

Human Oral Mucosa

Development, Structure, and
Function

Edited by

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Homologies in structure and function among mucosae: oral, esophageal, and vaginal mucosa

The oral mucosa shares much in common in terms of structure and function with the esophagus and vagina. As in the oral cavity, the soft tissues of the esophagus and vagina are everywhere covered by a stratifying squamous epithelium which is normally non-keratinized, although in the vagina this may tend toward parakeratinization at the midpoint of the menstrual cycle (Nauth, 1993). The epithelium is supported by an elastic connective tissue lamina propria, and there is an encircling smooth muscle layer. This structure will be described in more detail below.

9.1 ESOPHAGUS

The esophagus extends from the upper esophageal sphincter, which delineates it from the oropharynx, to the lower

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esophageal sphincter, representing the junction with the gastric mucosa (Gavaghan, 1999). The organization of the tissues reflects their function of transporting ingested food from the oral cavity to the stomach. The extensibility and motility of the mucosal lining is reflected in the presence of a non-keratinized mucosal surface resembling that of the oral lining mucosa. This is separated from the submucosa by a muscularis mucosa, consisting of a smooth muscle and elastic fiber layer, which may serve to reduce the excursion of the luminal lining mucosa as a result of the contractions of the external esophageal muscle, consisting of circular and transverse layers of striated or smooth muscle (Fig. 9.1).

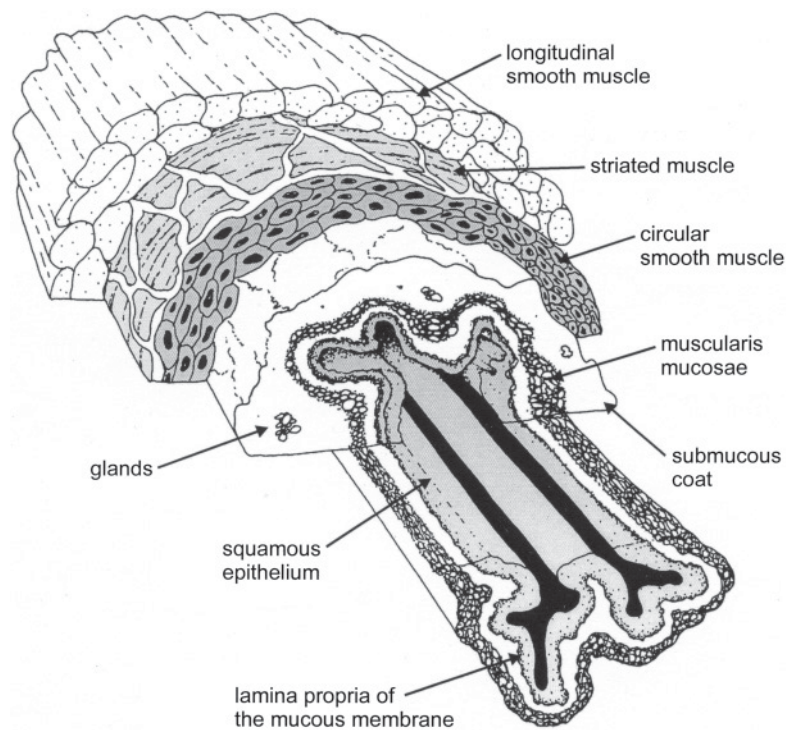


Figure 9.1 Drawing to show the organization of the tissues of the human esophageal lining. (Modified from Gavaghan, Copyright 1999, with permission from Elsevier.)

9.2 VAGINA

The vagina extends from the vestibule (vaginal introitus) to the uterus where it surrounds the vaginal portion of the uterine cervix, a short distance from the external orifice of the uterus. The vagina consists of an internal mucous membrane with a lamina propria that contains numerous elastic fibers. These extend toward the external smooth muscle coat.

The mucous membrane is continuous above with that lining the uterus. Its inner surface presents two longitudinal ridges, one on its anterior and one on its posterior wall; from these ridges, numerous transverse ridges or rugae extend outward on either side. The epithelium covering the mucous membrane is a non-keratinized stratified squamous tissue. The submucous tissue is very loose and contains numerous large veins together with smooth muscular fibers derived from the muscular coat, which consists of two layers: an external longitudinal layer, which predominates, and an internal circular layer. The longitudinal fibers are continuous with the superficial muscular fibers of the uterus. External to the muscular coat is a layer of fibrous connective tissue representing the adventitia (Fig. 9.2).

9.3 ORGANIZATION OF THE TISSUES OF ESOPHAGUS AND VAGINA

As pointed out in the first chapter of this volume, the major difference between the mucosa of the oral cavity and esophagus and the rest of the gastrointestinal tract is in the organization of the epithelium, which reflects the different functions of these regions. The lining of the stomach and the small and large intestine consist of a simple epithelium composed of only a single layer of cells which facilitates absorption across the tissue. The esophagus and vagina are lined by a stratified epithelium (Fig. 9.3) composed of multiple layers of cells which show a non-keratinized pattern of differentiation, although this may tend toward parakeratinization in vagina during the midpoint of the menstrual cycle

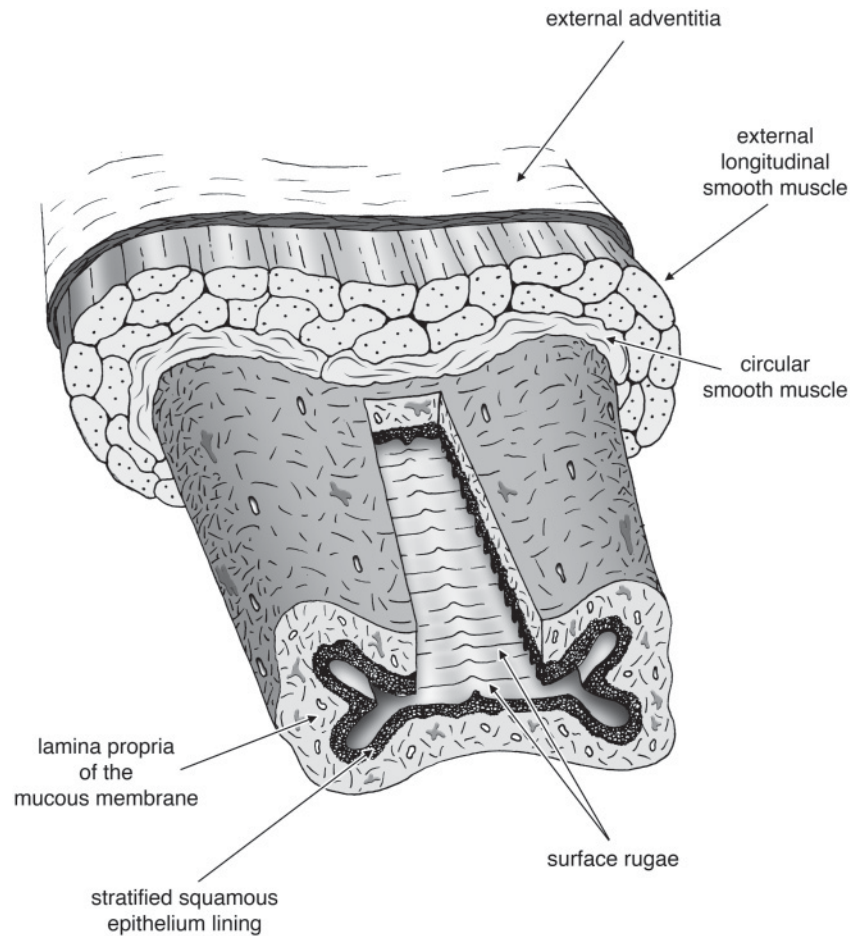


Figure 9.2 Drawing to show the organization of the tissues of the human vagina. (Original drawing by Sean Kelley.)

(see below). The mucosal lamina propria consists of cells, blood vessels, neural elements, and fibers embedded in an amorphous ground substance. The lamina propria shows regional variation in the proportions of its constituent elements, particularly in the concentration and organization of the fibers.

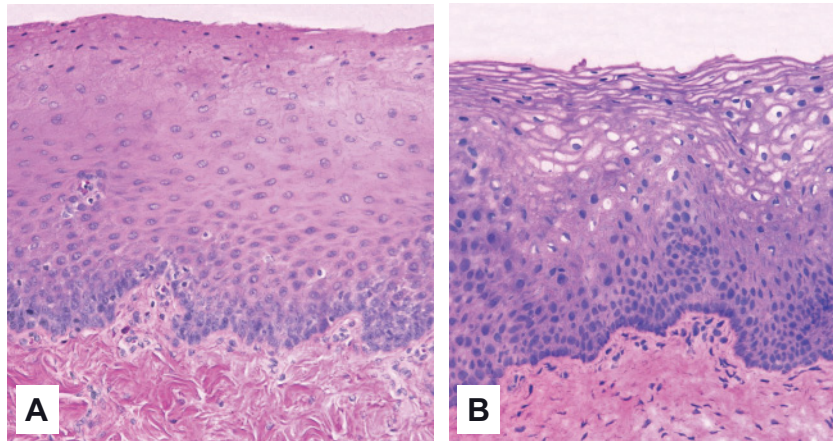


Figure 9.3 Histological sections showing the structure of the non-keratinized mucosa of (A) esophagus and (B) vagina. Note the similarities with the oral lining mucosa (Fig. 3.1C).

The glandular component of oral and esophageal mucosa is represented primarily by the minor salivary glands. These are concentrated in the submucosa, and the secretions reach the mucosal surface via small ducts. In the esophagus, the minor salivary glands can produce a secretion with high bicarbonate concentration to neutralize refluxing stomach acid (Long and Orlando, 1999). The vagina contains no true glands and the surface moisture is derived from those in the cervix and uterus and from Bartholin's glands at the introitus.

In the esophagus and vagina, there are nodules of lymphoid tissue consisting of areas extensively infiltrated by lymphocytes and plasma cells. Because of their ability to mount immunologic reactions, such cells play an important role in combating infections.

9.3.1 Epithelial differentiation

Keratinocytes of the esophagus and vagina are capable of division so as to maintain a constant epithelial population as cells are shed from the surface. Tissue homeostasis requires

differentiation and desquamation at the epithelial surface to be matched by cell division. Many factors, including aging and disease, can alter this balance so that an epithelium may become thicker (hyperplastic) or thinner (atrophic) than normal; in the vagina the fluctuations in estrogen production during the menstrual cycle also exert an effect on proliferation and differentiation of the epithelium (Schaller, 1990).

The progenitor cells are situated in the lower two to three cell layers; in the vagina the majority of proliferative activity take place in the suprabasal layer (Averette et al., 1970). Epithelial proliferation in the esophagus and vagina is controlled by the same biologically active substances, most of which are peptide growth factors collectively termed cytokines, as in the oral mucosa (see Chapter 3). Estimates of the rate of cell proliferation in various epithelia indicate that in general, the rate is higher for cells in thin non-keratinized regions such as floor of mouth than for thicker keratinized regions such as palate and skin (Thomson et al., 1999; see Table 9.1).

Apart from measurements of the number of cells in division (labeling index), it is also possible to estimate the turn-

Table 9.1 Epithelial cell proliferation and turnover in selected tissues.

Tissue region	Mean labeling index % ^a	Median turnover time (days) ^b
Small intestine	—	4
Floor of mouth	12.3	20
Buccal mucosa	10.2	14
Esophagus	—	21 ^c
Vagina:		
—premenopause	8.2	33
—postmenopause	6.2 ^d	27 ^d
Hard palate	7.2	24
Skin	—	27

^aBjarnason et al. (1999).

^bThomson et al. (1999).

^cSquier et al. (1976).

^dAverette et al. (1970).

over time; it can be seen that values for these parameters for the esophagus and vagina indicate a lower labeling index (and a slower turnover time) than for other non-keratinized human oral epithelia. However, because of the effect of estrogen during the menstrual cycle, cell proliferation increases in the vagina up to day 14 (midcycle and ovulation). This has been claimed to be associated with an increase in the number of desmosomes so that the epithelium becomes more cohesive and thickens from approximately 20 layers on day 10 to 45 on day 14 (Okada, 1990). Patton et al. (2000) have shown a significant decrease in number of layers between days 1–12 and days 19–24 although Ildgruben et al. (2003) were unable to detect any significant change in thickness between the follicular (days 1–14) and luteal phases (days 15–28). In terms of epithelial differentiation, there is an increase in glycogen within the cells and a tendency to parakeratinization. The reduction in estrogen levels at menopause results in a lower labeling index (see Table 9.1) and a thinner, atrophic mucosa (reviewed by Farage and Maibach, 2006). Thompson et al. (2001) have stated that the number of cell layers in postmenopausal vaginal epithelium ranges from 19 to 32.

Apart from the cyclical changes associated with menstruation, the principal patterns of differentiation are similar in the esophagus and vagina and resemble those of non-keratinized oral epithelium. During differentiation there is an accumulation of lipids and of cytokeratins in the keratinocytes, but this is less evident, and the change in morphology is far less marked than in keratinizing epithelia. The mature cells in the outer portion of non-keratinized epithelia become large and flat and possess a cross-linked protein envelope, but they retain nuclei and other organelles, and the cytokeratins do not aggregate to form bundles of filaments as seen in keratinizing epithelia. There are similarities in the types of cytokeratins in non-keratinized epithelia, but differences are evident between the esophagus and vagina (Table 9.2).

As cells reach the upper one-third to one-quarter of the epithelium, membrane-coating granules become evident at the superficial aspect of the cells and appear to fuse with the

Table 9.2 Cytokeratins in non-keratinized mucosae.

Tissue region	Cytokeratins
Non-keratinized oral epithelium	4, 5, 14, 19
Esophagus	4, 13, 15, 19
Vagina	4, 5, 6, 13, 14, 15, 16, 19

Sources: Barret et al. (1998); Bosch et al. (1988); Moll et al. (1983); Tomakidi et al. (1998).

Table 9.3 Permeability of non-keratinized mucosa to water.

Tissue region	Flux (dpm/cm ² /min) $\pm$ SD for tritiated water
Hard palate (keratinized)	1706 $\pm$ 93
Buccal mucosa	1963 $\pm$ 72
Esophagus	1220 $\pm$ 66
Vagina	4155 $\pm$ 70

Sources: Squier et al., 2008 and unpublished data.

plasma membrane so as to extrude their contents into the intercellular space. The membrane-coating granules found in non-keratinizing oral epithelia have already been described (Chapter 3); they have often been referred to as cored granules because of their appearance in transmission electron micrographs. Such granules have been observed in the esophagus (Hopwood et al., 1978), the vagina (Thompson et al., 2001), as well as the uterine cervix (Grubb et al., 1968). Only a small proportion of the granules in non-keratinized epithelium contain lamellae, which may be the source of short stacks of lamellar lipid scattered throughout the intercellular spaces in the outer portion of the epithelium (Wertz et al., 1993). It is the absence of organized lipid lamellae in the intercellular spaces that probably accounts for the greater permeability of these tissues non-keratinized tissues, although the least permeable of these do not differ greatly from the permeability of some regions of keratinized epithelium (Table 9.3), indicating the effectiveness of the barrier in non-keratinized mucosa.

The concept of epithelial homeostasis implies that cell production in the deeper layers will be balanced by loss of cells from the surface. The available evidence suggests a programmed breakdown of cell adhesion molecules, involving both lipids and proteins, probably by intercellular enzymes that might originate in the extruded membrane-coating granules (Madison et al., 1998). Regardless of the nature of the process, the rate at which cells leave the surface represents a defense mechanism by rapidly clearing the substrate to which many microorganisms adhere so that they are unable to produce toxic effects or invade.

9.4 NON-KERATINOCYTES IN ESOPHAGEAL AND VAGINAL MUCOSA

As already described in Chapter 3, non-keratinocytes represent a variety of different cell types, including pigment-producing cells (melanocytes), Langerhans cells, Merkel cells, and inflammatory cells such as lymphocytes.

Melanin is produced by the specialized pigment cells called melanocytes, which are situated in the basal layer of the epithelia. Cells with these characteristics have frequently been described in esophageal mucosa, as has melanin pigmentation and melanotic lesions (Chang and Deere, 2006; Yamazaki et al., 1991). Melanocytes, melanin pigmentation, and melanotic lesions are rarely observed in vaginal and cervical mucosa (Toncini and Innocenti, 1984).

Langerhans cells are another type of dendritic cell that are frequently present in the suprabasal layers of epidermis, oral, esophageal, vaginal, and cervical epithelium (Squier and Finkelstein, 1998; Terris and Potet, 1995). In vaginal and cervical epithelium, the numbers of Langerhans cells are highly variable, but this variation is not associated with stages of the menstrual cycle (Patton et al., 2000; Poppe et al., 1998).

The Merkel cell is situated in the basal layer of the oral and esophageal epithelium and epidermis (Harmese et al., 1999; Squier and Finkelstein, 1998). It has been observed in

association with the rich innervation of the vagina after immunochemical staining (Hilliges et al., 1995). This arrangement is in accord with neurophysiological evidence suggesting that Merkel's cell is a sensory cell responding to touch.

9.5 INFLAMMATORY CELLS

When sections of epithelium taken from clinically normal areas of mucosa are examined microscopically, a number of inflammatory cells can often be seen between the keratinocytes. These cells are transient and the cell most frequently seen is the lymphocyte, although the presence of polymorphonuclear leukocytes is not uncommon. In vagina, there is a widening of the intercellular spaces after ovulation facilitating the migration of leukocytes from the lamina propria (Okada, 1990). Lymphocytes present in vagina are predominantly CD4 or CD8 (Ildgruben et al., 2003) and, as for Langerhans cells, do not seem to vary in frequency during the stages of the menstrual cycle (Patton et al., 2000).

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