

# EPITHELIUM

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## Learning Objectives

1. Know the main characteristics of epithelium.
2. Understand the main functions of epithelium.
3. Be able to classify various epithelia based on their histology.
4. Understand epithelial polarity and surface specialization at various domains.
5. The major classes of cell adhesion molecules, the molecules involved and whether they are calcium-dependent or not.
6. The interactions of adhesion molecules with neighboring cells and with the stroma.
7. The structures that make up cell junctions and how they control the passage of materials across an epithelium.
8. Hemidesmosomes, structure and function.
9. Gap junctions, their makeup and how they work.
10. The composition of the basal lamina and how it is different from the basement membrane.
11. Difference between exocrine and endocrine glands.
12. Classification of exocrine epithelial glands.
13. The various types of secretion from epithelial glands and how these materials look in histological sections.
14. The difference modes of secretion and how this may affect the cells doing the secreting.
15. Definition and parenchyma and stroma.
16. The role of myoepithelial cells in epithelial glands.
17. Understand that epithelial cells are constantly being replaced.
18. Very significant numbers of tumors are of epithelial origin.

## 1. Main Characteristics of Epithelium

- An epithelium is a continuous sheet of connected cells that covers or lines a body surface (e.g. skin, intestine). Secretory glands (e.g. sweat, salivary, mammary) are derived from epithelium.
- An epithelium contains very little extracellular matrix.
- An epithelium sits on a basal lamina.
- Epithelium does not contain blood vessels. Nutrients reach the cells of the epithelium via diffusion from blood vessels outside the basal lamina. This feature places a limit to how thick an epithelium can be.

## 2. Main Functions of Epithelial Tissue

- Covering and lining of surfaces (eg. Skin)
- Absorption (eg. Intestine)
- Secretion (eg. Sweat glands)
- Sensation (eg. Neuroepithelium)
- Contractility (eg. Myoepithelial cells)
- Since epithelial cells cover all of the external and internal surfaces of the body, everything that enters or leaves the body must cross an epithelial barrier.

## 3. Classification of Epithelia

Epithelia are classified based on the number of cell layers and the shape of the cells at the uppermost layer.

Simple Epithelium --- Only one layer of cells, all of which are in contact with the basal lamina. Depending on the shape of the cells, simple epithelia can be further divided into:

Simple squamous --- One layer of flat cells. Examples: flat endothelium lines most blood and lymphatic vessels.

Simple cuboidal --- One layer of square cells. Example: cells of the proximal tubules of the kidney.

Simple columnar --- One layer of tall cells. Example: absorptive epithelium in the intestine.

Stratified Epithelium --- Two or more layers of cells. Only the cells of the bottom-most (basal) layer are in touch with the basal lamina. Mitosis takes place in the basal cells and, as the cells differentiate, they move upward in the epithelium. The classification is based on the shape of the cells in the superficial layer.

Stratified squamous --- the most commonly found stratified epithelium. This can further be divided into:

Stratified squamous non-keratinized --- multiple layers of cells with those in the outer layer displaying nuclei. Examples: esophagus, vagina.

Stratified squamous keratinized --- multiple layers of cells that are keratinized.

In the highly keratinized epithelium such as the epidermis of the skin, nuclei are absent in the outer layer. In the moderately keratinized (para-keratinized), nuclei may still be present in the outer cell layer (e.g. lining of the cheek).

Stratified cuboidal and Stratified columnar are less common and can be found in some secretory ducts. Example: large ducts in the salivary glands.

### Pseudostratified Epithelium

This kind of epithelium contains basal and columnar cells resting on the basal lamina. The basal cells sit on the basal lamina but do not reach upward. Only the columnar cells (also sitting on the basal lamina) reach the free surface. In a routine paraffin section the nuclei of the cells appear to be staggered and suggest a stratified arrangement, thus the name given in the good old days. In semi-thin and thin sections, it can be clearly seen that there is only one layer of cells. Examples: ciliated epithelium of the trachea.

### Transitional Epithelium

The transitional epithelium of the urinary passages is also called urothelium. The epithelium consists of superficial polygonal and basal cells. The cells of the surface layer are dome-like when the epithelium is not stretched (as in an empty bladder). The degree of “stratification” varies depending on if the organ is distended (2-3 layers of cells) or collapsed (several layers of cells). This epithelium will be discussed in more detailed in the section on the urinary system.

## 4. Epithelial Cell Polarity

Epithelial cells have structural and functional polarity. Each cell has two domains (regions with specialized structural and functional characteristics): an apical domain, and a basolateral domain.

The Apical Domain is the region of the cell that is exposed to the lumen or external environment. This region of some epithelial cells can have specialized structures:

Cilia --- Motile cell projections with the typical 9 + 2 microtubular doublet arrangement (an axoneme) originating from basal bodies. The basal body has a slightly different composition and is made up of 9 microtubular triplets. An epithelial cell in the trachea may have 250 cilia. Flagella are structurally similar to cilia but are much longer. There is usually only one flagellum per cell, eg. Sperm. Movements of these structures require ATP for energy.

Microvilli --- Non-motile, finger-like cytoplasmic projections resembling teeth of a comb, each with a core of cross-linked microfilaments (G-actin polymer). At the cytoplasmic end, bundles of actin extend into the terminal web (a network of filaments that helps to anchor the actin). The microvilli greatly increase the absorptive surface at the apex of the cell. These structures are coated with glycocalyx that may contain enzymes (disaccharidases, peptidases). Example: apical surfaces of absorptive cells in the intestine (striated border) and the apical surfaces of renal tubules (brush border).

Stereocilia --- Long and branching finger-like projections from the apical surface. Each contains a core of cross-linked actin. Stereocilia also increase the surface area of the cell and facilitate the movements of molecules into and out of the cell. Note that even though this structure has “cilia” in its name, the microtubular axoneme is absent and thus is nonmotile. The name is a carry over from the days when microscopy was not able to resolve the fine structure of this structure. Example: epithelial cells of the epididymis.

The Basal Domain is the part of the cell that sits on the basal lamina. The basement membrane includes the basal lamina and the connective tissues associated with it. The basal lamina/basement membrane will be discussed in greater details later in this chapter.

Due to the presence of cell junctions, the surfaces of the cell can be divided into the apical surface and the baso-lateral surface. As mentioned before, substances entering or leaving the body must cross an epithelium. The apical and baso-lateral surfaces have different characteristics (receptors, channels, pumps etc.) that make this process possible.

## 5. Cell Adhesion Molecules

A sheet of epithelium is made up of cells attached to each other and to the basal lamina. Cell adhesion molecules and specialized cell junctions secure inter-epithelial cell contact. Polarity of the cell is a result of this arrangement.

Cell adhesion molecules can be divided into two major classes:

Ca<sup>2+</sup>-dependent molecules, e.g. selectins, cadherins.

Ca<sup>2+</sup>-independent molecules, e.g. integrins and the immunoglobulin superfamily.

### Cadherins

These molecules connect the internal cytoskeleton of a cell and the exterior of another cell. There are over 40 different cadherins and they belong to a family of calcium-dependent molecules important in cell adhesion and differentiation.

E-cadherin (epithelial) is found on the lateral cell surfaces, important in keeping the cells together forming an epithelial sheet. N-cadherin (nerves) is found in the lens of the eye, in skeletal and cardiac muscles as well as the central nervous system. P-cadherin is present in trophoblasts in the placenta.

Linkage of cytoskeleton and the exterior

Cadherin has a cytoplasmic and an extracellular domain. The intracellular domain is linked to actin by proteins called catenins ( $\alpha$ ,  $\beta$  and  $\gamma$ ). The extracellular domains form dimers and bind to dimers of the same class of cadherin from an adjacent cell (homophilic interaction). The binding requires calcium.

Cadherins are also found between cytoplasmic plaques of zona and macular adherens (cell junctions).

These adhesion molecules not only play important roles in normal tissues, but also are also involved in development as well as in pathological processes. Loss of cadherin is associated with tumor metastasis.  $\beta$ -Catenin has been associated with formation of colorectal cancers.

Selectins are calcium dependent adhesion molecules that bind to carbohydrates. Each selectin has a carbohydrate recognition domain (CRD) with binding affinity to a specific oligosaccharide attached to a protein (glycoprotein) or a lipid (glycolipid).

There are three major classes of selectins:

P-selectin --- Present in platelets and activated endothelial cells lining the lumens of blood vessels. Interaction between P-selectin on the endothelial cell and its ligand on the leukocyte is a key step in the process of leukocyte extravasation (leaving the blood vessel and entering tissues).

E-selectin --- Present on activated endothelial cells.

L-selectin --- Present on leukocytes.

### Immunoglobulin Superfamily Related Adhesion Molecules

These cell adhesion molecules (CAM) have one or more folds in their extracellular domains and resemble the appearance of immunoglobulins. A molecule can bind to another CAM of the same class or to a CAM of another class. The binding is calcium independent.

N-CAM (neural cell adhesion molecules), V-CAM (vascular cell adhesion molecule) and I-CAM (intercellular adhesion molecule) are all involved in cell-cell adhesion and interactions.

Integrins are calcium independent adhesion molecules expressed by almost every cell. They are hetero-dimers formed by two associated  $\alpha$  and  $\beta$  subunits. They are involved in both cell-cell interactions and cell-matrix interactions.

The cytoplasmic  $\beta$  subunit is linked to actin filaments via connecting proteins ( $\alpha$ -actin, talin, vinculin etc.). The extracellular domain of integrins binds to laminin and fibronectin, components of the basement membrane. Laminin and fibronectin, in turn, bind to other extracellular matrix molecules such as collagens, entactin, and heparan sulfate proteoglycans.

## **6. Cell Junctions**

Adhesion molecules discussed above are reinforced by cell junctions, which provide further stability in the interaction.

Water, solutes, ions etc. can move through an epithelium by two different pathways. The transcellular pathway, with materials going through the cell, involves channels and transporter molecules. In the paracellular pathway, materials travel between adjacent cells and the process is regulated by cell junctions.

Occluding junctions (zonulae occludens, tight junctions) form a belt-like seal around the apical surfaces of two adjacent cells. They are not associated with cytoskeletal elements.

They junctions are “tight,” and prevent movements of lipids and proteins between adjacent cells thus setting up paracellular pathway barriers.

Occluding junction are symmetrical structures on opposite sides of two adjacent cells. They define epithelial cell polarity by separating the apical domain from the basolateral domain.

Occludin is an integral membrane phosphoprotein. Its intracellular domain interacts with the ZO-1, ZO-2, ZO-3 protein complex. Claudin is a transmembrane protein forming linear fibrils in the occluding junction. Together, these two proteins form the ‘seal’, which regulates the paracellular pathway.

With freeze-fracture EM, occluding junction appears as branching and interconnected strands. The more strands the “tighter” the seal.

Occluding junctions are not associated with cytoskeletal elements.

Anchoring junctions are found below the occluding junctions.

These belt- and spot-desmosomes provide strength and rigidity to an epithelial cell layer. They are symmetrical structures that anchor adjacent cells at the apical domains. The intercellular space at the site of these junctions is filled by interlocking cadherins. These junctions are associated with cytoskeletal elements.

Zonula adherens (belt desmosomes) is a belt-like junction and is associated with actin. It contains a dense plaque (containing desmoplakin and plakoglobin) that is attached to the cytoplasmic face of the plasma membrane and is associated with catenins ( $\alpha, \beta$  and  $\gamma$ ). Actin filaments (from the terminal web) in turn are attached to the catenins. Transmembrane proteins cadherins (desmocollins and desmogleins) are involved in bridging the intercellular space. One end of the cadherin molecules is anchored to the plaques while the other end forms links with cadherins of the opposite cell membrane. This interlocking, homophilic interaction is a calcium-dependent process.

Macula adherens (spot desmosomes) is a button-like junction associated with intermediate filaments (keratin filaments, tonofilaments) that are anchored to

cytoplasmic dense plaques (desmoplakin and plakoglobin). The intercellular space is occupied by cadherins that interlock by the calcium-dependent homophilic interaction.

### Junctional Complex

Tight junction, occluding junction and desmosome often occur in sequence, forming a junctional complex. A classical example is that found between epithelial cells in the intestine. (Zipper-Velcro-snaps) These structures may appear as terminal bar, little black dot at the apical part where two cells are attached to each other.

Hemidesmosomes are asymmetrical structures that anchor the basal domain of the epithelial cell to the basal lamina. They are associated with both intracellular and extracellular elements.

A hemidesmosomes consists of a cytoplasmic plate associated with intermediate filaments (keratin, tonofilaments). The plate is associated with a plaque that contains integrins and is located in the plasma membrane. Extracellular anchoring filaments (lamin5) link the hemidesmosome to the basal lamina.

Note that (i) hemidesmosomes occur at the basal domain of the cell and (ii) although the name contains “-desmosome,” the composition of the hemidesmosome is very different than the “real” desmosomes.

Communicating Junctions (gap junctions) are button-like structures made up of integral membrane proteins called connexins.

Six connexins subunits assemble in the plasma membrane to form a hollow cylinder called a connexon. Connexons from adjacent cells, when aligned together, form direct channels of communication between the cytoplasm of two cells. Connexons usually form patches and facilitate the movements of molecules such as  $\text{Ca}^{2+}$ , and messengers such as cyclic AMP between cells. A high concentration of calcium leads to the closure of the channels.

Gap junctions are responsible for the chemical and electrical “coupling” between adjacent cells. Examples include cardiac muscles and smooth muscles of the uterus. Gap junctions are present in most mammalian tissues, skeletal muscle, however, is an exception.

Occluding junctions are important in the regulation of the paracellular pathway and the permeability of epithelial sheets. Anchoring junctions are important in distributing mechanical stress and maintaining integrity of epithelial cell layers. Gap junctions are important in communications between cells. Defects in cell junctions can be found in a number of pathological conditions ranging from cancer to autoimmune diseases. Because many of the interactions involved with adhesion molecules are calcium-dependent, removal of calcium under experimental conditions will lead to dissociation of the epithelium.

## 7. Basal Laminae and Basement Membrane

All epithelium rests on a sheetlike extracellular structure called basal lamina that is not visible under the light microscope. This layer contains type IV collagen, laminin, entactin and proteoglycan. Under the electron microscope, the basal lamina appears as a dense layer, 20-100 nm thick, consisting of a delicate network of fine fibrils (lamina densa). There may be electron lucent layers (laminae rariae; singular – lamina rara, lamina lucida) on both sides of the lamina densa. Fibrils of collagen type VII anchor the basal lamina to the underlying connective tissue. The epithelial cells produce the basal lamina. In some instances, reticular fibers (formed by connective tissue cells) are closely associated with the basal lamina, forming the reticular lamina.

The term basement membrane describes a PAS-positive layer, visible with LM, beneath the epithelium. This usually contains two fused basal laminae or a basal laminae and a reticular lamina.

Two molecules associated with the basal lamina deserve further discussion.

Laminin is made up of three polypeptides ( $\alpha, \beta, \gamma$ ) and is cross-shaped. It contains binding sites for type IV collagen, proteoglycans, integrin, and entactin. Thus laminin can attach to cell surface, adhesion molecules and extracellular matrix. The epithelial cells that rest on the basal lamina synthesize it. Laminin and type IV collagen are the components of the basal lamina.

Fibronectin is made up of two proteins linked by disulfide bonds. It is made by fibroblasts and is the main adhesion molecule of extracellular matrix of the connective tissue. It binds to collagen, proteoglycans, cell surface and fibrin.

Note that the basal lamina is not found exclusively in epithelial tissues. It is also present in other cells types that are in contact with connective tissue, e.g. muscle, adipose and Schwann cells.

The functions of the basal lamina include: structural support, filtering, binding with growth factors (thus influencing cell proliferation and differentiation), organizing the proteins in adjacent plasma membrane, and serve as a guide for cell migration. Defects and disruptions of the basal lamina lead to many pathological conditions, e.g. glomerulonephritis.

## 8. Epithelial Glands

Epithelial glands are structures derived from epithelial cells that specialize in producing secretions. They usually develop as invaginations/ingrowths into the underlying connective tissue.

Exocrine glands are derived from specialized epithelial cells and have secretory portions and ducts that transport the products to the exterior of the glands. The duct may be made

up of squamous to stratified columnar cells. The secretory portion may be shaped like a test tube (tubular), a flask (acinar) or tubuloacinar.

Endocrine glands also derived from specialized epithelial cells. However, the connection to the exterior (duct) has disappeared. Products of the endocrine glands are released into blood vessels that are in close association with the secretory cells. We will deal with endocrine glands in greater details in a separate lecture.

### Classification of Exocrine Epithelial Glands

Unicellular Glands: isolated secretory cells located in a non-secretory epithelium.

Example: goblet cells among absorptive cells in intestinal epithelium.

Simple glands: The term “simple” applies to the duct portion that is unbranched. The secretory portion, however, can vary from straight tubular (intestine), coiled tubular (sweat), branched tubular (uterus) and branched acinar (sebaceous). Acinar (Lat. Grape) = alveolar (Lat. Small hollow sac).

Compound glands have ducts that branch repeatedly. The secretory portion can be tubular (pyloric stomach), acinar (pancreas) or tubuloacinar (salivary and prostate).

### The Type of Secretion

Exocrine glands can be mucous glands (glycoproteins and water), serous glands (protein and water), and mixed glands, containing both mucous and serous cells. Exocrine glandular epithelium can also secrete lipid material, eg. sebaceous glands.

Serous materials usually stain pink in routine H&E sections.

Mucous materials usually do not stain well in H&E and appear pale grey or purple.

They stain brightly magenta with PAS.

Lipid materials require special preservation and stains.

See ‘Introduction to Histology.’

### Mode of Release of the Secretory Products

Merocrine: The secretory granules leave the cell by exocytosis with no loss of other cellular material. Example: Exocrine pancreas.

Holocrine: The whole secretion-filled cell ruptures (and dies) and releases its products. Example: Sebaceous glands.

Apocrine: The secretory material is released along with a part of the apical cytoplasm in the form of “blebs”. The rest of the cell is intact and continues to function.

Example: Apocrine sweat glands.

## **9. Parenchyma and Stroma**

The terms parenchyma and stroma are used regularly to describe the functional and structural components of an organ. Here we use an exocrine gland as an example:

The functional portion of the gland associated with production and secretion (acini and ducts) is called the parenchyma.

Connective tissues usually form a capsule around an exocrine gland. Strands of connective tissue septa divide the gland into smaller functional portions (lobes and then lobules). This supporting tissue, along with blood vessels, is part of the stoma.

Ducts found among secretory units are intralobular ducts. Those found in the connective tissue septa are interlobular ducts. Eventually, the interlobular ducts will join to form lobar ducts. The “main duct” if present, drains the whole gland.

## 10. Myoepithelial Cells

In some exocrine glands (e.g. salivary, mammary, sweat), myoepithelial cells are present around the secretory acini and surrounding the ducts. These cells are located between the basal portion of the secretory cell and the basal lamina. The cytoplasm of the myoepithelial cell contains numerous actin filaments as well as myosin.

Contraction of the myoepithelial cells around the secretory acini and the ducts helps to propel the products out of the gland.

These cells are difficult to see in routine sections but are easily demonstrated with immunohistochemistry.

## 11. Renewal of Epithelial Cells

Cells of the epithelium are constantly being replaced by means of mitosis. The location of the active site of mitosis also varies from tissue. In the GU tract, the epithelial cells are constantly turning over. In the intestine, the epithelium is replaced in a matter of days; in the liver and the pancreas, the rate is considerably slower.

## 12. Clinical Collations

A significant numbers of tumors you will encounter are of epithelial origin.

Benign and malignant tumors can arise from epithelial tissues.

Carcinoma: malignant tumor of epithelial origin.

Adenoma: non-malignant tumor of epithelial origin.

Adenocarcinoma: malignant tumor derived from glandular epithelial tissue.

**12.1.** The basal lamina plays an important role in tumor biology. When cancerous cells break through the basal lamina, the tumor becomes invasive and may spread to distant sites (metastasis).