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Pathogenic Factors of *P. gingivalis* and the Host Defense Mechanisms

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1. Introduction

Periodontal diseases are the inflammatory diseases triggered specifically by some selected microorganisms, *i.e.*, periodontopathic bacteria, accumulated in and around the gingival crevice. Among periodontopathic bacteria, *Porphyromonas gingivalis*, a black-pigmented gram-negative anaerobic rod, has been implicated as a major pathogen of chronic periodontitis (Hamada et al., 1991; Lamont & Jenkinson, 1998). Recent studies using DNA-DNA hybridization that permits the examination of large numbers of species in large numbers of plaque samples also indicated the increased prevalence of *P. gingivalis* as well as other 'red complex species' (*P. gingivalis*, *Treponema denticola* and *Tannerella forsythensis*) in the subjects with chronic periodontitis (Socransky & Haffajee, 2002). However, it is also evident that the colonization of the putative pathogenic bacteria in subgingival plaque is not sufficient for the initiation/onset of periodontitis, since most periodontopathic bacteria including *P. gingivalis* may also be present at sound sites (Haffajee et al., 2009). Thus, the onset and progress of chronic periodontitis is based on the balance between the pathogenesis of the periodontopathic microorganisms and the host-defense against them (host-parasite relationship).

The pathogenic factors of *P. gingivalis* including fimbriae, hemagglutinin, capsule, lipopolysaccharide (LPS), outer membrane vesicles, organic metabolites such as butyric acid, and various enzymes such as Arg- and Lys-gingipains, collagenase, gelatinase and hyaluronidase, could contribute to the induction of chronic periodontitis in diverse ways; *P. gingivalis* could colonize to gingival crevices by the fimbriae-mediated adherence to gingival epithelial cells, the proteases may have the abilities to destroy periodontal tissues directly or indirectly, and the LPS could elicit a wide variety of inflammatory responses of periodontal tissues and alveolar bone losses. Although the complex interaction to the host response fundamentally responsible for chronic periodontitis cannot be reproduced in vitro, the studies with animal models that *P. gingivalis* can induce experimental periodontitis with alveolar bone losses (Kimura et al., 2000a; Oz & Puleo, 2011) clearly indicate that *P. gingivalis* is a major causative pathogen of chronic periodontitis, and its pathogenic factors could be potentially involved solely or cooperatively in every step of the onset and progression of the disease. A recent study that the DNA vaccine expressing the adhesion/hemagglutinin

domain of Arg-gingipain prevented the *P. gingivalis*-induced alveolar bone loss in mice (Muramatsu et al., 2011) may support in part the hypothesis.

In this chapter, we will address not the every pathogenic factor of *P. gingivalis* in tern, but the roles of the factors and their relationship in the pathogenic events of this microorganism, such as the colonization in gingival crevices, the invasion into gingival tissues, and the induction of inflammatory responses and alveolar bone losses.

2. Colonization in gingival crevices

The colonization of *P. gingivalis* in gingival crevices is the first step in the development of chronic periodontitis. However, it does not necessarily induce the periodontal destruction, but a prerequisite for onset of chronic periodontitis. In adults, *P. gingivalis* can be detected from periodontally healthy sites as well as diseased sites, although the number of the microorganisms is generally lower than that in diseased sites (Dzink et al., 1988; Hamada et al., 1991). In contrast, *P. gingivalis* is scarcely detected in the samples from oral cavities of children (Kimura et al., 2002; Kimura & Ohara-Nemoto, 2007). Our 2-year longitudinal study revealed that *P. gingivalis* as well as *Prevotella intermedia* and *T. denticola* appear to be transient organisms in the plaques of healthy children (Ooshima et al., 2003). From the point of view on host-parasite relationship in chronic periodontitis, the children's host-defense of antibiotic components in saliva and gingival crevicular fluid (GCF) could efficiently prevent the initial colonization and/or proliferation of these periodontal pathogens, resulting in the arrest of periodontal diseases in healthy children.

Nevertheless, it was also demonstrated that children whose parents were colonized by the BANA-positive periodontopathic species including *P. gingivalis*, *T. denticola*, and *T. forsythensis* were 9.8 times more likely to be colonized by these species, and children whose parents had clinical evidence of periodontitis were 12 times more likely to be colonized the species (Watson et al., 1994). The vertical transmission of *P. gingivalis*, however, has been still controversial; vertical as well as horizontal transmission was speculated in the research on 564-members of American families (Tuite-McDonnell et al., 1997), whereas vertical (parents-to-children) transmission has rarely been observed in the Netherlands (Van Winkelhoff & Boutaga, 2005), in Finland (Asikainen & Chen, 1999), and in the research of 78 American subjects (Asikainen et al., 1996). In the latter reports, since horizontal transmission of *P. gingivalis* between adult family members was considerable, it was suggested that *P. gingivalis* commonly colonizes in an established oral microbiota. According to these observations, it was also suggested that the vertical and horizontal transmission of *P. gingivalis* could be controlled by periodontal treatment involving elimination of the pathogen in diseased individuals and by oral hygiene instructions.

The major habitat of *P. gingivalis* is subgingival plaques in gingival crevices. However, *P. gingivalis* can be detected in the tongue coat samples from periodontally healthy and diseased subjects (Dahlén et al., 1992; Kishi et al., 2002). Clinical studies suggested that tongue coat could be a dominant reservoir of *P. gingivalis* (Kishi et al., 2002; Favari et al., 2006). Furthermore, our recent study with 165 subjects aged 85 years old indicated that *P. gingivalis* as well as *P. intermedia*, *T. denticola* and *T. forsythensis* was found more frequently in tongue coat samples from dentate than edentulous subjects, and the prevalence of *P. gingivalis* was significantly related to the number of teeth with a periodontal pocket depth ≥ 4 mm (Kishi et

al., 2010). Thus, it can be speculated that an adequately stable circulation of *P. gingivalis* between subgingival plaque and tongue coat occurs over time in dentate individuals. In addition, tooth loss, which is synonymous with loss of the gingival crevice, may affect the oral microflora population, resulting in a significant decrease in *P. gingivalis*.

Despite the host defense mechanisms in saliva and GCF, *P. gingivalis* can adhere and then colonize in gingival crevices to a variety of surface components lining the gingival crevicular cells and the tooth surface. The adhesive ability of *P. gingivalis* is mainly mediated by the fimbriae, although other bacterial components such as vesicles, hemagglutinin, and proteases may play an adjunctive role (Naito et al, 1993). Fimbriae are the thin, filamentous, and proteinaceous surface appendages found in many bacterial species, and these fimbriae are claimed to play an important role in the virulence of a number of oral and non-oral pathogens such as uropathogenic *Escherichia coli* and *Neisseria gonorrhoeae*. Fimbriae of *P. gingivalis* were first recognized on the outer surface by electron microscopic observation (Slots & Gibbons, 1978; Okuda et al., 1981), and were isolated and purified to a homogeneity from strain 381 by a simple and reproducible method using DEAE Sepharose chromatography (Yoshimura et al., 1984). Fimbriae of *P. gingivalis* 381 are composed of constituent (subunit) protein, fimbrillin, with a molecular weight of 40-42 kDa by sodium dodecyl sulfate-polyacrylamide gel electrophoresis (Ogawa et al., 1991; Hamada et al., 1994). Lee et al. (1991) compared fimbriae diversities of size and amino terminal sequence of fimbrillins from various *P. gingivalis* strains; they differed in molecular weights ranging from 40.5 to 49 kDa and were classified into four types (types I to IV) based on the amino terminal sequences of fimbrillins. Further molecular and epidemiological studies using PCR method to differentiate possibly varied bacterial pathogenicity revealed that *P. gingivalis* fimbriae are classified into six genotypes based on the diversity of the *fimA* genes encoding each fimbrillin (types I to V, and type Ib), and that *P. gingivalis* with type II *fimA* is most closely associated with the progression of chronic periodontitis (Amano et al., 1999a; Nakagawa et al., 2000 & 2002b) (Table 1). A recent study with the mutants in which *fimA* of ATCC 33277 (type I strain) was substituted with type II *fimA* and that of OMZ314 (type II strain) with type I *fimA* indicated that type II fimbriae is a critical determinant of *P. gingivalis* adhesion to epithelial cells (Kato et al., 2007).

<i>fimA</i> type	Odds ratio	95% confidence interval	<i>P</i> value
I	0.20	0.1 - 0.4	0.0000
Ib	6.51	2.9 - 14.6	0.0000
II	77.80	31.1 - 195.4	0.0000
III	2.51	1.1 - 5.8	0.0246
IV	7.54	3.5 - 16.0	0.0000
V	1.05	0.6 - 1.8	0.8525

Table 1. Relationship of *fimA* types in chronic periodontitis

P. gingivalis fimbriae possess a strong ability to interact with host proteins such as salivary proteins, extracellular matrix proteins, epithelial cells, and fibroblast, which promote the colonization of *P. gingivalis* to the oral cavity (Naito & Gibbons, 1988; Hamada et al., 1998). These bindings are specific and occur via protein-protein interactions through definitive

domains of fimbriae and host proteins. The real-time observation by biomolecular interaction analysis (BIAcore) showed specific and intensive interaction to salivary proteins and extracellular matrix proteins (Table 2). The binding components in saliva are acidic proline-rich protein (PRP), proline-rich glycoprotein (PRG), and statherin (Amano et al., 1996a, 1996b & 1998). *P. gingivalis* fimbriae also show significant interactions with extracellular matrix proteins including fibronectin and laminin (Kontani et al., 1996; Amano et al., 1999b). Therefore, *P. gingivalis* cells can bind to tooth surface and upper gingival crevice that is covered with saliva. Although a deeper portion of the gingival crevice could not be contaminated with saliva, *P. gingivalis* can bind directly to sulcular epithelial cells via interaction with extracellular matrix proteins.

In addition, Arg-gingipains produced by *P. gingivalis* can enhance the adherence of purified fimbriae to fibroblasts and matrix proteins; Arg-gingipains can expose a cryptotope in the matrix protein molecule, i.e. the C-terminal Arg residue of the host matrix proteins, so that the organism can adhere to the surface layer in gingival crevices through fimbrial-Arg interaction (Kontani et al., 1996 & 1997).

Host protein	k_a (1/M/s)	K_{dis} (1/s)	K_a (1/M)
PRP	2.61×10^3	1.60×10^{-3}	1.63×10^6
PRG	3.38×10^3	2.08×10^{-3}	1.62×10^6
Statherin	2.49×10^3	1.68×10^{-3}	1.48×10^6
Laminin	3.62×10^3	1.68×10^{-3}	2.15×10^6
Fibronectin	3.46×10^3	1.60×10^{-3}	2.16×10^6
Thrombospondin	3.01×10^3	1.33×10^{-3}	2.26×10^6
Type I collagen	3.04×10^3	1.10×10^{-3}	2.76×10^6
Vitronectin	4.16×10^3	1.10×10^{-3}	3.79×10^6
Elastin	3.72×10^3	1.21×10^{-3}	3.08×10^6
Anti-fimbriae IgG	6.11×10^3	5.00×10^{-3}	1.22×10^7

Table 2. Binding constants of *P. gingivalis* fimbriae to host proteins

In gingival crevices, serum antimicrobial components consecutively exude through the junctional epithelium, termed GCF. GCF originates from plasma exudates, thus contains IgG, IgA, complements and cellular elements. It is noted that 95% of the cellular elements are polymorphonuclear leukocytes (PMNL) and the remainder being lymphocytes and monocytes, even in the GCF from clinically healthy gingival crevices, indicating that PMNL are the principal cell of GCF (Genco & Mergenhagen, 1982). PMNL come into direct contact with plaque bacteria in the gingival crevice and actively phagocytose them. The protective function of PMNL in human periodontal diseases is demonstrated by the fact that patients with PMNL disorders, e.g. Chédiak-Higashi syndrome, lazy leukocyte syndrome, cyclic neutropeni, chronic granulomatous disease and diabetes mellitus, have usually rapid and severe periodontitis (Genco, 1996; da Fonseca & Fontes, 2000; Delcourt-Debruyne et al., 2000; Meyle & Gonzáles, 2001; Lalla et al., 2007). Furthermore, quantitative analyses using flow cytometer revealed that about 50% of the patients with localized and generalized

aggressive periodontitis exhibited depression of phagocytic function of peripheral blood PMNL (Kimura et al., 1992 & 1993), suggesting that the functional abnormalities of PMNL are implicated in the pathogenesis of both forms of aggressive periodontitis. Thus, PMNL could play an important role in gingival crevices as innate immunity to prevent the colonization and/or proliferation of *P. gingivalis*, resulting in the arrest of periodontal diseases in healthy subjects.

The gingival crevice is bathed in saliva that contains a lot of antibiotic agents, such as lysozyme, lactoferrin, peroxydase and secretory IgA. In addition, the sulcular epithelium acts as a physical barrier against intruders (Cimasoni, 1983). Furthermore, our recent study indicated that the sulcular epithelial cells could be a substantial producer of secretory leukocyte protease inhibitor (SLPI) that functions inhibitory to the pathogenic *P. gingivalis* infection (Ishikawa et al., 2010). SLPI has been recognized as not only a protease inhibitor but also an important defense component in innate immunity in mucosal secretory fluids. To elucidate the functional role in innate immunity in gingival crevices, we investigated the SLPI production from a gingival epithelial cell line, GE1, with or without the stimulation of the lyophilized whole cells of *P. gingivalis* (Pg-WC) and the LPS (Pg-LPS), and the inhibitory effect of SLPI on *P. gingivalis* proteases. The real-time RT-PCR analyses indicated that the unstimulated GE1 cells showed low, but significant levels of SLPI mRNA expression, which was augmented by the stimulation with Pg-LPS as well as Pg-WC (Fig. 1). The augmentation of SLPI mRNA expression in GE1 cells was accompanied by the inductions of IL-6, TNF- α and IL-1 β mRNA expressions. Although it was reported that IL-6 could induce macrophages to produce SLPI, the kinetics analyses suggested that the augmentation of SLPI production in GE1 cells could not be a second response to the IL-6 induced by the stimulant, but a direct response by the *P. gingivalis* antigens. Further experiments using rSLPI indicated that SLPI showed a direct inhibitory effect on the *P. gingivalis* protease of Lys-gingipain (Fig. 2). Thus the results suggested that the SLPI production by gingival epithelial cells could increase in response to *P. gingivalis* through the stimulation with its pathogenic constituents.

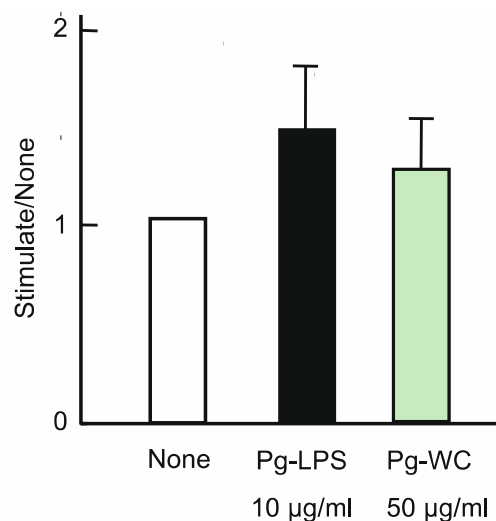


Fig. 1. SLPI mRNA expression of GE1 cells and the augmentation with *P. gingivalis* LPS. GE1 cells were incubated without or with Pg-LPS or Pg-WC. The mRNA levels of SLPI were measured by real-time RT-PCR. Mean \pm S.D.

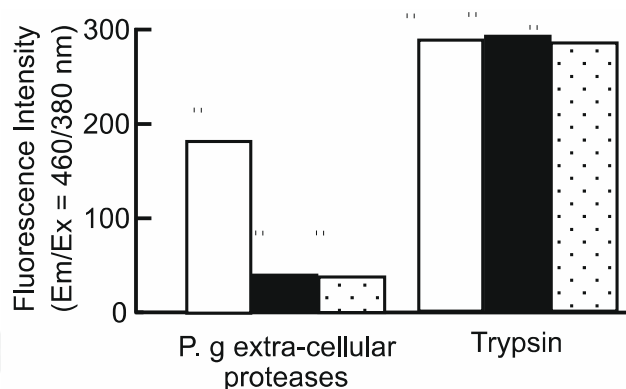


Fig. 2. Inhibitory effect of SLPI on the Lys-gingipain activity. Proteolytic activity toward His-Glu-Lys-MCA was measured with *P. gingivalis* extracellular proteases or trypsin without SLPI (open bar) or with 50 µg/ml (closed bar) and 100 µg/ml (dotted bar) of rSLPI.

3. Invasion into gingival tissues

Ultrastructural study demonstrated bacterial invasion in the apical gingiva of patients suffering from advanced chronic periodontitis (Frank, 1980; Saglie et al., 1986; Kim et al., 2010). In disease lesions, the barrier of PMNL present in the gingival crevice (periodontal pocket) is insufficient to prevent plaque bacterial invasion of the pocket walls, and subgingival plaque bacteria including *P. gingivalis* penetrate gingival epithelium. The bacterial penetration and access to the connective tissue is augmented by enlargement of the intercellular spaces of the junctional epithelium caused by destruction of intercellular junctions. *P. gingivalis* Arg- and Lys-gingipains are involved in degradation of several types of intercellular junctions and extracellular matrix proteins in host tissues. Intercellular presence of subgingival plaque bacteria was specifically demonstrated in the regions. However, intracellular bacteria have not been inevitably noticed in the cases of advanced chronic periodontitis except bacteria in phagocytic vacuoles of PMNL by ultrastructural studies.

On the other hand, invasion or internalization of *P. gingivalis* is observed in the cultures of gingival epithelial cells (Lamont et al., 1992 & 1995), oral epithelial KB cells (Duncan et al., 1993), and aortic and heart endothelial cells (Deshpande et al., 1998). Invasion of bacteria is quantitated by the standard antibiotic protection assay using gentamicin and metronidazole. Under optimal inoculation conditions at a multiplicity of infection of 1:100, approximately 10% of *P. gingivalis* are recovered intracellularly from epithelial cells at 90 to 300 min after incubation. The invasion efficiency for KB cells and endothelial cells is reported to be much lower, around 0.1%. With these cells, adherence of *P. gingivalis* to the cell surface commonly induces microvilli protruding and the attached bacterial cells are surrounded by microbilli on the cell surface (Fig. 3A). Adherence of *P. gingivalis* to eukaryotic cell surface is relevantly mediated with fimbriae, and it was reported that a fimbriae-deficient mutant exhibited a greater reduction in invasion compared with adherence (Weinberg et al., 1997). Therefore, it is speculated that fimbrillin interacts with cell surface receptor, permitting *P. gingivalis* invasion. Among the six *fimA* types, the adhesion to a human epithelial cell line was more significant in *P. gingivalis* harboring the type II *fimA* than those with other *fimA* types. Accordingly, invasion of the type II *fimA* bacteria was most efficiently demonstrated (Nakagawa et al., 2002b). Host receptor candidates including β 2 and α 5 β 1-integrin have been reported to interact with *P. gingivalis* fimbrillin.

Following the attachment of *P. gingivalis* to cells, the invasion process requires the involvement of both microfilament (actin polymerization) and microtubule activities. This property is similar to those of *N. gonorrhoeae* and enteropathogenic *E. coli*. In addition, proteolytic activity is involved in *P. gingivalis* invasion, whereas *de novo* protein synthesis both in *P. gingivalis* and eukaryotic cells are not inevitably needed (Lamont et al., 1995; Deshpande et al., 1998).

Although effects of staurosporine, a broad-spectrum inhibitor of protein kinases, on invasion are varied among targeted cells, protein phosphorylation is surely involved in *P. gingivalis* invasion. A recent report by Tribble et al. (2006) demonstrated that a haloacid dehalogenase family serine phosphatase, SerB653, secreted from *P. gingivalis* regulates microtubule dynamics in human immortalized gingival keratinocytes. The dephosphorylation activity of SerB653 is closely related to the optimal invasion and intracellular survival of the microorganism. The pull-down assay revealed Hsp90 and GAPDH as interactive candidates for SerB653. Both proteins are known to be phosphorylated and may play a role in modulation of microtubules for initiation of the bacterial invasion into epithelial cells.

We have recently succeeded in monitoring the *P. gingivalis* invasion process into porcine carotid endothelial cells in culture by time-laps movie (a part of the results is shown as Fig. 3B) (Hayashi M., Ohara-Nemoto, Y. & Kawamura, T., unpublished data of Cine-Science Lab. Co., Tokyo, Japan). Our movie clearly showed swift entering of the bacteria inside the cell through cell membrane. Intracellular movement of *P. gingivalis* was also observed, suggesting an interaction of the bacteria with microtubules. After 3-h invasion, *P. gingivalis* was located around the nuclei (Fig. 3B). This observation is in good accord with previous data, which showed accumulation of internalized recombinant FimA-microspheres around the epithelial cell nuclei (Nakagawa et al., 2002a).

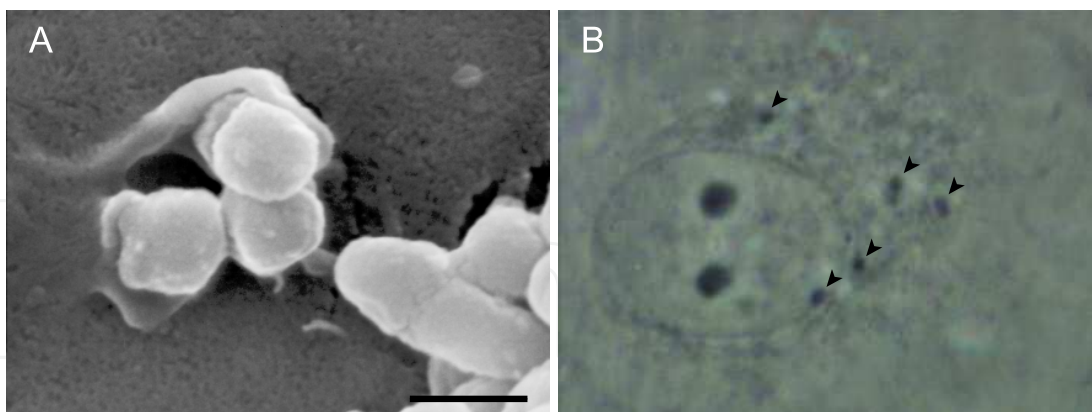


Fig. 3. Entry of *P. gingivalis* into endothelial cells. *P. gingivalis* ATCC 33277 was co-cultured with porcine carotid endothelial cells. (A) Scanning electron micrograph. *P. gingivalis* (observed in white) was surrounded by microvilli protruding from endothelial cell. Bar = 0.5 μm . (B) *P. gingivalis* inside the cell. A representative scene at 3 h after internalization from time-laps microscopic imaging with phase contrast microscopy. Arrowheads indicate *P. gingivalis* observed near the nucleus.

Molecular events of intracellular signal transduction that occur after invasion of *P. gingivalis* have been poorly defined. *P. gingivalis* invasion induces transient increase in cytosolic Ca^{2+}

concentration in gingival epithelial cells, suggesting an involvement of a Ca^{2+} -dependent signaling pathway (Izutsu et al., 1996). *P. gingivalis* internalization inhibits secretion of IL-8 by gingival epithelial cells (Darveau et al., 1998; Nassar et al., 2002), whilst interaction via integrin induced expression of IL-1 β and TNF- α genes in mouse peritoneal macrophages (Takeshita et al., 1998). Since challenge of oral bacterial substances or purified *P. gingivalis* LPS to an immortal mouse gingival epithelial cell line GE1 induced gene expression of IL-1 α , IL-1 β , IL-6, TNF- α and SLPI (Hatakeyama et al., 2001; Ishikawa et al., 2010), the cytokine production may be induced not only by bacterial invasion but also via a Toll-like receptor pathway activated by pathogen-associated molecular patterns in host cells. These findings raise a possibility that signal transduction caused by *P. gingivalis* invasion modulates cell promotion, resulting in gingival tissue destruction.

We monitored the dysfunction of endothelial cells for the first time on co-culture with *P. gingivalis* ATCC 33277 by time-laps microscopic imaging. Endothelial cell attachment became loose at 3 h after bacterial inoculation. Furthermore, cell atrophy was evident at 22 h (Fig. 4) (Hayashi M., Ohara-Nemoto, Y. & Kawamura, T., unpublished data). Therefore, it is of interest whether cellular dysfunction is caused by *P. gingivalis* invasion into host cells or mediated by intercellular signaling through host cell surface.

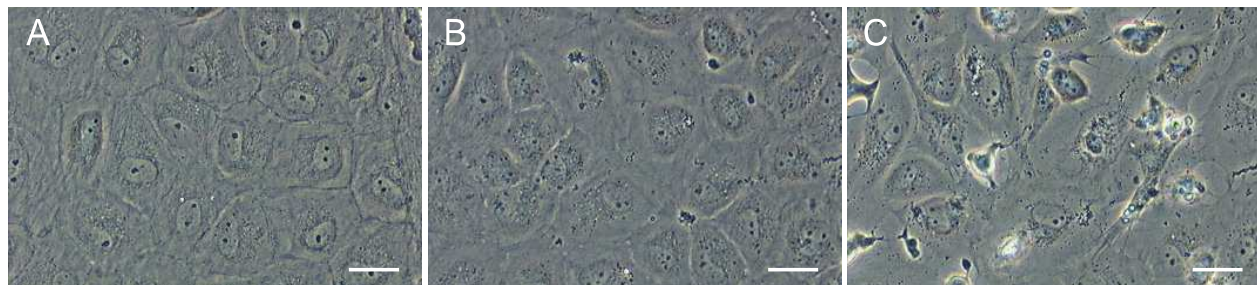


Fig. 4. Dysfunction of endothelial cells caused by co-culture with *P. gingivalis*. Porcine carotid endothelial cells were cultured with *P. gingivalis* ATCC 33277 at 37°C. Time-laps microscopic imaging was taken for 22 h. (A) Normal endothelial cells. Images at 3 h (B) and 22 h (C) after addition of *P. gingivalis*. Bar = 30 μm .

4. Induction of inflammatory responses

Chronic periodontitis is recognized as a B-cell-rich lesion that includes immunoglobulin G-producing plasma cells. However, the immunohistopathological studies revealed that B cell activation in periodontitis lesions by substances from plaque bacteria is, at least in major part, polyclonal, since the immunoglobulin showed a broad spectrum of antibody specificities, as is expected of polyclonal activation (Page, 1982). LPS from the outer membrane of gram-negative bacteria elicits a wide variety of responses that may contribute to inflammation and host defense. LPS stimulates various cell types including pre-B cells and B cells, and LPS activates most B cells (polyclonal B cell activation) without regard to its antigen specificity (Snow, 1994). Although *P. gingivalis* LPS is composed of unique constituents and exhibits characteristic immunological activities (Fujiwara et al., 1990 & 1994; Kimura et al., 1995 & 2000b), *P. gingivalis* LPS can be a potent polyclonal activator of B cells (Mihara et al., 1994), thus, it appears that *P. gingivalis* LPS could play a central role in the B cell activation in periodontitis lesions.

P. gingivalis LPS in gingival tissues could not only elicit a wide variety of responses of gingival fibroblasts and periodontal ligament fibroblasts to produce inflammatory cytokines (Agarwal et al., 1995; Yamaji et al., 1995), but also modulate immunocompetent cell responses, especially B cell activation, that may deteriorate the inflammatory condition. The immunoregulatory disorder is demonstrated in chronic periodontitis patients (Kimura et al., 1991).

It is also possible that the proteolytic enzymes of gingipains and collagenase produced by *P. gingivalis* could destroy periodontal tissue directly or indirectly, leading the progression of the disease (Holt et al., 1999; Potempa et al., 2000). Moreover, the organic metabolites such as ammonia, propionate and butyrate could exhibit the ability of disruption of the host immune system and the toxicity against the gingival epithelium (Tsuda et al., 2010). Thus, in chronic periodontitis, the pathogenic factors of *P. gingivalis* could contribute to the gingival inflammation in diverse ways, which results in the alveolar bone losses.

5. Induction of alveolar bone losses

In order to investigate the host-parasite relationship in periodontal diseases, animal models are critically important, since they provide the information about the complex pathogenic mechanism in periodontal diseases. To date, various models including rodents, rabbits, pigs, dogs, and nonhuman primates, have been used to model human periodontitis, and there are clear evidences from the literatures demonstrating alveolar bone losses in the animals infected with *P. gingivalis* (Holt et al., 1988; Kimura et al., 2000a, Wang et al., 2007; Oz & Puleo, 2011). In rodent models, however, a relatively large number of bacteria have often been used for a successful establishment (Klausen, 1991), since some periodontopathic bacteria including *P. gingivalis* are reported to be not easily established in the murine mouth (Wray & Grahame, 1992). In many instances, 10^8 - 10^9 bacteria in the suspension were applied into the oral cavity two or three times, with or without ligation (Oz & Puleo, 2011). In these studies, therefore, the precise inoculum size of the bacteria into the gingival crevice was unknown. Furthermore, it is possible that the pathogenicity of the bacteria with higher activity in the initial colonization in the oral cavity may have been overestimated, regardless of their bone resorbing potential. Then, we developed *P. gingivalis*-adhered ligatures on which 4.29 ± 0.23 logCFU/mm of *P. gingivalis* 381 cells were pre-adhered, and had applied it (1×10^5 *P. gingivalis* cells per mouse) on the first molar in the right maxillary quadrant of a mouse with sterile instruments (Kimura et al., 2000a). *P. gingivalis* was recovered in 95% of the infected mice on 1 week, and 58% on 15 weeks after the single infection with a *P. gingivalis*-adhered ligature in mouse gingival sulcus, indicating that, by means of this method, the establishment of *P. gingivalis* in murine mouths is not transient. The long-lasting infection of *P. gingivalis* in mice resulted in the site-specific alveolar bone breakdown on weeks 13 to 15, although sham-infected mice showed some alveolar bone breakdown in the ligation sites. These findings are supported by the linear regression analysis showing a significant positive correlation between the number of recovered *P. gingivalis* and alveolar bone loss. Furthermore, the *P. gingivalis*-induced alveolar bone loss seemed to be localized around the infected site. Thus, it is strongly suggested that the colonization of a critical amount of *P. gingivalis* for a certain period in gingival crevices may cause the periodontal breakdown at the site of colonization.

P. gingivalis could induce alveolar bone loss in diverse ways; *P. gingivalis* could influence both bone metabolism by Toll-like receptor signaling and bone remodeling by the receptor

activator of NF- κ B (RANK) signaling (Zhang et al., 2011). Among the pathogenic factors of *P. gingivalis*, a major causative factor in alveolar bone losses may be ascribed to the LPS. *P. gingivalis* LPS can induce in vitro the osteoclast formation directly, and also indirectly by the cytokine production from gingival fibroblasts (Slots and Genco, 1984; Zubery, 1998; Scheres et al., 2011). Moreover, an in vivo study indicated that *P. gingivalis* LPS injection resulted in significantly more bone loss versus PBS injections in both the rats with and without diabetes on normal diets (Kador et al., 2011).

In addition, an alternative hypothesis of etiology of development/onset of chronic periodontitis, 'polymicrobial pathogenicity', has been proposed, although a number of findings supporting the pathogenicity of *P. gingivalis* in periodontal diseases. The hypothesis is based on the observation in periodontitis patients that the colonization of 'red complex species' (*P. gingivalis*, *T. denticola* and *T. forsythensis*) strongly related to pocket depth and bleeding on probing (Socransky et al., 1998), and in a rat model that the rats infected with the polymicrobial consortium of the 'red complex species' exhibited significantly increased alveolar bone loss compared to those in the rats infected with one of the microbes (Kesavalu et al., 2007). However, the synergistic pathogenicity is still controversial; Orth et al. (2011) reported that co-inoculation with *P. gingivalis* and *T. denticola* induced alveolar bone losses synergistically in a murine model, whereas no synergistic virulence of the mixed infection with *P. gingivalis* and *T. denticola* was showed in a rat experimental periodontitis model (Verma et al., 2010).

The hypothesis of the synergistic polymicrobial pathogenicity does not exclude the pathogenicity of *P. gingivalis*, but acknowledges also the significant role of the local environmental conditions in subgingival plaques that could govern the periodontopathic potential of *P. gingivalis*. Further studies are obviously required to elucidate the mechanism of the polymicrobial pathogenicity in periodontal breakdown and what kinds of putative periodontopathic bacteria could participate in the synergistic pathogenicity with *P. gingivalis*.

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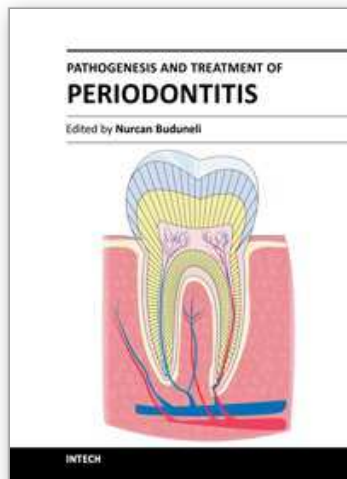
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