Chapter

Morphology of Salivary and Lacrimal Glands

Alpaslan Gokcimen

Abstract

Generally, the tissues consist of stroma and parenchyma. The epithelial tissue, which forms the basis of exocrine glands, is rich in parenchyma. The secretions of salivary glands are functionally related to the digestion, and the secretions of the lacrimal glands protect the eye surface and allow to maintain a proper vision. The parotid is a pure serous gland and consists of serous acinus. The submandibular gland is a mixed gland consisting of serous acini and mucous tubules, and the acinus is predominant. The sublingual gland is a mixed gland composed of serous acini and mucous tubules, such as the submandibular gland, but the mucous tubules are predominant. The secretions of salivary glands reach the oral cavity with the intercalated canal, the intralobular canal, the interlobular canal, and the main duct channel. "Stenon duct" in the parotid gland, "Wharton duct" in the submandibular gland, and "major sublingual" duct in the sublingual gland open into the oral cavity. The lacrimal gland is structurally similar to salivary glands. This gland was divided into lobules by irregular tight connective tissue. In the lobules, acinar cells and mucus tubules are located together.

Keywords: salivary glands, lacrimal glands, morphology, functions

1. Introduction

The smallest unit of a living organism is the cell and cells congregate to form tissues. The cells that make up the tissues do not only have similar shapes but also form a community to perform specified functions. Basically, the tissues consist of two parts: parenchyma and stroma. Stroma forms the skeleton of the structure. The parenchyma is the tissue's functional part and is located inside the stroma. Therefore, the tissue as a whole performs specific tasks and functions. In normal conditions, stroma and parenchyma are in certain ratios in each tissue. In some tissues parenchyma is predominant, as in epithelial tissue, while in a connective tissue, it makes up its minority. Basically, according to the rate of parenchyma and stroma, there are four kinds of tissues: epithelial tissue (epithelium), connective tissue, muscle tissue, and nerve tissue. In the second week of embryonic development, the bilaminar embryo disc forms, while the trilaminar embryo disc emerges at its third week. Tissues take origin from the different layers of this embryonic disc. The epithelial tissue originates from all of the embryonic germ leaves [1–3].

Ectoderm-derived epithelial structures are as follows: sweat glands and ducts, oral cavity, and vaginal and anal canal epithelium [1–3].

Mesoderm-derived epithelial structures include blood vessel endothelium, mesothelium that lines up body cavities, and epithelium covering genitourinary system and tubules [1–3].

The epithelial tissue originating from endoderm is located on the inner surface of the esophagus, as an epithelium covering the stomach-intestinal tract, an epithelium surrounding the gallstones, large glandules such as in the liver and pancreas, and an epithelium located in the respiratory system [1–3].

1.1 Features of epithelial tissues

a. Basal membrane: The epithelium is never found in space but is located on the basal membrane as single or multiple layers (**Figure 1a**, **b**). All cells are arranged on the basement membrane but with the exception of ependymal cells, mesangial cells, and macula densa [4, 5].

b. Diversity: We can summarize the main function of epithelial tissue as covering, protection, secretion, and absorption. It varies according to these functional differences. The epidermis covers the outer surface of our body and protects it (**Figure 2**). The covering function protects not only the body's external surface but also the inner part of the lumen structures such as the small intestine and colon, the trachea, and the urinary system (**Figures 3–6**). The epithelial cells progress in the lower connective tissue and form different gland structures such as tubular and simple branched tubular. In this way, mucous tubules and serous acini are formed. Therefore, suitable serous, mucous, or mixed secretions are produced. These glands give out their secretions through duct channels [4, 6].

c. Polarity: The epithelium has three surfaces. These include apical, lateral, and basal surface. There are membrane extensions on the apical surface such as cilia, microvillus, flagella, and stereocilia. Microvillus is especially important for these structures in food exchange. The small intestine is the best example of it (**Figure 3**). In particular, the microvillus is located in the proximal part of the kidney where the absorption occurs (**Figure 7**). The microvillus in the epithelial cells provides reabsorption of important substances. Reabsorption is also provided by basal invaginations. Basal invaginations can be observed in the ductus striata of the salivary glands and proximal and distal tubules of the kidney at best. The substances taken with the apical surface of the epithelial cell are given to the basal part by active transport [4, 6].

d. The cilia are mobile and they are located in the respiratory system (**Figure 5**). Cilia make the sweeping movement from the trachea to the oral cavity. In this way, harmful substances such as microorganisms and carbon particles are thrown out of the body. The cilia are also found in the uterus and tuba uterina of female genital system (**Figures 8**, **9a**, **b**). Cilia in the female genital system sweep the secretion to pass the zygote from the uterus into the uterine cavity. Flagella is seen in the spermium, and it provides the spermium moves in this way (**Figure 10a**, **b**) [4–8]. Stereocilia are a non-movement structure (**Figure 11**). Stereocilia increase the surface area of the epididymis and allow absorption of testicular fluid and phagocytosis of pathological sperm. Stereocilia which reside in the hair cells of the inner ear are involved in signal generation [4–8].

The lateral surface of the epithelium, there are intercellular binding complexes: non-permeable connections, anchor connections, and gap junction. Zonula occludens are non-permeable; zonula adherens, hemidesmosomes, and desmosome are anchors; and gap junction is the intercellular connections that provide communication.

Basal invagination is present in the epithelium. These are the finger in folds that the cell membrane makes at baseline and parallel to each other; there are abundant mitochondria in these recesses. Basal invaginations are known as ductus striata of salivary gland's duct channels. Basal invaginations are also present in the epithelium

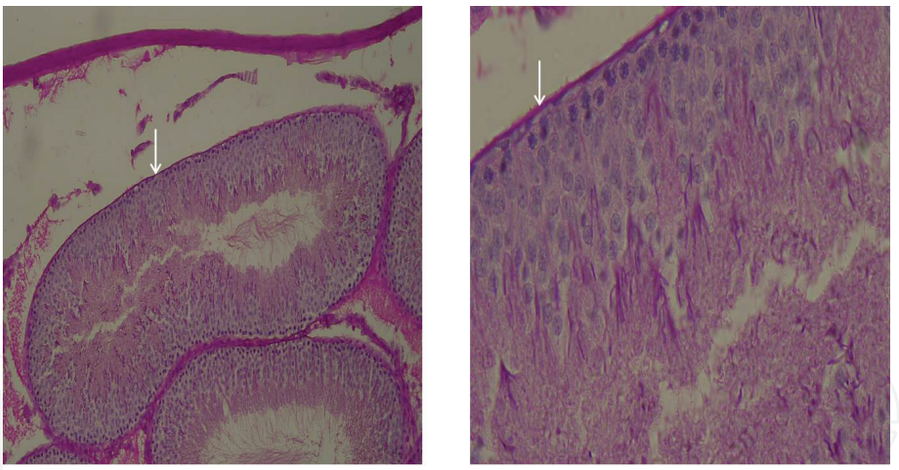


Figure 1.
(a, b) In the section taken from the testis, the basement membrane is seen as a red-pink line. Hematoxylin–eosin staining (Dr. Alpaslan Gokcimen).

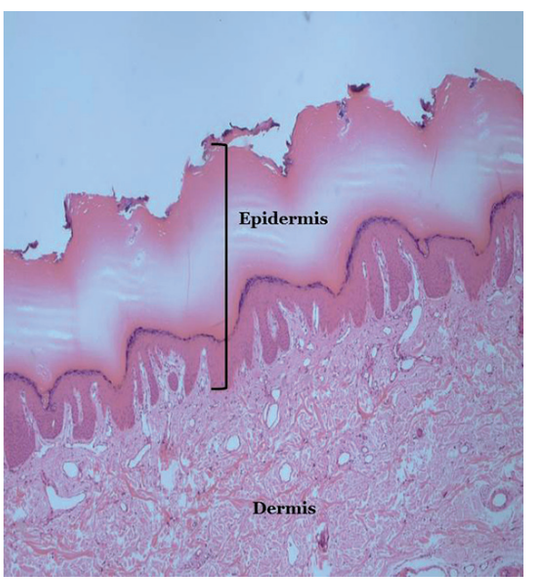


Figure 2.
Light microscopic image of the epidermis, skin. Keratinized stratified epithelium can be seen in the brackets. Hematoxylin–eosin staining (Dr. Alpaslan Gokcimen).

that forms the proximal and distal tubule, which allow the transport of the water and minerals. A rich capillary network exists around the basal invaginations. The cells pump the ions, glucose, sodium, potassium, and calcium through active transport from lumens of the tubes to the recesses. Thus, the water passes from the cytoplasm to the spaces that become hypertrophic and swell and expand, and then the collected water and ions pass into the veins [4, 9].

e. Avascularity: The epithelium is fed by diffusion through the blood vessels in the connective tissue below. In the feeding of multilamellar epithelium such as the skin, lip, esophagus, and vagina, the underlying connective tissue sends finger extensions into the epithelium. This is the name given to the "papilla" and thus feeding the epithelium [4, 5, 8].

f. Layer: The epithelial tissue can be classified according to the number of cell layers and the shape of cells. Different kinds/forms of epithelium are present in various organs, as shown in **Table 1**.

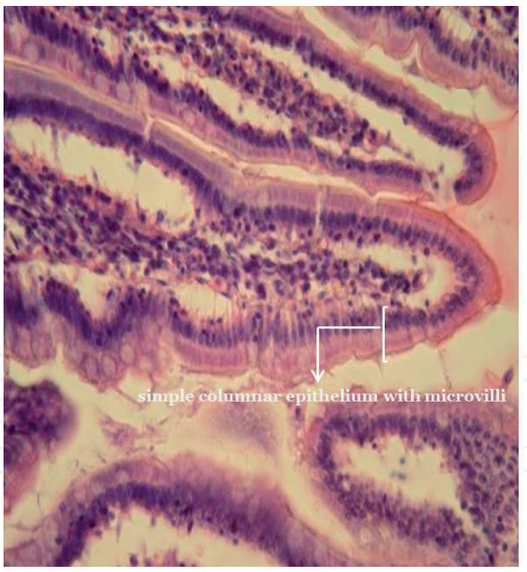


Figure 3.
Simple columnar epithelium with microvilli of the small intestine. Hematoxylin–eosin staining (Dr. Alpaslan Gokcimen).

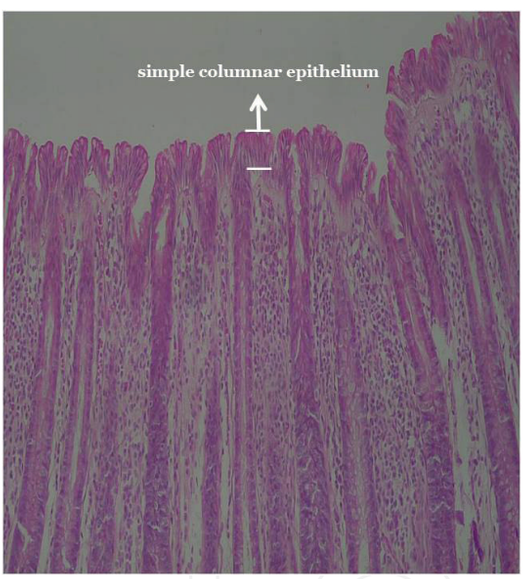


Figure 4.
Simple columnar epithelium of the large intestine can be seen between the lines. Hematoxylin–eosin staining (Dr. Alpaslan Gokcimen).

1.2 Functions of epithelial tissue

a. Protection against tearing and abrasion and protection against drying with keratin and mucus

b. Absorption of kidneys and intestines with microvilli

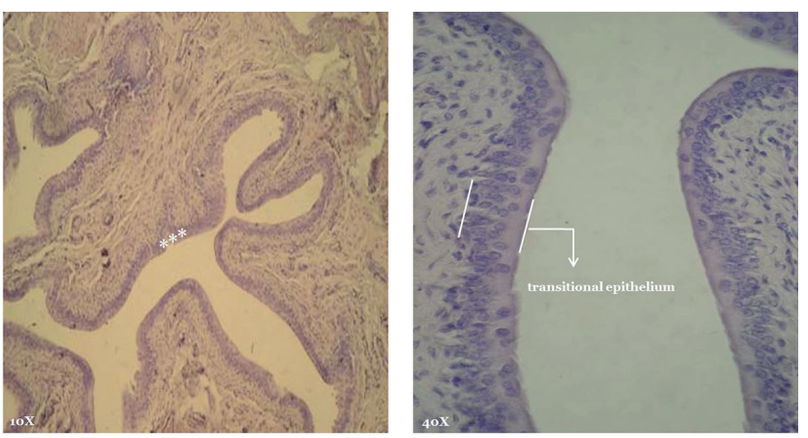
c. Surface transition: superficial transport with cell kinocilium

d. Secretion of hormones, digestive enzyme, and mucus

e. Sensory perception: taste buds, olfactory epithelium

f. Contraction: myoepithelial cells in glands [4, 6, 7, 10]

Figure 5.
Ciliated pseudostratified columnar epithelium of the trachea, Masson's trichrome staining (Dr. Alpaslan Gokcimen).



(a) (b)

Figure 6.
(a) The transitional epithelium of the bladder. (b) The transitional epithelium of the bladder is marked at larger magnification Light microscopic image of bladder with transitional epithelium. Epithelium is shown by stars and between the lines. Hematoxylin–eosin staining (Dr. Alpaslan Gokcimen).

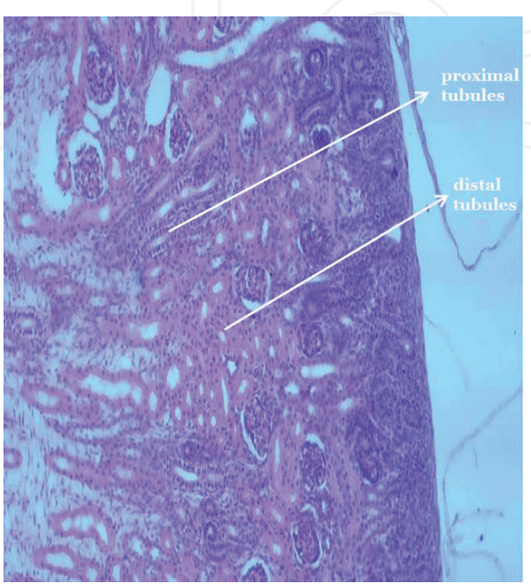


Figure 7.
Proximal and distal tubules of the kidney. Proximal tubules are the one which stained darker than the distal tubules. Hematoxylin–eosin staining (Dr. Alpaslan Gokcimen).

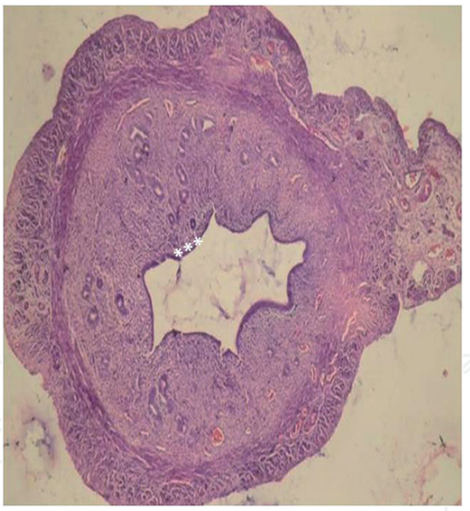


Figure 8.
Light microscopic image of the uterus with ciliated columnar epithelium. Epithelium is shown by stars. Hematoxylin–eosin staining (Dr. Alpaslan Gokcimen).

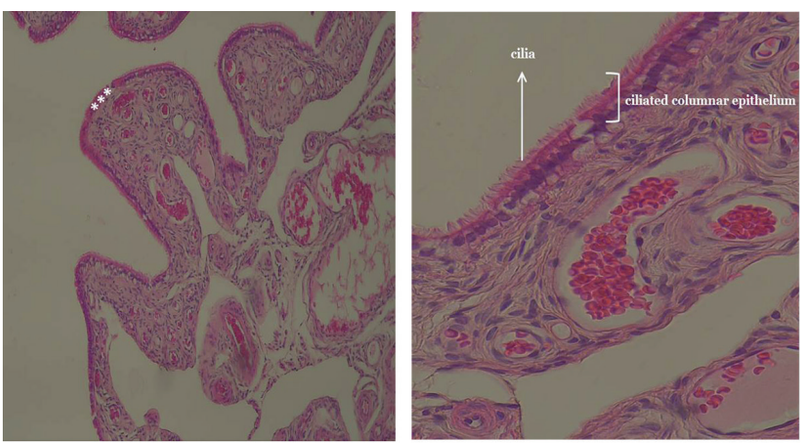


Figure 9.
(a) Light microscopic image of the tuba uterina with ciliated columnar epithelium. (b) Epithelium is shown by stars and between the lines. Hematoxylin–eosin staining (Dr. Alpaslan Gokcimen).

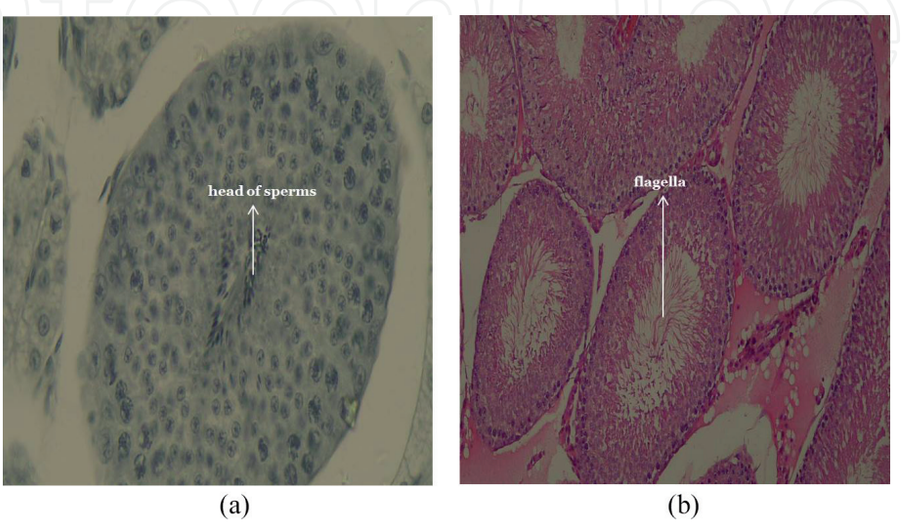


Figure 10.
(a) Light microscopic image of seminiferous tubules, testis. Head of sperms and their flagellas can be seen. \(b) The figures show the iron hematoxylin–eosin staining, respectively (Dr. Alpaslan Gokcimen).

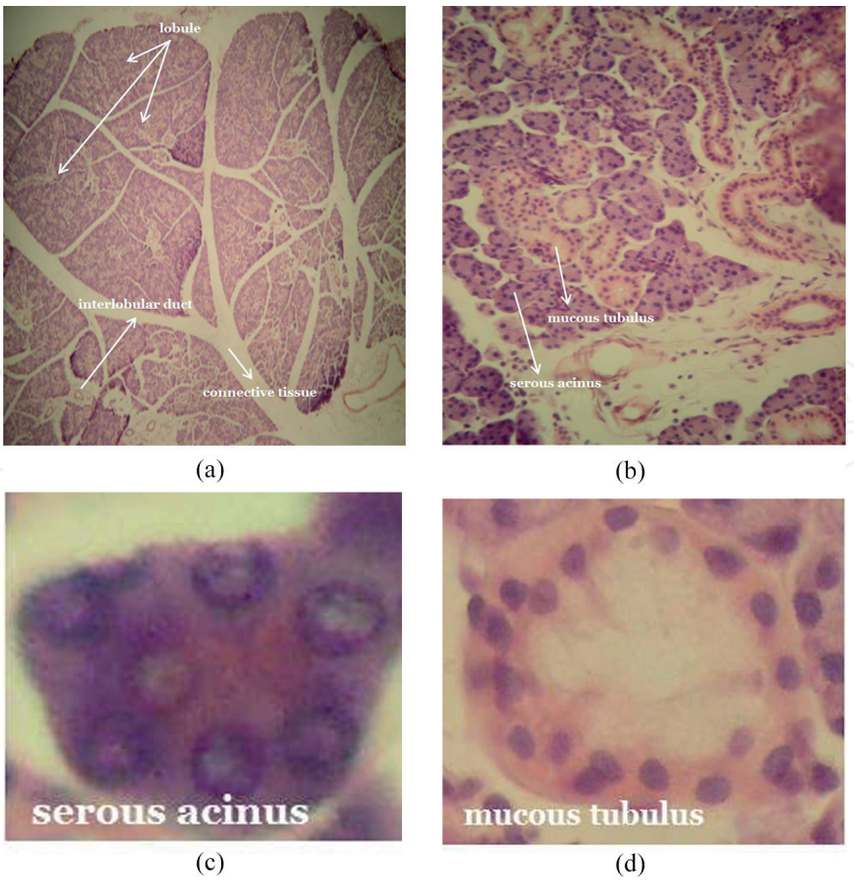


Figure 11.
(a) In the submandibular gland, irregular tight connective tissue is divided into lobules. Interlobular channels are seen in the connective tissue septa. (b) In the submandibular gland, serous acinus and mucous tubules are observed. Serous acini are predominant. (c) Serous acinus of the submandibular gland is observed. (d) The mucous tubule of the submandibular gland is seen (Dr. Alpaslan Gokcimen).

Type of epithelium	Places
Simple squamous epithelium	Parietal leaf of the kidney of Bowman capsule, serous membranes (peritoneum, pleura, mesothelium of the pericardium), vascular endothelium, type I alveolar epithelium laying lung alveoli.
Simple cuboidal epithelium	The proximal and distal of the kidney, the epithelium surrounding the colloid in the thyroid gland, the front face of the lens, the choroid plexus, the free face of the ovary, the most recent parts of the serous glands, the drainage channels of most glands and respiratory bronchioles. This type of epithelium allows the secretion and reabsorption of certain substances such as mucus, sweat, and enzyme.
Simple columnar epithelium	The stomach surface, small intestine and colon, gallbladder and uterine cavity.
Stratified squamous	This epithelium is divided into keratinized and non-keratinized. Keratinized epithelium is found in the skin and filiform papilla, non-keratinized epithelium is found in the lip, oral, pharynx, true vocal cords and vaginal epithelium.
Stratified cuboidal epithelium	Some sweat and salivary glands have this type of epithelium in the duct channels.
Stratified columnar epithelium	The female and male urethra, conjunctiva and large duct channels of some glands.
Transitional epithelium	In the urinary tract, from kidney and pelvis to a portion of the urethra. This epithelium is adapted to the short-term internal pressure

Table 1.
Types of epithelium and their locations [10].

1.3 Epithelium is classified as cover and secretory epithelium

1.3.1 Cover epithelium

The cover epithelium lines up the outer surface of the body and the inner surface of the hollow organs. The multilayer squamous epithelium, which forms the epidermis of the skin, has a protective effect by covering the outer surface of the body. Under the epithelium, there is a lamina propria and they are called as mucosa together and cover the inner surface of the cavities. Structures such as nasal mucosa, airway mucosa, digestive system mucosa, and urinary tract mucosa are good examples of laying lumen structures related to epithelial tissue [4–8].

1.3.2 Secretory epithelium

There are two types of glands—endocrine and exocrine.

a. The endocrine (hormone-producing) glands include the Langerhans islets of the pancreas, adrenal glands, and thyroid and parathyroid glands. Endocrine glands are supported by reticular fibers, arranged in cord or follicle. The most common cord shape is seen in the form of anastomoses around the capillaries or blood sinusoids. The produced hormone in the cell (adrenal gland, anterior lobe of the pituitary gland, parathyroid gland) is released through the appropriate signaling molecule or neural stimulus. In the follicular form of the endocrine gland, secretory cells surround the follicular cavity and store the produced hormone. The best example of this is the thyroid gland. Therefore, the endocrine glands do not have a discharge channel and deliver their secretions to the capillary network of the surrounding area [4].

b. Exocrine glands give their secretions to the external environment via a duct channel and are not rich in capillary network. Part of the pancreas, parotid, submandibular, and sublingual glands are the examples of exocrine glands [4–6, 8, 10].

There are irregular tight connective tissue sheath around the macroscopic glands which are parotid, submandibular, and sublingual gland. The connective tissue enters into the glands in the form of septa. The septa divide the gland into compartments. In the compartments, there may be acinus or tubules or both according to the type of the gland. Intralobulated duct channels are also included within the lobule. In the septa of connective tissue, interlobular channels are located. From these visible glands, the serous glands consist of acinus (alveolus), and the mucous glands are mucous tubules (**Figure 11a–d**). Exocrine glands can be subdivided into serous, mucous, and mixed glands according to the nature of the secretion they produce. Both serous- and mucous-secreting endpieces are covered with cubic epithelial cells which form intercalated (initial) ducts. Intercalated ducts combine to form the striated (intralobular) ducts. The intralobular ducts merge together to form the interlobular duct. These ducts are joined together and form "Stenson" in the parotid gland, "Wharton" in the submandibular gland, and "major sublingual" channels in the sublingual gland and open into the oral cavity. The most important features of intralobular ducts are the membrane folds extending from the cell basal to the nuclei. A large number of mitochondria were placed on the long axis of these folds. Such a location is particularly important for the salivary gland, which is functionally intense and consumes relatively more energy during its work. The parotid and the exocrine glands part of the pancreas are pure serous. The submandibular and sublingual glands are mixed glands [4–9].

1.3.3 Serous glands

The abundant zymogen granules in the serous glands are found in the upper part of the cell cytoplasm. Serous glands produce a smooth flow and protein secretion. The duct channels are narrower than the mucous glands. The nuclei of the cells are located in the middle and are round in shape. In the sections stained with hematoxylin–eosin, the basal part of the cell is stained with hematoxylin, and the apical portion is stained with eosin [4–8, 10] (**Figure 11c**).

1.3.4 Mucous glands

Mucous glands secrete carbohydrate properties. Since these granules are lost when preparing hematoxylin–eosin stained sections, these parts of the cells are often seen as empty. Therefore, these glands secrete in dense consistency and are lightly colored, and the discharge ducts are wider than the serous glands (**Figure 11d**) [4–9].

The epithelial cells of the gland are divided into three types according to the type of secretion:

1. Merocrine secretion: The secretory product is transported to the apical surface of the cell by vesicles. The vesicles are combined with the cell membrane and give their contents to the external environment by exocytosis. As in the pancreas, the most common form of secretion in the body is the merocrine type.

2. Apocrine secretion: While the secretory product is separated from the apical part of the cell membrane, it takes some cell membrane with it. This secretion occurs in the mammary glands, the apocrine of the skin, the ciliary (Moll's) of the eyelid, and the seromusin glands of the outer ear canal.

3. Holocrine secretion: Secretion product accumulates in the cell that continues to mature; then the secretory product is excreted into the outer environment together with the cell in which it is contained. The ovaries, the fat in the skin, and the Meibomian glands in the eyelid are the examples [4–8].

2. Structure of major salivary glands

a. The parotid gland is surrounded by irregular tight connective tissue called a capsule. The parts separated from the capsule move into the gland and are called septa. The septa separate the gland into lobules (**Figure 12a**). Each lobule is composed of spherical acini, which empty their serous secretion into intercalated ducts, from where it flows into striated (intralobular) ducts. We will see these ducts in the lobule. The intralobular ducts combine to form interlobular ducts. The interlobular ducts are located in the septa. Interlobular ducts leave the lobule and together with muscular arteries, veins, nerve, and lymphatic vessels. The interlobular duct channels are also known as excretory duct. Excretory ducts are emerged to form the main duct, "the Stenson." Round-shaped acinus is a part of the serous gland. The acinus (acinar cell) is formed by laying a single-layer cubic or prismatic epithelium on the basal lamina (**Figure 12b**). Fat cells which are one of the connective tissue cells are located between acini. Myoepithelial cells are located between epithelial cells and basal lamina. Contraction of myoepithelial cells accelerates the flow of saliva. Acinar secretion with serous content and secretion passes to intercalated ducts. Several intercalated ducts form an intralobular (striated) duct.

Prismatic-shaped epithelium is arranged on the basal lamina to form intralobular ducts. The basal cell membrane forms inward folds. A large number of mitochondria are located parallel to these basal invaginations. Basal invaginations are often seen in tissues and organs which allow water transport. The best example of this condition is the renal proximal and distal tubular epithelial cells and the striated duct in the salivary glands. Striated ducts have the ionic pump activity. These structures enable reabsorpsion of sodium and secretion of potassium and hydrogen ions, but reabsorption of sodium more than the potassium secretion. Thus, the secretion becomes hypotonic [7]. In this way, many substances which are reabsorbed from the apical are transported to the basal portion by active transport. The basal labyrinth is involved in transport of water and reabsorption of sodium from the saliva. Acinus and all excretory ducts are surrounded by a rich capillary network. The spherical-shaped nuclei of serous cells are in the middle of the cytoplasm. The organelles are well-developed granular endoplasmic reticulum and Golgi apparatus; the granular endoplasmic reticulum and ribosomes form ergastoplasm. Ergastoplasm is seen basophilic because it makes abundant protein synthesis. The ergastoplasm and Golgi complex together form secretory granules [4–10].

b. The submandibular gland as with the parotid gland has the irregular tight connective tissue that surrounds the organ and divides it into lobules (**Figure 11a**). The submandibular gland has both serous acinus and mucous tubules (the compound is a tubuloacinar gland), and the acinar cells were predominant. Hence, serous majority makes seromucous secretion. Acinus has the same structure as the parotid gland. The duct channels are also arranged in the same way as the parotid, and secretion is excreted in the oral cavity with "Wharton duct." The fat cells from connective tissue cells are located between the acinus and the mucous tubules. Myoepithelial cells are likewise located between the serous cells and the basement membrane and the basal membrane with mucous cells. A rich capillary system surrounds the organ. This system is accompanied by nerve vessels. Mucogenous granules are present in them because the mucous cells are pale. Since serous cells contain zymogen granules, they stained in dark color and have basophilic appearance. The ergastoplasm is dominant, and therefore, protein secretion is predominant to carbohydrate secretion [4–10].

c. The sublingual gland has the same structure as the other two major salivary glands. This gland is a mixed acinotubular. However mucous tubules are its predominant compound (**Figure 13a–d**). The duct channels of the gland, myoepithelial cells, and capillary and neural networks are as in the other two salivary glands, and salivary secretion reaches the oral cavity with a major sublingual duct. The fat cells are located between the functioning parenchyma [4–10].

d. The properties of macroscopic salivary glands are given in **Table 2**.

2.1 Structure of the lacrimal gland

The lacrimal gland is located on the upper lateral side of the orbit, beneath the conjunctiva (**Figure 14**). The lacrimal gland consists of several separate lobules formed by the tubuloacinar serous glands [7, 67]. The lacrimal gland is structurally similar to salivary glands. This gland was divided into lobules by irregular tight connective tissue. In the lobules, acinar cells and mucus tubules are located together. The acini have large lumens built with prismatic cells. Secretions produced in acinar and tubular structures are transmitted to the superior fornix

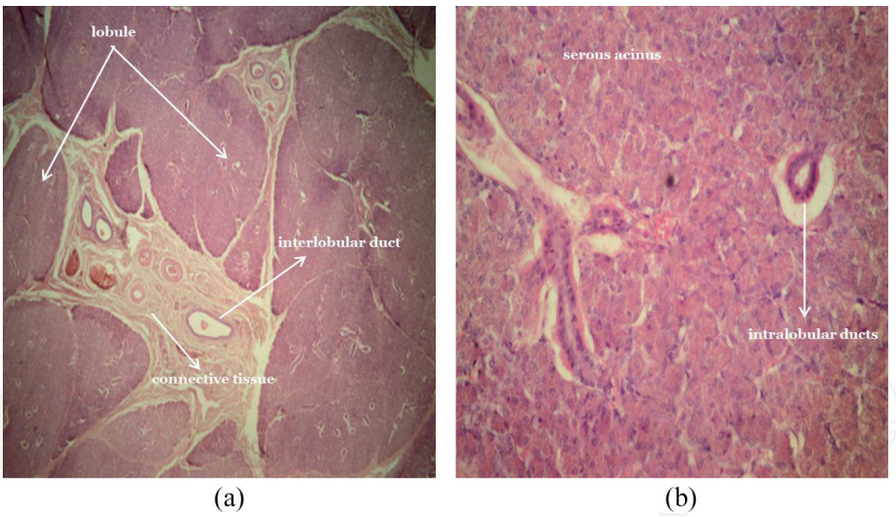


Figure 12.
(a) In the parotid gland, which is a pure serous gland, the irregular tight connective tissue is divided into the lobules. Interlobular ducts are seen. (b) Serous acinus and intralobular ducts are observed in the parotid section (Dr. Alpaslan Gokcimen).

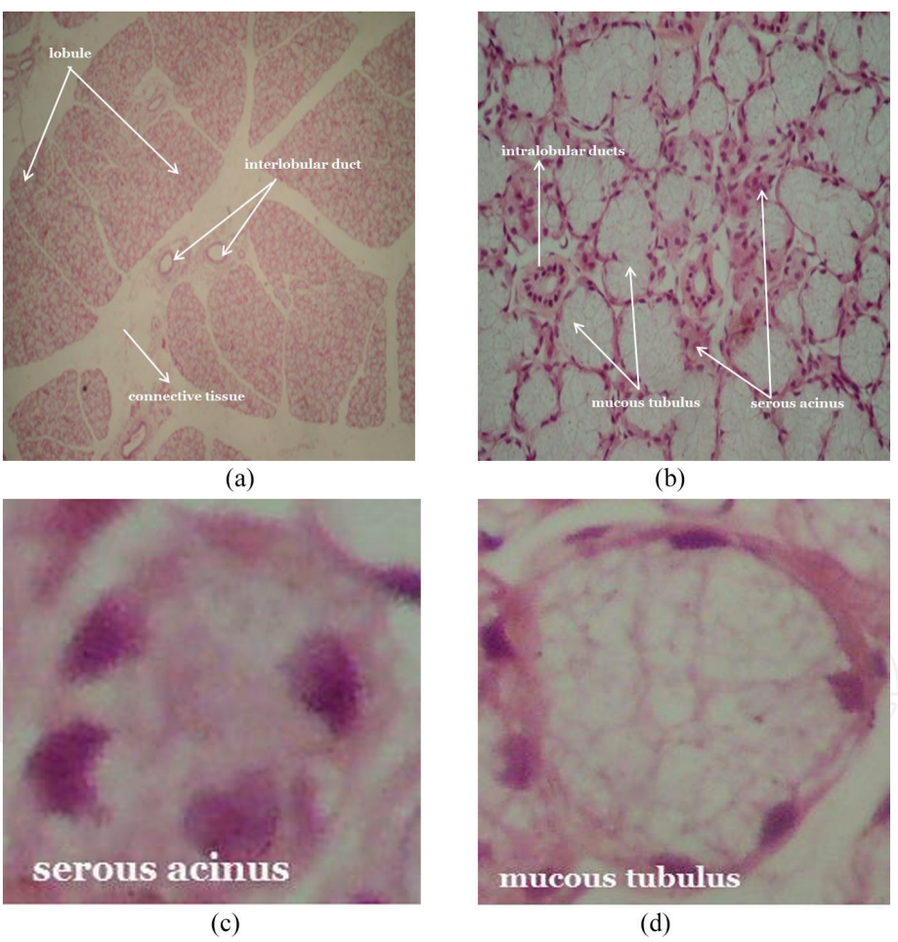


Figure 13.
(a) In the section stained with hematoxylin-eosin in the sublingual gland, the irregular tight connective tissue was divided into lobules. Interlobular ducts are observed. (b) The sublingual gland is a mixed gland consisting of mucous tubules and serous acini. Mucous tubules are predominant. (c) Serous acinus of the sublingual is observed. (d) The mucous tubule of the sublingual gland is seen (Dr. Alpaslan Gokcimen).

through the small duct channels. Tears drain in the inner aspect of the eye and then nasal cavity with the nasolacrimal duct (**Figures 15** and **16**), [10, 67]. The myoepithelial cells located between the epithelial cells and the basal lamina help this process [4, 7].

Name of the gland	Secretory content	Structural properties of gland	The opening of the excretory channels into the mouth
Parotid Pure serous	Zymogen granules	Stroma: Irregular tight connective tissue Parenchyma: Asinus (Compound alveolar gland)	Intercalated channel Intralobular channel Interlobuler channel Excretory channel Stenon channel
Glandula submandibularis	Mainly serous mixed (serous and mucous) Zymogen and mucinogen granules	Stroma: Irregular tight connective tissue and ve fat cells Parenchyma: Compound tubuloalveolar gland	Intercalated channel Intralobular channel Interlobuler channel Excretory channel Wharton channel
Glandula sublingualis	Mainly mucous mixed (serous and mucous) Zymogen and mucinogen granules	Stroma: Irregular tight connective tissue and ve fat cells Parenchyma: Compound tubuloalveolar gland	Intercalated channel Intralobular channel Interlobuler channel Excretory channel Major sublingual channel

Table 2.
Comparison of secretory content, structure and discharge channels of saliva glands.

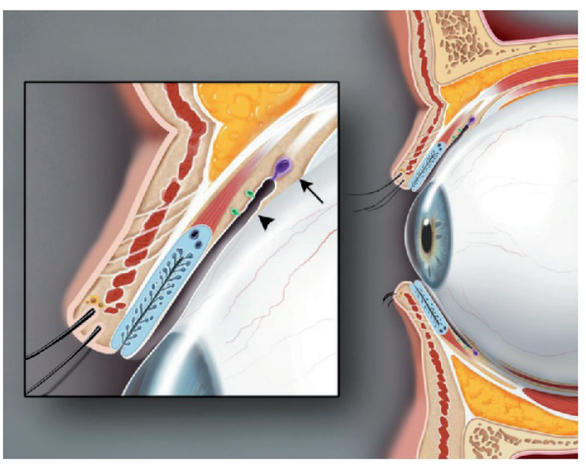


Figure 14.
Sagittal view of the upper and lower eyelids. The glands of Krause (arrow) are located in the superior conjunctival fornix. The glands of Wolfring (arrowhead) are found at the nonmarginal border of the tarsal plate [67] (with permission by Dr. Bhupendra Patel).

On the other hand, the lacrimal gland is made of several lobules separated by loose connective tissue. Each lobule consists of many acini, lined with columnar serous cells that produce a watery secretion. The central lumina of many units converge to form intralobular ducts, which unite to drain into 8–12 excretory ducts [11, 12].

2.2 The saliva and tear composition

Saliva is made up mostly of water (97–99.5%) originating from plasma of acinar cells [13]. The content of salivation has mucous, serous, or serous-mucous features. Mucous secretion is a thick form viscous fluid of highly glycosylated glycoproteins. Serous secretion is fluent and with clear consistency, forming thin, watery secretion containing proteins and glycoproteins. Seromucous form mixed secretin of intermediate thickness [14, 15]. Saliva is composed of a variety of electrolytes, including sodium, potassium, calcium, magnesium, bicarbonate, phosphates, immunoglobulins, proteins, enzymes, mucins, and nitrogenous products, such as urea and ammonia [16].

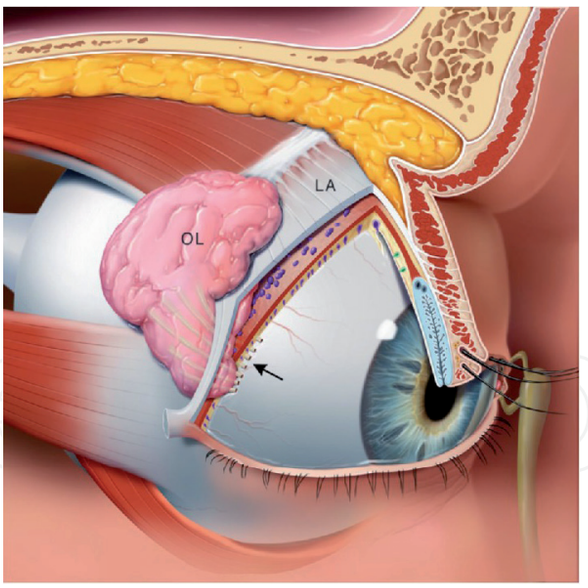


Figure 15.
Oblique view of the right orbit. Oblique view of the right orbit showing the main lacrimal gland divided into the orbital lobe (OL) and palpebral lobe by the lateral horn of the levator aponeurosis (LA). Note the excretory ducts coursing through the palpebral lobe and draining into the superior conjunctival fornix (arrow) [67] (with permission by Dr. Bhupendra Patel).

Histatins, the human salivary proline-rich proteins (PRPs) and statherin proteins are found in three kinds of protein saliva [17]. Histatins are a family of related neutral and basic histidine-rich peptides which are secreted mainly from parotid saliva and, to a lesser extent, submandibular saliva [18, 19]. A total of 12 salivary histatins have been isolated from human saliva.

The human salivary proline-rich proteins (PRPs) are a heterogeneous group of proteins that comprise about 70% of the parotid proteins. They are characterized by a predominance of the amino acids proline, glycine, and glutamic acid/glutamine (a total of 80% of all amino acids). PRPs are classified into three groups: acidic, basic, and glycosylated [20].

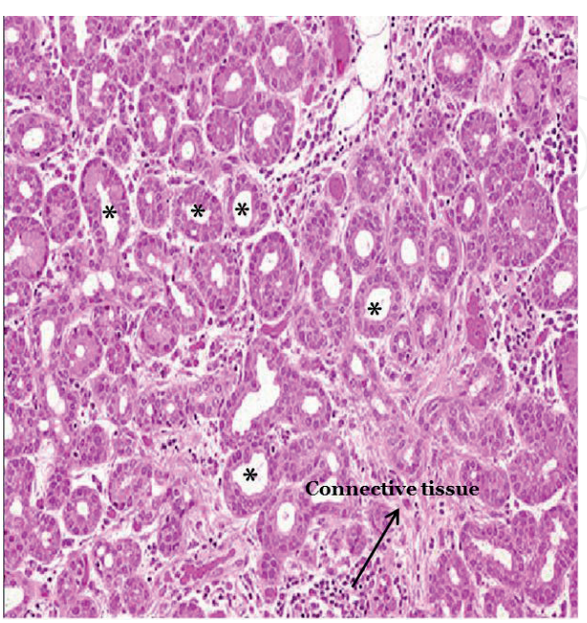


Figure 16.
Lacrimal gland histopathology. H&E staining of a normal lacrimal gland. The gland is composed of lobules separated by loose connective tissue. The lobules are composed of multiple acini lined by columnar secretory cells [67] (with permission by Dr. Bhupendra Patel).

Statherin is a low-molecular-weight acidic protein consisting of 43 amino acids. It is secreted by the parotid, submandibular, and von Ebner's salivary glands but is not present in labial saliva [21, 22].

Mucins are proteins that give the typical viscoelastic character to all the mucosal secretions (**Table 3**) [23–25].

Cystatins contain various kinds of endogenous proteinase inhibitors to regulate their protein metabolism or to protect tissues from proteolytic attacks by bacteria or viruses. Cystatins are important in the inhibition of several viruses, presumably by blocking necessary cysteine proteinases [26, 27].

Amylase is an abundant salivary component. It is produced mainly in the pancreas and salivary glands [17].

Secretory immune globulin A (sIgA) is a member of the adaptive immune response [28, 29]. IgA, which is a connective tissue cell and located in the stroma, is secreted into the saliva by plasma cells [7, 30, 31].

Lysozyme is called muramidase, for its antibacterial effect also. It is a widely distributed enzyme occurring in many human secretions (**Table 3**).

Extra-parotid glycoprotein (EP-GP), an acidic salivary glycoprotein, was originally isolated from submandibular and sublingual saliva and has been shown to have a strong affinity to hydroxyapatite. EP-GP can be localized only in the serous acinar cells of the submandibular glands and is absent in the parotid gland [32].

Kallikreins are a group of serine proteases that are found in glandular cells, neutrophils, and biological fluids. Glandular (tissue) kallikrein is found in a variety of tissues and biological fluids, including saliva [33].

	Saliva	**Tear fluid**
Mucins	++++	+
Asidic PRPs	++++	–
α-Amylase	++++	+
Basic PRPs	+++	–
Basic PRG	+++	–
Secretory IgA	+++	++++
Cystatins	++	+
Statherin	++	+
IgG	+	+
EP-GP	+	+
VEGh	+	++++
Histatins	+	–
Lysozyme	+	++++
Kallikrein	+	
Lactoferrin	+	++++
Lactoperoxidase	+	+
Haptocorrin	+	+
β-Microseminoprotein	+	+
IgM	+	+
Albumin	+	+
Zn-α2 Glycoprotein	+	+

Table 3.
Comparison of saliva and tear secretion [17].

Haptocorrin is an acidic glycoprotein that is present as a minor component in blood and other body fluids. It binds cobalamin (vitamin B12) but should be distinguished from two other vitamin B12-binding proteins: the intrinsic factor and transcobalamin. In human salivary glands, haptocorrin has been localized only in mucous acinar cells and in intercalated duct cells where it can be released via β-adrenergic receptor stimulation [34].

β-Microseminoprotein is present in various amounts in mucous secretions [17].

Table 3 shows the distribution of saliva and tear content [17].

Tear fluid is a complex solution intended to sustain the surface of the eye [35]. The lacrimal gland secretes tear fluid consisted mainly of water and electrolytes, and human tears have been disclosed to be isotonic with plasma [36]. In the secretion of the lacrimal gland, lysozyme, which is the antibacterial enzyme, contains electrolytes close to the plasma concentration [10].

Lysozyme is mainly present in saliva and tear fluid, and it plays an important role in the protection of the oral cavity and eyes from infection.

In addition to salivary secretions, statherin is also present in tear fluid and nasal and bronchial mucus. Statherin prevents excessive precipitation of calcium salts in these fluids [17].

Haptocorrin at the highest concentrations have been detected in tears and nasal secretion [34].

2.3 Function of saliva secretion

Saliva is mainly secreted by the parotid gland, submandibular gland, and sublingual gland [16, 37, 38]. In addition, the mucosa of the mouth, the tongue, and the soft palate also contains large amounts of microscopic salivary glands and helps secretion.

Different substances and factors in saliva have various functions. These functions are listed below:

1. Digestion: Basically, saliva is composed of water (~99.5%); electrolytes such as potassium, sodium, bicarbonate, calcium, phosphorus, and chloride; and various enzymes, among other important elements. Enzymes include amylase, lipase, lysozyme, immunoglobulins, thiocyanate, and urea. Alpha-amylase enzyme breaks the glycosidic linkages of carbohydrates 1–4 and provides digestion of carbohydrates [7, 30, 31, 39].

2. Lubrication and protection: Since the intraoral food is the first fragmentation place, the sensitive and delicate oral mucosa should not be damaged. For this purpose, saliva secretion protects the oral mucosa, and saliva contains mucins, which allow it to coat and lubricate [31, 40, 41]. The most important feature of salivary secretion is that it lubricates and protects the very sensitive oral mucosa. The best lubricating components of saliva are mucins. Mucins also cause an antibacterial function by selectively modulating the adhesion of microorganisms to oral tissue surfaces [42, 43]. Chewing, speech, and swallowing all are provided by the lubricating effects of mucins [43]. Glycosylated basic PRPs (PRGs) function as masticatory lubricants and have also been shown to interact with several types of microorganisms such as *Fusobacterium nucleatum* [44]. The physiological functions of the mucins include cytoprotection, lubrication, protection against dehydration, and maintenance of viscoelasticity in secretions [44, 45]. The viscoelastic properties of mucins play a role in lubrication and are considered to be an important characteristic of mucins [25, 46]. The capacity of mucins to protect epithelial surfaces depends largely

on their high content of oligosaccharides and their ability to form a gel layer together with other salivary proteins [47]. Kallikreins have been implicated in the regulation of local blood flow in salivary glands [48].

3. Buffering action and clearance: Bicarbonates, phosphates, and urea act to modulate pH and the buffering capacity of saliva. Saliva plays an active role in the sense of taste. We get the sense of taste with "gemma gustativa" known as taste buds. With microvilli of these taste buds, it is possible to bathe with saliva secretion continuously and thus to recognize different tastes. The saliva also forms a medium for the suspended food materials so that the environment for the stimulation of the taste buds is formed [30, 40, 41]. The acini of serous glands first produce an isotonic fluid; and when the secretion product reaches the ductus striata, it is absorbed back into the sodium and secreted into the secretory potassium and bicarbonate, resulting in salivary isotonic-hypertonic; and due to the high concentration of bicarbonate ions, it buffers the contents of the oral cavity [7, 49]. Statherin, together with the acidic PRPs, plays a role in the calcium homeostasis of saliva [50, 51].

4. Mucins play a role in mucosal surface coating, creating a chemical barrier, as a component of saliva decides on its viscosity, and are a part of the immune system and are important in the adherence of the microbial flora [52].

5. Maintenance of tooth integrity: Calcium, phosphate, and proteins work together as an antisolubility factor and modulate demineralization and remineralization [16]. The acidic PRPs bind Ca^{++} with a strength that indicates that they are important in pellicle formation and in maintaining supersaturation of ionic calcium in relation to phosphate ions in saliva [53]. Therefore, the acidic PRPs may be of biological significance in maintaining the calcium homeostasis of saliva and in preventing the formation of salivary stones [54]. Acidic PRPs inhibit apatitic crystal growth, suggesting that, when adsorbed on the tooth surface, they block specific mineral growth sites [55]. Statherin bound to the enamel surface can inhibit crystal growth of hydroxyapatite [17]. Cystatins have been reported to bind to hydroxyapatite [17] and therefore may play a role in acquired pellicle formation. Cystatins have been shown to inhibit hydroxyapatite crystal growth [56].

6. Antibacterial activity: Immunoglobulins, proteins, and enzymes provide antibacterial action [16]. With intraoral secretion flow, the mucosa of the mouth remains moist, and also food residues and microorganisms are sent into the lumen of the digestive tract. Saliva makes this function with proteins and peptides that will neutralize all kinds of microorganisms. Therefore, in-house flora and hygiene are formed in this way [30, 40, 41]. Macromolecule proteins and mucins serve to cleanse, aggregate, and/or attach oral microorganisms and contribute to dental plaque metabolism. Especially in dental caries, systemic microorganisms are effective, and saliva secretion reduces the risk of systemic infection [30, 40, 41]. Histatins possess antimicrobial properties against a few strains of *Streptococcus mutans* [29] and inhibit hemagglutination of the periopathogen *Porphyromonas gingivalis* [57, 58] and neutralize the endotoxic lipopolysaccharides located in the outer membranes of Gram-negative bacteria, which may be an important part of the host's defense system [59]. Histatins are potent inhibitors of the growth and germination of *Candida albicans* [17]. Another biological role of histatins in the oral cavity is the inhibition of the release of histamine from mast cells, suggesting that they play a role in oral

inflammation [59]. The PRPs are thought to serve as a defense mechanism against dietary tannins by forming precipitates, which reduce harmful effects of tannins [60]. Statherin adsorbed onto hydroxyapatite can promote adherence of a few oral bacteria, such as *P. gingivalis* and *Actinomyces viscosus* [61]. Mucins promote the clearance of various bacteria by masking their surface adhesins, a factor which inhibits bacterial colonization [17, 62]. Salivary immunoglobulin A (sIgA) associated response can be induced by local stimulation of mucosal membranes and secretory glands with antigens. Secretions of glands that are anatomically remote from the site of immunization, such as mammary, salivary, and lacrimal glands, can contain sIgA antibodies to antigens encountered through the respiratory or gastrointestinal tracts. Following this pathway, IgA-producing cells are induced by the common mucosal immune response, consisting of lymphoid tissues concentrated in special structures, such as the Peyer's patches [17]. The protective role of sIgA has been demonstrated in several experimental systems. Salivary immunoglobulin A can neutralize antigens (from viruses, toxins, and enzymes [63]. The enzymatic activity of lysozyme is able to cleave β-(l-4)-glycosidic bonds between muramic acid and N-acetylglucosamine residues in the peptidoglycan of the bacterial cell wall [64–66]. Haptocorrin play a role in the defense against microorganisms [17]. Beta-microseminoprotein has a protective function for the mucins by acting as a physiological inhibitor of endogenous mucin-degrading enzymes from leucocytes or by acting as an antibacterial agent [17].

7. Taste and digestion: Saliva plays an active role in the sense of taste. We get the sense of taste with "gemma gustativa" known as taste buds. With microvilli of these taste buds, it is possible to bathe with saliva secretion continuously and thus to recognize different tastes. The saliva also forms a medium for the suspended food materials so that the environment for the stimulation of the taste buds is formed [16, 30, 40, 41]. PRPs are involved in the bitter taste sensation [22].

2.4 Function of tear secretion

Tear secretion is extremely important for the health of the cornea and conjunctiva. Lacrimal secretions allow the creation of human tear film, made of the lipid, aqueous, and mucous layers. Tears, conjunctiva, and corneal epithelium are kept moist and remove foreign bodies. The tear film lubricates the surface of the eye, functions as a barrier against foreign body and microbial invasion, and supplies the avascular cornea with nutrients and oxygen [7, 67]. The tear covering the corneal surface in the form of a film layer is not homogeneous. Tear is mixture secretion and included the lacrimal glands, goblet cells, and eyelid tarsal gland secretions. The tear film layer includes proteins such as albumin and lactoferrin, enzymes such as lysozyme, lipids, metabolites, and electrolytes. The gland produces many proteins and aqueous fluid to add volume to the tear film. Furthermore, the lacrimal gland also secretes several bactericidal and fungicidal agents, akin to the salivary glands [11, 12]. Different isoforms of zinc α2-glycoprotein are present as a minor component in several body fluids, for example, serum, sweat, tears, and saliva [17].

"As a conclusion, the relation between the structure and function of exocrine glands is similar to other tissues. They produce normal secretions functionally as long as they maintain their normal shape and proper division of functions of individual cells. Saliva and tear secretion are necessary for survival, and these secretions are a barrier between environmental factors and internal organs. Tears

and saliva are often the first line of defense, part of immune system, and element of transmission of information. These secretions constitute an important and even indispensable part of the body's functionality."

Author details

Alpaslan Gokcimen
Medicine Faculty, Department of Histology and Embryology, Aydın Adnan Menderes University, Turkey

*Address all correspondence to: agokcimen@yahoo.com

References

[1] Moore LK, Persaud TVN. The Developing Human. 6th ed. Philadslphia: W.B Saunders Company; 1988. 87 p

[2] Basaklar CA, editor. Medikal Embriyoloji. 11th ed. İstanbul: Palme Yayıncılık; 2011; 67, 74, 82 p

[3] Irez T, Erkan M, editors. Embriyoloji. 6th ed. İstanbul: Istanbul Tıp Kitapevi; 2016. 30 p

[4] Gokcimen A. Genel Tıbbi Histoloji. 11th ed. Isparta: Süleyman Demirel Üniversitesi Basımevi; 2006. 14, 30, 177 p

[5] Junqueira LC, Carneiro J. Basic Histology. 10th ed. Rio de Janerio: Lange International Edition; 2003. 170, 385, 369, 375, 376 p

[6] Paulsen FD. Histology and Cell Biology. 4th ed. Rio de Janerio: Lange International Edition; 2000. 58 p

[7] Baykal B. Histoloji Konu Anlatımı ve Atlas. 6th ed. İstanbul: Palme Yayıncılık; 2014. pp. 113-121

[8] Gartner PL, Hiatt LJ. Color Textbook of Histology. 2nd ed. Philadslphia: W.B Saunders Company; 2001. 91-95, 325, 332, 333, 339 p

[9] Kristic RV. Human Microscopic Anatomy. 3rd ed. Switzerland: Springer-Verlag; 1991. pp. 183-191

[10] Young B, Heath JW. Functional Histology. 4th ed. Toronto: Churchill Livingstone; 2000. pp. 81-85

[11] Garg A, Zhang X. Lacrimal gland development: From signaling interactions to regenerative medicine. Developmental Dynamics. 2017;**246**(12):970-980

[12] Yao Y, Zhang Y. The lacrimal gland: Development, wound repair and regeneration. Biotechnology Letters. 2017;**39**:939-949

[13] Ship JA, Fischer DJ. The relationship between dehydration and parotid salivary gland function in young and older healthy adults. Journal of Gerentology. 1997;**52**(5):310-319

[14] Finkbeiner WE, Shen BQ, Widdicombe JH. Chloride secretion and function of serous and mucous cells of human airway glands. The American Journal of Physiology. 1994;**267**(2 Pt 1): 206-210

[15] Salivary Glands and Saliva. VIVO Pathophysiology. 2017. Available from: http://pediaa.com/difference-between-serous-and-mucous/

[16] Humphrey SP, Williamson RT. A review of saliva: Normal composition, flow, and function. The Journal of Prosthetic Dentistry. 2001;**85**(2):62-169

[17] Schenkels LC, Veerman EC, Nieuw Amerongen AV. Biochemical composition of human saliva in relation to other mucosal fluids. Critical Reviews in Oral Biology and Medicine. 1995;**6**(2):161-165

[18] Oppenheim FG, Xu T, McMillan FM, et al. Histatins, a novel family of histidine-rich proteins in human parotid secretion. The Journal of Biological Chemistry. 1988;**263**(16):7472-7477

[19] Khurshid Z, Najeeb S, Mali M, et al. Histatin peptides: Pharmacological functions and their applications in dentistry. Saudi Pharmaceutical Journal. 2017;**25**(1):25-31

[20] Carlson DM. Salivary proline-rich proteins: Biochemistry, molecular biology, and regulation of expression. Critical Reviews in Oral Biology and Medicine. 1993;**4**(3/4):495-502

[21] Hay DI, Smith DJ, Schluckebier SK, et al. Relationship between concentration of human salivary

statherin and inhibition of calcium phosphate precipitation in stimulated human parotid saliva. Journal of Dental Research. 1984;**63**(6):857-863

[22] Azen EA, Hellekant G, Sabatini LM, et al. mRNAs for PRPs, statherin and histatins in Von Ebner's gland tissues. Journal of Dental Research. 1990;**69**(11):1724-1730

[23] Marxena E, Mosgaarda MD, Pedersenb AML, et al. Mucin dispersions as a model for the oromucosal mucus layer in in vitro and ex vivo buccal permeability studies of small molecules. European Journal of Pharmaceutics and Biopharmaceutics. 2017;**121**:121-128

[24] Löfgren D, Johansson D, Bohlin L, et al. The challenge of measuring viscoelastic properties of human whole saliva to fit clinical purpose. International Journal of Oral and Dental Health. 2015;**1**(4):1-6

[25] Van der Reijden WA, Veerman EC, Nieuw Amerongen AV. Shear rate dependent viscoelastic behavior of human glandular salivas. Biorheology. 1993;**30**(2):141-152

[26] Kopitar-Jerala N. The role of cysteine proteinases and their inhibitors in the host-pathogen cross talk. Current Protein and Peptide Science. 2012;**13**(8):767-775

[27] Bjorck L, Grubb A, Kjellen L. Cystatin C, a proteinase inhibitor, blocks replication of herpes simplex virus. Virology. 1990:941-943

[28] Mestecky I, McGhee JR. Immunoglobulin A (IgA): Molecular and cellular interactions involved in IgA biosynthesis and immune response. Advances in Immunology. 1987;**40**:153-245

[29] MacKay BJ, Denepitiya L, Iacona VJ, et al. Growth inhibitory and bactericidal of human parotid salivary histidine-rich polypeptides on Streptococcus mutans. Infection and Immunity. 1984;**44**(3):695-701

[30] Schipper RG, Silletti E, Vingerhoeds MH. Saliva as research material: Biochemical, physicochemical and practical aspects. Archives of Oral Biology. 2007;**52**(12):1114-1135

[31] Carpenter GH. The secretion, components, and properties of saliva. Annual Review of Food Science and Technology. 2013;**4**:267-276

[32] Veerman EC, van den Keybus PA, Vissink A, et al. Human glandular salivas: Their separate collection and analysis. European Journal of Oral Sciences. 1996;**104**(4Pt1):346-352

[33] Wong RS, Madapallimattam G, Bennick A. The role of glandular kallikrein in the formation of a salivary proline-rich protein A by cleavage of a single bond in salivary protein C. The Biochemical Journal. 1983;**211**(1): 35-44

[34] Nexø E, Hansen M, Olsen PS, et al. Salivary secretion of rat haptocorrin and amylase is stimulated by vasoactive intestinal polypeptide. Digestion. 1987;**36**(1):18-23

[35] Rolando M, Zierhut M. The ocular surface and tear film and their dysfunction in dry eye disease. Survey of Ophthalmology. 2001;**45 Suppl 2**: 203-210

[36] Tiffany JM. Tears in health and disease. Eye. 2003;**17**:923-926

[37] Young B, O'Dowd G, Woodford P. Wheater's functional histology. In: A Text and Colour Atlas. 6th ed. Toronto: Churchill Livingstone; 2013. pp. 184-464

[38] Farnaud SJ, Kosti O, Getting SJ, et al. Saliva: Physiology and

diagnostic potential in health and disease. Scientific World Journal. 2010;**10**:434-456

[39] Karn RC, Malacinski GM. The comparative biochemistry, physiology, and genetics of animal co-amylase. Advances in Comparative Physiology and Biochemistry. 1978;**7**:1-103

[40] Dawes C, Pedersen AM, Villa A, et al. The functions of human saliva: A review sponsored by the World workshop on oral medicine VI. Archives of Oral Biology. 2015;**60**:863-874

[41] de Almeida PV, Grégio AM, Machado MA, et al. Saliva composition and functions: A comprehensive review. The Journal of Contemporary Dental Practice. 2008;**9**:72-80

[42] Slomiany BL, Murty VL, Poitrowski J, et al. Salivary mucins in oral mucosal defense. General Pharmacology. 1996;**27**:761-771

[43] Tabak LA. Structure and function of human salivary mucins. Critical Reviews in Oral Biology and Medicine. 1990;**1**:229-234

[44] Gillece-Castro BL, Prakobphol A, Burlingame AL, et al. Structure and bacterial receptor activity of a human salivary proline-rich glycoprotein. Journal of Biological Chemistry. 1991;**266**:17358-17368

[45] Levine MJ, Reddy MS, Tabak LA, et al. Structural aspects of salivary glycoproteins. Journal of Dental Research. 1987;**66**:436-441

[46] Gans RF, Watson GE, Tabak LA. A new assessment in vitro of human salivary lubrication using a compliant substrate. Archives of Oral Biology. 1990;**35**:487-492

[47] Bradway SD, Bergey EJ, Scannapieco FA, et al. Formation of salivary mucosal pellicle: The role of transglutaminase. The Biochemical Journal. 1992;**284**:557-564

[48] Berg T, Carretero OA, Scicli AG, Tilley B, Stewart JW. Role of kinin in regulation of rat submandibular submandibular gland blood flow. Hypertension. 1989;**14**:73-80

[49] Kondo Y, Nakamoto T, Jaramillo Y, et al. Functional differences in the acinar cells of the murine major salivary glands. Journal of Dental Research. 2015;**94**(5):715-721

[50] Hay DI, Schluckebier SK, Moreno EC. Saturation of human salivary secretions with respect to calcite and inhibition of calcium carbonate precipitation by salivary constituents. Calcified Tissue International. 1986;**39**(3):151-160

[51] Raj PA, Johnsson M, Levine MI, Nancollas GH. Salivary statherin. The Journal of Biological Chemistry. 1992;**267**:5968-5976

[52] Ruhl S. The scientific exploration of saliva in the post-proteomic era: From database back to basic function. Expert Review of Proteomics. 2012;**9**(1):85-96

[53] Gibbons RJ, Hay DI. Human salivary acidic proline-rich proteins and statherin promote the attachment of Actinomyces viscosus LY7 to apatitic surfaces. Infection and Immunity. 1988;**56**(2):439-445

[54] Saitoh E, Isemura S, Sanada K. Inhibition of calcium- carbonate precipitation by human salivary proline-rich phosphoproteins. Archives of Oral Biology. 1985;**30**:641-643

[55] Aoba T, Moreno EC, Hay DI. Inhibition of apatite crystal growth by the amino-terminal segment of human salivary acidic proline-rich proteins. Calcified Tissue International. 1984;**36**(1):651-658

[56] Fujikawa H, Matsuyama K, Uchiyama A, et al. Influence of salivary macromolecules and fluoride on enamel lesion remineralization in vitro. Caries Research. 2008;**42**:37

[57] Gusman H, Travis J, Helmerhorst EJ, et al. Salivary histatin 5 is an inhibitor of both host and bacterial enzymes implicated in periodontal disease. Infection and Immunity. 2001;**69**(3):1402-1408

[58] Murakami Y, Tamagawa H, Shizukuishi S, et al. Biological role of an arginine residue present in histidine-rich peptide which inhibits hemagglutination of Porphyromonas gingivalis. FEMS Microbiology Letters. 1992;**98**:201-204

[59] Sugiyama K, Ogino T, Ogata K. Rapid purification and characterization of histatins (histidine-rich polypeptides) from human whole saliva. Archives of Oral Biology. 1990;**35**:415-419

[60] Mehansho H, Butler LG, Carlson DM. Dietary tannins and salivary proline-rich proteins: Interactions, induction and defense mechanisms. The Annual Review of Nutrition. 1987;**7**:423-440

[61] Kim SG, Hong JY, Shin SI, et al. Prevalence of *Porphyromonas gingivalis* fimA genotypes in the peri-implant sulcus of Koreans assessed using a new primer. Journal of Periodontal and Implant Science. 2016;**46**(1):35-45

[62] Toribara NW, Gum JR, Culhane PJ, et al. MUC-2 human small intestinal mucin gene structure-repeated arrays and polymorphism. Journal of Clinical Investigation. 1991;**88**:1005-1013

[63] Palomares O, Akdis M, Fontecha M, et al. Mechanisms of immune regulation in allergic diseases: The role of regulatory T and B cells. Immunological Reviews. 2017;**278**(1):219-236

[64] Goodman H, Pollock JJ, Katona LI, et al. Lysis of Streptococcus mutans by hen egg white lysozyme and inorganic sodium salts. Bacteriology. 1981;**146**:764-774

[65] Ito T, Yoshida Y, Shiota Y, et al. Effects of lectins on initial attachment of cariogenic Streptococcus mutans. Glycoconjugate Journal. 2018;**35**(1):41-51

[66] Lenander-Lumikari M, Loimaranta V. Saliva and Dental Caries. Advances in Dental Research. 2000;**14**:40-47

[67] Conrady CD, Joos ZP, Patel BC. Review: The lacrimal gland and its role in dry eye. Journal of Ophthalmology. 2016;**2016**:7542929. DOI: 10.1155/2016/7542929. [Epub 2016 Mar 2]