodies, reside under the basal surface of the intestinal epithelial cells. The epithelial cells have a receptor on their basal surface that binds antibody. The receptor-antibody complexes are delivered to the apical surface via transcytosis.

Minus end of microtubules faces apical surface.



Microtubules are polarized in epithelial cells with their minus ends at apical side of the cell and their plus ends at basal side. This allows epithelial cells to use kinesins or dyneins to deliver material to their basal or apical side.

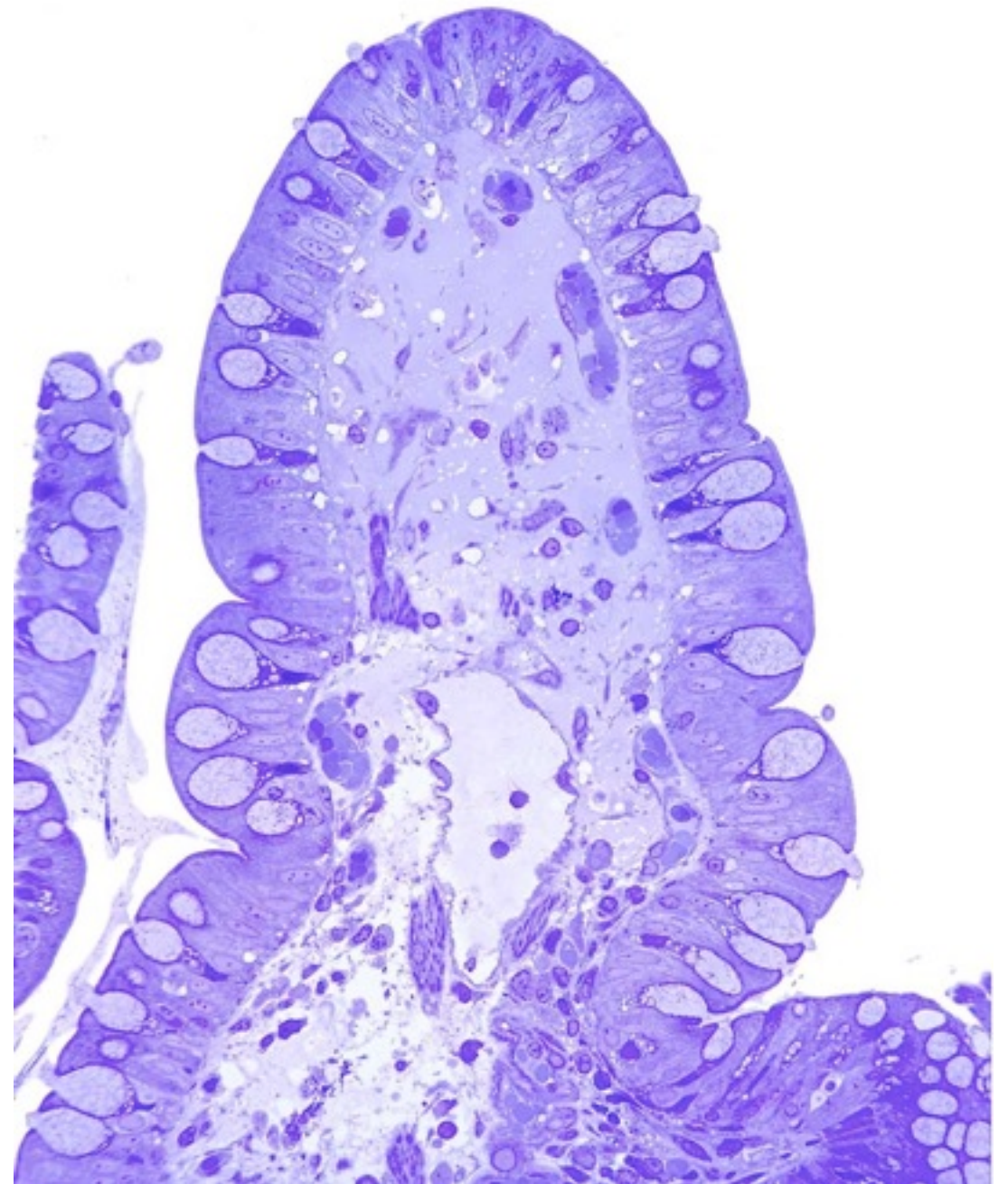
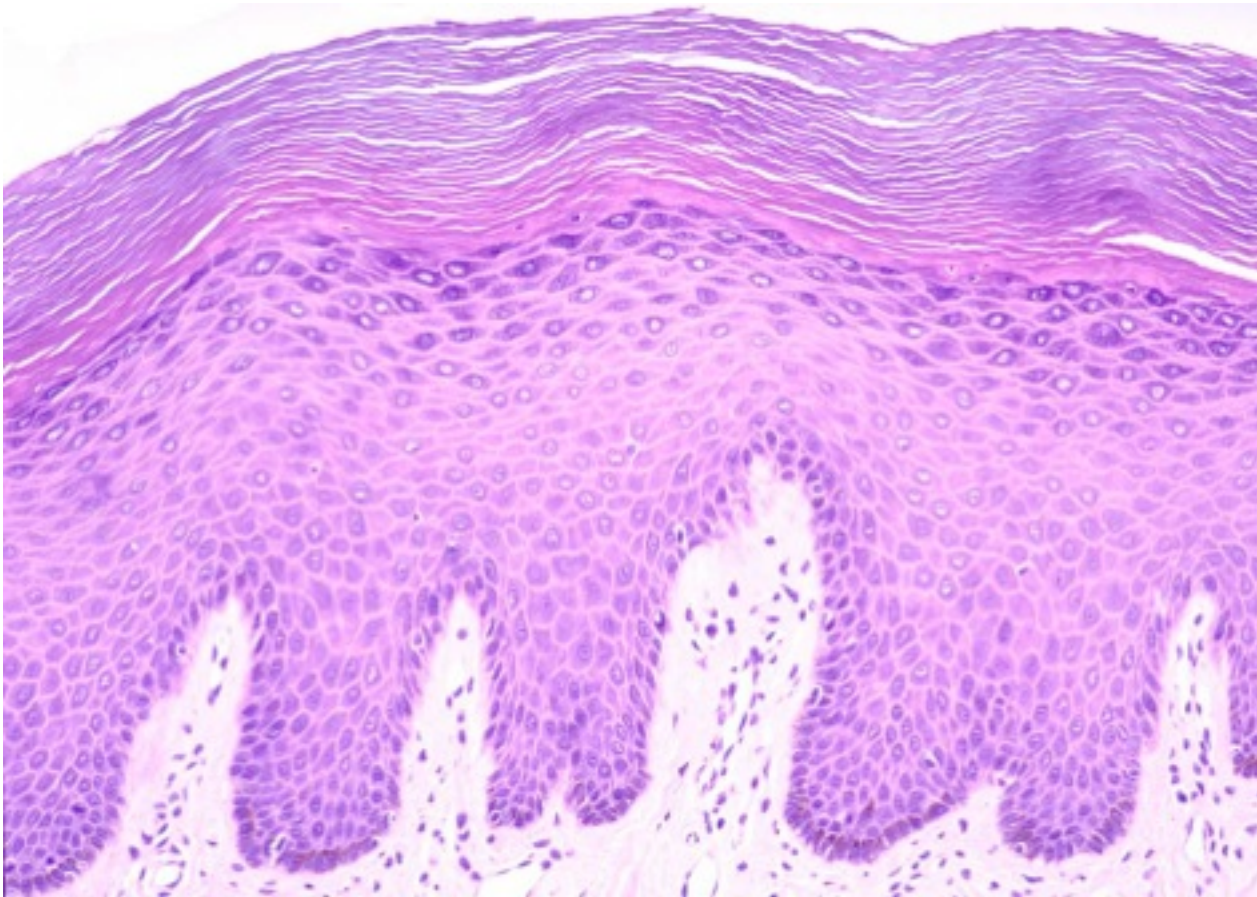
Tight junctions prevent diffusion of proteins between apical and basolateral domains.



Tight junctions not only function to restrict paracellular diffusion of small molecule but they also act as a diffusion barrier in the plasma membrane of epithelial cell to separate the apical and basolateral sides. Without tight junctions, proteins on the apical and basolateral side would mix because most proteins are able to diffuse within the plasma membrane. Consequently, polarity would be lost.

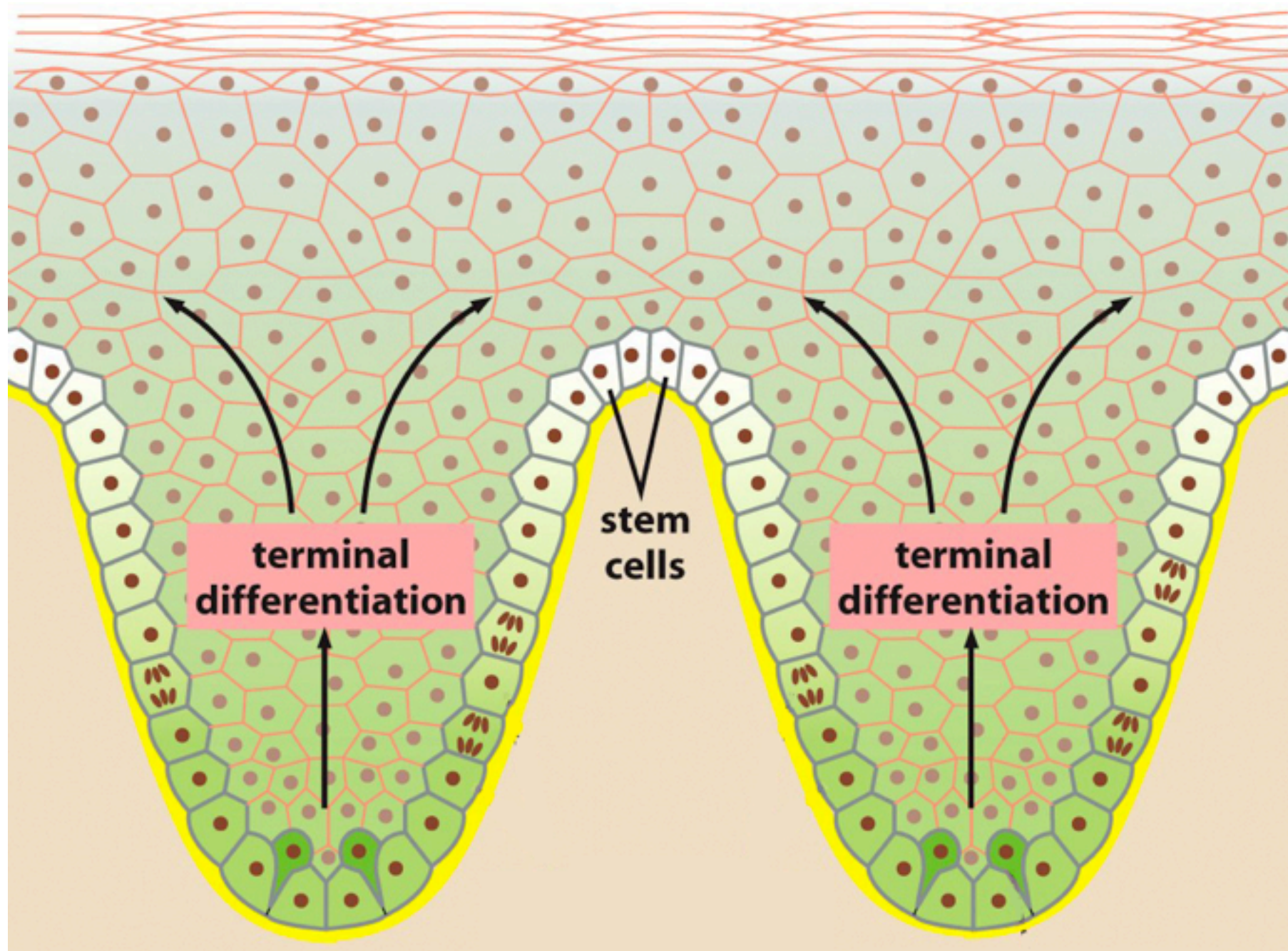
Renewal of Epithelial Cells and Cancer

The cells in many epithelia must be constantly replaced.



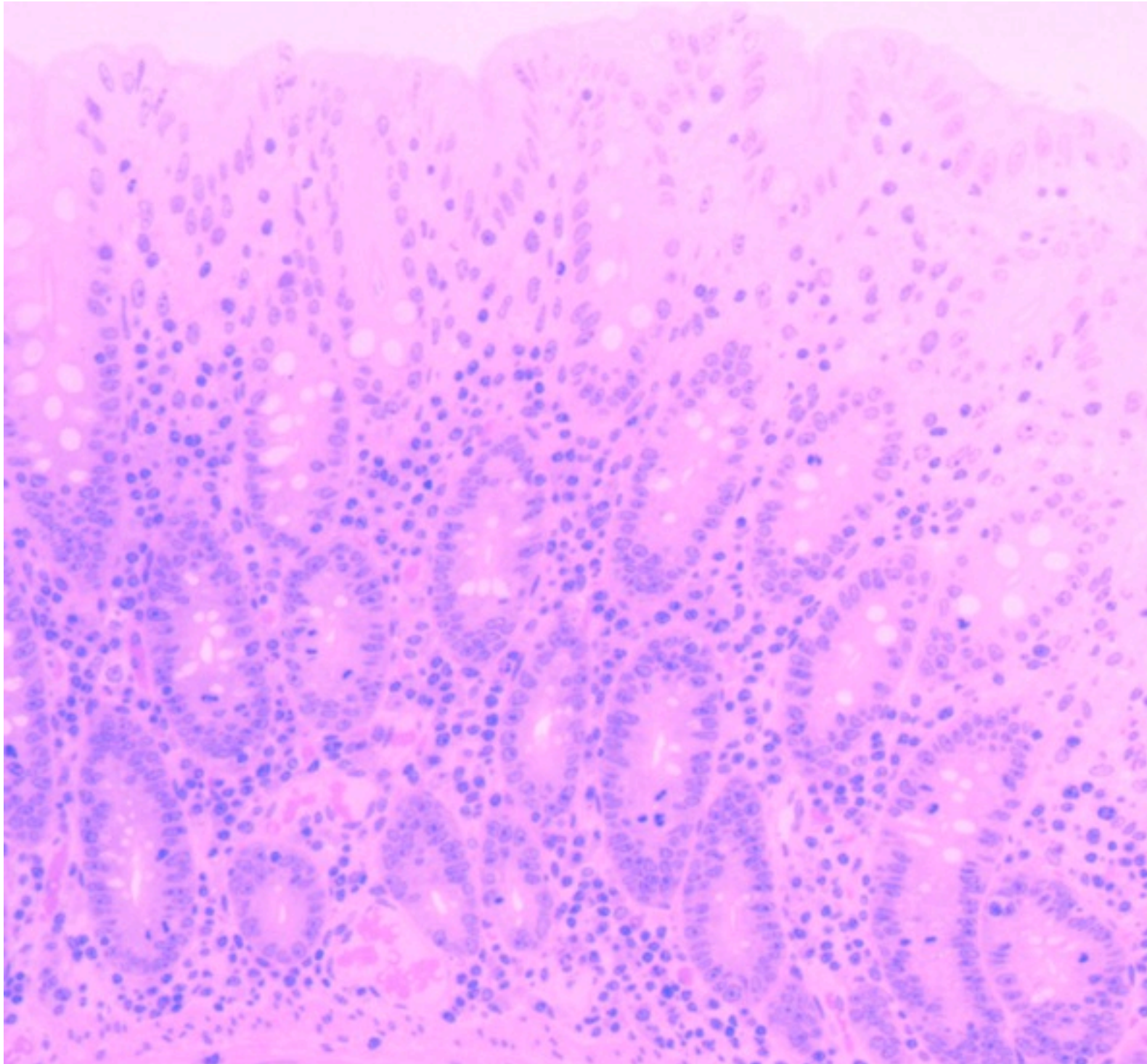
Many epithelia face external environment and lose cells due to mechanical strain and the natural aging of cells. In particular, the epithelia of the skin and intestine have high rates of cell loss. The epithelia of a typical villus in the small intestine turns over every 3 to 5 days, and the epidermis is completely replaced over 1000 times over the lifetime of an individual. To replace cells, epithelia need a pool of stem cells that proliferate and differentiate into a specific type of epithelial cells. Because the skin and intestine require many a steady supply of new cells, both epithelia have high rates of cell division and are prone to developing cancers.

Epidermal stem cells reside in certain locations in the basal layer.



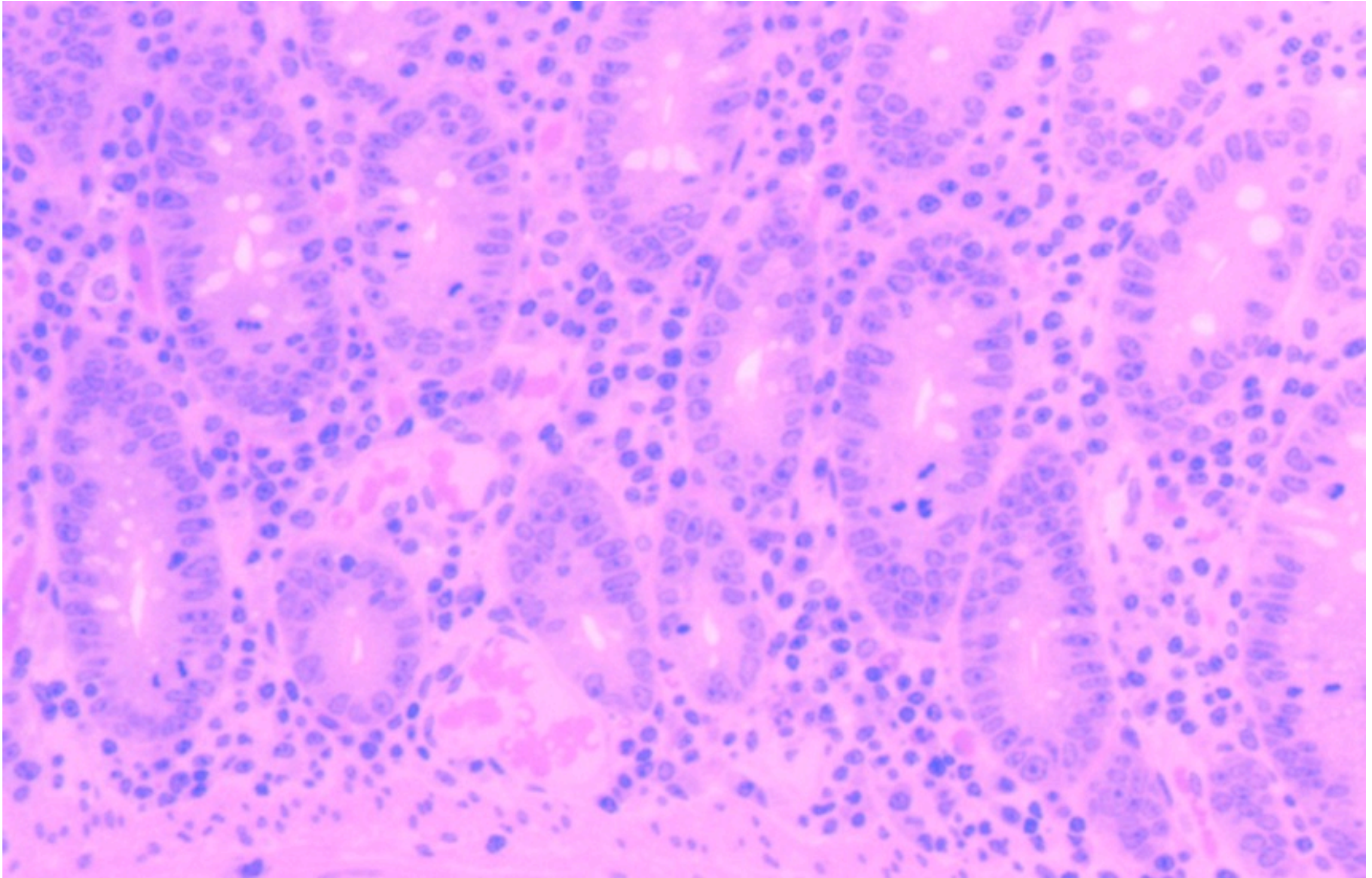
In many epithelia, the stem cells reside in discrete locations called niches. Non-epithelial cells around the niches produce growth factors and mitogens that regulate the division and differentiation of the stem cells. In the skin, stem cells reside in dermal papillae. They give rise to cells that divide more rapidly and differentiate into basal cells of skin as they migrate down the papillae. The basal cells differentiate into squamous cells as they migrate upward through the epidermis.

Intestinal epithelial stem cells resides in crypts at the base.



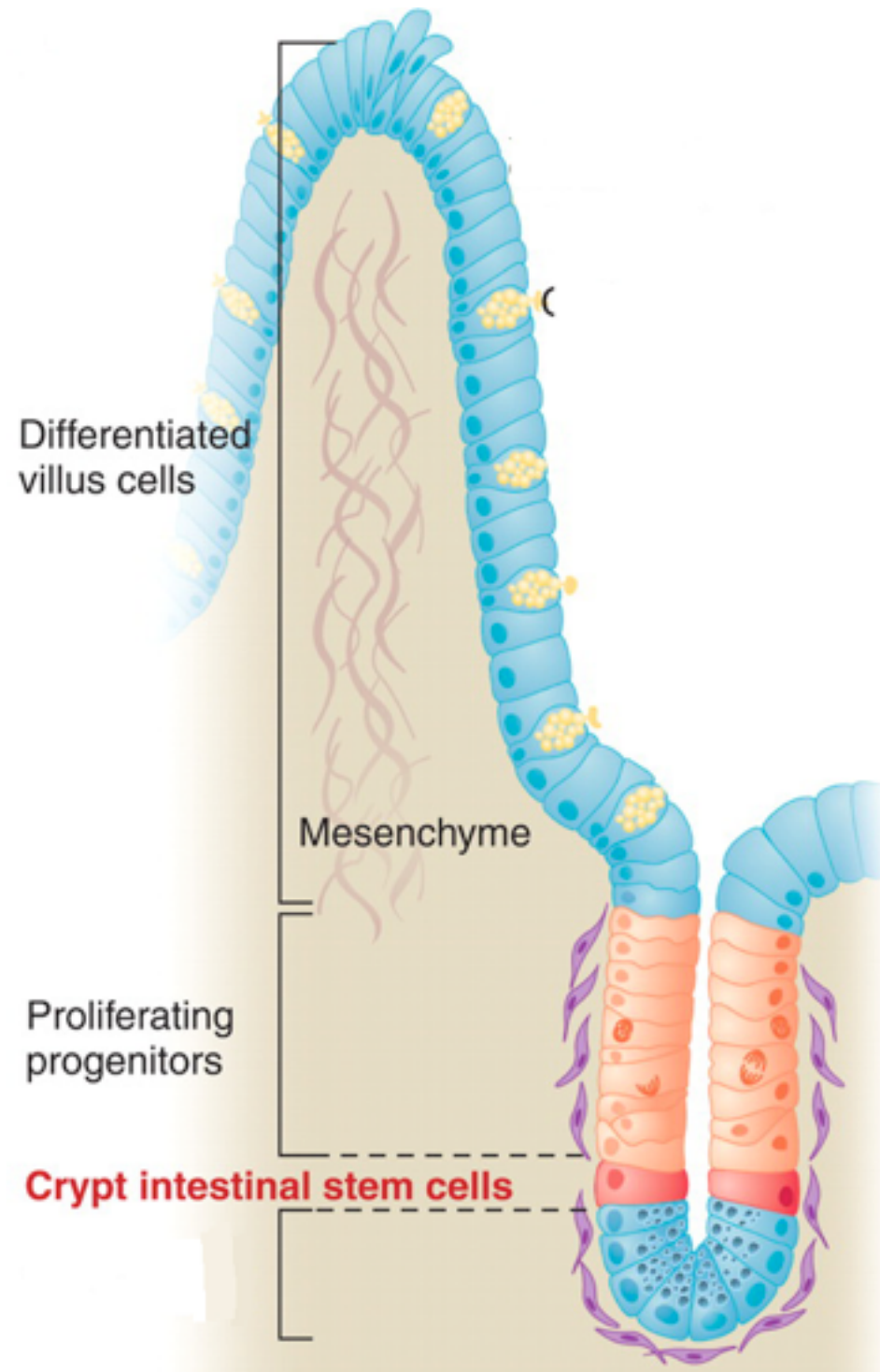
The epithelium of the small intestine is a single layer of cells. The stem cells reside in one domain of this layer which is located at the base or crypts of the villi. These cells give rise to faster dividing cells that differentiate into intestinal cells as they migrate up the villi.

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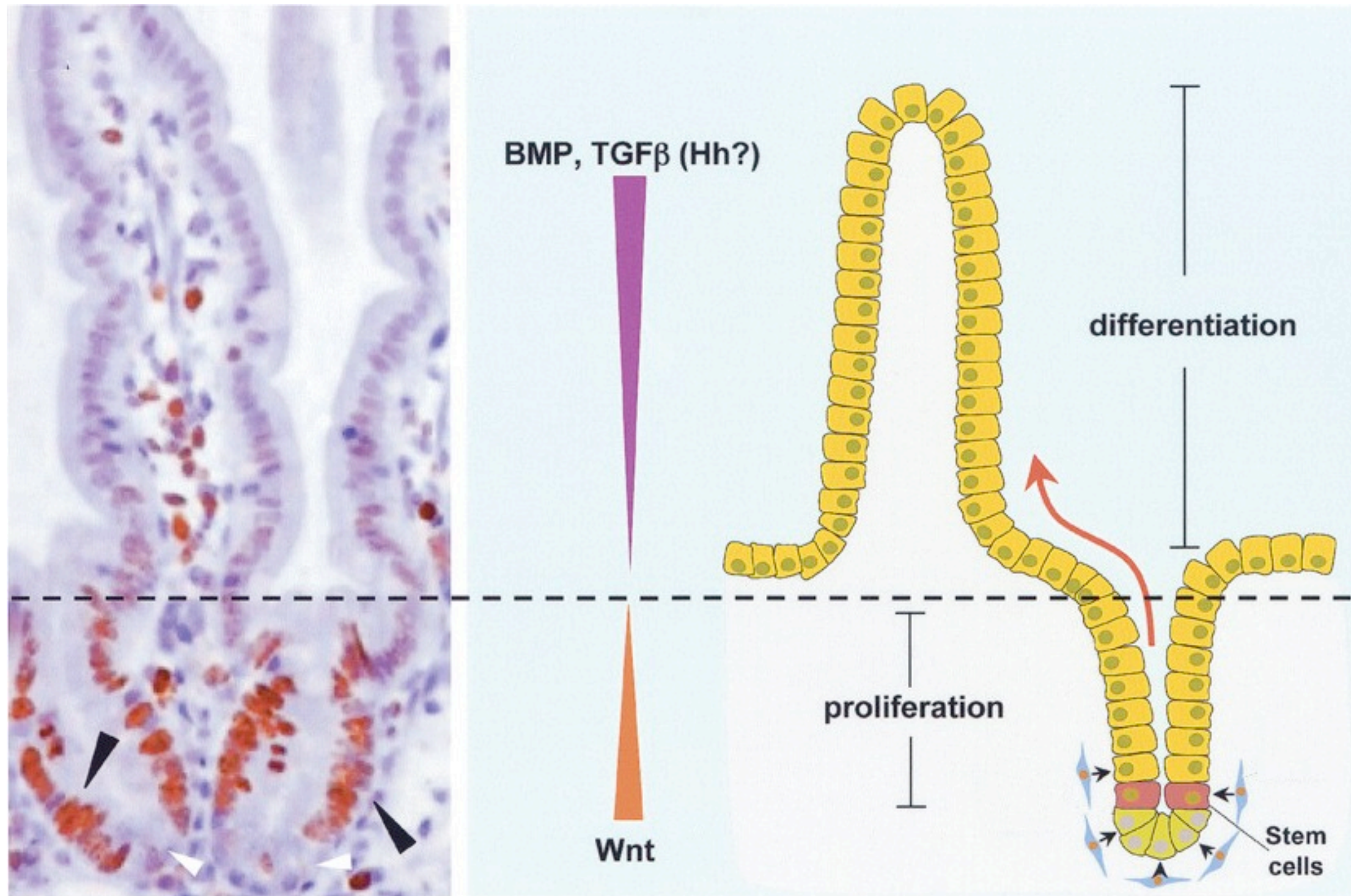
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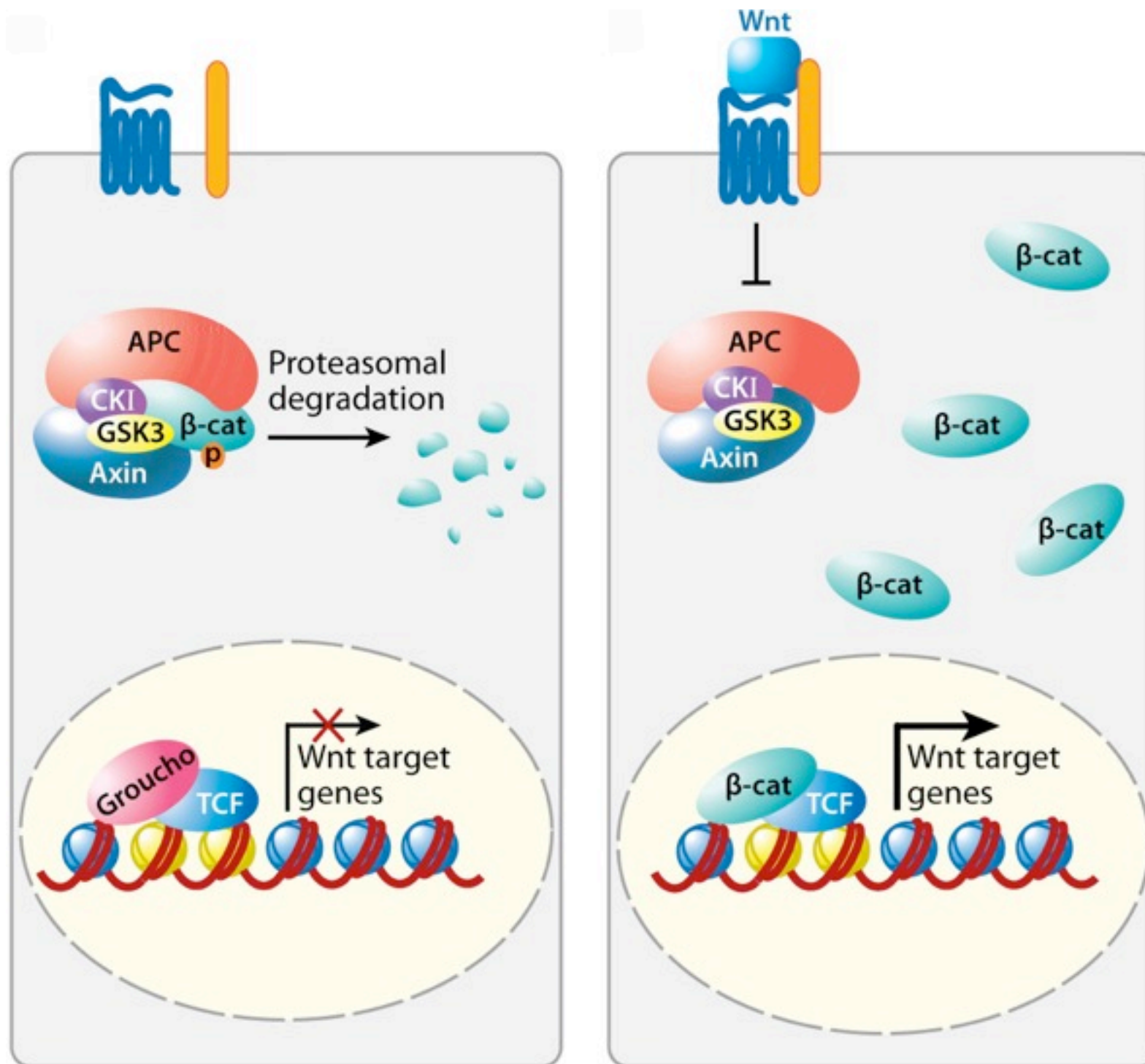
The epithelium of the small intestine is a single layer of cells. The stem cells reside in one domain of this layer which is located at the base or crypts of the villi. These cells give rise to faster dividing cells that differentiate into intestinal cells as they migrate up the villi.

Wnt maintains stem cell niche in intestinal epithelia.



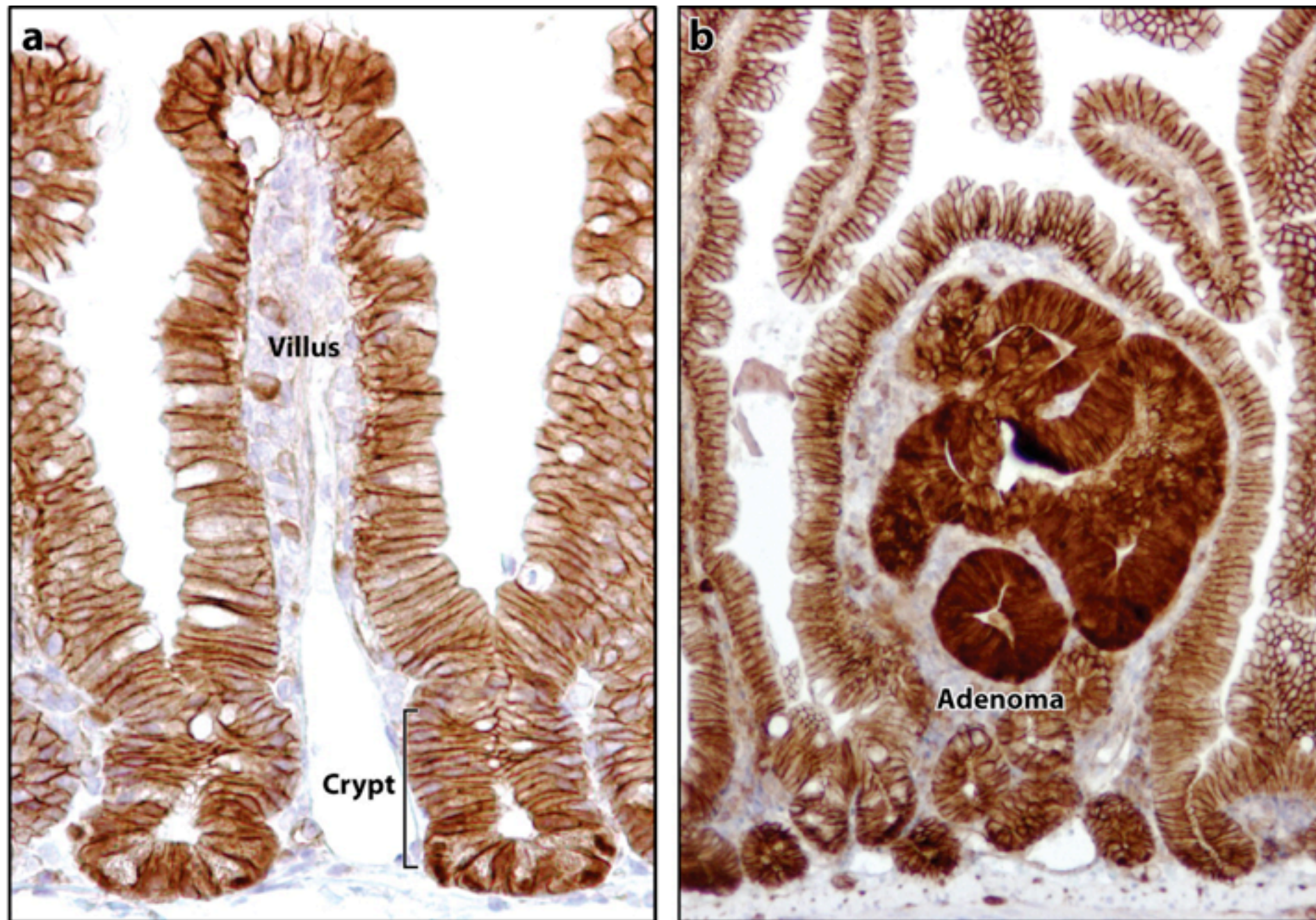
The cell division of the stem cells and differentiated cells in the intestine is regulated by mitogens and anti-mitogens. Wnt stimulates cell proliferation in crypts of intestinal epithelium, whereas anti-mitogens (BMP, TGF- β) inhibit cell proliferation further up the intestinal epithelium.

APC is tumor suppressor that mediates degradation of beta-catenin.



A key regulator of cell division in intestinal epithelial cells, is APC (adenomatous polyposis coli) which is part of a complex that keeps the amount of cytosolic beta-catenin low. APC, along with other proteins, phosphorylates beta-catenin targeting it for degradation. Consequently, beta-catenin cannot activate transcription of genes that encode proteins that trigger cell division. Stem cells in the intestine reside in an area with a high concentration of Wnt. Wnt activates a signaling pathway that inhibits the activity of the APC complex resulting in elevated cytosolic levels of beta-catenin. Cytosolic beta-catenin enters the nucleus and turns on expression of genes that stimulate entry into the cell cycle.

Mutated APC leads to elevated beta-catenin in nucleus and cell proliferation.



By inhibiting the activity of beta-catenin, APC functions as a tumor suppressor. Mutations in APC can lead to colon cancer. In normal color (left), beta-catenin (brown stain) localizes to the plasma membrane because it is associated with cadherins and cytosolic beta-catenin is degraded. In APC mutants, the amount of cytosolic beta-catenin increases leading to increased cell division and the development of adenomas.

Take home points...

- Epithelial cells come in a variety of shapes and layers to optimize their functions
- Tight junctions regulate the paracellular diffusion of small molecules and ions across an epithelium
- The basement membrane provides structural support and separates epithelia from underlying tissue
- Epithelia cells are polarized and can target proteins to apical and basolateral surfaces
- Stem cells allow replacement of epithelial cells and reside in niches