An Overview of Epithelium

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Abstract*— The first line of defense against bacterial invasion in periodontal disease is provided by the epithelium, which functions as a physical barrier to separate the biofilm from the gingival tissue. Inflammation results from the disruption of the gingival epithelial barrier and the subsequent entry of exogenous pathogens into the host tissues, which leads to the development of a chronic infection. This review aims to discuss in-depth knowledge of the different types of oral epithelium, cell junctions, and cellular ultrastructure.

Indexed Terms*— Epithelium, Columnar, cuboidal, Keratinization

I. INTRODUCTION

The human body is made up of about 200 distinct types of cells, which are arranged and cooperatively grouped into four basic tissues: epithelial, connective, muscular, and nervous tissue. In this context, the nipple is the tiny capillary containing papillae of connective tissue that project into the epithelium. The word epithelium is derived from the Greek words epi, which means upon, and thelium, which means nipple. Surface epithelia and solid organs are both included in the diverse group of tissues known as epithelia. One or more layers of cells make up the continuous sheets that make up surface epithelia. All of the body's surface cavities and tubes are covered by it or lined with it, forming the boundary between the various biological compartments. Immunohistochemistry, a technique used to diagnose histopathology and classify challenging malignant tumours, is used to recognise an epithelial phenotype in most of the epithelial cells. Blood vessels never enter the epithelium[1].

II. ORIGIN

After going through a number of divisions, the fertilised ovum or zygote eventually develops into a morula. The morula grows larger and develops a central cavity, eventually turning it into a hollow sphere due to continuous mitosis. The implantation in the uterine wall takes place during the blastocyst stage. The blastocyst develops an inner cell mass that gives rise to the embryo and a delicate outer layer of cells called trophoblast prior to implantation. Zona pellucid endures up until implantation, after which it degrades. The trophoblast divides into two layers: an outer syncytiotrophoblast made up of fused trophoblast cells and an inner cytotrophoblast layer that protrudes solidly into the uterine lining. An internal amniotic cavity develops within the inner cell mass[2]. The portion of the inner cell mass that makes up the amniotic cavity's floor differentiated into a bilaminar embryonic disc, whose upper layer is an epiblast and its lower layer a hypoblast. Each of the three layers develops from the epiblast. Gastrulation is the process of a trilaminar disc developing from three germinal layers. The epiblast cells migrate between the epiblast and hypoblast at the medial site on the epiblast primitive groove, and then they enter the hypoblast. Mesoderm is created when cells move between two layers. Endoderm develops from the cells that enter the hypoblast. The epiblast is produced by the cells that are still present. All three layers can produce epithelial tissue, and the ectoderm produces the oral and nasal mucosae, cornea, skin's epidermis, skin glands, and mammary glands. The uriniferous tubule of the kidney, the lining of the male and female reproductive systems, the endothelial lining of the circulatory system, and the mesothelium of body cavities are all

products of mesoderm. Liver, pancreas, and the lining of the respiratory and gastrointestinal tract are all descended from endoderm[3].

III. ORAL EPITHELIUM

After the buccopharyngeal membrane ruptures at around 26 days of gestation, the embryonic stomatodeum and foregut fuse to form the primitive oral cavity, which is lined with epithelium made of ectoderm and endoderm. The tongue, epiglottis, and pharynx are examples of structures that develop in the branchial arches and are covered by endoderm-derived epithelium, whereas the palate, cheeks, and gingivae are covered by ectodermal-derived epithelium. The primitive oral cavity's single cell layer has divided into two by the time a pregnancy is five to six weeks old, and by the eighth week, the vestibular dental lamina complex region has thickened. At 10 to 14 weeks, the cells covering the cheek area and the alveolar mucosa separate in the central region of this thickening, resulting in the formation of the oral vestibule. The lingual begins to show specialisation at around 7 weeks. All oral epithelia thicken between 13 and 20 weeks of pregnancy[4]. Langerhans cells and melanocytes start to appear in the epithelium during this time. The epithelium's surface layers exhibit orthokeratinization and parakeratosis. The epithelial cells can be high columnar, cuboidal, or low squamous in shape and size. The spherical, elongated, or elliptical shapes of epithelial cell nuclei are distinctive. The shape of epithelial cells and the form of their nuclei are roughly equivalent. Squamous cells, which are cuboidal in shape, have a flattened nucleus. Because the boundaries between the cells are indistinguishable with light microscope the form of cell nucleus is important to determine the shape and number of the cells. In order to determine whether the cells are arranged in layers, nuclear form is important[4].

IV. TYPES OF EPITHELIUM

A single layer of flattened cells makeup the simple squamous epithelium, an epithelial membrane (squamous means scale like). It is referred to as pavemented epithelium because it is made up of flattened, irregularly shaped cells that form a continuous surface. seen in the pleural and peritoneal cavities, the loop of Henle, the parietal layer of the Bowmen capsule, the inner and middle ears, and blood and lymphatic vessels. Simple cuboidal epithelium: The cells appear to be square with a centrally located round nucleus when viewed in a section cut perpendicular to the surface. It can be seen in the numerous glands that cover the kidney tubules and the ovary[1].

A single layer of tall, rectangular cells with ovoid nuclei situated in the basal half of the cell make up a simple columnar epithelium. It is present in the lining of the oviduct, the ductuli efferentes of the testis, the uterus, the small bronchi, the majority of the digestive tract, the gall bladder, and the large ducts of some glands.

Squamous non-keratinized stratified epithelium: It is thick, made up of several layers of cells, and only the deepest layer is in contact with the basal lamina. The cuboidal, polymorphous, and flattened cells that make up the epithelium's free surface are found in its most basal cells, which are also its most numerous. usually visible when wet, and it can be found lining the vagina, oropharynx, oesophagus, and mouth.

Stratified squamous keratinizing epithelium: Since the cells of the basal layer are typically cuboidal in shape, the classification of the stratified epithelia is based on the shape and structure of the surface cells. A tough, non-living surface layer of squames made of the protein keratin is formed when the epithelial cells accumulate cross-linked cytokeratin intermediate filaments during a process known as keratinization. encased in lingering plasma membrane. The matrix of developing epithelial cells gradually condenses before disappearing. It makes up the skin's epidermis. Only two layers of cuboidal cells are present in the stratified cuboidal epithelium. lines the larger excretory ducts of the exocrine glands, such as the salivary glands, and the sweat gland ducts. Stratified columnar epithelium: This type of epithelium has a superficial layer of columnar cells and a deeper layer that is low polyhedral to cuboidal and in contact with the basal lamina. It can be found in the male urethra, large excretory ducts, and the conjunctiva of the eye[3].

Between stratified columnar and stratified squamous epithelia, it is known as a transitional epithelium. The urinary tract, which runs from the renal calyces to the

urethra, is lined with it, and it is only found in the urinary system. It is made up of many layers of cells, and the cells at the bottom are low columnar or cuboidal in shape. Several layers above the basal cells are made up of polyhedral cells. The largest, occasionally binucleated, and rounded dome-topped cells of the empty bladder have lumen-bulging dome tops. When the bladder is inflated, these dome-shaped cells flatten and the epithelium thins[5]

Pseudostratified columnar epithelium: It has a single layer of cells despite appearing to be stratified. Only a few cells make it to the epithelium's surface, though all are in contact with the basal lamina. Cells that don't reach the surface have a wide base that narrows to a point at the apex.

Taller cells have an expanded apical surface and a narrow base in contact with the basal lamina. They also reach the surface. Since the height of the cells in this epithelium varies, so do the locations of their nuclei. The male urethra, epididymis, and larger excretory ducts of glands are where you can find this. The majority of the traches and primary bronchi, the auditory tube, a portion of the tympanic cavity, the nasal cavity, and the lacrimal sac all have pseudo stratified columnar ciliated epithelium lining them[4].

V. CELL SURFACE SPECIALISATIONS

The apical pole and basal pole of epithelial cells are opposite sides that face a space or connective tissue, respectively. The apical pole's surface is referred to as the free surface, and the surfaces that are in opposition to neighbouring cells are referred to as lateral surfaces. Intercellular junctions: Specialized junctions form at the precise sites on contacting cell membranes when cells come into contact with one another and occasionally with the extracellular matrix. Occluding and tight junctions are different types of cell junctions (Zonula occludens)[5].

Adhesive junctions

a) Cell to cell - I) Zonula adherens

II) Macula adherens (Desmosomes)

b) Cell to matrix - I) Focal adhesions

II) Hemidesmosomes

Communicating (Gap junctions)

Tight junctions, also known as zona occludens, are structures where transmembrane adhesive proteins are arranged in anastomosing strands to hold opposing cell membranes tightly together. At the tight junctions, the intercellular space is completely destroyed. Occluding members of the claudin family are transmembrane adhesive proteins. A number of cytoplasmic proteins, such as polarity-related proteins, vesicular-related proteins, a tumour suppressor protein, and a transcription factor, associate with the intracellular proteins of the transmembrane proteins[6]. A few of the tight junctions' cytoplasmic proteins interact with the actin filaments. The movement of the substance through the intercellular spaces is regulated by tight junctions. Latin terms for belt and membrane fusions include zonula and occludens. The so-called sealing strands that hold the membranes together are made up of transmembrane proteins. Stitch is made up of two molecules of the transmembrane protein claudin, one of which is a crucial component of every opposing plasma membrane. The actin cytoskeleton is connected to the tight junctions on the cytoplasmic side of the plasma membrane[10].

3 COMPONENTS: 1) Transmembrane proteins – occluding

2) Cytoplasmic adapter

3) Cytoskeletal filaments

Cells are held together by adhesive junctions. Cell-cell adhesive junctions have a 20 nm-wide intercellular space. In cellular signalling, these are crucial. Cadherins, which are calcium ion dependent proteins, are the main transmembrane proteins. The cytoplasmic adapter proteins are catenin family members[6]. The transmembrane cadherin molecule's cytoplasmic domain, the cytoskeleton, and other proteins, such as tumour suppressor molecules, are all interacting with catenins. E-cadherin is a member of the cadherin family in zonula adherens, along with and catenin, which function as cytoplasmic adapters and actin filaments as cytoskeletal elements. On the cytoplasmic side of the cell membrane, there is an accumulation of actin and catenin filaments[11].

VI. DESMOSOMES

Desmoglein and desmocollin are the cadherins. The middle of the intercellular space at the desmosome is the result of the interaction of these transmembrane proteins with those from the neighbouring cell. On the cytoplasmic side of the desmosome, desmoplakina and plakoglobin combine to form an electron-dense plaque. The intermediate filaments in the cytoskeletal desmosome components have a place to attach to this plaque[7].

VII. CELL-MATRIX JUNCTIONS/ FOCAL ADHESIONS

A member of the integrin family of adhesion molecules, the transmembrane component. Different & subunits are heterodimers that make up integrins. There are 24 different ways that the 18 known subunits can be combined. The actin binding proteins actinin, vinculin, and talin are among the cytoplasmic adapter proteins that connect the transmembrane proteins with the actin cytoskeleton. Integrin 64 is a transmembrane adhesive molecule found in hemidesmosomes that binds specifically to the laminin and collagen 17 found in the basal lamina. Hemidesmosomes connect the cell to the rest of the extracellular molecules as well as to the basal lamina. Bulbous pemphigoid antigen 230 and plectin, two cytoplasmic adapter proteins that serve as an attachment for intermediate filaments, form a dense plaque on the cytoplasmic surface of the hemidesmosomes[8].

VIII. GAP JUNCTIONS

The transmembrane proteins of the connexin family form aqueous channels between the cytoplasm of neighbouring cells in plaque-like regions of the cell membrane where intercellular space is 2 to 3 nm. A connexon with 6 molecules and a central channel with a diameter of 2 nm is formed. A channel is created when connexons in one cell pair with those in the adjacent cell[9].

IX. ORAL EPITHELIUM

The primary barrier between the oral environment and deeper tissues is the oral epithelium, a tissue that makes up the surface of the oral mucosa. The oral epithelium is a stratified squamous epithelium made up of cells that are closely packed together and arranged in a variety of clear layers. In order to replace shed cells, cells produced by mitotic divisions in the deepest layers of the oral epithelium migrate to the surface in a process known as continuous cell renewal. Consequently, there are two distinct functional populations of epithelial cells. Progenitor population and maturing population are listed first[12].

X. EPITHELIAL PROLIFERATION

The progenitor cells are located in the thin epithelia's basal layer. A small number of progenitor cells, which are stem cells and cycle slowly, are responsible for producing basal cells and maintaining the tissue's capacity for cell division. Amplifying cells make up the majority of the progenitor compartment; their purpose is to increase the number of cells.

XI. EPITHELIAL MATURATION

Cells that divide in the epithelium's basal or parabasal layers either stay in the progenitor cell population or go through one of two patterns of maturation[11].

XII. THE TWO TYPES OF KERATINIZATION ARE

- KERATINIZATION: The masticatory mucosa's epithelial surface, which includes the hard palate, gingiva, and specialised mucosa on the dorsum of the tongue, is rigid, tough, abrasion-resistant, and closely bound to the lamina propria. The development of a surface layer of keratin, also known as cornification or keratinization, produces the mucosal surface. A layer of cuboidal or columnar cells called the basal layer is found next to the basement membrane. This layer, which can divide, is referred to as the proliferative or germinative layer. Several rows of larger elliptical or spherical cells, also known as the prickle cell layer or stratum spinosum, are located above the basal layers.

This term describes the appearance of cells that have been prepared for histological examination. These cells frequently separate from one another and only make contact at intercellular bridges or desmosomes. The cells have a spiny or prickle-like appearance as a

result of this alignment. Greek prickle is used to describe an increased thickness (acanthosis) or a separation of cells brought on by the breakdown of intercellular bridges in pathology descriptions (acantholysis). The basal and prickle cell layers make up one-half to two-thirds of the epithelium's thickness[13].

Large flattened cells with small granules that strongly stain with acid dyes, such as hematoxylin, are found next to this layer. The granules in this layer, known as the stratum granulosum, are known as keratohyaline granules. Flat cells (squamous) that do not have nuclei and stain brightly with eosin make up the surface layer. This layer consists of the keratinized, stratum corneum, cornified, and horny layers. The surface layer of the parakeratinized epithelium stains for keratin, but the shrunken or pyknotic nuclei are still present. Compared to orthokeratinized areas, there are fewer keratohyaline granules. In the epidermis but is a normal occurrence in the oral epithelium and does not indicate disease. Psoriasis is connected with parakeratinization[12].

- NON KERATINIZATION: The lips, buccal mucosa, alveolar mucosa, soft palate, underside of the tongue, and floor of the mouth all have non-keratinized epithelium as part of the oral cavity's lining mucosa. This mucosa is thicker than keratinized epithelium in thickness. The non-keratinized epithelium has slightly larger basal and prickle cell layers, but less obvious intercellular prickles. The superficial layer's cells lack a granular layer and have frequently swollen nuclei.
- ULTRASTRUCTURE OF EPITHELIAL CELL: Oral epithelial cells in the basal layer have the least amount of differentiation. In addition to organelles, they also have a few distinctive structures that mark them as epithelial cells. Tonofilaments, which are filamentous strands, and desmosomes, which are intercellular bridges, are these structures. Tonofilaments are long filaments with an approximate diameter of 8 nm. They are fibrous proteins produced by the ribosomes. They are a part of the intermediate filaments, which are crucial for the structure of the cell. Chemically, the filaments are cytokeratins, a group of intracellular proteins that are essential components of epithelial tissues. Keratins are categorised as epithelial tissues' constituents. According to their size and charge, keratins are categorised; the types of keratin that are present differ between various stratified epithelia and even between the various cell layers within a single stratified epithelium. when they group together to form tonofibrils, bundles of filaments.

The 30 different proteins known as keratins have a low molecular weight of 40 kDa, which is present in glandular epithelium and simple epithelia. the stratified epithelia's middle molecular weight. those in the keratinized stratified epithelium that have the highest molecular weight, 67kDa. As a result, keratins 5 and 14 are present in all stratified oral epithelia. However, keratinized oral epithelium contains keratins 1, 6, 10, and 16, whereas non-keratinized oral epithelium contains keratins 4, 13, and 19. The ability of any epithelium to act as a barrier is a crucial characteristic that heavily depends on the cohesiveness or close contact of the epithelial cells.

In pemphigus, the epithelium blisters, or the epithelial layers split, resulting in bullous or vesicular lesions inside the epithelium. This splitting results from the breakdown of some desmosomal attachments' constituent parts. Cellular events during maturation: In both types of epithelia, the synthesis of more structural proteins in the form of tonofilaments, the emergence of new organelles, and the production of intercellular matrix occur concurrently with changes in cell size and shape. When moving from the basal to the prickle cell layer, the cells of both epithelia enlarge, but more so in the non-keratinized epithelium. Tonofilament synthesis takes place in both types of epithelium, but in keratinized epithelium, tonofilaments group together to form tonofibrils, whereas in non-keratinized epithelium, they are dispersed and less noticeable. A new organelle, such as membrane coating or lamellate granules, is visible in the upper portion of the prickle cell layer. These tiny, membrane-bound granules, which are about 250 nm in size and comprise glycolipids, come from the Golgi complex. They are long, elongated keratinized epitheliums that have parallel lamellae[15].

The granules in non-keratinized epithelium have an amorphous core and a circular appearance. The keratinized epithelium's granular layer and non-

keratinized epithelium's intermediate layer both contain larger, more flattened cells than the prickle cell layer does. The membrane coating granules appear to be fused with the superficial cell membrane in both keratinized and non-keratinized epithelia, releasing their contents into the intercellular substance. A lipid-rich permeability barrier that restricts the movement of aqueous substances through the intercellular spaces of the keratinized layer in the keratinized oral epithelium is formed as a result of this discharge of granule contents. The inner aspect of the membrane of cells in the superficial part of the granular layer thickens noticeably, providing resistance to chemical solvents. The protein involucrin is one of the main components of this thickening[14].

- KERATINIZED EPITHELIUM: Ribosomes produce the irregularly shaped, 0.5–1 nm-sized keratohyaline granules found in the granular layer of keratinized epithelium. They help the cytokeratins of the keratinized layer to aggregate and form cross-links because they are linked to tonofibrils. Filaggrin, a type of protein, makes up most of the granules. Loricrin, a substance rich in sulphur, is also present.

The organelles, such as the nuclei and Keratohyaline granules, vanish as the cells of the granular layer meet the keratinized layer. Cells in the keratinized layer become packed with filaments that are connected by disulphide bonds as they dehydrate. The keratinized layer's dehydrated cells flatten and take on the shape of hexagonal desks called squames, which are lost during the desquamation process and replaced by the cells from the deeper layers. There are 20 layers of squames that make up the keratinized layer in the oral cavity. The parakeratinized epithelium exhibits incomplete removal of organelles from the cells of the granular layer, and the nuclei still appear as shrunken pyknotic structures[14].

- NON-KERATINIZED EPITHELIUM: In the intermediate cell layer, there is a slight increase in cell size, and the surface layer's cells have a buildup of glycogen. In contrast to keratinized epithelial granules, keratohyaline granules are regular, spherical structures surrounded by ribosomes and are not connected to tonofilaments. They don't contain loricrin or filaggrin. The cells in the superficial layer have a flatter appearance than those in the layers below and have tonofilaments and nuclei that are scattered throughout. The non-keratinized epithelium's surface layer is made up of cells filled with slackly arranged filaments that are not dehydrated[14].
- NON KERATINOCYTES IN THE ORAL EPITHELIUM: The oral epithelium contains cells known as "clear cells," which include melanocytes, Langerhans cells, Merkel cells, and inflammatory cells, and are distinguished from other epithelial cells by having a clear halo around their nuclei (Lymphocytes). Desmosomal attachment cells to neighbouring cells are present in merkel cells. Tonofilaments are absent from all of the cells, and they are not involved in the maturation process[13].
- MELANOCYTES: At around 11 weeks of gestation, they begin to emerge embryologically from the neural crest ectoderm and enter the epithelium. Their long dendritic processes extend between the keratinocytes, but they lack desmosomes and tonofilaments. Melanosomes, which are tiny structures made inside of melanocytes and released into the cytoplasm of nearby keratinocytes by their dendritic processes, are responsible for the production of melanin. Several pigmented lesions in the oral mucosa are developed by melanocytes. Oral melanotic macules resemble freckles in appearance and microscopic examination reveals increased melanin pigment production without melanocyte proliferation. A nevus or mole is a benign melanocyte proliferation. Melanoma is a rare, fatal tumour of melanocytes that develops in the oral cavity[12].
- LANGERHANS CELLS: Above the basal layers of the skin's epithelium and the oral epithelium is another dendritic cell. It appears as a clear cell and has no desmosomal attachments to neighbouring cells. It is distinguished by a tiny flask- or rod-shaped granule, also known as the Birbeck granule ultrastructurally. They come from bone marrow. In order to present antigenic material to the T lymphocytes, they recognise and process it after it enters the epithelium from the outside environment. Local lymph nodes can receive Langerhans cells that have moved from the epithelium[12].

- MERKEL CELLS: Situated in the oral epithelium's and the epidermis' basal layer. In addition to having keratin, tonofilaments, and desmosomes that connect it to nearby cells, the Merkel cell is not dendritic. The small membrane-bound vesicles in the cytoplasm, which are located close to a nerve fibre connected to the cell, are its defining characteristic. These granules may release a transmitter substance across the synapse-like junction between the Merkel cell and the nerve fibre, resulting in the generation of an impulse. Sensory Merkel cells react to touch. These cells develop from the division of an epithelial cell[12].
- GLANDULAR EPITHELIUM: The connective tissue is penetrated by expanding epithelial cells. They could come into contact with the surface or not. The formation of exocrine glands occurs when contact is maintained. Endocrine glands form when contact is broken. Endocrine gland cells are organised in follicles or cords. The second primary division of epithelial tissue is represented by epithelial glands. Unpaired glandular cells make up unicellular glands. Clusters of cells make up multicellular glands.

A basal lamina is created around glandular epithelia. The parenchyma of the gland is made up of the secretory units and their ducts, whereas the stroma of the gland is made up of the connective tissue that invades and supports the parenchyma. Additionally, it produces its goods intracellularly through the synthesis of macromolecules, which are typically contained and stored in vesicles referred to as secretory granules[12].

CONCLUSION

Epithelia are obviously more than just a physical barrier. They are active participants in the host defence system with sensors, signalling circuits, and molecules that carry out a graduated response to microbes. These epithelial responses molecules and pathways are currently the subject of extensive research. Identification of potential targets in the airway epithelium for intervention requires a thorough understanding of the mechanisms that start the development and progression of gene transcription or translation. It would also be simple to incorporate additional facets of cell biology, like cell division or apoptosis, or active behaviours, like migration, oscillations, and fluid pumping. Additionally, numerical simulations are required to study how disorder and noise affect the morphology of epithelial sheets.

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