Japanese Dental Science Review (2018) 54, 59—65

Contents lists available at ScienceDirect

Japanese Dental Science Review

journal homepage: www.elsevier.com/locate/jdsr

Review Article

Histological and immunological characteristics of the junctional epithelium

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Received 6 June 2017; received in revised form 23 October 2017; accepted 14 November 2017

KEYWORDS
The junctional epithelium;
Intraepithelial lymphocytes;
ICAM-1;
Cytokines;
Chemokines;
Enamel organ

Summary The continuity of epithelial tissue is collapsed by tooth eruption. The junctional epithelium (JE) is attached to the tooth surface by hemidesmosomes, which constitutes the front-line defense against periodontal bacterial infection. JE constitutively expresses intercellular adhesion molecule-1 (ICAM-1), and neutrophils and lymphocytes penetrate into JE via interaction between ICAM-1 and LFA-1 expressed on the surface of these migrating cells. JE also expresses cytokines and chemokines. These functions of JE are maintained even in germ-free condition. Therefore, the constitutive expression of adhesion molecules, cytokines, and chemokines might be used not only for anti-pathogenic defense but also for maintaining the physiological homeostasis of JE. In this review, we have mainly focused on the structural and functional features of JE, and discussed the function of intraepithelial lymphocytes in JE as a front-line anti-microbial defense barrier and regulator of JE hemostasis.
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https://doi.org/10.1016/j.jdsr.2017.11.004
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1. Introduction

Epithelial tissues form junctional complexes to maintain a continuous demarcation against the external environment and prevent the invasion of foreign substances inside the living body. Tooth eruption collapses the continuity of epithelial tissue in the oral cavity. Erupted teeth are surrounded by the gingival epithelium, which is one of the most specialized tissues of the body because the discontinuity of the gingival epithelial sheath renders it susceptible to bacterial infection from dental plaques and periodontal disease [1—3].

The gingival epithelium consists of the oral gingival epithelium (OGE), oral sulcular epithelium (OSE), and junctional epithelium (JE) (Fig. 1A, B). Among them, the JE attaches to the tooth surface via hemidesmosomes, which forms the front-line of defense against periodontal bacterial infection [4,5]. In rodents, the JE is clearly distinguished from OSE (Fig. 2). The JE originates from the enamel organ and constructs the gingival epithelium along with OGE and OSE, which are derived from the oral epithelium [6,7]. The OGE and OSE are keratinized squamous epithelial cells with narrow intercellular space [8,9]. On the contrary, the JE is non-keratinized epithelium and has wide intercellular space (Fig. 3A, B). In addition, many migrating cells such as polymorphonuclear cells (PMNs) and lymphocytes are located within JE [10—15] (Fig. 3A, B). The JE shows rapid turnover, which might contribute to its defense against dental plaque [16,17]. The structure of the gingival epithelium

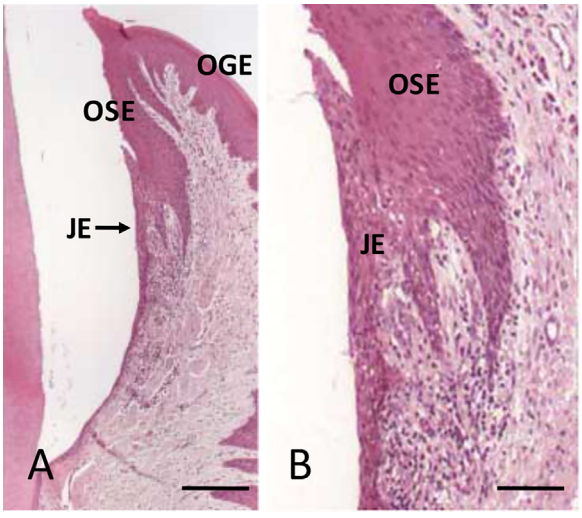

Figure 1 Human gingiva. A: Inner gingival epithelium consists of OSE and JE. Bar = 250 μm. B: Higher magnification of the JE. Bar = 100 μm.

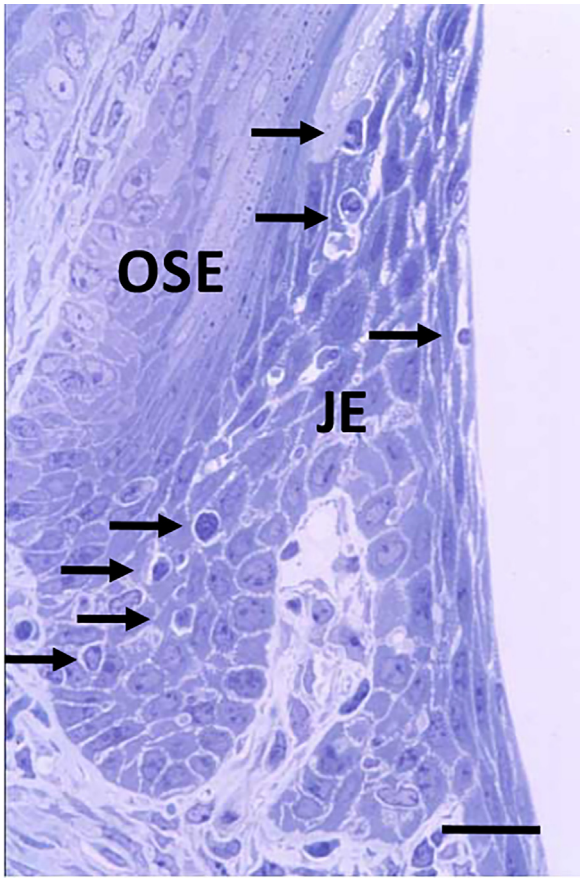

Figure 2 Mouse gingiva. The JE is clearly distinguished from OSE. Many migrating cells (arrows) are detected in the JE. Bar = 50 μm.

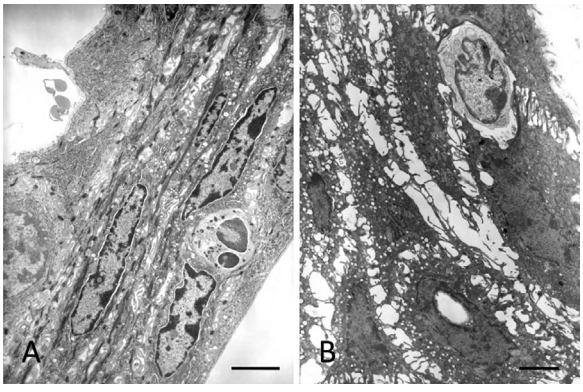

Figure 3 Ultrastructure of the JE showing wide intercellular space. Neutrophil (A) and lymphocyte are migrating within the JE. Bars = 10 μm.

is maintained by the coordination of epithelial tissues of two different origins. Therefore, the structure, origin, and function of the JE at the dento-gingival junction have been the subject of interest and controversy.

2. Structure of the JE

JE is classified as non-keratinized stratified squamous epithelium. Intercellular junctions formed in JE are relatively loose and contain only few desmosomes, adherens junctions, and gap junctions, which allow tissue exudate and inflammatory cells to penetrate toward the gingival sulcus [1,4,5,18—20].

JE has a true basement membrane towards the connective tissue of gingiva (called the external basal lamina, EBL) and a simple ECM (called the internal basal lamina, IBL) against the enamel [21] (Fig. 3A, B). The EBL contains structures that are identical to those of a typical basement membrane, with the lamina lucida against the basal keratinocytes and the lamina densa towards the underlying connective tissue. The protein composition of the IBL differs significantly from that of a typical basement membrane. The IBL does not contain any typical basement membrane-forming proteins such as laminin 111, laminin 511, type IV and VII collagens, and perlecan [22]. The main cell adhesion protein identified so far in the IBL is laminin 332 [22—24]. Furthermore, reports show the presence of type VIII collagen and versican at the JE-tooth interface [25,26]. These proteins were not detected in other typical basement membranes. These findings indicate the uniqueness of JE and provide important information regarding the biological relationship between dental implants and the gingival epithelium to establish the effective interface.

In general, epithelial cells form basement membranes for survival in cell culture systems [27—30]. However, detailed studies regarding the protein composition of basement membrane are lacking. Therefore, an extensive study of the protein composition of epithelial cell basement membranes in culture might clarify the structure and function of the JE basement membrane.

3. Origin of the JE

The structure and the function of the JE are influenced by the underlying connective tissue and by contact with a solid substratum, such as enamel, dentin or cementum, the exact mechanisms that lead to the formation and regeneration of the JE remain unclear. Common notion posits that during tooth development, the primary JE is formed by the fusion of the reduced enamel organ, which is replaced in time by a secondary JE derived solely from cells of the OE [31—35]. The reduced enamel epithelium is composed of reduced ameloblasts and papillary cells located at the side of the connective tissue. The histological analysis clearly distinguishes OSE from the JE. The function of JE is also entirely different from OSE. Therefore, is might be reasonable that the JE is derived from the reduced enamel epithelium.

We previously demonstrated that the constitutive expression of ICAM-1 in the gingival epithelium is restricted in the JE of erupted molar teeth of mouse [36] (Fig. 4A, B). The expression of ICAM-1 in the JE was also reported in human and experimental animal gingiva [37—39]. The expression of ICAM-1 is constitutively maintained even in the JE of germ-free mouse [36].

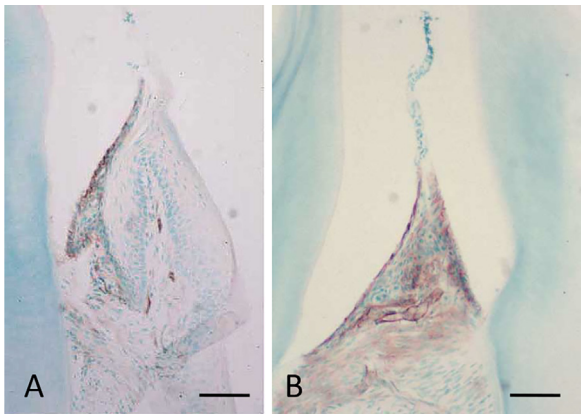

Figure 4 Immunohistichemical localization of ICAM-1 in the JE of labial side (A) and intertooth area (B) of a germ-free-mouse. Intensive immunoreactions are detected at the JE. B: The JE between the two molars. Endothelial cells beneath the JE also expressed ICAM-1. Bars = 80 μm.

Studies demonstrated that keratinocytic ICAM-1 expression in dermatological disease is localized precisely in the lymphocyte infiltration site of the epithelium. Keratinocytes do not express ICAM-1 after recovery from disease [40—42]. These results indicate that the expression of ICAM-1 is regulated by pro-inflammatory cytokines such as interluekin-1 (IL-1) and tumor necrosis factor-α (TNF-α) [43—46]. Therefore, regulation of ICAM-1 expression and differences in ICAM-1 levels in JE might be regulated not only by bacteria-derived LPS, which stimulates macrophages to produce cytokines [46], but also by intrinsic factors. In fact, JE constitutively express IL-1β, which regulates the expression of ICAM-1 in JE [36,47].

During tooth development, the inner enamel epithelium differentiates into the secretary, transitional, mature, and reduced stages of ameloblasts, and the stratum intermedium, adjacent to the secretary stage of ameloblasts, differentiates into the papillary layer [48,49]. ICAM-1 expression is initiated during the formation of the papillary layer (Fig. 5A, B). However, all stages of ameloblasts do not express ICAM-1. The papillary layer adheres to the oral epithelial tissue during tooth eruption. These results indicate that the JE might have originated from papillary layer cells and not the reduced ameloblasts. ICAM-1 expression may be regulated by certain autocrine or paracrine factors regulating cell death of ameloblasts at the transition stage. Although IL-1β might be the key molecule for ICAM-1 expression [43—46], further studies are required to clarify the mechanism of ICAM-1 expression during tooth development.

4. Functional specificity of the JE

The JE has several specific functions that differ from those of other oral epithelium. JE expresses defensive factors such as β-defensins, secretory leukocyte protease inhibitor (SLPI), and S100A8 against inflammation [50—52]. β-Defensins are

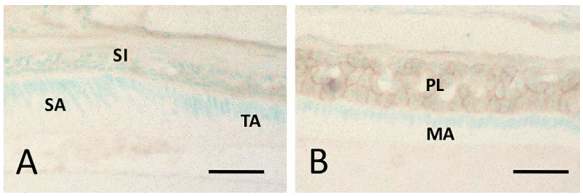

Figure 5 Immunohistochemical localization of ICAM-1 during the tooth development. A: ICAM-1 is not detected at the stratum intermedium adjacent to the secretoru stage of ameloblasts and expresses form the transition stage of ameloblasts at the papillary layer. B: The papillary layer cells highly express ICAM-1 at the maturation and the reduced stages of ameloblasts. SI: stratum intemedium, SA: secretory stage of ameloblast, TA: transition stage of ameloblast, PL: papillary layer, MA: maturation stage of ameloblast. Bars = 30 μm.

small cationic peptides that contribute to innate host defense against bacterial challenge [50,52]. SLPI protects the intestinal epithelium from proteases secreted as part of the inflammatory response and is associated with the maintenance of tissue integrity [53]. S100A8 and S100A9 form a heterodimeric complex and constitute calprotectin, an antimicrobial peptide [54].

The JE constitutively produces chemokines and cytokines, such as keratinocyte-derived chemokine (KC), macrophage inflammatory protein-2 (MIP-2), and IL-1β in conventional and germ-free mice [47]. KC and MIP-2 are potent chemoattractants for neutrophils. The expression of these chemokines is up-regulated by bacterial stimulation.

The JE also constitutively express follicular dendritic cell-secreted protein (FDC-SP) and odontogenic ameloblast-associated protein (ODAM) [55—57]. The genes encoding FDC-SP and odontogenic ameloblast-associated protein appose at the gene cluster for secretory calcium-binding phosphoproteins [58,59]. Secretory calcium-binding phosphoproteins interact with several bioactive molecules to regulate cell adhesion, migration, proliferation, and tumorigenesis [60,61]. Furthermore, the gene encoding FDC-SP lies adjacent to the cluster of genes encoding C—X—C chemokines [58]. These results suggest a close association between the expression of pro-inflammatory cytokines and chemokines and the expression of FDC-SP and odontogenic ameloblast-associated protein.

Histological and immunohistological investigation indicates massive infiltration of lymphocyte function-associated antigen-1 (LFA-1)-positive PMNs and lymphocytes in the JE [36,37]. The interaction of LFA-1 and ICAM-1 plays a key role in the migration of these cells in JE. Endothelial cells and fibroblasts underlying the JE also express ICAM-1, which might provide a pathway for granulocytic and lymphocytic migration into JE.

5. Role of commensal microflora

All the factors mentioned above are up-regulated in conventional conditions [47]. The commensal microflora plays a critical role in the postnatal development of the system, as the physiological inflammatory response in the gut during early postnatal ontogenesis is essential for the development of the immune system and its appropriate functioning. An interaction between commensal bacteria and the innate defense system of the periodontal tissue has also been reported [62]. Hayashi et al. observed the increased expression of SLPI in the JE compared to that in oral gingival epithelium [50]. The expression of SLPI is regulated by a cross-talk between epithelial cells and neutrophils. Thus, the constitutive expression of these factors and the migration of neutrophils in the JE might be induced by intrinsic genetic regulation rather than by bacterial infection for the maintenance of the functional specificity of the JE.

Histological examination indicated an increase in the JE area in conventional mice [47]. Immunohistochemistry also indicated an increase in the number of PCNA-positive epithelial cells within the JE upon bacterial infection [47]. Furthermore, the number of neutrophils and the expression of chemokines (KC and MIP-2) in the junctional epithelium are significantly higher in conventionalized mice than in germ-free mice [47]. Tsukamoto et al. evaluated the relationship between epithelial cell proliferation and inflammation in clinically healthy and inflamed human gingival tissue and found that epithelial cell proliferation and epithelial thickness were associated with gingival inflammation [63]. Similarly, chemokines were induced by bacterial lipopolysaccharide [64,65]. Thus, commensal bacteria might be important for up-regulating the physiological barrier function of the JE.

6. Intraepithelial cells in the JE

Intraepithelial cells (IELs) are lymphocytes located within the epithelial layer of mucosal tissues such as the gastrointestinal and reproductive tract. IELs were localized in the middle layer of the JE as indicated by mucosa associated lymphoid tissue (MALT) [66]. IELs are characterized by the presence of higher numbers of TCRγδ$^+$ lymphocytes than those in the systemic immune organs such as the spleen and lymph nodes [67].

The vast majority of TCRγδ$^+$ IELs expresses CD8αα, but a small proportion lacks CD8α and CD8β, which is obviously different from the TCRγδ$^+$ T cells located in lymphoid tissues, which show no CD8 expression [68,69]. The TCR repertoires of IELs in each mucosal tissue were restricted by the in situ microbial colonizations in the tissue [70]. In humans, the γδ TCRs expressed by IELs predominantly use the Vγ1 gene and Vδ1, whereas in mice, Vγ5 T cells are enriched in the intraepithelial tissues of the gut [71,72].

Non-classical molecules such as the thymus leukemia antigen or the major histocompatibility complex (MHC) class I-like molecules are candidate ligands for TCRγδ. TCRγδ$^+$ T cells, including IELs, may be involved in a totally distinct type of host defense, whereas TCRαβ-positive T cells, a major population in peripheral lymphoid organs, elicit the MHC class II-restricted or MHC class I-restricted immune responses [73,74].

The TCRγδ$^+$ lymphocytes play an important role in the defense mechanism as a front-line competent cell population. IELs are frequently exposed to a number of microbial antigens and might be cytotoxic against infected epithelial cells [73,74]. IELs have also been suggested to be involved in graft-versus-host diseases and abrogation of oral tolerance

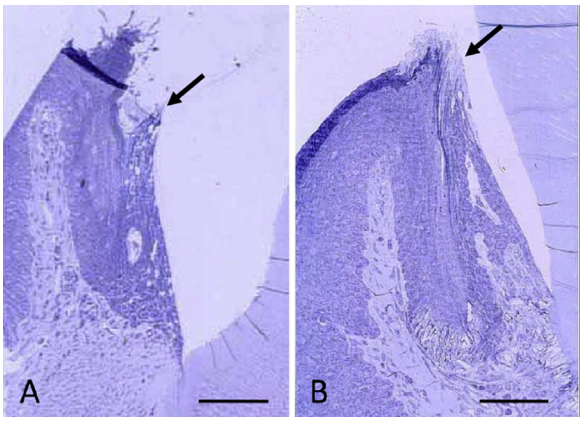

Figure 6 The effect of cyclosporine A on the JE. Mice are intraperioneally injected with cyclosporine A (25 mg/kg) for 21 days. A: Normal JE. The tip of the JE (arrow) is lower than the OSE. B: By cyclosporine A treatment, the JE elongated and the tip of the JE (arrow) reaches almost to the same level with the OSE. Bars = 50 μm.

[75,76]. In contrast, IELs produce growth factors to regulate the epithelial cell proliferation [77—79].

IELs in the JE express TCRγδ and CD3 in conventional and germ-free mice [36,47]. The existence of TCRγδ T cells in the JE was also reported in humans [80]. Furthermore, TCRαβ-expressing T cells and B cells could not be detected in the JE, whereas in other mucosal epithelial tissues, TCRαβ-positive T cells constituted the main population of IELs [73,81]. These results suggest that the JE might be a specialized mucosal tissue in the body. The identification of TCR repertoires might be the next step for clarifying the exact function and IEL antigens in JE.

7. The expected function of IELs in the JE

Previous studies from our and other laboratories indicated that IELs in the duodenum and jejunum induced enterocyte apoptosis within 30 min after activation by anti-CD3ε antibody treatment [82—84]. Cytotoxic activity of IELs is inhibited by immunosuppressive agents such as cyclosporine A (CsA) and FK506, which induce the elongation of intestinal villi and decrease enterocyte activity [82,84].

As mentioned above, the JE plays an active role in the synthesis of a variety of molecules that are involved in anti-bacterial defense. Therefore, the balance between cell death and mitotic activity is critical for maintaining the number of JE cells, which affects the defensive properties of the JE, and eventually, disease progression.

The JE and OSE form the inner gingival epithelium. The origins of these two epithelial tissues are different. The JE and OSE have a high rate of cell turnover. The JE shows higher proliferation than the OSE [16,85]. To maintain the structure of the inner gingival epithelium over time, either the cell cycle of the two epithelial tissues must be identical or cells of the epithelium showing high proliferative activity should be eliminated.

Three weeks treatment with CsA (25 mg/kg) induced the elongation of JE. In normal conditions, the tips of the JE are always located under the OSE, while the tips of the JE are guided to a position higher than the OSE by CsA treatment (Fig. 6A, B). which indicate that the cytotoxic activity of IELs expressing TCRγδ might be inhibited by CsA. These results suggest that IELs in the JE regulate epithelial cell survival for maintaining barrier function against bacterial stimulation similar to that in the gastrointestinal tract. The inhibition of rapid turnover of JE might decrease the survival activity and the barrier function of JE, and permit the easy penetration of bacterial LPS into the gingival connective tissue.

8. Conclusion

The JE is the only discontinuous epithelial tissue in the body. The JE functions as a front-line barrier against foreign antigens with structural and functional features such as adhesion to tooth surface via formation of basal lamina, large intercellular space, expression of several cytokines and chemokines, and the penetration of neutrophils and lymphocytes to play as the front-line innate immune system and to maintain the JE homeostasis. Further understanding of the structure and function of the JE would provide better understanding of systemic host defense system and specificity of the oral mucosal tissue.

Conflicts of interest

The author declare that no competing financial interests exist.

Acknowledgment

This study was partially supported by the Grants-in Aid for Scientific Research (24592777, 15K11022) from the Ministry of Education, Culture, Sports, Science and Technology of Japan.

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