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Epithelium - An Overview and an Insight on Gingival Epithelium: A Literature Review

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ABSTRACT

Epithelium is comprised of cells that cover the exterior surfaces of the body and line both the internal closed cavities of the body and those that communicate with the exterior.
The cells forming epithelium are in close apposition with one another, they may be arranged in multiple layers. In some locations cells are found aggregated in close apposition with one another but lack free surface. They are called epithelial like or epithelioid tissues. It is a tissue composed of a layer of cells which lines both the outside (skin) and the inside (e. g. intestine) of organisms. The epithelium serves as a barrier to protect the body from pathogens and functions to maintain homeostasis. In this review we will focus on organization and function of the epithelium with its distinctions among epithelia which includes fundamentals of organization, adhesion, polarity, and mechanical coordination and its role in oral mucous membrane.

Keywords: Epithelium, cell junctions, gingival epithelium,basal lamina.

INTRODUCTION

Epithelia (Greek- epi-upon + thele, nipple) line all external and internal surfaces of the body and all substances that enter or leave an organ must cross this type of tissue). Epithelial tissues are composed of closely aggregated polyhedral cells adhering strongly to one another and to a thin layer of extracellular matrix (ECM), forming cellular sheets that line the cavities of organs and cover the body surface. The epithelial structures that accomplish this and other tissue-specific functions vary widely and can be classified according to cell shape, orientation, and interactions with one another. While these diverse morphologies correspond to divergent specialized roles, most epithelia also share many of the following core functions,[1] which include protection, sensation, transport, secretion, clearance, and repair. Epithelial function is characterized by the polarization of the epithelial cell, the formation of specific plasma membrane domains (PLMs), the localization of target proteins, and the organization of the cell's cyto-skeletal system. Coordinated action of trans membrane transport proteins (TMTPs) as well as trans paracellular flux (e.g., the tight junction) facilitate vectorial transport. Disorders of epithelial function can cause and contribute to disease.

The principal functions of epithelial tissues include the following:

- Covering, lining, and protecting surfaces (e.g.-epidermis)
- Absorption (e.g., the intestinal lining)
- Secretion (e.g., parenchymal cells of glands) [2]

Embryology

- Embryology includes development, differentiation, morphogenetic processes (cell migration, transformation, folding,

invagination, evagination, apoptosis, etc.) and controlled growth.[3]

- As early as the morula stage, desmosomes and gap junctions are essential to maturation from the solid morula to the hollowed-out blastocyst. As the blastocyst develops further, it gives rise not only to the tissues and organs of the embryo but also to a number of structures that support the embryo and help it to acquire nutrition.
- Eventually, three germ layers develop and each gives rise to unique epithelia: The skin, renal tubules, and gut are formed from ectoderm, mesoderm, and endoderm, respectively.[4]

These are the three-germ layers. All tissues of the body are derived from one or more of these layers. Functional differentiation of cells of germ layers and organogenesis takes place during the embryonic period. The contributions by various germ layers are:

Ectoderm: gives rise to the epithelium of the skin (the outer epithelium). The ectoderm differentiates into surface ectoderm, neuroectoderm and neural crest cells.[5]

Endoderm: from endoderm originates the epithelial lining of the digestive tract, respiratory system. [6]

Mesoderm: Gives origin to the lining enclosing the peritoneal cavities. These peritoneal linings are most often called as Mesothelium. The mesoderm derived lining of blood vessels, lymphatics and heart are commonly known Endothelium. The intraembryonic mesoderm is divided into three parts, i.e., Paraxial, intermediate and lateral plate mesoderm. The musculoskeletal, blood vascular and parts of urinary and genital systems develop from them. [7]

CLASSIFICATION

The modern view is that the human body is composed of tissues and body fluids, and that there are four basic tissue types[TABLE-1],

The older concepts described these body parts as structural and functional parts of organs, whereas it is now common place to consider a tissue to be a grouping of similar cells with a variable amount of extracellular matrix. The development of the microscope as a useful tool in human anatomy shifted focus from tissues to cells and led to changes in the definition of tissue and the classification of tissues.

The four basic tissues of the human body are derivatives of germ layers. They are as follows:

1. Epithelial tissue: Epithelium consists of cells arranged in the form of continuous sheets. Epithelia line the external and internal surfaces of the body and of body cavities.
2. Connective tissue: Connective tissue proper includes loose connective tissue, dense connective tissue and adipose tissue. Blood, cartilage and bone are special connective tissues.
3. Muscular tissue: This is of three types:
   1) skeletal
   2) cardiac
   3) smooth.
4. Nervous tissue: This tissue consists of neurons (nerve cells), nerve cell processes (axons and dendrites) and cells of neuroglia.[8]

TABLE-1 Characteristics of four types of tissues.[9]

Tissue	Cells	ECM	FUNCTIONS
Epithelial	Aggregated polyhedral cells	Small amount	Lining surface or body cavities; glandular secretion
Connective	Fixed & wandering cells	Abundant	Support &protect
Muscle	Elongated & contractile	Moderate	Body movements
Nervous	Elongated & fine processes	Very small	Transmission of nerve impulses.

FUNCTIONS OF EPITHELIUM

Sensation: Specialized epithelial tissue containing sensory nerve endings is found in the skin, eyes, ears, nose and on the tongue. The whole subepithelial space, including glands and blood vessels, is densely innervated by afferent somatosensory nerve endings, which functions are detecting thermal, mechanical, and chemical stimuli, and releasing mediators that interact with other cells.[10]

Protection: Epithelial cells from the skin protect underlying tissue from mechanical injury, harmful chemicals, invading bacteria and from excessive loss of water. Each organ resides in a unique environment. For example, the skin is regularly exposed to physical abrasion that can remove one or more epithelial layers. This would be an insurmountable challenge for the epithelium, which is composed of a single epithelial layer, but is easily managed by the multilayered stratified skin epithelium.[11]

Absorption: Epithelial cells form barriers that separate distinct compartments, one of which is often the external environment. The permeability of these barriers varies, such that epithelia can be classified as either leaky or tight. Certain epithelial cells lining the small intestine absorb nutrients from the digested food.[12]

Secretion: In glands, epithelial tissue is specialized to secrete specific chemical substances such as enzymes, hormones and lubricating fluids. Epithelia transport ions, water, and other substances that hydrate the surface. At many sites, the epithelial cells also elaborate mucins to aid in surface lubrication and support mucosal homeostasis. For example, mucins secreted by intestinal goblet cells contribute significantly to the mucosal barrier and, among other functions, limit contact between microbes and the epithelium. lacrimal and salivary gland secretions that lubricate the eye and oral cavity, respectively.[13]

Excretion: Epithelial tissues in the kidney excrete waste products from the body and reabsorb needed materials from the urine. Sweat is also excreted from the body by epithelial cells in the sweat glands. Many epithelial cells have cilia, which aid in moving substances within the lumen and may also sense fluid pressure and flow. Ciliated columnar epithelial cells are essential for transport of mucus containing entrapped bacteria and pollutants out of the airways.[14]

Diffusion: Many epithelia are involved in active and passive transcellular and passive paracellular transport. In many cases, this is facilitated by morphological specializations that markedly increase membrane surface area, such as intestinal microvilli. Simple epithelium promotes the diffusion of gases, liquids and nutrients. Because they form such a thin lining, they are ideal for the diffusion of gases (e.g., walls of capillaries and lungs).[15]

CHARACTERISTICS

Epithelial cells are located throughout the body and have many different functions based on morphology and location. Cells have a structural polarity that causes three distinct regions or domains (apical, basal, and lateral).

Epithelial cells:

- Located on the basal lamina
- Are avascular (contain no blood vessels)
- Have almost no extracellular space
- Renew basally
- Are derived from all three germ layers.

Classification

Epithelial cells are organized according to their shape and number of layers.

Simple epithelial cells contain one layer, whereas stratified cells contain two or more layers. Pseudostratified epithelial cells contain only one layer of cells, but the cells are of different sizes, so cells appear to be stratified or layered. In regards to the shape of epithelial cells, there are three main shapes, squamous, cuboidal, columnar. Squamous cells are flat sheet-like cells, cuboidal cells are cube-like with an equal width, height, and depth, and columnar cells

are taller than they are wide making them rectangular.[16]

Epithelial cells are classified by the following three factors.[TABLE-2][17]

- Shape
- Stratification (number of layers)
- Specialization

TABLE-2 Epithelial classiffication

SHAPE	STRATIFICATION	SPECIALIZATIONS
Squamous	Simple	Keratinized
Cuboidal	Stratified	Non keratinized
Columnar	Pseudostratified with cilia	Non-ciliated
Transitional		Ciliated

1. Based on shape and number of cell layers, Epithelium is further divided
   I. Simple squamous
   II. Simple cuboidal
   III. Simple columnar

2. Based on Stratification (number of layers)

STRATIFIED EPITHELIUM

I. More than one layer of cells.
II. The superficial layer is used to classify the layer.
III. Only one layer touches the basal lamina.
IV. Stratified cells can usually withstand large amounts of stress.

Stratified epithelia can be:

- Stratified squamous
- Stratified cuboidal
- Stratified columnar

3. Based on Specialization

Stratified squamous epithelium can be divided into two types—

I. Keratinized
II. Non-keratinized

I. Keratinized cells contain keratin (a cytoskeletal protein). While keratinized epithelium occurs mainly in the skin, it is also found in the mouth and nose, providing a tough, impermeable barrier.

The keratinized epithelium has four layers

i. The stratum Basale,
ii. The stratum spinosum,
iii. The stratum granulosum and
iv. The stratum corneum

II.Non-keratinized stratified squamous epithelium:

In situations where the surface of the squamous epithelium remains moist, the most superficial cells are living and nuclei can be seen in them. This kind of epithelium is described as non-keratinized stratified squamous epithelium. Non-keratinized stratified squamous epithelium covers wet surfaces exposed to wear and tear. It is seen lining the mouth, the tongue, the Oro and laryngopharynx, the oesophagus, and the cornea. Under pathological conditions the epithelium in any of these situations may become keratinized.[18]

SURFACE DOMAINS

Epithelial cell membranes have three regions (domains) different in structure and function. This feature is called membrane polarity. Each membrane pole exhibits various features. These can include receptors and channels for transportation of substances that the epithelial cell needs to internalize or expel, or membrane specializations.[19]

Epithelial cells have 3 surface domains:

I. Apical
II. Lateral
III. Basal

I. APICAL DOMAIN

Free surface always directed toward exterior or lumen of the enclosed body cavity. May have surface modifications depending upon specific function i.e.

Microvilli
Stereocilia
Cilia

II. LATERAL DOMAIN

The lateral membrane contains proteins for cell-cell adhesion, intercellular signaling, and cell-cell communication and is the only region of the plasma membrane where an epithelial cell interacts with other epithelial cells. The relationship between the lateral membrane and intercellular interaction is especially important for non-cell-autonomous processes such as mechano-regulation of cell-cell adhesion. Hence, the lateral membrane plays a permissive role in the strengthening of cell-cell adhesion and the maturation of adhesion complexes.

III. BASAL DOMAIN

Basal surface domain facing the extracellular matrix and underlying tissue or, in case of hepatocytes, the sinusoidal blood. Controlled interaction between the cells and the extracellular matrix (ECM) is essential for many processes, including normal development, migration and proliferation The integrin-based cell–matrix adhesions are spot-like structures that are dynamically regulated to ensure communication between the cell's interior and the ECM cross-talk between the diverse cell–cell and cell–extracellular matrix junctions has been found, with the help of cell junctions.[20]

CELL JUNCTIONS

DEFINITION

Cell junction is the connection between the neighboring cells or the contact between the cell and extracellular matrix. It is also called membrane junction.

CLASSIFICATION

1. Occluding junctions (tight junctions or zonula occludens)
2. Communicating junctions (Gap junction)
3. Anchoring junctions. (Zonula adherens)

The tight junction occupies the most apical position, followed by the adherens junction (adhesion belt) and then by a special parallel row of desmosomes; together these form a structure called a junctional complex. Gap junctions and additional desmosomes are less regularly organized.[21]

CELL ADHESION MOLECULES

- Cell adhesion molecules (CAMs) or cell adhesion proteins are the protein molecules, which are responsible for the attachment of cells to their neighbors or to basal lamina (or basal membrane).
- CAMs form the important structures of intercellular connections and are responsible for structural organization of tissues.[22]

Two types:

I. Calcium dependent
II. Calcium independent

CALCIUM DEPENDENT

i. Cadherins
ii. Integrins
iii. Selectins

CALCIUM INDEPENDENT

a. Neural cell adhesion molecules
b. Intercellular adhesion molecules

CYTOKERATINS

Cytokeratin's are a subfamily of intermediate filament proteins and are characterized by a remarkable biochemical diversity, represented in epithelial tissues by at least 20 different polypeptides

CLASSIFICATION

The cytokeratin's are divided into the type I and type II subgroups, the type II family members comprising the basic to neutral cytokeratin's 1-8, while the type I group comprises the acidic cytokeratin's 9-20.[23]

BASEMENT MEMBRANE

Epithelial cells rest on a thin basement membrane.

Under the EM a basement membrane is seen to have a basal lamina (nearest the epithelial cells) and a reticular lamina or fibroreticular lamina (consisting of reticular tissue and merging into surrounding connective

tissue). The major molecular constituents of basement membrane include Collagen IV, Laminin-entactin/Nidogen complex and Proteoglycans.

The basal lamina (often called basement membrane) is a layer on which epithelium rests. This layer is composed of an electron-dense layer (lamina densa) between two electron-lucid layers (lamina lucida), and is approximately 40-50 nm thick the lamina densa is composed of type IV collagen. The lamina lucida is adjacent to the epithelial cells and contains the glycoprotein laminin.[24]

The two layers of the basal lamina typically sit on top of the lamina reticularis, which is synthesized by cells from the underlying connective tissue and contains type IV collagen.

Also, it plays a role in differentiation and repair of the epithelium.[25]

TYPE IV Collagen

Structure:

Kefalides (1971) was the first to recognize that basement membrane contains a unique collagen as a major component, which is different from collagen types I, II and III. He named it as type IV collagen. They form a macromolecular network in which they are cross linked via their like ends (Timpl et al). Strands of two or three triple helical segments of different molecules twisted around each other into superhelices have been observed. (Yurcheno and Ruben,1987).[26]

LAMININ

Laminin is a ubiquitous basement membrane component, as demonstrated in numerous immune-histological and cell-culture studies (Timpl et al 1983). Laminin, a major component of basement membranes, has numerous biological activities including promotion of cell adhesion, migration, growth, and differentiation, including neurite outgrowth, promote cell attachment, chemotaxis, and cell differentiation.

NIDOGEN

The nidogen family, also known as Entactin's, consists of a number of sulfated monomeric glycoproteins ubiquitously present in the basement membrane. Because of their wide range of binding partners, they have been considered as adapter proteins in this specialized extracellular matrix. Based on molecular structure they are divided in two types nidogen 1, nidogen 2.

Functions of Basement membrane

a) It provides adhesion on one side to epithelial cells (or parenchyma); and on the other side to connective tissue (mainly collagen fibers).
b) It acts as a barrier to the diffusion of molecules. The barrier function varies with location (because of variations in pore size). Large proteins are prevented from passing out of blood vessels, but (in the lung) diffusion of gases is allowed.
c) Recent work suggests that basement membranes may play a role in cell organization, as molecules within the membrane interact with receptors on cell surfaces. Substances present in the membrane may influence morphogenesis of cells to which they are attached.
d) The membranes may influence the regeneration of peripheral nerves after injury, and may play a role in re-establishment of neuromuscular junctions.[27]

Gingival Epithelium

Overview

The mucous membrane that lines the structures within the oral cavity is known as *oral mucosa*.The oral mucosa comprises an epithelium with an underlying connective tissue layer termed the lamina propria, Masticatory mucosa, where the epithelium is keratinized, is found in areas subjected to significant loading such as the hard palate and Lining mucosa, where the epithelium is non-keratinized, is subjected to far less stress and is found in regions such as the lip,

cheek and floor of mouth. The anterior two-thirds of the dorsum of the tongue is partly keratinized and is lined by a specialized gustatory mucosa containing various papillae and taste buds.

The oral mucosa shows specialization's that allow it to fulfil several roles:

- It is protective mechanically against both compressive and shearing forces.
- It provides a barrier to microorganisms, toxins and various antigens.
- It has a role in immunological defense, both humoral and cell-mediated.
- Minor glands within the oral mucosa provide lubrication and buffering as well as secretion of some antibodies. The viscoelastic mucous film also acts as a barrier, helping to retain water and electrolytes.
- The mucosa is richly innervated, providing input for touch, proprioception, pain and taste.[28]

Development of gingival epithelium

Cell Proliferation and Differentiation

Proliferation is a property of stem cells of the basal cell layer and their immediate progeny, the transit-amplifying cells. The proliferation compartment contains two pools of dividing cells: stem cells and transit-amplifying cells. Stem cells located in the basal cell layer are slow-cycling cells. Transit-amplifying cells, derived from the division of stem cells, divide one to five times while migrating laterally and upward toward the epithelial surface, producing a clone of differentiating cells.[29]

Differentiation starts when recently divided cells detach from the underlying extracellular matrix. The regulatory signals that must be activated to initiate keratinocyte differentiation are clearly complex. As differentiating cells mature, they are pushed toward the epithelial surface by pressure generated in the underlying proliferation compartment.

Terminal differentiation of Stratified squamous epithelium (SSE) follows either one of two major pathways. Fully cornified dead cells (squames) are formed in the epidermis, hard palate, and oral gingival epithelium (OGE). In contrast, in lining mucosa, the outer-level cells are non-cornified. Site-specific differentiation also gives rise to epithelial appendages, such as the filiform papillae of the tongue.[30]

The valid classification of different mucous membranes of the oral cavity is attributable to Bodecker[31]and Orban and Sicher[32].

According to these authors' proposals, three types may be differentiated:

(1) keratinizing masticatory mucosa, i.e., the gingiva and the mucosa of the hard palate.

(2) the specialized mucosa of the dorsum of the tongue; and

(3) Non keratinizing "lining mucosa" including the alveolar mucous membrane, the mucosa of the vestibular fold, the cheek and lip, the ventral sides of the tongue, and the soft palate.

Masticatory Mucosa

Masticatory mucosa is the epithelium covering the gingiva and hard palate The gingiva is that part of the masticatory mucosa which covers the alveolar process and covers the cervical portion of the teeth.

Gingiva and Epithelial Attachment

In the oral mucosa, the gingiva surrounds the cervical of the teeth and extends apically to the mucogingival junction.

The gingiva is divided into three zones. They are as follows: (1) the free or marginal zone, which encloses the tooth and defines the gingival sulcus; (2) the attached gingiva, that portion of the epithelium attached to the neck of the tooth by means of junctional epithelium; and (3) the interdental zone (groove), the area between the two adjacent teeth beneath their contact point. The free and attached gingivae have an indistinct groove on the surface of the epithelium separating them. This groove is termed the free gingival groove.[33]

Interdental Papilla and Col

Gingiva located between the teeth and extending high on the interproximal area of the crowns on the labial and lingual surfaces is known as the interdental papilla. This tissue fills the space created by the constricted cervical areas of the adjacent crowns. In the interproximal area, between the lingual and vestibular papilla, is a concave zone of the gingiva that follows the contour of each crown.[34]

Hard Palate

The roof of the mouth, or hard palate, is covered with keratinized stratified squamous epithelium. This epithelium is similar to that of the gingiva in the midline of the hard palate, where there is no submucosa.

Specialized Mucosa

Specialized mucosa is located on the dorsum of the tongue. It contains specialized mucosal structures the lingual papillae and taste receptors. The heterogenous pattern of keratin expression in the tongue is complex and in part is responsible for generating the papillary architecture of the lingual epithelium.[35]

Lining Mucosa

Lining mucosa is distensible and relatively loosely bound to adjacent structures by connective tissue that is rich in elastin. It is found over mobile structures such as the lips, cheeks, soft palate, alveolar mucosa, vestibular fornix, and the floor of the mouth.

Lips

The inner oral surface of the lips is lined with moist surface, stratified squamous cells, and nonkeratinized epithelium and is associated with small, round seromucous glands of the lamina propria. Beneath the lamina propria is the submucosa, in which fibers of the orbicularis oris muscle are located. Nonkeratinized mucosa of the lips is distinguished by a red border known as the vermilion border. Also observable in the skin of the lips are hair follicles and their associated sebaceous glands, erector pili muscles, and sweat glands. Ectopic sebaceous glands can be seen at the angles of the mouth. They are not associated with hair follicles. These glands are known as Fordyce spots.[36]

Several layers of cells of distinct morphologies may be recognized in lining the oral cavity:

i. Basal layer (stratum germinativum or stratum Basale)
ii. Prickle cell layer (stratum spinosum)
iii. Granular layer (stratum granulosum)
iv. Keratinized (cornified) layer (stratum corneum).

Keratinized epithelium can be:

a) Orth keratinized
b) Para keratinized

In Para keratinization, the cells retain pyknotic and condensed nuclei and other partially lysed cell organelles until they desquamate. i.e. they appear almost as if they are keratinizing.

The keratinized epithelium is present in regions which are subjected to abrasion as well as drying.

E.g., skin, vermilion border of the lip, gingiva.

TABLE-3 Difference between Orth keratinized and Para keratinized

Ortho-keratinized	**Para-keratinized**
1.Epithelial maturation is present in superficial layers. [keratin]	1.Immature form ortho-keratinized epithelium.
2.No nuclei in the stratum corneum.	2.Pyknotic nuclei/shrunken nuclei is retained.
3.Well defined stratum granulosum is present.	3.Stratum granulosum is indistinct/absent.
4.Shedding of superficial layer of epithelium is absent.	4. Shedding of superficial layer of epithelium. (Keratin +nuclei)

Cells of Gingival Epithelium

The epithelium consists of two types of cells—

1. keratinocytes and
2. Non-keratinocytes

1. Keratinocytes
   Keratinocytes are the predominant cell type of gingival epithelium. They are formed from stem cells present in basal layer.

2. Non-keratinocytes-Include melanocytes, dendritic cell of Langerhans and cells of Merkel.

From morphologic and functional point of view gingival epithelium is divided into:

1. 1.Oral or outer epithelium
2. 2.Sulcular epithelium
3. 3.Junctional epithelium

1. Oral or outer epithelium

The oral or outer epithelium covers the crest and outer surface of the marginal gingiva and the surface of the attached gingiva. The oral gingival epithelium is cornified, impermeable to water-soluble substances, and attached firmly to a base of dense gingival connective tissue. Four clearly defined cell layers are present: the basal cell layer, the spinous cell layer, the granular cell layer, and the cornified cell layer.

On an average, the oral epithelium is 0.2 to 0.3 mm in thickness. It is keratinized or Para keratinized or presents various combinations of these conditions. The basal cells make up the proliferation compartment of the epithelium, and the remaining layers form the differentiation compartment. In keeping with the complete maturation, histo-enzyme reactions for acid phosphatase and pentose shunt enzymes are very strong.[37]

Para keratinized areas express K19, which is usually absent from Orth keratinized normal epithelia. Keratins K1, K2 and K10 to K12, which are specific to epidermal-type differentiation, are immunohistochemically expressed with high intensity in Orth keratinized areas and with less intensity in Para keratinized areas. K6 and K16, characteristic of highly proliferative epithelia, and K5 and K14, stratification-specific cytokeratin's, also are present.[38]

2. Oral Sulcular epithelium

The sulcular epithelium lines the gingival sulcus. It is a thin non keratinized stratified squamous epithelium without rete pegs, and it extends from the coronal limit of the junctional epithelium to the crest of the gingival margin. Regular and prolonged chemical and mechanical tooth cleaning can lead to a condition in which there is almost no sulcus. However, most individuals who practice good oral hygiene have clinically healthy gingiva. This condition is characterized by a shallow gingival sulcus (less than 3.0 mm), no bleeding on probing, moderate numbers of inflammatory cells in the connective tissue and JE, a small loss of collagen matrix beneath the OSE and JE, and a minimal flow of gingival fluid.[39]

The sulcular epithelium lacks granulosum and corneum strata and K1, K2 and K10 to K12 cytokeratin's, but contains K4 and K13, the so-called esophageal cytokeratin's also expresses K19 and does not contain Merkel cells. Histochemical analyses have consistently revealed a lower degree of activity in the sulcular than in the outer epithelium, particularly in the case of enzymes related to keratinization.[38]

3. Junctional epithelium

The junctional epithelium is the epithelial component of the dento-gingival unit that is in contact with the tooth surface."

D.D. Bosshardt and N.P. Lang

"A single or multiple layers of non-keratinizing cells adhering to the tooth surface at the base of the gingival crevice."

-AAP- Periodontal literature review 1996

Development of junctional epithelium

Beginning orally and ending at the cementoenamel junction (Schroeder and Listgarten, 1977) 3 to 4 (Ten Cate, 1998) yrs later, the reduced enamel epithelium gradually converts into junctional epithelium, a multilayer non-keratinizing squamous epithelium (Glavind and Zander, 1970; Listgarten, 1972; Schroeder, 1996).

Theories of junctional epithelium

The ultrastructure of the oral gingival epithelium was studied by (Listgarten, 1964), where he named junctional epithelium as the "epithelial attachment". Gottlieb (1921) had reported that the "epithelial attachment" is organically united to the tooth surface. Waerhaug (1952) concluded that the "epithelial attachment" belongs to the lining of the "physiological pocket", that its cells adhere only weakly to the tooth surface, and that the bottom of that pocket is to be found at the cementoenamel junction. subsequent research emphasized the importance of the junctional epithelium in the peripheral host defenses against infection (Schroeder and Listgarten, 1997).

THE EARLY STUDIES: MAX LISTGARTEN, HUBERT SCHROEDER

The nature of the epithelial attachment apparatus in man was unveiled primarily by Max. It consisted of hemidesmosomes and a basement lamina, resembling that at the epithelium-connective tissue interface (Listgarten, 1966).

The epithelial attachment is mediated by a basement lamina produced by the attachment epithelium, that this attachment extends from the cementoenamel junction to the gingival sulcus bottom, and that it withstands any mechanical force applied. Hubert used the term "junctional epithelium", which had been suggested by Anderson and Stern (1966).

“It was concluded that the junctional epithelium is a non-keratinizing, non-differentiating, fast-renewing epithelium with distensible intercellular spaces that serve as a pathway for an inflammatory exudate and neutrophilic granulocytes, as a residence for lymphocytes and monocytes, as well as for the inward diffusion of foreign molecules.”

Three zones have been described in junctional epithelium:

1. APICAL – shows cells with germinative characteristics.
2. MIDDLE – adhesiveness
3. CORONAL – greater permeability

Length of junctional epithelium

Gargiulo et al., 1961 – 0.97 mm average with a range of 0.71 mm-1.35 mm

Carranza - 0.25 to 1.35 mm.

At its apical and lateral aspects, the junctional epithelium is bordered by soft connective tissue and, at its coronal-most portion, also by the sulcular epithelium.

Toward the tooth surface, the junctional epithelial cells form and maintain the epithelial attachment (Schroeder and Listgarten, 1977).[40]

BASAL ATTACHMENT APPARATUS

Basal cells of stratified squamous epithelia are bound to underlying connective tissue by an attachment apparatus comprising cytoplasm, plasma membrane, and extracellular proteins. Nondividing basal cells of SSE often develop major cell processes (pedicles) that project into the connective tissue, thereby increasing the surface area for attachment. Pedicles are plentiful in areas of the skin and mucous membranes (such as the oral gingival epithelium and hard palate) that are exposed to high shearing forces.

Molecular associations for attachment are concentrated in button like structures, the hemidesmosomes. They serve as sites for binding keratin inter- mediate filaments to the basal lamina via several plaque and transmembrane proteins. The basal lamina is in turn joined to collagen fibers by a system of anchoring fibrils (type VII collagen) and connective tissue anchoring plaques.[41]

The basal lamina densa, a dense network of collagen type IV, laminin, nidogen

(entactin), and heparan sulfate proteoglycan (perlecan), forms adjacent to the basal surface of the basal cells. The lamina densa is constructed of type IV collagen molecules assembled to form a meshwork whose pore size ranges from 8 to 20 nm, depending on the epithelial site. Laminin 1 also undergoes self-assembly to form a meshwork. The laminin mesh forms without covalent bonding and thus is less stable than the collagen IV network. The two networks combine through the interaction of nidogen bridges to create a scaffold containing other constituents, such as perlecan, fibronectin, and other glycoproteins.[42]

Collagen types VI and XV are also localized to the basement membrane zone, where they appear to provide additional adherence between the epithelium of skin and oral mucosa and the underlying connective tissue. Fibrillin, a matrix protein that forms microfibrils about 10 to 12 nm wide, also participates in the attachment of epidermis to connective tissue. The fibrillin microfibrils form a network that projects downward from the collagen VII anchoring fibrils.[43]

Type IV collagen

Type IV collagen is a nonfibrillar collagen that constitutes the major fraction of the basal lamina densa. Type IV procollagen molecules are heterotrimers assembled from six genetically distinct (IV) chains. Each chain consists of a long linear collagenous do- main of about 1,400 amino acids. Several short, non- collagenous segments that impart flexibility to the molecule interrupt the collagenous domain. The most common heterotrimer is made up from two alpha 1 (IV) chains and one alpha 2(IV) chain.[44]

Type VII collagen

Type VII procollagen molecules are composed of three identical alpha chains. Each chain contains a central collagenous domain and two non-collagenous terminal domains. The collagenous segments of three alpha chains associate in a triple helical arrangement to form a type VII procollagen molecule. Following cleavage of the carboxy non-collagenous terminal domains, dimer formation occurs by side-to-side aggregation of partially overlapping procollagen molecules.

Type VII collagen is made by epithelial cells and by fibroblasts of the lamina propria. Monocultures of both cell types produce small quantities of type VII collagen; however, cocultures of epithelial cells and fibroblasts produce larger amounts of the protein, indicating that epithelial-mesenchymal interaction is necessary for the efficient production of anchoring fibrils. The expression of type VII collagen is strongly dependent on the stimulatory effect of TGF-beta.[45]

Cell surface proteoglycans (syndecan and epican)

Oral keratinocytes synthesize extracellular and cell- associated heparan sulfate-rich proteoglycans. Syndecans are a family of cell surface proteoglycans expressed in all cell types. Four genetic types, with different tissue distribution patterns, have been identified: syndecan 1 (the original syndecan), syndecan 2 (fibro glycan), syndecan 3 (N-syndecan), and syndecan 4 (amphiglycan). Syndecan 1 is strongly expressed in the stratum spinosum of stratified squamous epithelia but present in only small amounts in the basal cell layer.[46]

Epican is similar to syndecan, in that it carries heparan sulfate and chondroitin sulfate glycosaminoglycan side chains on its extracellular domain. It is a form of CD44 cell surface protein, expressed primarily by epidermal cells. It plays a role in mediating keratinocyte cell-to-cell adhesion in a low-avidity, hyaluronan-dependent, calcium-independent attachment mechanism. Integrins and cadherins form the molecular basis of the high-avidity adhesion system between keratinocytes. The syndecan and epican proteoglycans belong to the mucopolysaccharide intercellular "cement" described in the older scientific literature.[47]

Non-collagenous components of the basal lamina

Nidogen (entactin)

The nidogen molecule is rod shaped with globular domains at both the carboxy and amino terminals. Nidogen binds to type IV collagen, laminin, and perlecan. Because laminin does not have the ability to bind to collagen type IV, nidogen appears to play a crucial role in the assembly of the basal lamina by acting as a bridge between collagen type IV and laminin. At the epithelial-mesenchymal junction, nidogen is localized in the basal lamina and attachment plaques. In vitro studies indicate that, although fibroblasts produce nidogen, the assembly of a basal lamina requires participation of epithelial cells.[48]

Perlecan

Perlecan is a large proteoglycan (400 to 450 kDa) found within basal laminae, including those of the oral mucosa.[327] The main producers of perlecan are fibroblasts adjacent to the basal lamina. Perlecan binds to other molecules of the basal lamina such as fibronectin, nidogen, and laminin. In addition to its structural contribution to the basal lamina, perlecan has significant interactions with growth factors. Growth factors such as basic fibroblast growth factor and TGF alpha are bound and stored at the heparan sulfate chains of perlecan. Release of basic fibroblast growth factor via the action of heparinase occurs during wound healing.[49]

Laminins

Laminins are large, extracellular, cross-shaped adhesion proteins consisting of three polypeptide chains. The alpha chain is the largest of the three. It has three globular domains separated by numerous EGF repeats in its amino terminal. A large component consisting of five subunits characterizes its rather large carboxy terminal. The smaller beta and gamma chains contain two domains in the amino terminal. The ex-helical domains of the three chains form a coiled-coil structure stabilized by interchain disulfide bridges.

At least eight different genetic polypeptide chains and seven distinct heterotrimeric molecular assembly patterns have been characterized. Laminin-1 is a major component of most basal laminae. It is a ligand for integrin receptor. The location of binding sites for perlecan, nidogen, various integrins, and other molecules to laminin.[50]

Epithelial-mesenchymal interactions

Oral epithelium demonstrates regionally specific patterns of cytodifferentiation and morphogenesis, from simple non-cornified epithelium of the ventral surface of the tongue to more complex patterns that determine the structure of the filiform appendages of the dorsal surface of the tongue. These patterns are pre- served over the life span of the organism, despite continued and rapid turnover of the cell populations. There are numerous examples of necessary epithelial-mesenchymal interactions in embryonic development of tooth formation constitutes a prime example- but their importance in adult tissues, such as oral mucosa, is less clear.

In general, the epithelial tissues maintain the same pattern of cytodifferentiation characteristic of their site of origin when grown in combination with heterogenous connective tissue. In such cases, the connective tissue is said to have a permissive effect on the epithelium. However, there are combinations in which the differentiation pattern of the epithelium changes to reflect the site of origin of the connective tissue. It has become increasingly clear that cytokines and growth factors arising in the supporting connective tissue control, in part, variations in gene expression that are responsible for epithelial tissue heterogeneity. In fact, there is a constant interplay, or cross talk, mediated by soluble factors emanating from and acting on both tissues. This interplay of epithelial and mesenchymal signals controls embryonic development as well as the maintenance of the adult phenotype. [51]

Renewal or homeostasis of gingival epithelium

Oral epithelium maintains its structural integrity by a process of continuous cell renewal in which cells produced by mitotic divisions in the deepest layers migrate to surface to replace those that are shed.

The cells of the epithelium considered to consist of 2 functional populations:

Progenitor Population: whose function is to divide and provide new cells.

Maturing Population: where cells are continually undergoing a process of differentiation or maturation to form a protective surface layer.

Epithelial proliferation

The progenitor cells are situated in the basal layer in thin epithelia (e.g. floor of mouth) and in lower 2 to 3 cells layers in thicker epithelia (e.g. cheeks and palate).

The progenitor compartment is not homogenous but consists of 2 functionally distinct sub-population of cells.

1. A small population of progenitor cells cycles very slowly and is considered to represent stem cells whose function is to produce basal cells.
2. The larger portion of progenitor compartment is composed of amplifying cells, whose function is to increase the number of cells available for subsequent maturation.
3. Proliferating cells are most commonly identified by immmunocyto chemistry following administration of bromodeoxyuridine. Apart from measuring the number of cells in division it is possible to estimate the time necessary to replace all cells in the epithelium. The turnover time of the epithelium is derived from knowledge of time it takes for a cell to divide and pass-through entire epithelium.[52]

In general, turnover time of: -
skin – 52-75 days
Gut – 4-14 days
Gingiva-41 -57 days
Cheek – 25 days

Epithelial maturation

Cells arising by division in the basal and parabasal layers of epithelium either remains in the progenitor cell population or undergo a process of maturation as they move to the surface.

The mitotic rate is higher in nonkeratinized areas and is increased in gingivitis, without significant gender differences. Opinions differ as to whether the mitotic rate is increased or decreased with age.

Regarding JE, it was previously thought that only epithelial cells facing the external basal lamina were rapidly dividing. However, evidence suggests that a significant number of cells, such as basal cells along the connective tissue, are capable of synthesizing DNA, demonstrating their mitotic activity.

Rapid shedding of cells effectively removes bacteria adhering to the epithelial cells and therefore is an important part of the antimicrobial defense mechanisms at the dentogingival junction.[53]

Antimicrobial peptides and their role in microbial ecology

Several families of natural anti-microbial peptides and proteins are expressed in epithelia as well as in neutrophils as part of the barrier.

These peptides have broad specificity with activity against gram (+ve) and gram (-ve) bacteria.

Antimicrobial peptides defined as proteins with less than 100 amino acids with mol. weights ranging from approximately 3,500 to 6,500D include, α and β defensins which are localized in different sites in gingiva suggesting they are likely to serve different roles. The human β defensin-1(hBD1) and hBD –2 is expressed in areas of inflammation and differentiation, but are expressed poorly or not at all in the J.E. On the other hand, the α defensins are present in high amounts in neutrophils that migrate through J.E into gingival sulcus.

Thus, the JE is protected by α-defensi ns released from neutrophils whereas differentiated stratified epithelia are protected by β defensins.[54]

Role of epithelia in integrating innate and acquired immune response

Epithelial cells also respond to bacteria by altering cell signaling events.

Langerhans cells function as antigen presenting cells and serve as one of the connecting links between epithelium and acquired immunity. cathelicidin acts as a neutrophil chemo-attractant and stimulates expression of proteoglycans associated with wound healing.

Thus, epithelium responds to the presence of bacteria and during this process T cell and macrophages and stimulated, providing a connection of the innate responses of the epithelial cells with acquired immune response for specific and long-term recognition of foreign antigens.[55]

CONCLUSION

To summarize, epithelium has an active role in keeping the oral environment healthy by its effective barrier function, crucial in preventing in infections by production of antimicrobial peptides such as defensins which have the ability to inhibit the growth of microbes. Epithelial cells also produce chemokine and cytokine expression to environmental stimuli such as injury. These signaling molecules help to regulate the immune response by attracting immune cells to the site of inflammation there by aiding in the defense against pathogens and tissue repair. It's a dynamic system that constantly adapts to different changes and challenges is a testament to its role in ensure the well being of the oral tissues.

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