Junctional Epithelium: A dynamic seal around the tooth

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Junctional epithelium located at an interface of gingival sulcus and periodontal connective tissue, provides a dynamic seal around the teeth, protecting the delicate periodontal tissue from offending bacteria, which is critical for health of supportive periodontal tissue, and hence tooth as a whole. Its rapid turnover is important for maintaining tissue homeostasis. It plays a more active role in innate defense than what was thought earlier. In addition, it expresses some mediators of inflammation involved in immune response. Its unique structural and functional adaptability maintains the anti-microbial security. Detachment of JE from tooth surface is the hallmark of initiation of periodontal pocket, and hence periodontitis. This review article has made an attempt to put light on various aspects of this unique tissue.

INTRODUCTION

Junctional epithelium represents the epithelial component of the dento-gingival complex that lies in contact with the tooth surface, at the interface between the gingival sulcus and the periodontal ligament fibers¹. It forms an intimate seal around the tooth, the so-called ‘epithelial attachment’, that serves as an effective barrier, protecting the delicate periodontal tissues from exterior¹. It provides definite anti-microbial defense by the barrier action, as well as by secreting different anti-microbial peptides. Junctional epithelium shows a markedly high turnover rate, and plays an important role in tissue homeostasis². Schroeder and Listgarten first clarified the ultra-structure of dento-gingival junction (using electron microscope) in a monograph named ‘Fine structure of developing epithelial attachment of human teeth’³. After that, various research works have been done on this and the knowledge has been reviewed in number of articles. The aim of this article is to discuss various structural and functional aspects of this tiny unique tissue, called junctional epithelium.

HISTORICAL ADVANCEMENT

There was little information available regarding the junction of tooth and epithelium in early twentieth century. G.V. Black (1915) opined that a ‘sub-gingival space’ extends up to Cemento-enamel Junction, under loosely fitting gingiva. It was Gottlieb, who first depicted the connection between tooth and gingiva (1921). He believed in existence of an organic union between tooth and gingiva, which he referred as ‘epithelial attachment’ (epithelansatz). This was accepted universally until
Waerhaug (1952) challenged Gottlieb’s idea and disagreed any organic union. He declared that gingiva is separated from tooth by a capillary space forming ‘epithelial cuff’. The conflict between two schools of thought went on until Orbans, a disciple of Gottlieb, agreed to both and put forward the concept of ‘epithelial attachment cuff’. Later Stern (1962) demonstrated in rat incisor that the dento-gingival junction consists of basal lamina and hemi-desmosomes. Four years later, with Anderson, he coined the term ‘junctonal epithelium’. Finally Schroeder and Listgarten (1971), with electron microscopic study, gave detailed description of the ultra-structure of juncional epithelium [5].

**DEVELOPMENT**

The Junctional Epithelium forms with the eruption of tooth crown into the oral cavity [6]. It arises from the Reduced Enamel Epithelium, forming a collar around the cervical part of the tooth along cemento-enamel junction; while it’s free surface forms the floor of sulcus [4]. Its development takes place in the following way:

At the late bell stage, the crown an erupting tooth, is covered by reduced enamel epithelium, consisting of reduced ameloblasts and the remaining cell layers of enamel organ before the emergence of tooth into the oral cavity [6]. When the crown is about to breach the oral mucosa, cell transformation process begins from cuspal/ incisal margin towards cemento-enamel junction [6,2,1]. At the time of transformation, the reduced ameloblast changes their shape from short columnar to flattened cells, lying parallel to the enamel surface and the cells present externally regain mitotic activity after undergoing a structural change [2]. These transformed ameloblast cells migrate coronally, exfoliating at the base of sulcus, and are being replaced by the external cells [2]. Within 1-2 years, reduced enamel epithelium gradually converts into multi-layered junctional epithelium [1,7,8,2]. The primary Junctional epithelium develops from cells of inner layers of reduced enamel epithelium, but later on the external cells of the transformed amelo blast gradually replace them, forming secondary Junctional epithelium [2]. The juncional epithelium, that was originally derived from the reduced enamel epithelium, can be replaced by a junctional epithelium developed from basal cells originating from the gingival epithelium [9]. This holds true, at least, for *de novo* formation of the juncional epithelium [10,11]. Even, basal cells other than those of gingival origin also can regenerate a junctional epithelium [12, 13, 14, 15]. According to the recent studies, the primary junctional epithelium develops more specifically from the reduced amelo blast associated proteins and amelotin which also has the capacity for regeneration of junctional epithelium [16,17,18].

**MICROSCOPIC FEATURES**

Junctional epithelium is a non-keratinized stratified squamous epithelium that surrounds the tooth like a collar with a wedge like cross-section [19]. Externally it is attached to the tooth surface, whereas internally it is being supported by the gingival connective tissue [20]. Again, periodontal ligament limits its apical extent, and coronally it is continuous with sulcular epithelium [20].

- **Thickness**: 15-30 cell layers at the coronal end, which tapers to 1-3 cells layers at the apical end.
- **Length in average**: 0.25mm-1.35mm

This non-keratinizing stratified squamous epithelium is made up of two strata: bas**al layer and the supra-basal layer [20].

- Basal layer – consisting of cuboidal cells, are arranged along the connective tissue interface [20].
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Junctional epithelium is attached to gingival connective tissue by an external basal lamina, while it is attached to the tooth surface by internal basal lamina. The single layer of cell, lying in contact with tooth surface, is referred to as DAT (Directly attached to tooth) cells [20]. Recent studies indicate that they are capable of undergoing cell division [21]. The existence of a proliferating population of epithelial cells (DAT cells) in a supra-basal location, several layers away from the connective tissue, is a unique feature of the junctional epithelium. This possibly results from specific permissive or instructive signals provided by the internal basal lamina matrix on the tooth surface. Therefore, any structural/ molecular changes in the internal basal lamina can influence the DAT cells homeostasis and also, its antimicrobial defense or vice versa. The interaction between the IBL and cell surface macro-molecule is fundamental for cell motility, adhesion, synthetic capacity, tissue stability, regeneration and response to external signal [22]. DAT cells possess the capacity to form and renew the components of epithelial attachment [23,24].

The cells of junctional epithelium present following features:

1. These cells contain dense cytoplasm, abundant rough endoplasmic reticulum, Golgi complex, few tonofilaments, lysosomal bodies and numerous polyribosomes [2,4].

2. Cytokeratins (CK) are the intermediate filament proteins of cytoskeletal family and form the main structural proteins of these Junctional epithelial cells [25,26]. They express CK5, CK10, CK13, CK 14, CK16 and CK19 [2, 27,28,29,30]. The expression of CK19 being high, found in almost all the layers of junctional epithelium, have been regarded as the characteristic histological marker for Junctional epithelium [27,28,29,30].

3. The cells exhibit relatively loose intercellular junctions comprising of few desmosomes, adherens junctions and occasional gap junctions [31,32,9, 33-35]. The fluid-filled inter-cellular spaces are responsible for remarkable permeability [35].

4. Intercellular spaces are occupied by mononuclear leukocytes of varied nature. Different types of cells like the polymorphonuclear leukocytes, lymphocytes, macrophages, antigen-presenting cells, Langerhans cells are seen to exist in and around the junctional epithelium cells [31, 36,1,37].

5. It is also being innervated by sensory nerve fibers [38,39]. Therefore, it aids in neuro-sensory pain conduction, by releasing Neuropeptides, that helps in plasma extravasation and immigration of leucocytes with endocytic activities [40,41].

Junctional epithelium presents two basal-lamina: one facing the gingival connective tissue is the external basal lamina, while the other facing the tooth surface represents the internal basal lamina. External basal lamina contains the structures similar to that of typical basement membrane, with the lamina densa supporting the underlying connective tissue and lamina lucida lying in between the lamina densa and the basal keratinocytes [2,42].

Internal basal lamina lacks true basement membrane components like: collagen IV and VII, laminin 111, laminin 511, perlecan, heparan sulfate proteoglycan, fibronectin, nidogen [43,2]; while it contains cell-adhesion protein- laminin 332, laminin 5 [22,43,44,45]. Epithelium-tooth interface contains versican and type VIII collagen (usually absent in typical basement membrane); hence
now-a-days it is considered as a specialized extracellular matrix \[46,47\].
The gingiva (specifically junctional epithelium) is adherent to tooth through a structural complex, referred to as epithelial attachment apparatus \[4\]. This consists of hemidesmosomes and a basal lamina, i.e. internal basal lamina, to which the cells are attached through hemidesmosomes \[4,13,49\].
The hemidesmosome comprises of an attachment plaque, cytokeratin filaments and a sub-basal lamina dense plate \[50\]. They are believed to act as sites for signal transduction. The interaction between IBL and cell surface macro-molecule helps in cell motility, adhesion, synthetic capacity, tissue stability, regeneration and response to external signal \[51\].
The elements of attachments are produced and renewed by the adjacent DAT cells \[24\]. This attachment mechanism are shown to exist on dental calculus layer in a bacteria-free environment (Listgarten & Ellegaard, 1973) \[50\].
The connective tissue supporting junctional epithelium is different from that of outer and sulcular epithelium both structurally and functionally \[3\]. It contains extensive blood vascular plexus, and varying amount of inflammatory cells, such as PMNs and T-cells, migrate into the gingival sulcus and oral fluid \[3\].
Junctional epithelium can be considered as “Incompletely developed striated squamous epithelium. Alternatively, it can be viewed as a structure that evolves along a different pathway and produces the components of epithelial attachment instead of progressing further into a keratinized epithelium” (Nanci & Bosshardt, 2006).
The special nature is attributed to the connective tissue supporting it. Thus it is functionally different as it provides instructive signals for the normal progression of stratified squamous epithelium which is absent in other parts of gingiva \[52,53\].

Function:
1. Barrier: junctional epithelium forms a dynamic seal around the tooth, protecting delicate periodontal tissues from external environment, and acts as a physical barrier \[1\].
2. Rapid turnover: junctional epithelium shows exceptionally high turnover rate, which not only maintains a structural integrity but also adopts itself as per need \[54,33,55,21\].
3. Anti-microbial function: junctional epithelium has no keratinized layer at its free surface, some special structural and functional characteristics compensate for absence of this barrier, thereby help to maintain a potent anti-microbial mechanism, which is a unique property of J.E \[2,31\].

- **Antimicrobial mechanisms in junctional epithelium**
  I. In the coronal part, rapid cell exfoliation occurs due to high turnover rate and funneling of cells towards the sulcus prevents bacterial colonization \[51\].
  II. Laterally, the (external) basal lamina forms an effective barrier against invading microbes \[51\].
  III. Active antimicrobial substances are produced in junctional epithelial cells. These include β-defensins, secretory leucocyte protease inhibitor (SLPI1), S100A8 and lysosomal enzymes \[56-58,60\]. β-defensins are anti-microbial peptides which function as innate defense mechanism against the bacterial challenge \[57,58\]. SLPI-1 is responsible for the maintainance of tissue integrity while S100A8 & 9 form a heterodimeric complex, thus forming an antimicrobial peptide \[61,62\].
Junctional epithelium cells activated by the antimicrobial substances secrete variety of cytokines (like keratinocyte derived chemokine, macrophage inflammatory protein 2) that bring and activate neutrophils. In addition, the junctional epithelial cells express follicular dendritic cell secretory protein and odontogenic ameloblast associated protein. The genes encoding these proteins lie adjacent to the cluster of genes encoding for C-X-C chemokines. These interactions are suggestive of a close association between the expression of pro-inflammatory cytokines and the expression of products by the junctional epithelium as mentioned above.

IV. These cells also have an endocytic capacity equal to that of macrophages and neutrophils and this activity is protective in nature.

- **The role of the epithelial attachment in tooth resorption of primary teeth**
  Bernice S et al suggested that during tooth resorption, the epithelial attachment proliferates apically, destroying the attachment fibers either by a lytic or pressure effect, causing degeneration and detachment of the principal fibers. The fibers below the epithelial attachment remain attached to the viable cementum. Then an inflammatory process accompanies the migrating epithelium. This process continues until the epithelium reaches the resorbing area of tooth structure aiding in the final exfoliation of the deciduous tooth.

- **The Role of junctional epithelium in formation of periodontal pocket**
  The transformation of the junctional epithelium into pocket epithelium is regarded as a hallmark in the development of periodontitis. The initiation of formation of periodontal pocket may be either due to the detachment of DAT cells from the tooth surface or it may due to the development of an intra-epithelial split. Progressive inflammation of gingiva causes destruction of collagen fibers just apical to junctional epithelium, and the area becomes occupied by inflammatory cells and edema. Consequently cells from apical end of junctional epithelium proliferate along root surface. When relative volume of cellular infiltrates reach 60%, the tissue loses cohesiveness, and coronal part of the junctional epithelium gets detached from tooth surface and gets converted to sulcular epithelium, and subsequently the base of the sulcus shifts apically. Thus gingival sulcus is transformed to periodontal pocket, with the commencement of periodontitis.

- **Regeneration of Junctional Epithelium**
  Waerhaug (1981) studied healing of the junctional epithelium after the use of dental floss at premolars in 12-year-old humans. He observed that detachment of cells persisted for 24 hrs after flossing ceased. Then new attachment of junctional epithelial cells started 3 days after flossing ceased. Finally the cell populations on the experimental and control surfaces were again indistinguishable after two weeks.

  In general, a new junctional epithelium after gingivectomy forms within 20 days.

- **Junctional epithelium in relation to implants**
  The junctional epithelium around implants originate from epithelial cells of the oral mucosa. Structurally, the peri-implant epithelium closely resembles the junctional epithelium around teeth. Many molecules are involved in the defensive activity against the bacterial challenge which are being expressed in the peri-implant epithelium.
So, a functional adaptation occurs when oral epithelia forms an epithelial attachment around implants (70).

CONCLUSION
Junctional epithelium, as stated earlier, represents a dynamic seal around the tooth, at a strategically important interface of oral cavity (flushed with oral fluid containing innumerous pathogens) and delicate periodontal tissues. This is a specialized unique tissue, capable enough to act as a barrier against the bacterial challenge by adapting both structurally and functionally as per the requirement. The integrity of this tiny tissue carries extreme importance for the health of supportive periodontal structures, and virtually the tooth. Detachment of junctional epithelium from tooth surface initiates formation of periodontal pocket, and hence periodontitis. So further understanding of the structure and function of junctional epithelium would enable us to attain knowledge regarding its uniqueness and also develop new therapeutic strategies against the microbial infection and subsequent tissue destruction.

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