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Original Article

Unfolding Various Concepts of Junctional Epithelium

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Abstract

The Gingival epithelium comprises of three different areas based on their anatomical and functional points of view 1) the oral or outer epithelium (OGE), 2) Sulcular epithelium (SE) and 3) Junctional epithelium (JE). The junctional epithelium may be regarded as the most interesting structure of the gingiva. . The formation of junctional epithelium in the implant/ mucosal interface can be considered as the first barrier of defense against oral micro flora. Any kind of disruption of this barrier will lead to initiation and progression of progression of periodontal disease. Hence, in this review we made an attempt to wrap various concepts of junctional epithelium formation, its role in disease progression and its relation to the implant surface.

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Introduction

Junctional epithelium (J.E) rather than simply providing an attachment to the tooth surface it actively participates in host defense mechanisms. Hence it is regarded as the most interesting structure of gingiva. [1] The key function of J.E is to clear and thwart the continuous bacterial challenge by allowing the cells and substances to emigrate from the sulcus into the gingival connective tissue considering it as an 'open system'. [2] Amongst the gingival epithelium a spot light on J.E is important because of its location anatomically and as because it is the site of host-bacterial interaction in the initiation of periodontal disease.

Definitions

"A unique squamous non-keratinized epithelium that forms the base of the gingival sulcus and adheres to both tooth and the underlying lamina propria at the base of the gingival crevice formerly called as epithelial attachment" – AAP. [3]

"The Junctional epithelium is the epithelial component of the dento-gingival unit that is in contact with the tooth surface" – Bosshardt and Lang. [2]

Terminologies

Epithelial attachment – Gottelieb 1921
Epithelial cuff – Waerhaug 1952
Attached epithelial cuff – Orban 1956
Junctional epithelium – Stern 1967

Concepts of Junctional Epithelium

The history of the development, structure and dynamics of the epithelial attachment, has been reviewed and retold since many years.

G.V. Black (1915) suggested that as the tooth erupts into the oral cavity, the oral and odontogenic epithelium fuse to form a continuous lining. According to Black, at the CEJ the apical end of the sulcular epithelium was only attached. [4]

Microscopically the presence of a firm attachment around the tooth was first demonstrated by Gottelieb (1921) which he termed as "epithelial attachment". [5]

Holton (1937) concluded that there was no real connection found to exist between enamel and epithelium with the introduction of dyes into the attachment.

Waerhaug (1952) observed that the epithelial cells attached to the surface of artificial crowns which were in contact with the pocket epithelium was due to adhesion and described this junction as the EPITHELIAL CUFF. [6]

Orban (1960) demonstrated a firm attachment of epithelial cells to the teeth in his experimental study where he inserted steel blades into the sulci of dogs and monkeys. This experiment was in agreement with the Gottelieb's concept of firm attachment.[7]

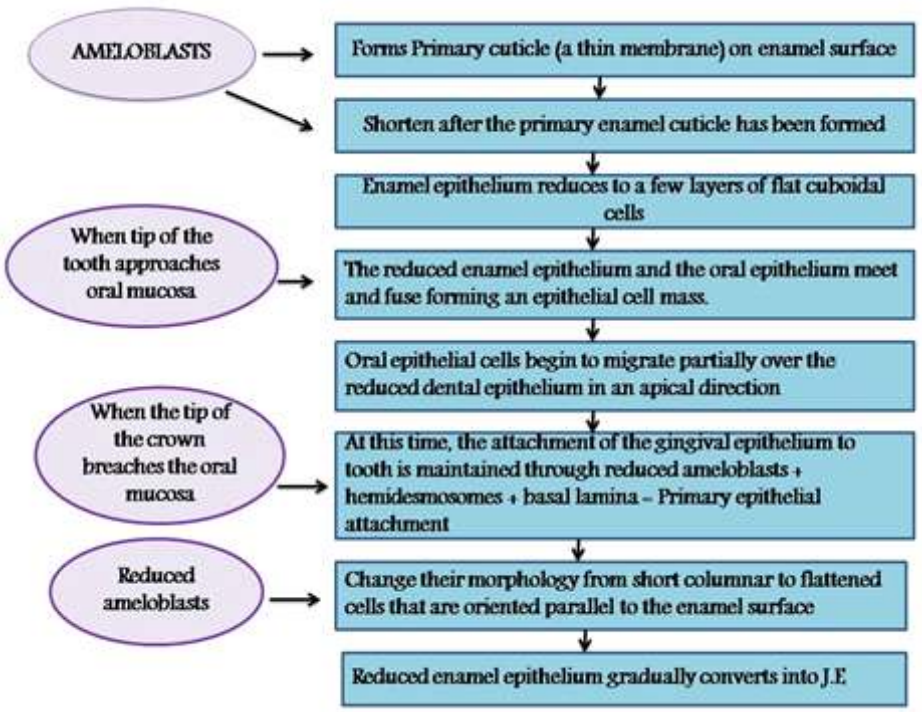
Listgarten (1966) felt that epithelial cells attach to the tooth by means of hemidesmosomes and a basement membrane (basal lamina) despite their origin, whether derived from reduced ameloblasts or oral epithelium. Since cells move along the tooth surface from the apical portion of the epithelial attachment to the base of the sulcus this attachment is not considered static.[5]

Stern (1981) reported a width of lamina lucida is 400 A°.[6]

Sabag et al (1981) described that 4 to 8 hemidesmosomes at the coronal zone and 2 hemidesmosomes in the apical zone mediate the epithelial attachment to the cementum root surface concluding that more adhesion is exhibited by the coronal zone of cemental surface when compared to apical zone.[6]

The opinion that attachment to the tooth surface may occur even without the cuticle being present and the cuticle only represents an accumulation of material from metabolites of plaque, which was suggested by Friedman in 1993.[7]

Development of the Junctional Epithelium:



The final conversion of reduced enamel epithelium to a stratified squamous epithelium may not occur until 3-4years after the tooth has erupted.[8]

The development of the dento-gingival junction may be regarded as complete, immediately after all the reduced enamel epithelium has been transformed into the squamous epithelium.

At this time, it extends to the cemento-enamel junction and its epithelial component consists of junctional epithelium, formed largely by transformation of reduced

enamel epithelium. Interface between J.E and the tooth surface forms ? secondary epithelial attachment.[9]

Anatomy of the Junctional Epithelium:

Junctional epithelium is stratified squamous non keratinizing epithelium which forms a collar like band peripheral to the cervical region of tooth. JE coronally terminates as a free surface which is located at the base of sulcus. Length of JE is 0.25 to 1.35 according to Carranza; and according to Gargiulo is 0.71 mm-1.35 mm. [10] The epithelial seal extends from CEJ to marginal gingiva under pristine conditions which is 2mm in height and is attached to the tooth surface (epithelial attachment) by the internal basal lamina and to the gingival connective tissue (basal layer) by an external basal lamina.[11](Figure 1)

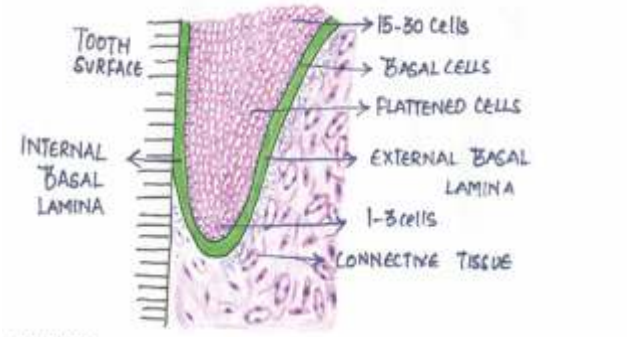


FIGURE 1.

Histological diagram showing the number of junctional epithelial cells 1 to 3 cells at the apical zone where as15-30 cells at the coronal zone

Cellular inclusions of Junctional Epithelium:

The basal cell layer and the adjacent 1 to 2 suprabasal cell layers are cuboidal to slightly spindle shaped and the remaining layers of suprabasal cell layers are flat, oriented parallel to the tooth surface, and closely resemble each other. (Figure 2)

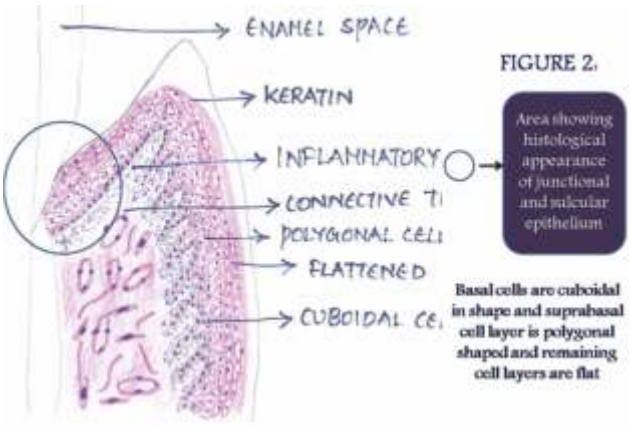


FIGURE 2.

Basal cells are cuboidal in shape and suprabasal cell layer is polygonal shaped and remaining cell layers are flat

The inner most suprabasal cells facing the tooth surface are also called as DAT cells (Directly Attached to Tooth) (Salonen *et al.*, 1989).[12]

In general, the transformation of gingival sulcus to periodontal pocket is the result of disturbances or imbalance between microbial attack and host defence mechanisms. Locally, this process includes the degeneration and detachment of coronal DAT cells from the tooth surface. DAT cells forms and maintains the 'internal basal lamina' that faces the tooth surface and these cells may also share some additional characteristics with the basal cells since they have the ability to form an attachment. [13] Morphologically, DAT cells vary from low cuboidal to flatten cells. This variation in cell morphology did not correlate with the cells potential to synthesize DNA instead the prerequisite for DNA synthesis is the capability of attachment of individual suprabasal cells to the tooth surface.[14]

Along with the DAT Cells, lysosomal bodies, cytokeratins, polymorph nuclear lymphocytes are found in J.E cells.

Lysosomal bodies are found in more numbers in J.E cells. Enzymes contained within these lysosomes share a role in the eradication of bacteria.[15]

Cytokeratins belong to intermediate filament (IF) protein family that provides mechanical support and fulfil a variety of functions in epithelial cells. [16] Cytokeratin distribution varies in different epithelia; its distribution in oral epithelium is different from junctional epithelial complex which is adjacent to the tooth surface.

Various cytokeratins detected immune histochemically in J.E are CK 19, CK 16, CK 14, CK 13, CK 6, CK 5, and CK 4. According to the findings of Juhl et al CK13 is more frequently found in the coronal part of JE and is considered to be a differentiation marker for non-

keratinized squamous epithelia. [17] A study was done by Feghali-Assaly et al to identify the above mentioned cytokeratins in partially erupted human dentition and concluded that the following cytokeratins are seen in PJE (Primary junctional epithelium)[18]

PJE In Basal layers - CK 19, 16, 13 and 4 mRNAs were abundant
In Supra basal layers - CK 19 less concentrated but CK 13 and 4 is abundant } PJE

Neutrophilic granulocytes are the immune defense cells of the J.E, also called as polymorphonuclear leukocytes, neutrophils and PMNs. They are abundantly found in the central region of the J.E (Schroeder and Listgarten 1997).[19] > 50% of the leukocytes infiltrating the J.E and 90% of the leukocytes isolated from the crevicular fluid are neutrophils. The periodontal tissues neutrophilic concentration exceeds the blood neutrophil concentration.[20] (Table 1)

Table 1

TISSUE	COUNT OF NEUTROPHILS
Connective tissue of minimally infiltrated gingiva	2.5×10^7 PMN/cm^3
Junctional epithelium of minimally inflamed gingiva	1.7×10^8 PMN/cm^3
Blood levels of neutrophils range	1×10^6 to 4×10^6 PMN /cm3

The epithelial attachment: The basement membrane is made up of external and internal basal lamina. The external basal lamina lies between internal basal lamina and basal cells of J.E. The internal basal lamina is found to be continuous with the external basal lamina at the apical end of junctional epithelium. [21] By means of internal basal lamina together with the hemidesmosomes the junctional epithelium is attached to the tooth surface. This is called epithelial attachment (Figure 3 and 4).

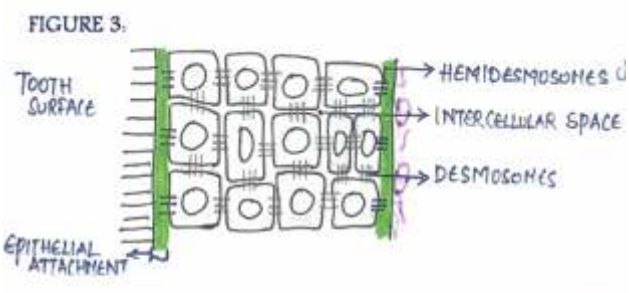


FIGURE 3.
Diagrammatic representation of various intercellular junctions (hemidesmosomes and desmosomes)

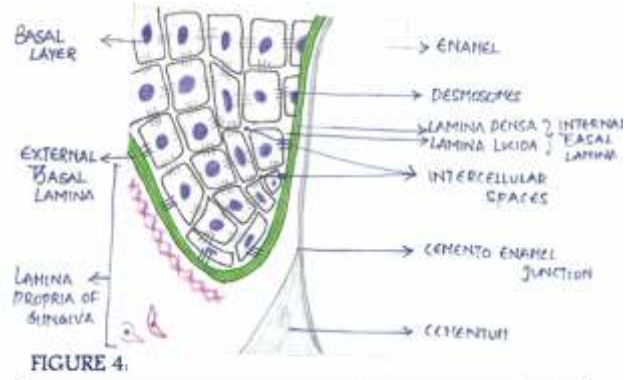


FIGURE 4.
Diagrammatic representation showing internal and external basal lamina

Basement membrane operate special functions like

1. Compartmentalization (physical barrier function),
2. Filtration (selective permeability barrier function),
3. Cell polarization,
4. Migration,
5. Adhesion, and
6. Differentiation[22]

Internal basal lamina consists of;

a) Lamina lucida also called as Lamina rara
b) Lamina densa
c) Lamina Fibroreticularis also called as Sub-basal lamina.

Sub basal lamina faces the connective tissue and forms a layer of reticular and anchoring fibrils. Generally, basement membrane matrix typically constitutes type IV and type VII collagen, laminin, heparan sulfate, proteoglycan, fibronectin, nidogen (entactin), and the proteoglycan perlecan, while the basement membrane of J.E lacks most of these constituents like as collagen types IV and VII, most laminin isoforms, perlecan.[23] Thus, the internal basal lamina of J.E cannot be regarded as basement membrane as it has its own characteristics.

Intercellular Junctions

There are various cell junctions in epithelial tissues and play a key role in enabling communication between neighbouring cells via specialized proteins called communicating junctions.

Generally, there are three major types of cell junctions:

a) Anchoring junctions

b) Gap junctions (communicating junction)
c) Tight junctions (occluding junctions)[24]

Three types of anchoring junctions are noticed; they are desomosomal junctions, hemidesmosomal junctions and adherens junctions and they differ from one another in their cytoskeleton anchor and the Trans membrane linker.[25] (Table 2)

Table 2

Junction	Desmosomes	Hemides-mosomes	Adherens junctions
Cytoskeleton anchor	Intermediate filaments	Intermediate filaments	Actin filaments
Transmembrane linker	Cadherin	Integrins	Cadherin / Integrins
Ties cell to	Other cells	EC matrix	Other cells / EC matrix

Gap junctions are also called as nexus or macula communicans and are specialized intercellular connections which directly connect the cytoplasm of two cells. These gap junctions allow various molecules, ions and electrical impulses to directly pass through a regulated gate between the cells.[26]

Tight junctions also known as occluding junctions or zonulae occludentes (Singular, Zona occludens) are composed of a branching network of sealing strands. Therefore, the efficiency of the junction in preventing ion passage increases exponentially with the number of strands.[27]

J.E cells are interconnected by few desmosomes and occasional gap junctions contrary to stratified squamous gingival epithelium whose cells are connected by all the three types of junctions.

Innervations

The junctional epithelium is well innervated by sensory nerve fibers especially the basal cell layers, which have been subsequently been confirmed by immunocytochemical studies.[28,29] These studies observed that several dense nerve plexus are distributed and detected in the apical two-thirds of the epithelium, near the gingival sulcus and the enamel surface. Tanaka and co-workers they employed substance P, calcitonin gene-related peptide (CGRP) and neurokinin-1 receptor and demonstrated the existence of nerve terminals. In the intercellular spaces between basal cells of junctional epithelium substance P- axon profiles were detected immune histochemically.[30]

Dynamics of the Junctional Epithelium

Knowledge about progressive alteration of cellular and extracellular aspects of J.E is important as these dynamics are crucial in maintaining its protective and regenerative functions.[31] The characteristic feature of J.E in primates is its high cellular turn over which

is about 1week to 10 days.[32] Turn over happens by mitotic cell division which is seen at the basal cell layers and DAT cells and the subsequent migration of cells towards the coronal direction resulting in gradual exfoliation of daughter cells from the free surface of J.E. Also, Since the DAT cells are connected to the basal lamina the DAT cells are said to migrate towards the bottom of the sulcus. Thus, the epithelial attachment is dynamic not static.[33]

Role of JE in Antimicrobial Defence

A variety of molecules are transported by the tissue fluid to the bottom of gingival sulcus through the J.E. These molecules along with PMNs they represent host immune defense mechanism against the bacterial insults. Approximately 30,000 PMNs per minute migrate into the oral cavity through the J.E in the absence of clinical signs of inflammation. Thus, gingival fluid is considered as an exudate and its flow rate is directly proportional to the degree of inflammation.

Various mechanisms involved in antimicrobial defense:

1. High turnover rate of J.E is crucial in antimicrobial defense
2. The surface area of J.E is 50 times larger and hence allows for effective flow of epithelial cells and impedes bacterial colonization and thus acts as an effective barrier. This is called as Funnelling effect.
3. Defensins and lysosomal enzymes produced by the cells of J.E which functions as antimicrobial defense

4. Chemokines which are secreted by activated epithelial cells attracts various cells like defensins and lymphocytes which activate further inflammatory process.[2]

Role of the Junctional Epithelium in the initiation of Pocket Formation

Pocket formation initiates by detachment of DAT cells from tooth surface. A biologically relevant and clinically important question raised by Schroeder (1996) is: 'what happens to the junctional epithelium under conditions of sub-gingival microbial attack, *i.e.*, in context with pocket formation and deepening?' This question still awaits resolution but meanwhile several researchers have attributed the formation of pocket to a loss of cellular continuity in the coronal-most portion of the J.E.[34]

Clinically, factors of both microbial and host origin alter the JE in several ways like the attachment apparatus between the JE and the teeth can be broken down (or) the biosynthetic function of the DAT cells can be altered (or) cell lysis can be induced (or) renewal of the DAT cells can be inhibited.[35]

Takata and Donath (1988) [36] studying pocket formation in humans, observed degenerative changes in the second or third cell layer of the DAT cells in the coronal-most portion of the junctional epithelium facing the bacterial biofilm. Similar observations were made in a dog model. [37] Several attempts to explain the reason for the cleavage within the junctional epithelium have been made. With increasing degrees of gingival inflammation, both the emigration of PMNs and the rate of gingival crevicular fluid passing through the intercellular spaces of the junctional epithelium increase. [38] Moderately distended intercellular spaces are not considered to interfere with the structural and functional integrity of the junctional epithelium. However, an increased number of mononuclear leukocytes, *i.e.*, T- and B-lymphocytes and monocytes/ macrophages, together with PMNs, are considered as factors that contribute to the focal disintegration of the junctional epithelium. [39] Apart from the view that the host itself is the major source of factors contributing to the disintegration of the junctional epithelium, other possibilities have to be considered as well.

Various factors of both microbial and host origin which can clinically alter J.E, they are:

1. The attachment apparatus between the JE and the teeth can be broken down
2. DAT cells biosynthetic function can be altered
3. Stimulation of DAT cell lysis
4. DAT cell lysis renewal inhibited

All these mechanisms ultimately lead to degenerative changes in JE which further promote detachment of epithelium from the root surface and subsequently lead to periodontal pocket formation. But, this is not thoroughly being studied and the development of optimal model systems is still in progress. Thus, the development of pocket is attributed to detachment of the DAT cells or to the development of an intra-epithelial split.

Junctional Epithelium and Microbiota

The Junctional epithelium allows various cells and molecules to migrate into the sulcus from gingival connective tissue which helps in fighting against continuous bacterial invasion, and

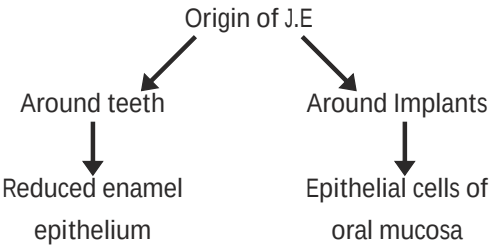
in contrast bacterial cells are also permeable to enter into J.E hence it is considered as “Open system”. It has already been studied that the pocket formation results due to subgingival spread of microbiota under impaired defense conditions.[40] So, various authors have further extended their studies[41,42,43] to know about various mechanisms exercised by microbiota in the destruction of J.E. However, amongst all microbiota, a keen interest is paid to know the mechanisms played by Actinobacillus actinomycetemcomitans (A.A comitans) and Porphyromonas gingivalis (P. gingivalis) to adhere, replicate and invade epithelial cells.

Cysteine proteinases produced by P.gingivalis commonly regarded as Gingipains[44], specially degrade cell-cell epithelial junctional complexes leading to proteolysis of focal contact components, adhesion signaling molecules, adherens junction proteins, reduced adhesion to

extracellular matrices, changes in morphology, impaired motility, and apoptosis.

Various studies have also reported that Gingipains disrupts the ICAM-1-dependent adhesion of PMNs to oral epithelial cells allowing P.gingivalis to enter J.E leading to proteolytic disruption of the epithelial integrity, a significant factor in pocket formation initiation.

Junctional Epithelium adjacent to Oral Implants



Hence, it is the subject of interest whether or not these 2 J.E is identical in their structural and functional characteristics. However, although the 2 epithelia resemble similar structurally [45,46,47], few dissimilarities have been reported[48,49,50] (Figure 6)

Table 3:

	HEALTHY TEETH	HEALTHY IMPLANTS
Sulcuar depth	Shallow in absence of disease	Sulcular depth varies, depending upon the length of abutment and restorative margin.
J.E	On the enamel surface	On the metal surface of the implant
Biologic width	Supracrestal	Subcrestal
Gingival fibres	Fibres inserted on to the	Collagen fibres are arranged in parallel fashion
	cementum above the crest of the bone and arranged in a complex manner	
Crest of the bone	1-2 mm apical to CEJ	Crest of the bone varies - According to the design of the implant - If the implant surface is threaded then the crest of the bone lies about the first thread
Physical characteristics	Slight mobility is present and normal because of the visoelastic properties of periodontal ligament	No mobility present and resembles ankylosed unless infected
Adaptive characteristics	Adaptive capacity varies according to the amount of occlusal forces	No adaptive capacity present due to the abscence of periodontal ligament.
Proprioception	Good proprioception because of presence of high sensitive receptors	No proprioception.

FEW KEY SIMILARITIES BETWEEN IMPLANT-EPITHELIUM JUNCTION & JUNCTIONAL EPITHELIUM:

- Epithelial cells in both the epithelia are attached to the tooth by hemidesmosomes.
- A viable biologic seal exists between both the epithelia
- Sulcus around the implant is also lined by sulcular epithelium which is continuous with J E
- Capillary loops under both the epithelia appear to be similar
- Certain marker molecules of defense mechanism against bacterial challenge like t- PA, ICAM-1, cytokeratin profile etc., appear similar to that of gingival J.E

Histochemical Aspects of normal Junctional Epithelium[51,52]

Histochemical techniques are considered important as they provide knowledge regarding various enzyme systems and chemical components that appear in normal gingiva which help us in appreciating physiologic processes in the gingiva and the changes that occur in disease. Following are various cellular and intercellular substances and enzymes that can be appreciated in the normal gingiva.

Cellular and intercellular substances

1. Heteropolysaccharide which stains PAS +ve is an intercellular ground substance seen between the cells of

the epithelium.

2. Acid mucopolysaccharides, hyaluronic acid, chondroitin sulfate A, C and B etc., PAS –ve are present between the epithelial cells, and are considered by some investigators to be intercellular cementing substance and by others to be certain stained portions of intercellular attachment apparatus.
3. PAS +ve glycogen is present in the epithelium in concentrations inversely related to the amount of keratinisation.
4. Normally sulfhydryls and disulfides bonds are present in the gingival epithelium.
5. The DNA and RNA activity of the epithelium at the gingival margin and junctional epithelium is greater than in the remaining oral mucosa.

Enzymes

Various enzymes found to be present in the J.E are:

- ã Collagenase
- ã Alkaline phosphatase
- ã Lysosomes
- ã Diphospho and triphosphopyridine nucleotide reductase
- ã Cytochromic oxidase

Regeneration of the junctional epithelium:

Because of its anatomical location, injury of J.E may occur through various mechanical methods or clinical probing or through some intentional trauma.

- ã Clinical Probing:

  Clinical probing disrupts J.E cells mechanically from the tooth surface. Several studies focused on whether and how fast a new epithelial attachment can be reformed. An experimental study done in marmosets was shown that 5 days after complete separation of J.E following clinical probing, a new epithelial attachment was established.

In another study it was shown that epithelial seal around implants was re-established within about the same time period following clinical probing.[53] Based on the findings of these 2 studies, clinical probing around implants and natural teeth does not lead to irreversible damage of the soft tissue components.

Ø Oral Hygiene Practices:

Regular oral hygiene practices may cause unintentional trauma to J.E. Waerhaug (1981) reported that following the use of dental floss in 12-year-old humans at premolar regions and after cessation of flossing there is detachment of cells which persisted for 24 hours and then new epithelial reattachment started within 3 days.[54]

ã Gingivectomy :

Oral hygiene never completely removes J.E from tooth surface. However, the application of gingivectomy techniques would completely remove J.E. Subsequently, the formation of a new J.E must occur from basal cells of the oral gingival epithelium.

In humans, a new J.E after gingivectomy may form within 20 days indicating that it is a highly dynamic tissue with a fast self-renewal capacity.[55]

ã Scaling And Root Planing

JE forms in 2 weeks after phase I therapy.[56]

ã Open Flap Debridement

Formation of long J.E occurs in 4-6 months.[57]

ã Mucogingival Surgery :

It takes 3-4 weeks and the stages involved are: - adaptation, proliferation, attachment and maturation.[58]

Conclusion

Junctional epithelium is a unique tissue that fulfils a challenging function at the border between the oral cavity, colonized by bacteria, and the tooth attachment apparatus. It is structurally and functionally very well-adapted to control the constant bacterial ingress. Its structural alteration is clearly the first step towards the progression of disease. The conversion of the J.E to pocket epithelium is regarded as a hallmark in the development of periodontitis. Thus, understanding the molecular architecture and function of the junctional epithelium attachment may aid in the understanding the onset and progression of periodontal disease and may provide new possibilities for manipulating periodontal healing.

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