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Biological Sealing and Defense Mechanisms in Peri-Implant Mucosa of Dental Implants

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1. Introduction

Much attention during the early stages of basic and clinical research on dental implants has been focused on the bone (jaw)-to-titanium (implant) interface, because direct bone contact with the implant was thought to be a critical factor in implant therapeutics. However, since wide acceptance of the important concept of "osseointegration", developed by Branemark et al. (1977) in the late 1960's, biomaterial implants, usually titanium, have been shown to be able to bind directory and tightly to the bone surface at the engraftment sites, with no tissue intervention. This concept also avoids the risk of fibrous encapsulation, indicating that successful biological and clinical sealing can occur at the bone-to-implant interface (Kajiwara et al., 2005). The applications of titanium implant therapy have therefore increased for patients in medical and dental clinics.

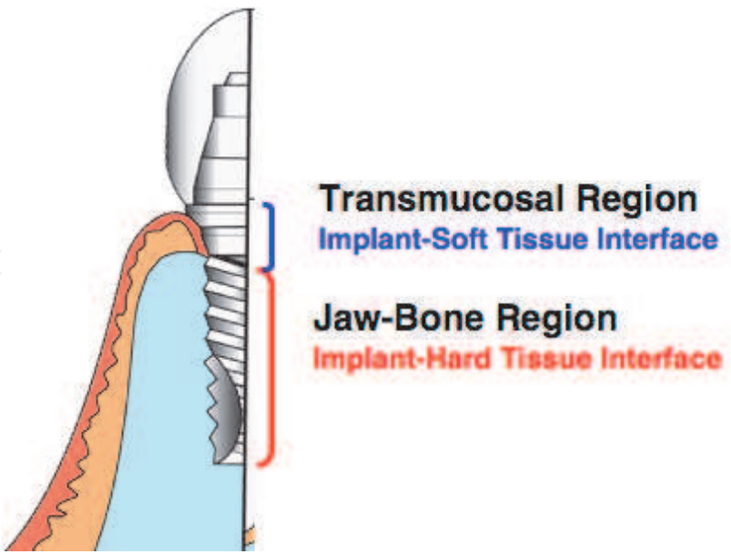

Fig. 1. Schema of biological region around dental implants. A unique part of dental implants is their pierce through oral mucosa. The dental implants are hided in jaw-bone to support the implant body. For functional and aesthetic matters, dental implants expose to the oral cavity. The surrounding tissue of dental implants is biologically divided into two regions; jaw-bone and transmucosal regions.

To date, several factors have been considered to improve the outcomes of clinical dental implants. The functional and aesthetic constraints on dental implants require their insertion through the oral mucosa/gingiva, thus inevitably establishing a transmucosal region between the oral cavity and the dental implant body (Figure 1). This environment exposes dental implants to several external stimuli from the oral cavity through the implant-soft tissue interface. Inflammation of the area surrounding the dental implant is one of most critical problems associated with the clinical failure and short- and long-term maintenance of dental implants, in a similar manner to the problems of tooth-loss caused by periodontal disease (Baillie et al., 2004; Esposito et al., 2010). Bacterial invasion of the transmucosal region leads to the progressive destruction of the peri-implant tissues and their subsequent failure (Mombelli, 1999), indicating that effective protection of the peri-implant mucosa is mandatory (Pontoriero et al., 1994; Tonetti & Schmid, 1994) (Figure 2). Regeneration of firm soft tissues surrounding dental implants, especially in the transmucosal region, is thus required for the long-term success of therapeutic dental implants (Grusovin et al., 2008; Canullo et al., 2011).

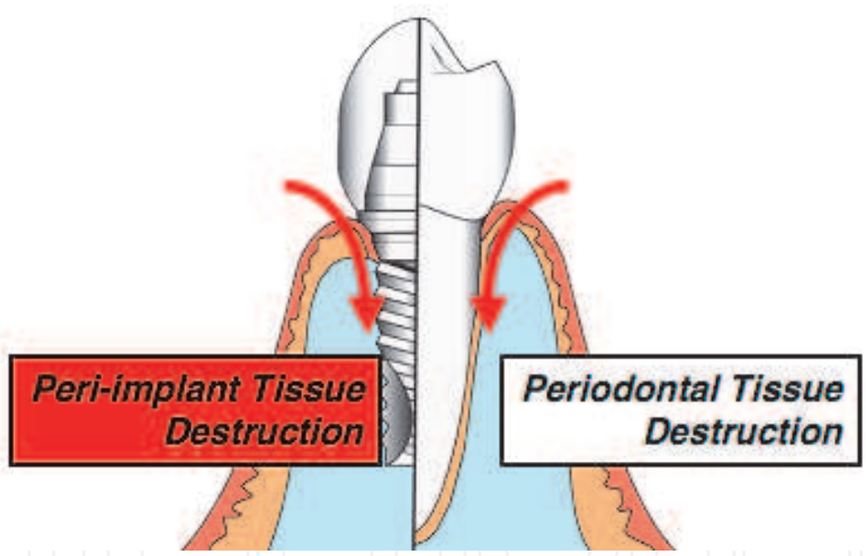

Fig. 2. Schema of a clinical importance of the transmucosal region around dental implants. A variety of oral pathogens (red arrows), likely bacteria and their products, are able to penetrate into the submucosal tissue around dental implants through the transmucosal region around dental implants, followed by causing the destruction of peri-implant tissue, similar to the destruction of periodontal tissue around tooth.

Dental implant research has focused on the interface between dental implants (titanium) and the surrounding soft tissues (Cairo et al., 2008; Grusovin et al., 2008). *In vivo* and *in vitro* investigations can help to understand the structural, functional and molecular properties of

the biological seal and defense mechanisms acting at the interface between the peri-implant mucosa and dental implants (Baschong et al., 2001; Chai et al., 2010). Histological analysis of *in vivo* models, including animal and human subjects, is one of the gold standard methods for investigating the mechanisms at the implant-soft tissue interface. However data on peri-implant tissue from human subjects are scarce because of the limited collecting opportunities and ethical issues (Piattelli et al., 1993, 1997a, 1997b; Arvidson et al., 1996; Corpe et al., 1999; Baschong et al., 2001), animal models have therefore been widely used (Albrektsson et al., 1985; Buser et al., 1992; Berglundh et al., 1994; Berglundh & Lindhe, 1996; Weber et al., 1996; Abrahamsson et al., 1998, 2001, Fujii et al., 1998, 2003; Kawahara et al., 1998; Moon et al., 1999; Hermann et al., 2000, 2001). Peri-implant tissue contains both hard (bone) and soft (mucosa) tissues, which presents a challenge in terms of the histochemical examination of the intact implant-soft tissue interface.

This chapter reviews the morphological and functional features of the soft tissue surrounding dental implants, with emphasis on the epithelial interface between the implant and the peri-implant mucosa. The evidence is based on recent animal studies, especially our investigations using a unique oral implant rat model (Ikeda et al., 2000, 202; Atsuta et al., 2005a, 2005b; Yamaza et al., 2009). This *in vivo* model uses a 4-week implantation system, immediately after tooth extraction (maxillary first molar). Screw-type pure titanium implants (4 mm long, 2 mm in diameter) were inserted, and a complete peri-implant mucosa developed around the titanium body. Furthermore, this model allows the preserved implant-soft tissue interface to be examined at the ultrastructural level, including cellular features (e.g., microvilli, cytoplasmic processes, cytoplasmic organelles of epithelial cells, nerve fibers and terminals, blood vessel components, immune cells) and the epithelial attachment apparatus (basal lamina and hemidesmosomes).

2. Topological features of peri-implant mucosa

A tissue surrounding tooth, known as periodontium, is characterized by four types of tissue: periodontal ligament, cementum, alveolar bone, and gingiva (Schroeder, 1986). These components play critical roles in the support, maintenance, and repair of the tooth and the supporting tissue under both physiological and pathological conditions. The gingiva is a special oral mucosa that surrounds the tooth surface enamel, and covers the alveolar bone that supports the tooth (Schroeder & Listgarten, 1997). This mucosa is composed of connective tissue and epithelial components (Figures 3a and 4a). The gingival connective tissue component, the lamina propria, attach directly and tightly to the alveolar bone, while the gingival epithelium, which overlies the lamina propria, faces the oral cavity and the tooth surface. A tiny slit between the tooth surface and the gingival epithelium, known as oral sulcus, is present even under healthy conditions. This narrow space forms a route for outward flow from the sub-epithelial tissue, as well as an inward pathway into the connective tissue.

To achieve their therapeutic function based on recent established clinical techniques, dental implants pierce the oral mucosa and are inserted into the alveolar bone (Branemark et al., 1977). A tissue surrounding dental implant, known as peri-implant tissue, exhibits various morphological and structural similarities to the natural periodontium; it contains implant-supporting jaw bone and surrounding oral mucosa (peri-implant mucosa), but no

intercalated tissue between the bone and implant surface equivalent to the periodontal ligament and cementum.

The peri-implant mucosa is specifically acquired after dental implant surgery, and resembles the natural gingiva, consisting of peri-implant connective tissue and peri-implant mucosal epithelium (Ikeda et al., 2000) (Figures 3b and 4b). The peri-implant connective tissue integrates with the surface of the jaw bone supporting the dental implant body, while the peri-implant mucosal epithelium faces the oral cavity and the implant surface. There is also an acquired fissure between the implant surface and the peri-implant mucosa, known as the peri-implant sulcus.

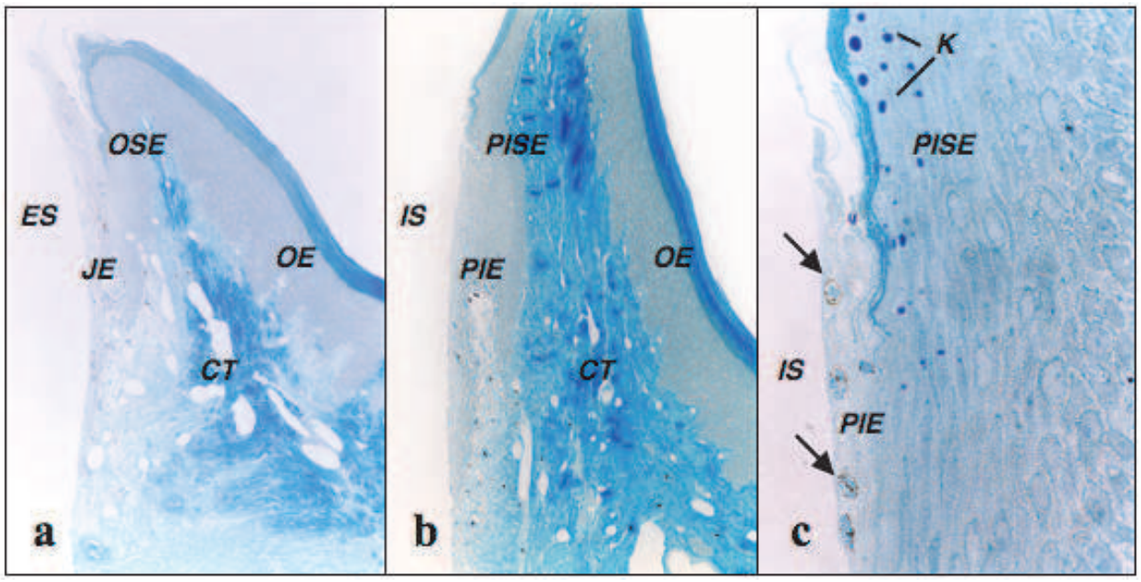

Fig. 3. Light micrographs of healthy gingiva and peri-implant mucosa in rats. (a) Healthy gingiva consists of an epithelial component and a connective tissue component (*CT*). The gingival epithelium can be divided into three parts: oral epithelium (*OE*), oral sulcular epithelium (*OSE*), and junctional epithelium (*JE*). *ES*: enamel space. (b, c) The components of peri-implant mucosa resemble those of the healthy gingiva. The peri-implant mucosa epithelium consists of oral epithelium, peri-implant sulcular epithelium (*PISE*), and peri-implant epithelium (*PIE*). The oral epithelium and peri-implant sulcular epithelium in the peri-implant mucosa, as well as the oral epithelium and oral sulcular epithelium in healthy gingiva, are keratinized, stratified squamous epithelia, while the PIE and junctional epithelium are non-keratinized epithelia with invading neutrophils (arrows). Blood vessels are developed under the PIE and junctional epithelium. *IS*: implant space. *K*: keratohyaline granules. Toluidine blue staining.

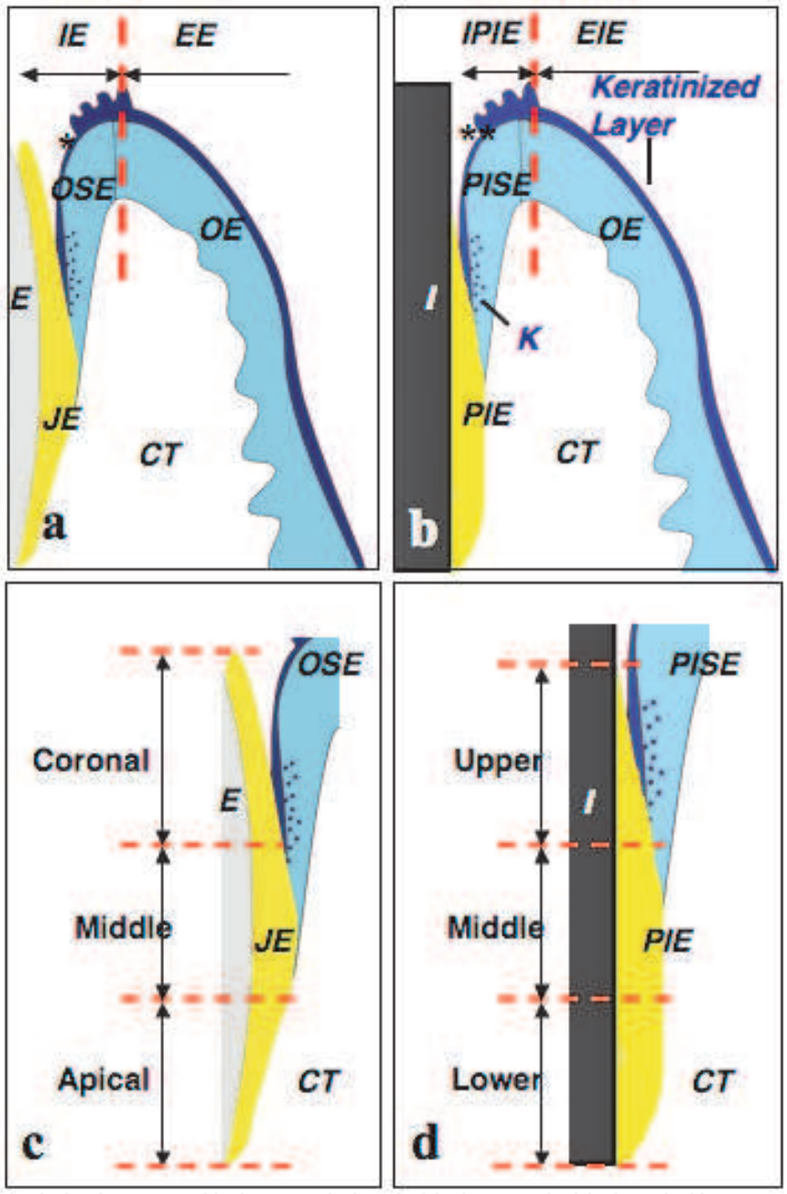

Fig. 4. Schemata of gingiva and peri-implant mucosa. (a) The gingival epithelium can be divided into oral epithelium (*OE*), oral sulcular epithelium (*OSE*), and junctional epithelium (*JE*). The external marginal epithelium (*EE*) covers the gingiva facing the oral cavity, while the inner marginal epithelium (*IE*) covers the gingiva facing the tooth. The space (asterisk) between the enamel (*E*) and inner marginal epithelium is the oral sulcus. *CT*: connective tissue. (b) Epithelia in the peri-implant mucosa consist of the oral epithelium, peri-implant sulcular epithelium (*PISE*), and peri-implant epithelium (*PIE*). The external peri-implant epithelium (*EPIE*) faces the oral cavity, while the inner peri-implant epithelium (*IPIE*) faces the implant (*I*). The peri-implant sulcus (double asterisk) comprises a narrow space between the inner peri-implant epithelium and the implant surface. (c) Natural junctional epithelium is divided into three regions: the coronal, middle and apical regions. (d) The PIE is also divided into three regions: the upper, middle and lower regions.

3. Peri-implant mucosal epithelium

The peri-implant mucosal epithelium exhibits histological and structural features similar to those of the natural gingival epithelium (Ikeda et al., 2000, 2002) (Figures 3 and 4). This epithelium is classified as a stratified squamous epithelium, and consists of three parts: oral epithelium, peri-implant sulcular epithelium, and peri-implant epithelium (PIE) (Figures 3b and 4b), equivalent to the parts of the natural gingival epithelium: oral epithelium, oral sulcular epithelium and junctional epithelium (Figures 3a and 4a). The junctional epithelium is considered to be unique among the three types of gingival epithelium, and participates in forming a fixed tooth-gingiva interface (Schroeder, 1986; Schroeder & Listgarten, 1997).

Topologically, the peri-implant mucosal epithelium is also divided into two parts in relation to the dental implant surface (Ikeda et al., 2000, 2002; Atsuta et al., 2005b) (Figures 4a and 4b). The external-implant marginal epithelium is the part of the epithelial component facing the oral cavity, and consists of the oral epithelium, and the inner-implant marginal epithelium lies directly against the implant surface and the peri-implant sulcus.

3.1 Oral epithelium

The oral epithelium of the peri-implant mucosal epithelium is directly exposed to the oral cavity, forming the external-implant marginal epithelium of the peri-implant mucosal epithelium (Ikeda et al., 2000, 2002) (Figures 3b and 4b). This epithelium is common to the natural gingival epithelium. Histologically, the oral epithelium forms a keratinized stratified squamous epithelium (Figure 3b). The most superficial layer of this epithelium contains keratin, which helps to protect the oral epithelium from foreign stimuli.

3.2 Peri-implant sulcular epithelium

The peri-implant sulcular epithelium shares histological and topological properties with the natural oral sulcular epithelium (Ikeda et al., 2000, 2002). This epithelium, which forms part of the inner-implant marginal epithelium, forms a collar around the peri-implant sulcus (Figures 3b and 4b). The peri-implant sulcular epithelium is keratinized, similar to the oral epithelium, but also contains keratohyaline granules, indicating a keratinized barrier (Figure 3c). The basal layers of both the oral and peri-implant sulcular epithelia form general epithelial-connective barriers, including basement membrane and hemidesmosomes, which join the epithelium to the sub-epithelial tissue. The peri-implant sulcus provides a direct connection to the oral cavity, and acts as a passage for foreign substances into the peri-implant tissue (Ikeda et al., 2002) (Figure 5a), in a similar manner to the oral sulcus (Schroeder & Listgarten, 1997).

3.3 PIE

The PIE, the other part of the inner-implant epithelium, demonstrates unique and specific characteristics, forming a solid transmucosal interface around the dental implant (Ikeda et al., 2000, 2002) (Figures 3 and 4). The topological and structural features of the PIE resemble those of the tooth-enamel interface epithelium, the junctional epithelium, suggesting an important function for the transmucosal region around dental implants in biological sealing and defense.

4. Biological characteristics of the PIE

4.1 Topological and ultrastructural features of the PIE and PIE cells

PIE is formed by epithelial cells derived from the oral epithelium and/or residues of the junctional epithelium after tooth extraction (Fujii et al., 1998; Atsuta et al., 2005a). The epithelial cells move and grow down along the implant surface whilst secreting laminin 5, resulting in reorganization of the intercalated epithelial tissue to form the PIE (Atsuta et al., 2005a).

PIE and PIE cells show some structural and cellular phenotypic similarities to natural junctional epithelium and junctional epithelial cells (Ikeda et al., 2000). The PIE is a non-keratinized and stratified squamous epithelium (Figures 3b, 3c), consisting of basal and supra-basal cell layers. It is located between the surface of the dental implant and the lamina propria of the peri-implant mucosa (Figure 5a, 5b). Blood vessels, especially post-capillary venules, mostly occur under the sub-PIE connective tissue, compared to other sub-peri-implant epithelial tissue (Figure 3b).

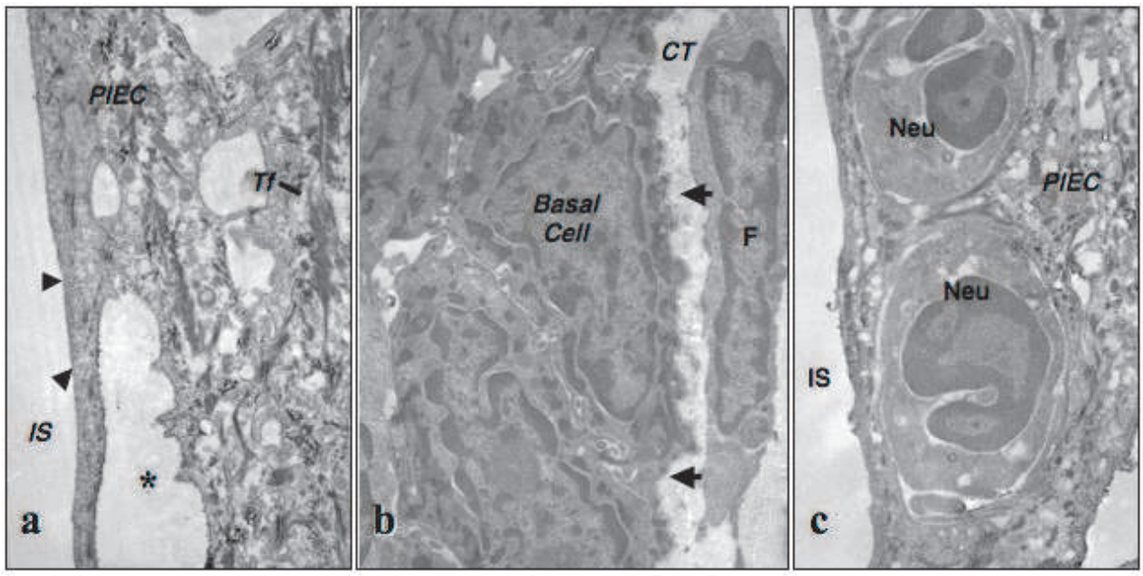

Fig. 5. Electron micrographs of the transmucosal region of the peri-implant mucosa. (a) Typical electron micrograph of the suprabasal peri-implant epithelium (*PIE*), especially the lower PIE. PIE cells (*PIEC*) are arranged parallel to the implant surface, are flattened, and contain a variety of vesicles and vacuoles. Tonofilaments (*Tf*) are localized within the PIE cells. Wide intercellular spaces (asterisk) are found between the cytoplasmic processes. Internal basement lamina (arrowheads) is laid on the innermost PIE cell. *IS*: implant space. (b) The basal part of the PIE consists of cuboidal cells (*Basal Cell*) lining the external basal lamina (arrows). *CT*: connective tissue, *F*: fibroblast. (c) Neutrophils (*Neu*) migrate into the intercellular spaces between PIE cells.

PIE cells are flattened, undifferentiated epithelial cells with few organelles, such as mitochondria and endoplasmic reticulum (Ikeda et al., 2000) (Figure 5a). The PIE cells are arranged parallel to the implant surface. They extend their cytoplasmic processes to other PIE cells, and connect via desmosomes to form wide intracellular spaces (Figure 5a). Neutrophilic granulocytes leak from the blood vessels of the sub-epithelial connective tissue

and invade into the PIE (Ikeda et al., 2000; Yamaza et al., 2009) (Figure 5c). These ultrastructural characteristics support the idea that the PIE acts as a pathway not only for foreign molecules penetrating into the sub-epithelial connective tissue of the peri-implant mucosa (Ikeda et al., 2002), but also for the flow of peri-implant cervicular fluid from the sup-epithelial tissue (Eley et al., 1991). Both inward (McDougall, 1971; Romanowsky et al., 1988; Yamaza et al., 1997) and outward (Golub et al., 1976; Tanaka 1984; Tanaka and Sakano, 1987) flow are also recognized in the junctional epithelium.
The PIE cells also contain tonofilaments (Figure 5a) that associate with desmosomes and hemidesmosomes (Schroeder, 1986). Many lysosomal vesicular and vacuolar structures are located in the cytoplasm (Ikeda et al., 2000; Yamaza et al., 2009) (Figures 5a and 10c).

4.2 Ultrastructural features of transmucosal epithelial attachment around dental implants

4.2.1 Epithelial attachment around natural teeth

Epithelial attachment components in the junctional epithelium are located throughout the tooth-gingiva interface. The attachment apparatus includes hemidesmosomes and basement lamina, which in turn comprises the external basement lamina (EBL) and the internal basement lamina (IBL) (Schroeder, 1986). The EBL, which is formed between the basal cells of the junctional epithelium and the connective tissue, shows a typical basement-membrane structure. The IBL, however, is a unique and specific adhesive structure at the interface between the innermost junctional epithelial cells and the enamel surface. Both the IBL and the EBL consist of two laminal structures, known as the lamina densa and the lamina lucida. These contain the major components of the basal lamina, laminin-1 and laminin-5 (Sawada et al., 1990; Hormia et al., 1998; Mullen et al., 1999). Hemidesmosomes are arranged in the cytoplasm under the plasma membrane of the junctional epithelial cells to anchor the IBL and EBL (Schroeder, 1986).

4.2.2 Epithelial attachment around dental implants

The PIE is divided to three regions: the upper, middle and lower regions (Ikeda et al., 2000) (Figure 4c), equivalent to the three regions of the junctional epithelium: the coronal, middle, and apical regions (Tanaka, 1984) (Figure 4d). The upper region of the PIE is closest to the peri-implant sulcus, while the lower region is connected to the sub-PIE tissue. The middle region is intercalated between the upper and lower regions. The PIE expresses a unique distribution of epithelial attachment, compared to the junctional epithelium (Ikeda et al., 2000; Atsuta et al., 2005b).
Several studies have demonstrated the formation of attachment structures at the titanium-epithelium interface both *in vivo* and *in vitro* (Gould et al., 1984; Mckinney et al., 1985; Donley & Gillette, 1991). At the internal interface between the implant and the PIE, the epithelial attachment apparatus, including the basal lamina and hemidesmosomes, are limited to the lower region of the PIE (Ikeda et al., 2000; Atsuta et al., 2005b) (Figures 5a and 6c). The hemidesmosomes lie beneath the plasma membrane of the innermost PIE cells. The basal lamina of the IBL shows structural similarity with the lamina densa and lamina lucida of the natural junctional epithelium. Laminin-1 and laminin-5 are strongly expressed and distributed heterogeneously in both the lamina densa and lamina lucida of the PIE IBL-like structure similar to the IBL of the junctional epithelium (Ikeda et al, 2000: Atsuta et al., 2005b) (Figure 6c). This indicates that the lower PIE provides epithelial attachment structures similar to those in the natural junctional epithelium. However, no comparative

studies have yet elucidated the distribution of hemidesmosomes at the internal interface of the PIE.

In the upper and middle regions of the innermost interface, the innermost PIE cells are close to the implant surface, but epithelial attachment structures are absent or rare (Ikeda et al., 2000; Atsuta et al., 2005b) (Figure 6b). The innermost PIE cells extend short cytoplasmic processes to the titanium surface, probably forming a loose attachment (Ikeda et al., 2000) (Figure 6b). Laminin-1 and laminin-5 are located in the innermost cells, but are not deposited on the interface (Ikeda et al., 2000; Atsuta et al., 2005b) (Figure 6b).

The external interface is formed between the basal PIE cells and the sub-epithelial connective tissue (Figure 5b). Basal lamina and hemidesmosomes are located throughout the external interface (Ikeda et al., 2000; Atsuta et al., 2005b). The basal lamina contains laminin-1 and laminin-5 and shows feature in common with the EBL of the natural junctional epithelium. Some part of the EBL of the PIE, especially in the lower region, is discontinuous, indicating epithelial migration of PIE/PIE cells (Atsuta et al., 2005b).

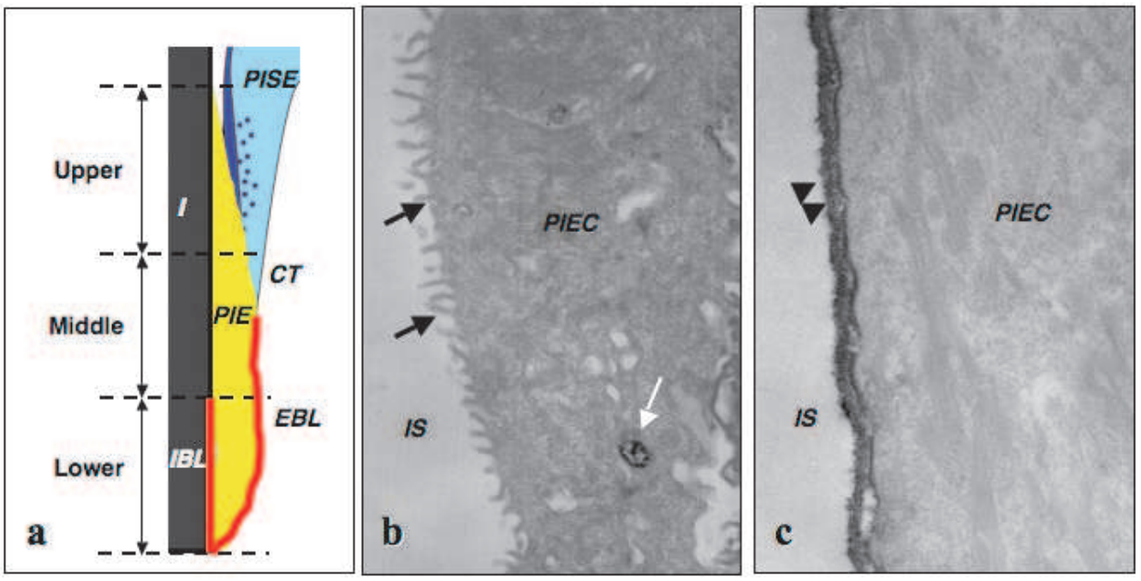

Fig. 6. Interface of the transmucosal region of the peri-implant mucosa (a) Schema of the transmucosal region of the peri-implant mucosa. The transmucosal region consists of the peri-implant epithelium (*PIE*). Only the inner interface of the lower portion of the PIE has an internal basement lamina (*IBL*), and IBL-like structure is lacking in the other portions. The external interface, the external basement lamina (*EBL*), is found through the PIE. *I*: implant, *PISE*: peri-implant sulcular epithelium. *CT*: connective tissue. (b, c) Immunoelectron micrographs showing the localization of laminin 5 at the inner interface (*IS*) of the PIE. (b) No specific epithelial attachment structures are found in the upper region of the PIE. An innermost PIE cell (*PIEC*) extends short cytoplasmic processes (arrows) to the implant surface. No laminin 5 is detected at the interface between the PIE cell and titanium, but laminin 5 is recognized in vesicles within PIE cells (white arrow). (c) In the lower region, IBL-like structure is found between the innermost PIE cell and the implant surface. Laminin 5-immunnoproducts (arrows) are deposited in the IBL structures, the lamina densa and lamina lucida.

4.3 Innervation of PIE by sensory nerve fibers

The natural junctional epithelium, as well as its sub-epithelial connective tissue, is abundantly supplied by nerve fibers derived from the trigeminal ganglion (Byers & Holland, 1977; Kondo et al, 1992; Sugaya et al., 1994). The sensory nerve fibers contain the neuropeptides, calcitonin gene-related peptide (Byers et al., 1987; Nagata et al., 1992, 1994) and substance P (Nagata et al., 1992, 1994; Tanaka et al., 1996; Kido et al., 1999), and terminate close to endothelial cells, neutrophils, and junctional epithelial cells (Kondo et al, 1992; Tanaka et al., 1996).

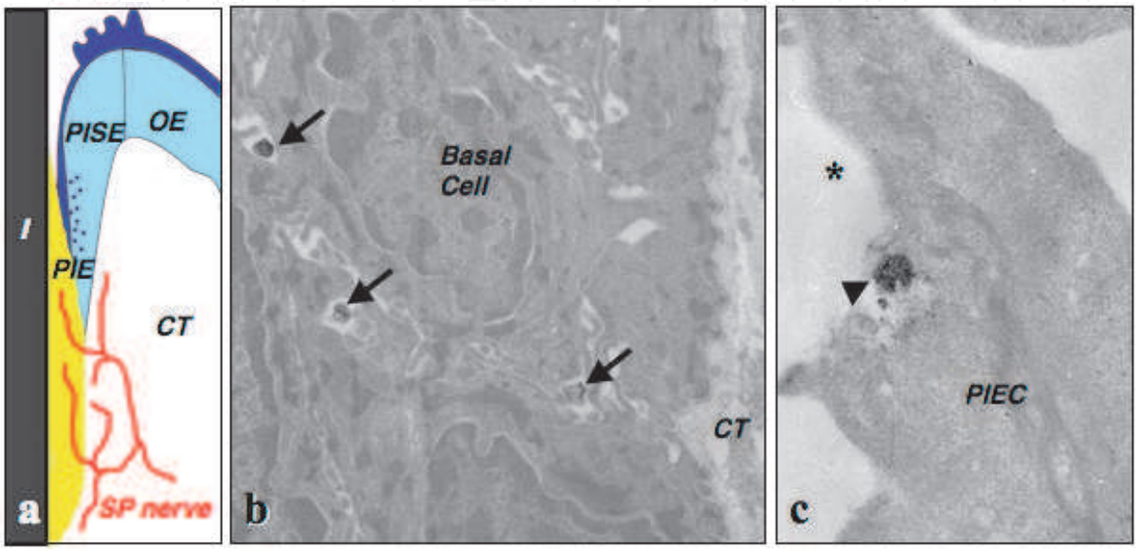

Fig. 7. Distribution of sensory nerve fibers in the transmucosal region of the peri-implant mucosa. (a) Schema of innervation by substance P-containing fibers (*SP nerve*) in peri-implant mucosa. The peri-implant epithelium (*PIE*) is rich in substance P-containing nerve fibers, compared to other epithelia. *CT*: connective tissue, *I*: implant, *OE*: oral epithelium, *PISE*: peri-implant sulcular epithelium. (b, c) Immunoelectron micrographs showing the localization of substance P-containing nerve fibers in the PIE. Nerve fibers with substance P immununoproducts (arrows) penetrate into the PIE via the intercellular spaces between basal PIE cells (*Basal Cell*) (b). The substance P-positive nerve ending (arrowhead) is closely localized to a PIE cell (*PIEC*) (c) Asterisk: intercellular space between PIE cells.

The peri-implant mucosa is also supplied with sensory nerves containing calcitonin gene-related peptide (Fujii et al., 2003) and substance P (Yamaza et al, 2009) (Figure 7a). The innervation of the PIE is denser than in other parts of the epithelium (peri-implant sulcular epithelium and oral epithelium) (Figure 7b). The free ends of the nerve fibers terminate close to PIE cells (Figure 7c), neutrophils and endothelial cells (Yamaza et al, 2009). In addition, neurokinin-1 receptors, which are receptors for substance P, are expressed on the extra- and intra-epithelial nerve fibers, endothelial cells and PIE cells (Yamaza et al, 2009) (Figures 8a, 8b, and 8d). These receptors are also localized in neutrophils invading into the intercellular spaces between PIE cells (Figure 8c). Overall, the PIE shows a similar distribution of substance P-containing sensory nerve fibers and their neurokinin-1 receptors, compared to junctional epithelium (Kondo et al, 1992; Tanaka et al., 1996; Kido et al., 1999).

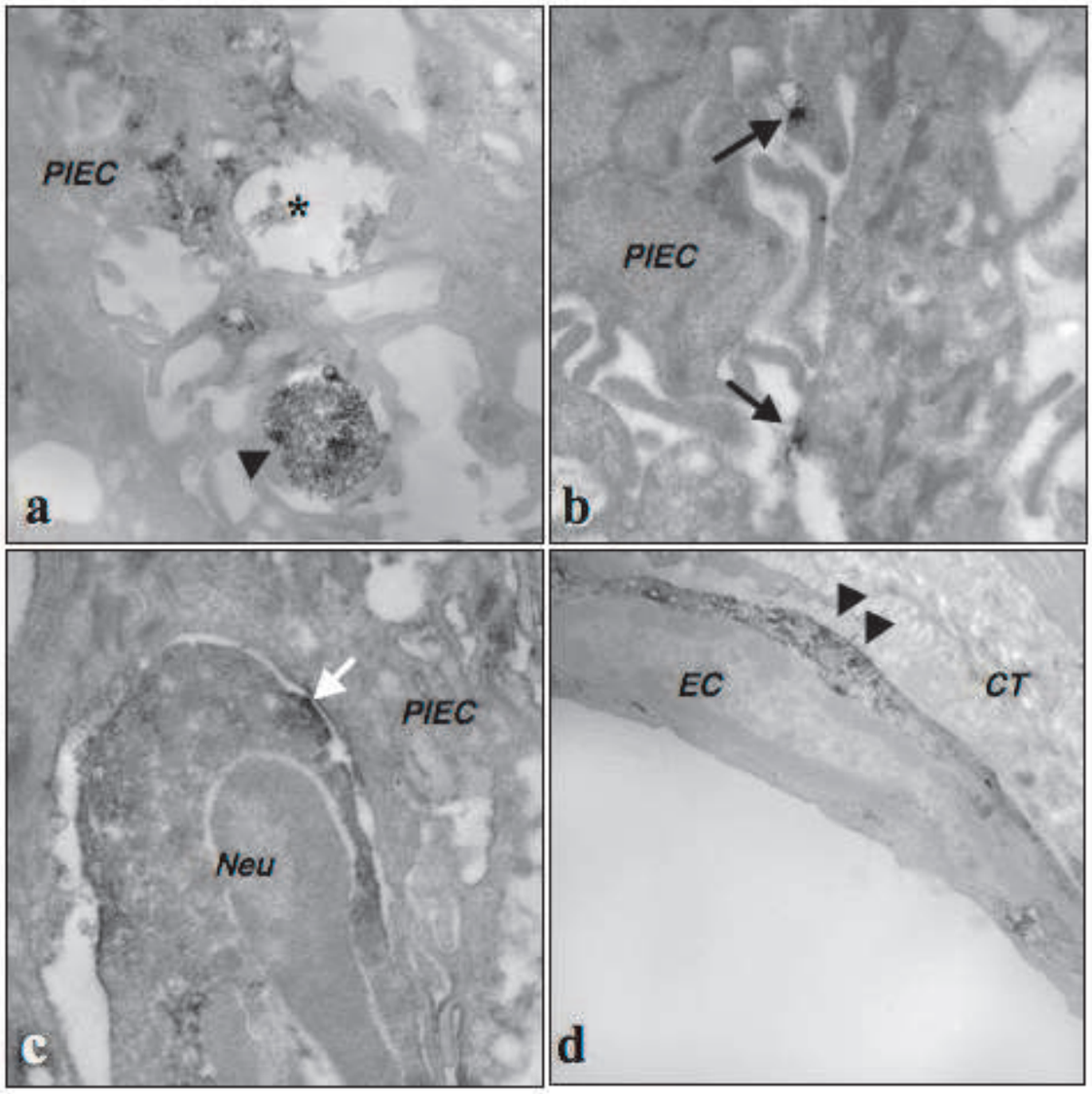

Fig. 8. Distribution of neurokinin 1 receptors in the peri-implant epithelium (*PIE*). (a) Neurokinin 1 receptor-positive products (arrowhead) are seen in a nerve ending close to a PIE cell (*PIEC*). Asterisk: intercellular space between PIE cells. (b) Neurokinin 1 receptor-positivity (arrows) can be detected on the plasma membrane of a PIE cell. (c) An invading neutrophil (*Neu*) was positive for neurokinin 1 receptors (white arrow). (d) A nerve fiber close to an endothelial cell (*EC*) was also positive for neurokinin 1 receptors (double arrowhead). *CT*: connective tissue.

5. Biological sealing and defense mechanisms in the transmucosal region around dental implants

The junctional epithelium is a critical transmucosal region for innate defense against periodontal inflammation. Various mechanisms of peripheral host defense have been demonstrated in this epithelium (Schroeder & Listgarten, 1997) (Figure 9): (1) phagocytosis

and anti-bacterial activity of neutrophils infiltrating into the junctional epithelium (Yamasaki et al., 1979, Tanaka et al., 1988), (2) outward flow of gingival sulcular fluid through the junctional epithelium (McDougall, 1970; Tanaka, 1984; Tanaka and Sakano, 1987), (3) fast turnover or apoptosis of junctional epithelial cells (Schroeder, 1986, Ekuni et al., 2005), (4) continuous epithelial attachment via the IBL throughout the enamel surface (Squier, 1991; Bartold, et al., 2000), (5) endocytotic capacity of junctional epithelial cells for external pathogens (Yamasaki et al., 1979; Tanaka 1984; Tanaka & Sakano, 1987; Ayasaka et al., 1989, Yamaza et al., 1997), and (6) neurotrophic modulation in the junctional epithelium (Kondo et al., 1995; Tanaka et al., 1996; Kido et al, 1999).

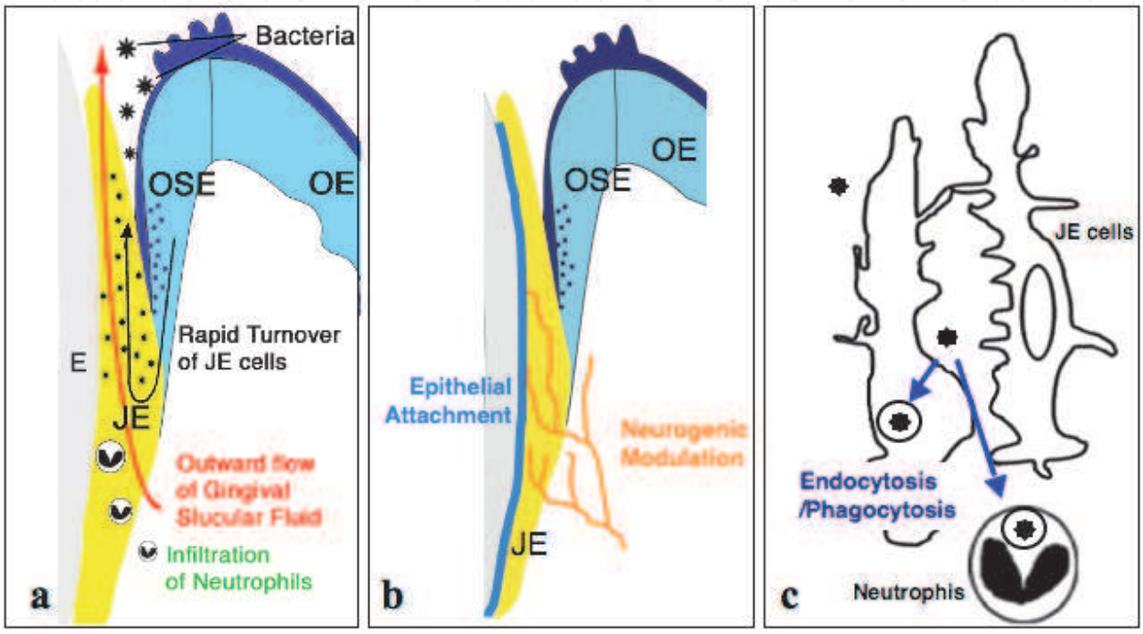

Fig. 9. Schemata of defense mechanisms in the junctional epithelium (JE) around natural teeth. To block invading pathogens, JE has defensive mechanism of (a) outward flow of gingival sulcular fluid through the junctional epithelium (red arrow), fast turnover or apoptosis of junctional epithelial cells (black arrow), and neutrophils infiltrating into the junctional epithelium, (b) continuous epithelial attachment via the internal basement lamina throughout the enamel surface (blue line, and neurotrophic modulation by sensory nerve innervation in the junctional epithelium (orange lines), and (c) endocytotic capacity of junctional epithelial cells and phagocytosis of neutrophils for external pathogens (blue arrows). E: enamel, OE: oral epithelium, OSE: oral sulcular epithelium.

The ultrastructural findings support the idea that the PIE can allow the penetration of foreign molecules into the sub-epithelial connective tissue, indicating that the PIE acts as a first line of defense in protecting against the invasion of several pathogens (Ikeda et al., 2000, 2002). Transmucosal defense around dental implants is suggested to involve the acquisition and maintenance of a similar defense system to that shown by the junctional epithelium. This review considers three aspects of the mucosal defense system around dental implants; (1) PIE-titanium barrier (2) endocytotic system in the PIE, and (3) neurogenic regulation in the PIE (Figure 13).

5.1 Epithelial attachment of PIE-titanium barrier

Laminin-1 and laminin-5 are major components of the basal lamina, and participate in the formation of a molecular network in the basal lamina (Tryggvason, 1993; Burgeson et al., 1994; Aumailley & Krieg, 1996). They also play important roles in cell differentiation, migration, and adhesion, as well being involved in determining cell phenotype and survival (Timpl, et al., 1979). Laminin 5 forms anchoring filaments in hemidesmosomes and promotes their assembly, indicating a strong binding function in the basal lamina (Green & Jones, 1996). This suggests that IBL- and hemidesmosome-like structures contribute, at least in part, to the formation of a tight attachment at the inner interface between the PIE and the dental implant (Ikeda et al., 2000; Atsuta et al., 2005b).

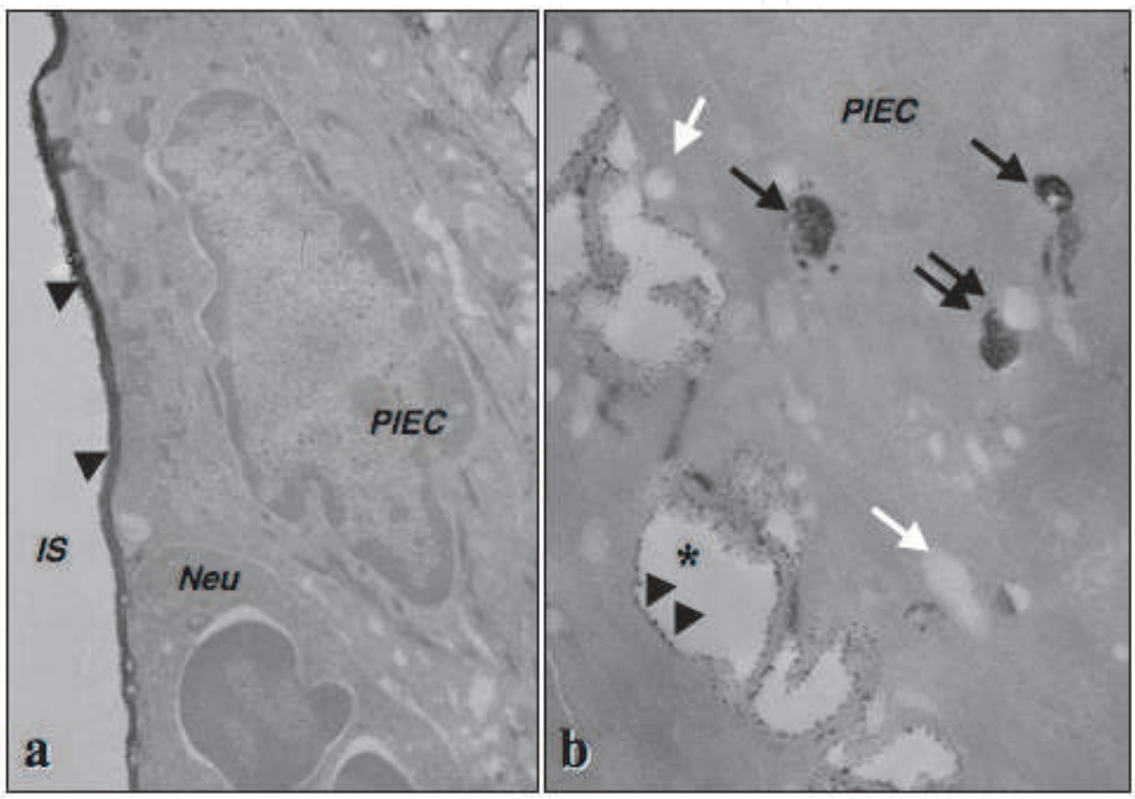

Fig. 10. Electron micrographs showing the localization of applied horseradish peroxidase in the periimplant epithelium. (a) Horseradish peroxidase-reactive products (arrowheads) were found in the internal basement lamina in the lower PIE. However, horseradish peroxidase was not found in the intercellular spaces between PIE cells (*PIEC*). *Neu*: neutrophil, *IS*: implant space. (b) Horseradish peroxidase-reactive organelles show several feature in PIE cells. Endosome-like structures in the cells contained various densities of horseradish peroxidase-reactive products (arrows). Horseradish peroxidase-negative endosomes (white arrows) were also found in PIE cells. Some endosomes were fused with other horseradish peroxidase-negative endosomes (double arrow). Horseradish peroxidase-reactive products (arrowheads) were deposited on the plasma membrane of PIE cells. Asterisk: intercellular space between PIE cells.

The application of horseradish peroxidase (HRP) as a tracer in the mucosa around dental implants or teeth shows a different distribution at each transmucosal interface (Ikeda et al., 2002) (Figures 10, 11). At the natural interface, abundant HRP is stopped at the coronal region of the junctional epithelium and IBL (Yamaza et al., 1997). In contrast, high levels of horseradish peroxidase are widely distributed from the upper to middle regions of the PIE around the dental implants (Ikeda et al., 2002) (Figures 10a, 11a). The lower region also contains HRP, but in smaller amounts (Figures 10b, 11a). The IBL of the lower PIE accumulates exogenous HRP, suggesting a functional role for the IBL in protecting against external invasion (Ikeda et al., 2002) (Figure 11). These findings indicate that the IBL in the PIE participates in local defense around dental implants (Figure 13a).

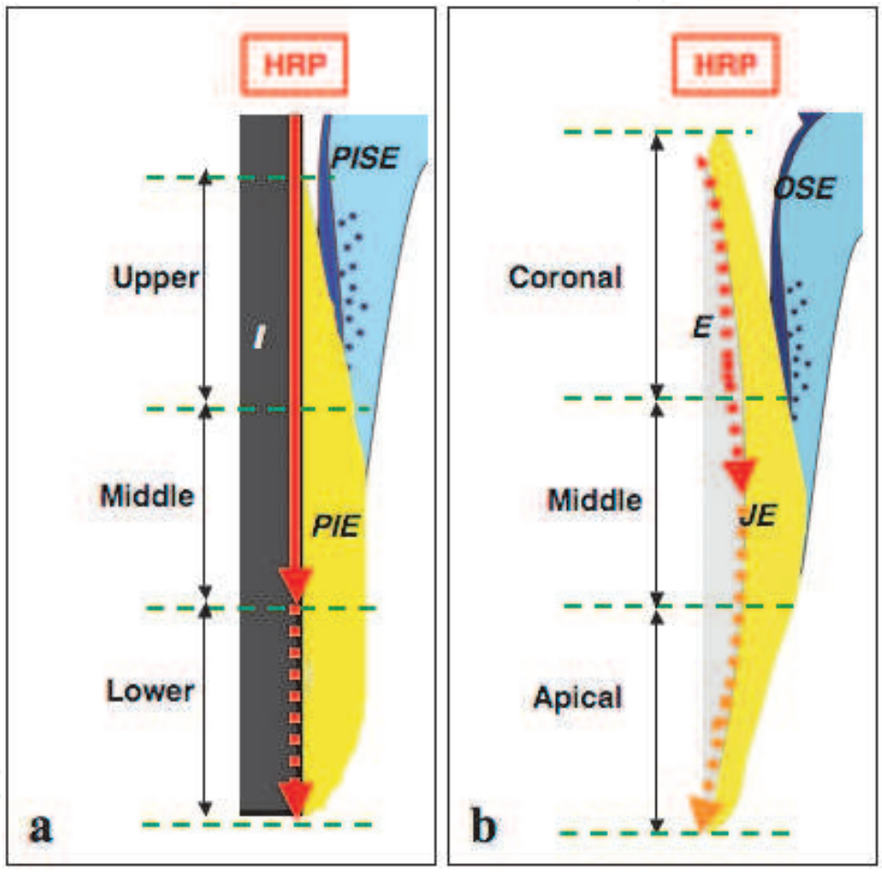

Fig. 11. Schema of the difference of barrier capability of internal basement lamina in the peri-implant epithelium (*PIE*) and junctional epithelium (*JE*). (a) In the PIE, only the lower region has a solid epithelial attachment structure, not in the middle and upper portions. Locally applied horseradish peroxidase (HRP) is easy to penetrate into the PIE thorouth the direct interface between the dental implant (*I*) and PIE (red arrow), but the lower interface showing basal lamina structure defend the penetration (red dot arrow). *PISE*: peri-implant sulcular epithelium. (b) In the natural teeth, basal lamina structure is present throughout the interface between enamel (*E*) and junctional epithelium (*JE*). Loccaly appile HRP is hard to invade along not only to the internal interface of the coronal to middle portion of JE (red dot arrow), but also to the middle to lowe interface (orange dot line).

5.2 Endocytotic system in PIE

Neutrophils generally play an important role in the front-line defense against foreign bodies, through their phagocytotic capacity. They infiltrate into the PIE (Ikeda et al., 2002), suggesting that they are resident or transient leukocytes in the PIE, as well as in the natural junctional epithelium (Yamaza et al., 1997), and function effectively to prevent peri-implant inflammation/disease by their phagocytotic capacity (Ikeda et al., 2002).

Junctional epithelial cells have the ability to endocytose foreign substances (Tanaka et al., 1984; Yamasaki et al., 1985; Ayasaka & Tanaka, 1989; Yamaza et al., 1997). These cells can also digest materials using the intracellular lysosomal system containing aspartic proteinase, cathepsin D (Ayasaka et al., 1993), and the cysteine proteinases, cathepsins B and H (Yamaza et al., 1997). Lysosomal compartments participate in intracellular degradation using lysosomal enzymes (Mellman et al., 1986). The cathepsins show high protein degradative activities (Barrett & Kirschke, 1981), especially in the case of cathepsin B and H (Nishimura et al., 1988). Periodontal pathogens can invade the gingival epithelial cells (Lamont et al., 1995; Rautemaa et al., 2004). PIE cells also contain a variety of intracellular endosome/lysosome systems, suggesting a capacity to take up and digest foreign materials in the vesicles and vacuoles (Ikeda et al., 2000, 2002). PIE cells also show the ability to endocytose HPR applied locally to the peri-implant mucosa, indicating their digestive capacity against foreign materials (Ikeda et al., 2002) (Figure 10b). These results suggest that the endocytotic system of PIE cells, as well as the presence of neutrophils, may play a role in the local defense of the transmucosal region around dental implants (Figure 13).

Cystatin C is an endogenous cysteine proteinase inhibitor (Abrahamson et al., 1986) expressed in junctional epithelial cells, and secreted extracellularly (Yamaza et al., 2005). This natural inhibitor also plays a role in the anti-bacterial activity against the periodontal microorganism, *Porphyromonas gingivalis* (Blankenvoorde et al., 1998), which releases a specific cysteine proteinase (Chen et al., 1992). Cystatin C is present in gingival cervicular fluid (Ulker et al., 2008), supporting the extracellular secretion of this inhibitor into gingival tissues, including the intercellular spaces of the junctional epithelium. Secreted cystatin C from junctional epithelial cells may participate in the inhibition of *P. gingivalis*-derived proteinase activity and suppression of *P. gingivalis* growth, suggesting that cystatin C also acts as a candidate molecule governed by the PIE cell-mediated defense system. Thus several functions of PIE cells may contribute to local defense in the transmucosal region around dental implants.

5.3 Neurogenic regulation in PIE

Substance P is a nociceptive neuropeptide responsible for transmitting pain stimuli, such as those due to chemical irritants, heat, cold or other noxious stimuli. It is expressed in sensory nerves of the peripheral nervous system and participates in the afferent transmission of pain impulses from the mucosa through sensory receptors at the nerve endings (Lundy & Linden, 2004) (Figure 12). In contrast, this transmitter is also released efferently from nerve endings on stimulation by noxious phenomena (Figure 12). Released substance P can affect the responses of the target cells through direct interaction with neurokinin-1 receptors (Scholzen et al., 1998) (Figure 12). The presence of substance P in gingival cervicular fluid supports the release of this neuropeptide from nerve terminals (Linden et al., 1997). Acting via neurokinin-1 receptors, substance P induces several cellular responses (Figure 12), In the endothelial cells, vasodilation, and modulates blood flow and plasma leakage are occurred

by the substance P-nurokin 1 receptor binding (Lembeck & Holzer 1979; Nicoll et al., 1980; Otsuka & Yoshida 1993). The substance P-neurokinin-1 receptor pathway can also enhance endocytosis in neutrophils (Bar-Shavit et al., 1980; Tanabe et al., 1996). Substance P also stimulates the chemotaxis of neutrophils and macrophages, the proliferation and migration of keratinocytes and fibroblasts, degranulation of mast cells, the expression of various adhesion proteins on endothelial cells, and the release of inflammatory cytokines from immune cells (Kähler et al., 1993; Ziche et al., 1994; Scholzen et al., 1998; Koon et al., 2006; Liu et al., 2007). Furthermore, substance P-binding neurokinin-1 receptors are known to regulate the innate immune system (Tuluc et al., 2009; Douglas & Leeman, 2011), and participate in immunomodulation in immune diseases (Koon & Pothoulakis, 2006).

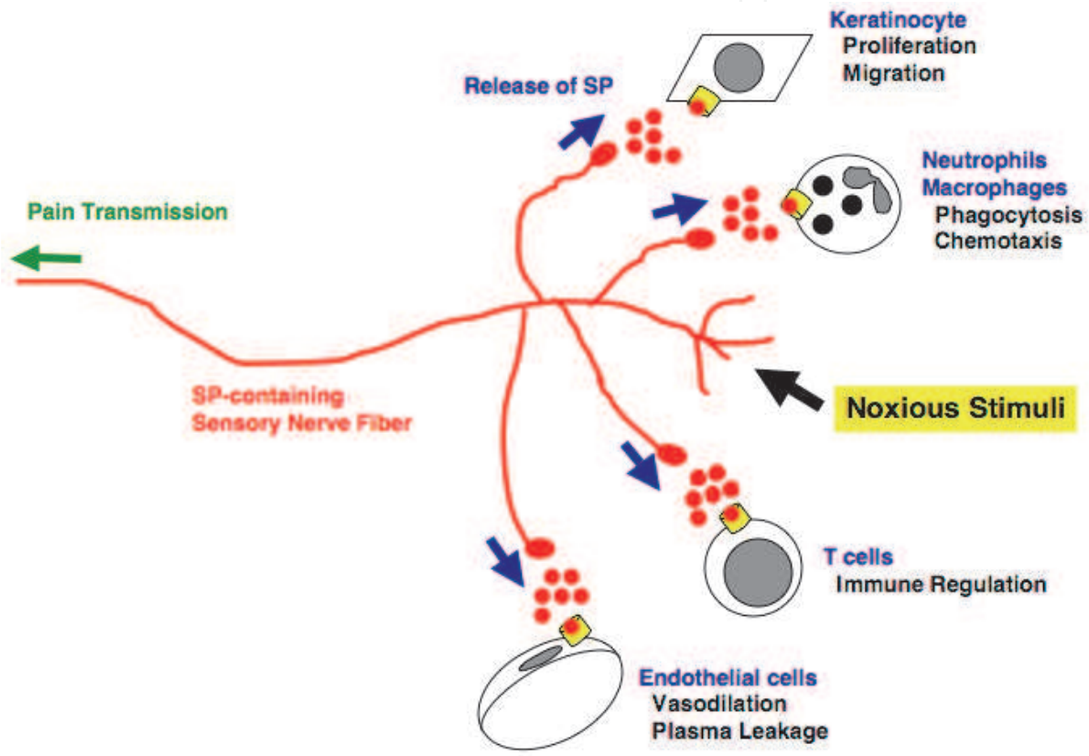

Fig. 12. Scheme of biological functions of substance P. Once the nerve ending catch noxious stimuli such as chemical irritants, heat, cold stimuli, (black arrow) to substance P-containing nerve fibers, substance P has a capable of transmitting pain stimuli (green arrow). On the other hand, substance P can be released from the free nerve endings by the noxious stimuli (blue arrows). Released substance P (red dots) are able to bind to their receptors neurokinin 1 recetors (yellow squeares) on the several types of cells, such as keratinocytes, neutrophils, macrophages, endothelial cells of blood vessels, and T cells to induce a variety of cellular functions, as shown on the scheme.

The distribution of substance P-containing sensory nerve terminals and neurokinin-1 receptors in the PIE (Yamaza et al., 2009) suggests that released substance P may bind to neurokinin-1 receptors on PIE cells, endothelial cells, and intraepithelial neutrophils, and induce a variety of innate defense mechanisms in the PIE (Figure 13). These mechanisms might include the induction of neutrophil infiltration from blood vessels into the PIE, the

promotion of plasma extravasation from blood vessels beneath the PIE subjected to peri-implant sulcular fluid, and up-regulation of the endocytotic capabilities of PIE cells and neutrophils.

Substance P is also known to have anti-microbial activity (Kowalska et al., 2002; El Karim et al., 2008; Douglas & Leeman, 2011). Substance P released from nerve terminals into the intercellular spaces between the nerve endings and neurokinin receptor-bearing cells may inhibit intraepithelial growth of peri-implant bacteria in the PIE. Thus substance P-neurokinin-1 receptor function could, at least partly, govern the local defense mechanisms in this transmucosal region around dental implants, as in the natural junctional epithelium (Kido et al., 1999; Brogden et al., 2005).

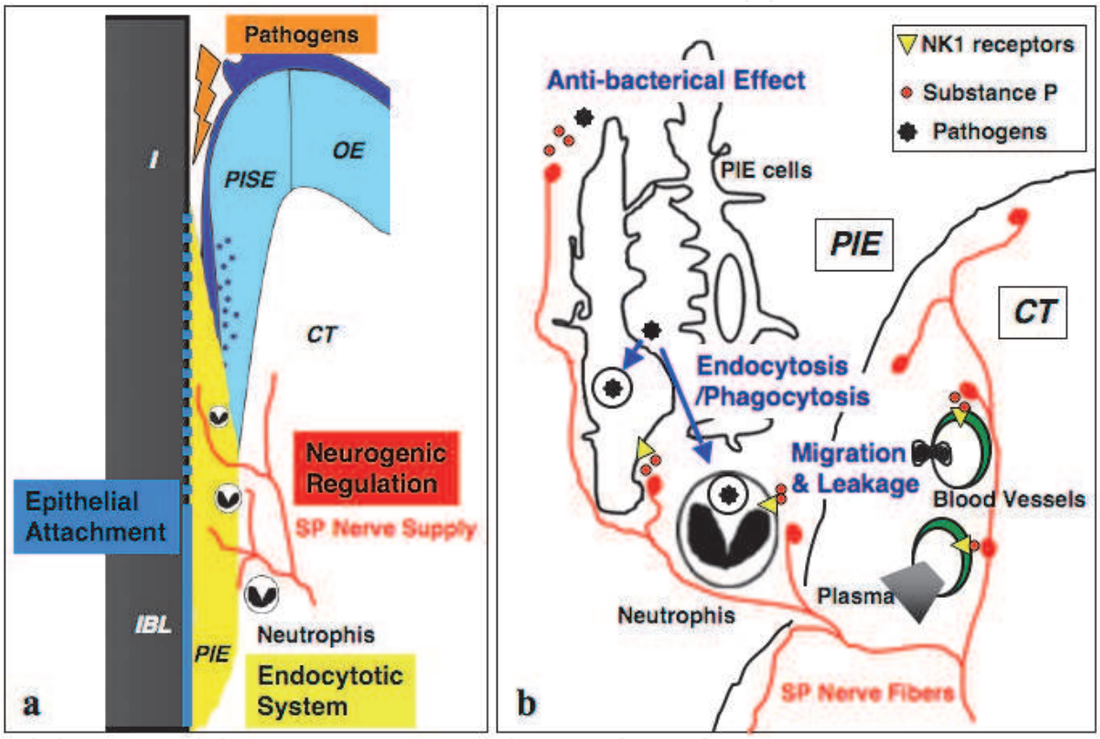

Fig. 13. Schemata of defense mechanisms in the transmucosal region around dental implants. (a) Epithelial attachment structure, internal basement lamina (*IBL*) and substance-P (SP) nerve supply in the peri-implant epithelium (*PIE*) and its subepithelial connective tissuesuggests the restoration of biological seals and defenses against several pathogens (bacteria or their products) from the oral cavity. *CT*: connective tissue, *I*: implant, *OE*: oral epithelium, *PISE*: peri-inplant sulcular epithelium. (b) Invaded pathogens stimulate the release of substance-P from the nerve endings of extra-and intra-epithelial nerve fibers. The released substance-P induces various cellular functions by binding to neurokinin-1 (NK1) receptors localized on endothelial cells, neutrophils, and peri-implant epithelial cells. This linkages result in migration of neutrophils from blood vessels into the peri-implant epithelium, and increased permeability of blood vessels to pass outwardly throughout the peri-implant epithelium. The cascades also promote the endocytosis or phagocytosis of peri-implant epithelial cells or neutrophils. The released substance P may also leads to act as a direct anti-bacterial agent.

6. Conclusion

The transmucosal region around dental implants demonstrates similar anatomical and biological features to the natural interface between the tooth enamel and the junctional epithelium. Regeneration of the PIE with its defense functions will produce a more secure implant-soft tissue interface, and thus improve the success of clinical dental implant therapy.

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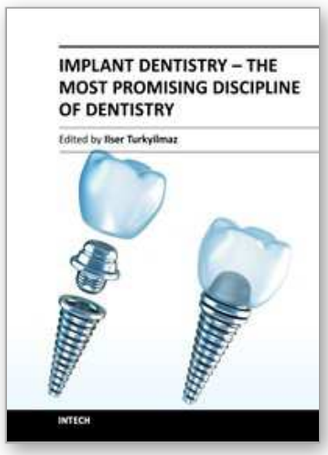

Implant Dentistry - The Most Promising Discipline of Dentistry

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Since Dr. Branemark presented the osseointegration concept with dental implants, implant dentistry has changed and improved dramatically. The use of dental implants has skyrocketed in the past thirty years. As the benefits of therapy became apparent, implant treatment earned a widespread acceptance. The need for dental implants has resulted in a rapid expansion of the market worldwide. To date, general dentists and a variety of specialists offer implants as a solution to partial and complete edentulism. Implant dentistry continues to advance with the development of new surgical and prosthodontic techniques. The purpose of Implant Dentistry - The Most Promising Discipline of Dentistry is to present a comtemporary resource for dentists who want to replace missing teeth with dental implants. It is a text that integrates common threads among basic science, clinical experience and future concepts. This book consists of twenty-one chapters divided into four sections.

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