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# The Impact of Bacteria-Induced Adaptive Immune Responses in Periodontal Disease

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## 1. Introduction

More than one microorganism causes periodontal disease, like many infectious diseases in humans. Because of the complexity of “polymicrobial infections”, their study requires a multidisciplinary approach, employing specific in vitro techniques, and various animal models (Bakaletz 2004). Inherently, no one approach or animal model can completely elucidate the mechanisms of periodontal disease. Notwithstanding these difficulties, animal models do provide critically important information regarding periodontal disease pathogenesis (Graves 2008). Another layer of complexity resides in the fact that different strains of bacteria, as in the case of *P. gingivalis* (*Pg*)-induced disease, cause different levels of disease in the same mouse strain (Baker and Roopenian 2002). Similarly, differences in disease susceptibility can result from the same bacterium strain, as in the case of *Aggregatibacter actinomycetemcomitans* (*Aa*) infected rodents (Fine et al. 2009). Furthermore, different strains of rodents exhibit different susceptibilities to challenge from the same strain of bacterium, such as *Pg* (Baker et al. 2000). This finding also holds true for *Aa* (Schreiner et al. 2011). These observations resemble findings in human disease, especially in the case of *Aa*-related disease where the JP2 strain of *Aa* appears to be more virulent than other *Aa* strains, and where individuals of African heritage appear to be more susceptible to *Aa*-induced periodontal disease than Caucasian individuals (Haubek et al. 2008). The similarities between rodent and human bacterial-induced periodontal diseases lend credence to the validity of the animal model designed to assess this disease (Fine 2009).

The virulence factors elaborated by pathogenic microorganisms and the host immunologic responses to such factors play a major role in disease induction and progression. It has been established that *Aa*, a gram-negative facultative capnophilic rod, is the causative agent in localized juvenile periodontitis (LJP) (Zambon 1985). This agent is also a key pathogen for localized progressing and severe forms of adult periodontitis (Dzink et al. 1985; Zambon et al. 1988). *Aa* possesses several virulence factors, including endotoxin and leukotoxin (Fives-Taylor et al. 1999). *Aa* secretes a protein toxin, Leukotoxin (LtxA), which helps the bacterium evade the host immune response during infection, by specifically targeting white blood cells

(WBCs) (Kachlany 2010). The ability of LtxA to bind WBCs from humans and Old World primates, by interacting with lymphocyte function antigen-1 (LFA-1) on susceptible cells, has opened a window of opportunity for the use of LtxA as a novel therapeutic agent in leukemia (Kachlany et al. 2010). *Aa* also produces cytolethal distending toxin (Cdt), which is a potent immunotoxin that induces G2 arrest in human lymphocytes (Shenker et al. 2007). The immunologic and systemic impact of these bacterial toxins in periodontal disease is yet to be clarified.

The binding of *Aa* to buccal epithelial cells (BEC) was shown to be mediated by two *Aa* autotransporter adhesions (ApiA and Aae), which work, in concert to modulate *Aa* binding to BEC, specifically in humans and Old World Monkeys (Yue et al. 2007). The type and extent of the immunologic response mounted in response to oral pathogen will undoubtedly depend on the particular microbial pathogen(s), the virulence factors invoked and the genetic background of the host. The immunologic reactions mounted in response to oral pathogens have a potential to precipitate other unforeseen systemic diseases of grave importance. The connection between immunologic responses to oral pathogens and systemic diseases is mostly unexplored, at present.

## 2. Immune responses to microbial pathogens

Our understanding of periodontal pathogenesis has evolved over the years, and has transformed from periodontitis being considered an almost ubiquitous condition in which the role of plaque was thought to be the sole aetiological factor to today where concepts of inflammation and individual susceptibility are considered (Preshaw and Taylor 2011). Neutrophils are a critical arm of the host defense in periodontitis, but bacterial evasion of neutrophil microbicidal machinery, together with delayed neutrophil apoptosis can transform neutrophil from defender to perpetrator (Nussbaum and Shapira 2011). In the recent Seventh European Workshop on Periodontology, aimed at understanding cellular and molecular mechanisms of host microbial interactions, a consensus was reached that "PMNs are important in the pathophysiology of periodontal disease but there is limited evidence on their much quoted destructive potential". Cytokine networks are enormously complex and we are really at the beginning of understanding their role in the disease process (Kinane, Preshaw and Loos 2011). Thus, there is an emerging appreciation for the complex role played by the adaptive immune system in responses to periodontal pathogens.

### 2.1 Humoral Immune responses to microbial pathogens

In early studies, significantly elevated serum immunoglobulin G (IgG) antibody levels to *B. gingivalis* were seen in adult and advanced destructive periodontitis patients, suggestive of distinctive host-parasite interactions in this disease (Ebersole and Cappelli 1994; Ebersole et al. 1986). Analysis of the proportion of various cell types present in gingival biopsies retrieved from subjects with severe chronic periodontitis showed that the proportion of B cells was larger than that of T cells, plasma cells and neutrophils. Furthermore, about 60% of the B cells were of the autoreactive B-1a sub-population (CD19<sup>+</sup>CD5<sup>+</sup>) (Donati et al. 2009). The plasma cells that developed were shown to derive from both B-2 cells (conventional B cells) and B-1a cells. There is strong evidence that B cells serve as antigen presenting cells in periodontitis (Gemmell et al. 2002; Mahanonda et al. 2002). Indeed, upregulation of the co-stimulatory molecule, CD86 (B7.2), and the dendritic cell marker, CD83, on B cells in

periodontal lesions, have been reported (Gemmell et al. 2002). Thus, it is likely that the B cells found in periodontal tissue might present bacterial antigens to host T cells, leading to the elaboration of a whole range of cytokines, the nature of which would depend on the type of bacteria, and the host.

Altered CD4/CD8 T-cell ratios and autologous mixed-lymphocyte reaction in LJP, suggested a potential regulatory role of T cells in periodontitis. Using immunohistochemical and *in situ* hybridization techniques, a higher frequency of CD4<sup>+</sup>CD45RO<sup>+</sup> cells expressing IL-4 has been seen in lesions from individuals with chronic periodontitis compared to normal tissue (Yamazaki et al. 1994). Comparing two different compartments (peripheral blood vs. periodontal tissue), it was noted that even though mRNA for IL-12 and IL-13 were similar between the two compartments, the level of IFN- $\gamma$  was higher in circulating cells than in gingival cells. Inversely, IL-10 expression was higher in the gingival cells (Yamazaki et al. 1997). Moreover, the frequency of IL-10 expressing CD14<sup>+</sup> cells was higher in peripheral blood of chronic periodontitis, but not acute periodontitis patients, compared to healthy controls (Yamazaki et al. 1997).

In periodontal disease, the development of gingivitis involves Th1 cells, while in periodontitis, there is a shift toward Th2 cells (reviewed in (Berglundh and Donati 2005)). Autoimmune reactions do occur in periodontitis lesions; however, the role of autoantibodies in the regulation of host response in periodontitis needs to be clarified (Berglundh and Donati 2005). In studies conducted with *Aa*-induced periodontal disease rat model, we observed an early increase in serum IgG2a antibody 2-4 weeks post inoculation. This was accompanied by a concomitant increase in LtxA-specific IgG production, suggesting that the immune response was mediated by *Aa* (Li et al. 2010). An increase in B and CD4 T cell numbers in draining cervical and submandibular lymph nodes accompanied this *Aa*-specific antibody production. CD8 T cell numbers were not examined in this study (Li et al. 2010). In agreement with this observation, there was an increase in the expression of CD70 (TNFSF7) in B cells harvested from draining lymph nodes in rats infected by *Aa* (Li et al. 2010). CD70 has been shown to be expressed on a subpopulation of germinal center B cells (Hintzen et al. 1994).

## 2.2 Cytokines in periodontal disease

Innate immunity is mediated by macrophages, dendritic cells (DCs), neutrophils, monocytes, epithelial cells and endothelial cells that recognize and temporarily respond to pathogen associated molecular patterns (PAMPS), like LPS on gram-negative bacteria. The adaptive immune system, on the other hand, uses specific antigen recognition structures on T and B cell. Such responses are specific and maintained by the generation of memory. Various cytokines generated by macrophages and DCs create a milieu, which determines the differentiation of particular effector T-cell subsets as well as the class and subclass of immunoglobulin (Ig) antibodies synthesized. Cytokines act in concert with other signalling pathways and, especially, cell-to-cell interactions via antigen presentation and co-stimulatory molecules (Preshaw and Taylor 2011).

The role of inflammatory cytokines, such as interleukin (IL)-1 $\beta$ , tumor necrosis factor- $\alpha$ , and IL-6, has been the most understood (reviewed in (Preshaw and Taylor 2011)). Inhibition of IL-1 and tumor necrosis factor (TNF) resulted in amelioration of bone loss in experimental periodontitis (Assuma et al. 1998; Graves et al. 1998). In our studies on *Aa*-induced periodontal disease, the early induction of *Aa*-specific IgG and IgG2a antibodies in *Aa*-fed rats is of interest since mRNA for Th1 cytokines TNF and lymphotoxin beta (LT $\beta$ ) (Abbas,

Murphy and Sher 1996) were upregulated early (2-4 weeks) in the inflammatory response, which could explain the significant switch in *Aa*-specific antibody production to IgG2a. This is consistent with the observation that Th1 cytokines drive isotype switching to IgG2a in inflammatory responses of atherosclerosis (Schulte, Sukhova and Libby 2008).

### 2.2.1 Th1/Th2 paradigm

Cytokines mediate and sustain the development and function of CD4<sup>+</sup> Th cell subsets. In the original description of Th cell dichotomy, Th1 cells secrete interferon- $\gamma$  (IFN- $\gamma$ ), and promote cell-mediated immunity by activating macrophages, natural killer (NK) cells and cytotoxic CD8<sup>+</sup> T-cells, whereas Th2 cells secrete IL-4, IL-5 and IL-13 and regulate humoral (antibody-mediated) immunity and mast cell activity (Mosmann and Coffman 1989). It was conjectured that the dynamic interaction between T-cell subsets might result in fluctuations in disease activity and that a Th1 response (providing protective cell-mediated immunity) underlies a “stable” periodontal lesion, and a Th2 response (leading to activation of B-cells) mediates a destructive lesion possibly through enhanced B-cell-derived IL-1 $\beta$  (Gemmell, Yamazaki and Seymour 2007; Seymour and Gemmell 2001). It is now becoming clearer that the Th1/Th2 model alone is inadequate to explain the role of T-cells in periodontal disease process (Gaffen and Hajishengallis 2008).

### 2.2.2 Role of Th17 cells

Th17 cells secrete the IL-17 cytokines (which have a number of pro-inflammatory activities in common with IL-1 $\beta$  and TNF $\alpha$ ) and IL-22, and are crucial for immunity against extracellular bacteria (Miossec, Korn and Kuchroo 2009). Th17 cells have been implicated in the pathogenesis of several autoimmune and inflammatory disorders, and *in vitro* polarization of human and mouse Th17 cells is under the influence of Notch1 (Keerthivasan et al. 2011). Studies have shown that IL-17A produced by Th17 cells stimulate the development of osteoclasts (osteoclastogenesis) in the presence of osteoblasts (Zhang et al. 2011), and expression of IL-17 has been observed in gingiva from patients with periodontitis (Cardoso et al. 2009).

In our studies on *Aa*-induced rat model for periodontal disease, we observed upregulation in IL-17 in CD4<sup>+</sup> T cells (2.8 fold) and B cells (2 fold), in lymph nodes from *Aa*-infected rats, compared to control rats. This level of expression was below our stringent criterion of four-fold differential gene expression in this study. However, this finding is in conformity with the observation that IL-17 might be involved in inflammatory response and bone resorption in periodontal disease animal models (Oseko et al. 2009) (Xiong, Wei and Peng 2009). It should, however, be noted that T cells exhibit “functional plasticity” that is influenced by the cytokine milieu (Bluestone et al. 2009). For instance, Th17 cells can differentiate into Th1 cells, under the influence of IL-12 (Korn et al. 2009), and follicular T helper cells (Thf), present in the B cell follicles of lymph nodes, are dependent on IL-6 and IL-21 for their development, and are capable of secreting a cytokine profile corresponding to Th1, Th2 or Th17 cells (Korn et al. 2009).

### 2.2.3 Role of regulatory (Treg) cells

It has been established that naturally arising Foxp3<sup>+</sup>CD4<sup>+</sup>CD25<sup>+</sup> (Treg) cells play a central role in the maintenance of immunological tolerance (Sakaguchi 2005). Treg cells secrete transforming growth factor- $\beta$  (TGF- $\beta$ ) and IL-10 which are critical in regulating other T-cell



subsets and maintaining tolerance against self-antigens, thereby preventing autoimmunity (Josefowicz and Rudensky 2009). Gingival mononuclear cells from mice infected with *Pg* were found to exhibit increased levels of Treg cells 30 days post infection, suggesting that there are potential roles for Treg cells during the chronic stage of periodontitis in the regulation of gingival inflammation and alveolar bone loss (Kobayashi et al. 2011). FoxP3<sup>+</sup>CD8<sup>+</sup> T cells, with suppressive function have recently been identified in simian immunodeficiency virus infected rhesus macaques, and in HIV-1 infected humans. Expansion of CD8<sup>+</sup> Tregs correlated directly with acute phase viremia and inversely with the magnitude of antiviral T cell response (Nigam et al. 2010). Using transgenic OT-I mice, the administration of ovalbumin (OVA) enabled osteoclasts to cross-present OVA to Ag-specific CD8<sup>+</sup> T cells to induce their proliferation, and secretion of IL-2, IL-6, and IFN- $\gamma$ . CD8<sup>+</sup> T cells activated by osteoclasts expressed FoxP3, CTLA4 and RANKL. Those CD8<sup>+</sup> T cells were found to be anergic and suppressed dendritic cell priming of naive responder CD8<sup>+</sup> T cells (Kiesel, Buchwald and Aurora 2009). The role of this novel group of CD8<sup>+</sup> Treg cells in periodontal disease requires further examination.

#### 2.2.4 Novel cytokine roles in periodontal disease

In our studies on *Aa*-induced periodontal disease rat model, we observed upregulation in mRNA for a number of cytokines, not normally ascribed to periodontal disease. IL-16 was upregulated in CD4 T cells in the early phase of the response (Li et al. 2010). IL-16 has been shown to be involved in the selective migration of CD4 T cells, and participates in inflammatory diseases (Akiyama et al. 2009). It was detected in gingival crevicular fluid (Sakai et al. 2006). IL-19, a novel cytokine of the IL-10 family, was also upregulated in CD4 T cells in response to *Aa*. IL-19 produced by synovial cell in Rheumatoid arthritis (RA) patients promotes joint inflammation (Sakurai et al. 2008). IL-21, which has recently been shown to induce receptor activator of nuclear factor kappaB ligand (RANKL) and was implicated in arthritis (Jang et al. 2009), was upregulated in B cells responding to *Aa*. There was also an induction of IL-24 by 12 weeks in CD4 T cells responding to *Aa*. Studies conducted on RA showed an increase in IL-24 in the synovium of RA patients, and this cytokine was implicated in recruitment of neutrophil granulocytes (Kragstrup et al. 2008). B-cell-activating-factor (BAFF, or TNFSF13B) and a proliferation-inducing ligand (APRIL), members of the TNF family, were upregulated in B cells and CD4 T cells, respectively, in response to *Aa* infection. Both of these factors were found to be upregulated in children with atopic dermatitis (Jee et al. 2009), and thus would represent factors that characterize *Aa*-induced periodontal disease.

IL-23, a proinflammatory cytokine composed of IL-23p19 and IL-12/23p40 subunits, is known to promote the differentiation of Th17 cells. Studies showed that IL-23 and IL-12 were expressed at significantly higher levels in periodontal lesions than in control sites, suggesting that IL-23-induced Th17 pathway is stimulated in inflammatory periodontal lesions (Ohyama et al. 2009). IL-33 is a new member of the IL-1 family, which plays a role in inflammatory response. Injection of TNF transgenic mice, overexpressing human TNF, with IL-33 or IL-33R agonistic antibody inhibited the development of spontaneous joint inflammation and cartilage destruction. Furthermore, *in vitro*, IL-33 directly inhibits mouse and human M-CSF/receptor activator for NF- $\kappa$ B ligand-driven osteoclast differentiation, suggesting an important role for IL-33 as a bone-protecting cytokine with potential for treating bone resorption (Zaiss et al. 2011).

### 2.2.5 Role of RANKL and related molecules

RANKL plays a role in T cell-mediated bone resorption. Interference with RANKL by systemic administration of osteoprotegerin (OPG), the decoy receptor for (and inhibitor of) RANKL, was found to result in abrogation of periodontal bone resorption in a rat model (Taubman et al. 2005). Studies in humans have demonstrated that RANKL levels in gingival crevicular fluid (GCF) were low in health or gingivitis, but increased in periodontitis. On the other hand, OPG levels were higher in health than periodontitis, or gingivitis groups (Bostanci et al. 2007). Thus, GCF RANKL and OPG levels were oppositely regulated in periodontitis, but not gingivitis, resulting in an enhanced RANKL/OPG ratio. In our studies with *Aa*-induced periodontal disease rat model, while the bone resorption protein RANKL (TNFSF11) was induced in CD4 T cells from *Aa*-fed rats, its soluble decoy receptor OPG (TNFSF11b) was also induced in the CD4 T cells (Li et al. 2010). Developments in the field of osteoimmunology, which examine the crosstalk of immune cells and bone, have uncovered a novel role for the RANKL-RANK-OPG system in other processes such as in controlling autoimmunity or immune responses in the skin (Leibbrandt and Penninger 2010). Despite the sustained upregulation of OPG, bone resorption still occurred. The critical balance between osteoblast-mediated bone formation and osteoclast-mediated bone resorption has been described as “coupling” of bone formation to bone resorption (Parfitt 1982).

### 2.2.6 Role of BMPs and GDFs in periodontal disease

Bone morphogenic proteins (BMPs) and growth differentiation factors (GDFs) are members of the transforming growth factor- $\beta$  (TGF- $\beta$ ) superfamily. They play important roles during development and organogenesis in delivering positional information in both vertebrates and invertebrates, and are involved in the development of hard as well as soft tissue (Herpin, Lelong and Favrel 2004).

BMPs can also act locally on target tissues to affect proliferation and survival (Rosen 2006). BMP2, even though dispensable for bone formation, is a necessary component of the signaling cascade that governs fracture repair (Tsuji et al. 2006). In our studies, BMP2 was induced in B cells early (week 4) of an inflammatory process, at the same time that RANKL was induced in CD4 T cells (Li et al. 2010). This suggests that bone repair mechanisms were induced early, well ahead of impending bone resorption. However, by 12 weeks of infection by *Aa*, BMP2 was shut down, as bone resorption proceeded. BMP3 was also upregulated at week 4 in B cells responding to *Aa*. BMP3 has been shown to be a negative regulator in the skeleton, as mice lacking BMP3 have increased bone mass. Transgenic mice over-expressing BMP3 had altered endochondral bone formation resulting in spontaneous rib fractures (Gamer et al. 2009). On the other hand, it has been suggested that BMP2 and BMP3 might be co-regulated. BMP-2 was found to enhance BMP-3 and -4 mRNA expressions in primary cultures of fetal rat calvarial osteoblasts. The enhancement of BMP-3 and -4 mRNA expressions by BMP-2 was associated with an increased expression of bone cell differentiation marker genes (Chen et al. 1997). It is of interest that BMP2 and BMP3 were upregulated in B cells at the same time (4 weeks post infection), and were shut down at 12 weeks, at which time bone resorption was evident.

In our studies with *Aa*- rat model for periodontal disease, we found that B cells responding to *Aa* upregulated BMP10 at all time points (Li et al. 2010). BMP10 has been shown to regulate myocardial hypertrophic growth (Chen et al. 2006), and may function as a tumor

suppressor and apoptosis regulator for prostate cancer (Ye, Kynaston and Jiang 2009). To our knowledge, our work is the first report on the production of BMP10 by B cells responding to infection. The expression pattern of BMP10 in our studies, suggests that it might be involved in inflammation, as well as in bone resorption. Furthermore, the involvement of BMP10 in cardiac hypertrophy and cancer, suggests that it might represent one of the possible “missing links” between periodontal disease and other systemic diseases like heart disease and cancer. Evidence for this is provided in the modeled biological interaction pathway depicted in Fig 1.

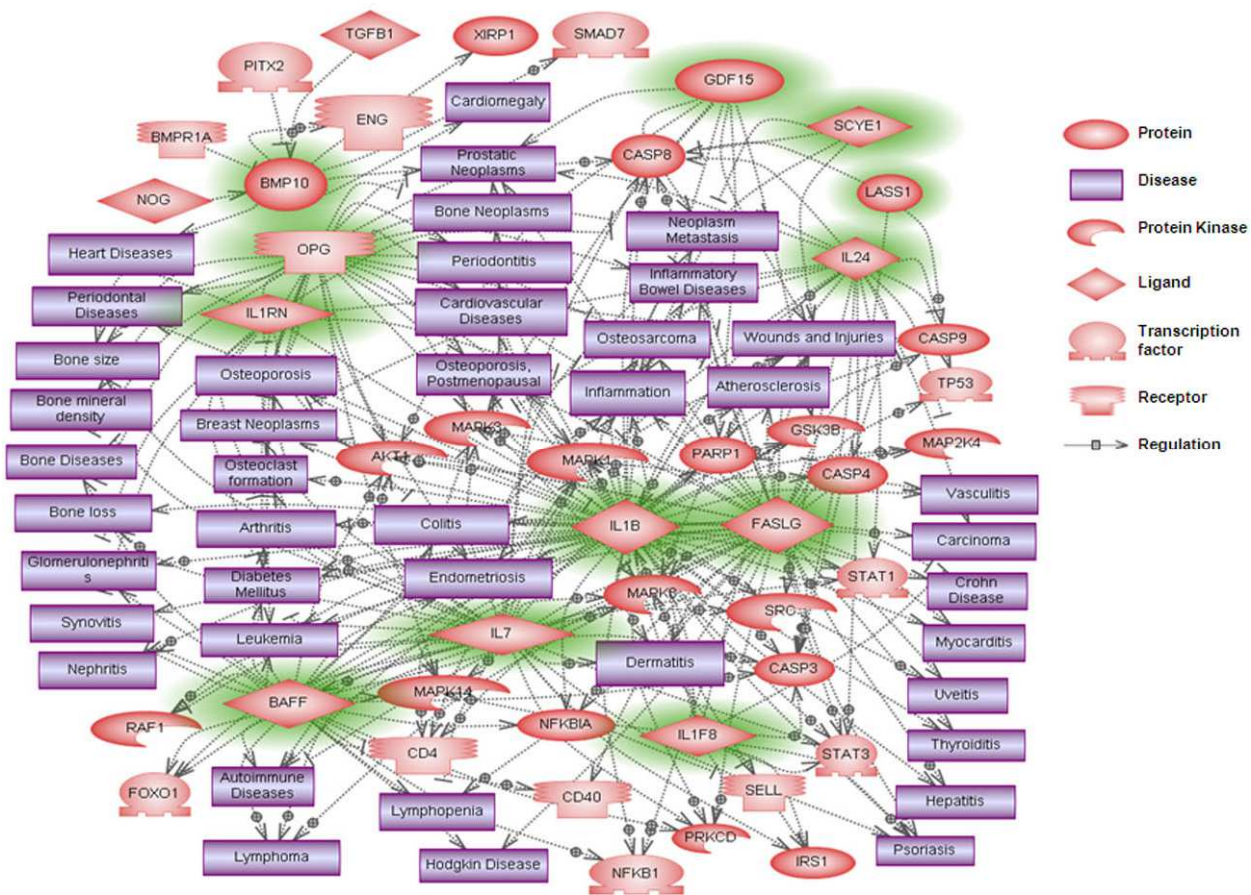


Fig. 1. Proposed biological interaction network of differentially expressed genes from B and CD4 T cells of *Aa*-fed rats at 12 weeks post infection by *Aa*, and their relationship to disease. Genes upregulated by at least four-fold (i.e. Log<sub>2</sub> fold greater than 2) in B and CD4 T cells derived from cervical and submandibular lymph nodes of *Aa*-fed rats, in comparison to B and CD4 T cells from control rats, were imported into Pathway Studio (Ariadne Genomics, Inc., Rockville, MD, USA) (Yuryev et al. 2006) for analyses. The picture shows interactions between upregulated genes in the expression data (shown as green highlights) and their interactions with related genes and diseases. The biological relationships revealed by the network are depicted in the pallets at the right of the figure. The relevance of the expression data to various diseases, as determined by the mining of the published Resnet 7 database in Pathway Studio, is indicated in the network. Reprinted with permission from Li Y *et al.* Molecular Oral Microbiology 2010; 25:275-292.



Growth differentiation factor 11 (GDF11) or BMP11, plays an important role in establishing embryonic axial skeletal patterns (McPherron, Lawler and Lee 1999). Transfection of GDF11 gene was found to stimulate a large amount of reparative dentin formation in amputated dental pulp of canine teeth in vivo (Nakashima et al. 2003). In our studies with *Aa*-induced periodontal disease rat model, GDF11 was upregulated at 12 weeks post infection, in both B and CD4 T cells, at the time of bone resorption. This suggests that GDF11 may have a novel role in bone resorption. The fact that GDF11 activation has been observed in cancer (Yokoe et al. 2007), may also provide another possible link between periodontal disease and cancer.

Growth differentiation factor 15 (GDF15), was upregulated in both B and CD4 T cells of *Aa*-infected rats at 12 week, coinciding with the time of bone resorption. However, there are conflicting reports on the role of GDF15 in bone resorption and other systemic diseases. Studies have shown that pure GDF15 and the GDF15-containing growth medium of 1,25(OH)<sub>2</sub>-vitamin D<sub>3</sub>-treated prostate adenocarcinoma LNCaP cells suppress osteoclast differentiation (Vanhara et al. 2009). In addition, elevation in GDF15 has been associated with cardiovascular disease (Kempf and Wollert 2009), and colorectal cancer metastasis (Xue et al.). Thus, GDF15 may also contribute another possible link between periodontal disease and systemic diseases.

### 3. Conclusions

The nature of the adaptive response to oral microbial insult is vastly dependent on the nature of the microbe, the host (including genetic background), as well as the milieu of prevailing cytokines and chemokines. The *Aa*-induced rat model and *Pg*-induced mouse model for periodontal disease have provided extensive knowledge about role of several previously uncharacterized genes in periodontal disease, however, much more work needs to be done. Therefore, examination of B and CD4 T cells from lymph nodes draining the oral cavity of *Aa*-fed rats showed that inflammatory processes are initially activated early (2-4 weeks) post infection. This, ultimately, leads to activation of bone resorption pathways that end in overt bone resorption by 12 weeks post infection. Apart from induction of known inflammatory cytokines (such as TNF $\alpha$ , IL-1 $\beta$ , and LT $\beta$ ), other cytokines and TGF- $\beta$  superfamily member genes, not previously associated with bone resorption, were found to be upregulated in B and/or CD4 T cells. Some of these genes have known effects on systemic diseases such as heart disease, cancer, autoimmune disease, and diabetes. The role of CD8 T cells in adaptive immune responses to periodontal pathogens is not yet clarified. This evidence suggests a subtle link between periodontal disease and other systemic diseases. In conclusion, animal studies have played an important role in unraveling key elements of our understanding of microbial pathogenesis in many human diseases (Shea et al. 2010). The availability of new and more complete data from mouse and rat genome studies coupled with the access to powerful tools that can uncover microbial and host expression can provide novel ways to examine periodontal disease pathogenesis. Application of these tools can allow for comparisons to common pathways with respect to other infectious diseases. This chapter has presented some data derived from the application of one of these new immune response pathway tools to microbial-induced periodontal disease in a rat model.

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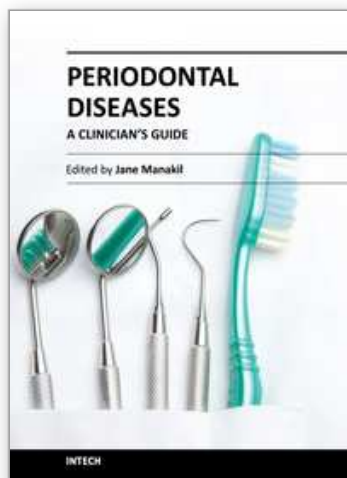
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## **Periodontal Diseases - A Clinician's Guide**

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"Periodontal diseases" is a web-based resource intended to reach the contemporary practitioners as well as educators and students in the field of periodontology. It is fully searchable and designed to enhance the learning experience. Within the book a description is presented of the current concepts presenting the complex interactions of microbial fingerprint, multiple genotypes, and host modulations. In addition, an overview is given of the clinical outcome of the disease's progression, as influenced by the epigenetic factors. Emerging concepts on periodontitis as a risk factor for various systemic diseases and as a bilateral modulating factor have been elucidated in detail as well.

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