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Guest Editorial

The new concept of periodontal disease pathogenesis requires new and novel therapeutic strategies

Focused Perspective on Bostanci et al., J Clin Periodontol 2007; 34: 370–376.

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Abstract

In this issue Bostanci et al. (2007) demonstrate that receptor activator of NF-κB ligand (RANKL) and osteoprotegerin (OPG) were oppositely regulated in gingival crevice fluid (GCF) from periodontitis patients. RANKL, RANK and OPG are key molecules that regulate osteoclast recruitment, differentiation and activation. New concepts of the pathogenesis of periodontitis have implicated inflammation triggered by host immune response to periodontal biofilm microorganisms(s) in disease. Host response to bacteria involves activation of T and B cells in the inflammatory infiltrate which bear abundant RANKL that promotes osteoclastic bone resorption. Periodontal tissue destruction can be ameliorated by immunobiological interference with immune cell RANKL expression or function. The new disease concepts provide a foundation to build biological approaches to target RANKL production in periodontal lesions.

In an article in this issue, Bostanci et al. (2007) demonstrate that receptor activator of NF-κB ligand (RANKL) and osteoprotegerin (OPG), two molecules belonging to the tumour necrosis factor (TNF) ligand/receptor families, were oppositely regulated in gingival crevicular fluid (GCF) from periodontitis patients. Thus, OPG (which antagonizes RANKL-mediated bone resorption) levels were higher in healthy subjects than in those patients with periodontitis. Importantly, RANKL/OPG ratios were significantly elevated in the GCF of three forms of periodontitis. This parameter, i.e., RANKL/OPG ratio, in tissues seems to be a major indicator of potential bone resorption (Theill et al. 2002, Valverde et al. 2004). Bostanci and colleagues suggest that the relative RANKL/OPG ratio in GCF is indicative of periodontitis and, as such, may provide clinical diagnostic potential. There is now considerable evidence to support the findings that periodontitis patients exhibit higher RANKL expression in GCF (Mogi et al. 2004, Vernal et al. 2004) or gingival tissues (Nagasawa et al. 2002, Crotti et al. 2003) than periodontally healthy subjects. These combined findings signal the emergence of a new concept of periodontal disease pathogenesis.

RANKL and Its decoy receptor OPG

RANKL, its receptor RANK, and a decoy receptor, OPG, are three key molecules that regulate osteoclast recruitment and function (Boyle et al. 2003). RANKL-binding to its receptor, RANK, expressed on osteoclast precursor cells elicits their differentiation and activation. On the other hand, OPG-binding to RANKL interrupts RANKL–RANK ligation; consequently, OPG inhibits the ability of RANKL to induce osteoclastogenesis. RANKL is not only been reported to be involved in physiological osteoclastogenesis, but also in pathological bone loss (Boyle et al. 2003). It was demonstrated that the level of RANKL mRNA was highest in inflammatory cells and epithelium of advanced periodontitis patients compared with those of moderate periodontitis and healthy subjects and may be associated with the activation of osteoclastic bone destruction in periodontitis (Liu et al. 2003).

Importantly, RANKL has two forms: (1) membrane-bound RANKL (mRANKL) and (2) soluble RANKL (sRANKL) (Nakashima et al. 2000). Accumulating lines of evidence imply that sRANKL is more functionally potent in eliciting osteoclastogenesis than mRANKL (Mizuno et al. 2002). Returning to the finding by Bostanci et al. the RANKL detected in the GCF appears to be sRANKL. However, the origin of sRANKL and OPG present in GCF is still to be elucidated. To provide

a clue to this question, studies of human periodontal lesions have, thus far, indicated abundant RANKL expression on the T and B cells of patients with chronic periodontitis (Kawai et al. 2006). It has also been found that these cells could cause osteoclast differentiation and bone resorption in vitro (Kawai et al. 2006). Furthermore, both forms of sRANKL and mRANKL appeared to be expressed from T and B cells (Kawai et al. 2006). Sakata et al. showed that dental mesenchymal cells, such as gingival fibroblasts, produce OPG in vitro (Sakata et al. 1999). Therefore, it is plausible that sRANKL and OPG found in the GCF originate from lymphocytes (T and B cells) and dental mesenchymal cells, respectively.

Osteoimmunology Supports Periodontitis Pathogenesis

Approximately 6–7 years ago, several important discoveries were made indicating a close relationship between the immune and skeletal systems. RANKL has been shown to be expressed not only by osteoblasts and bone marrow stromal cells, but also by T and B cells (Lacey et al. 1998, Kong et al. 1999). In addition, osteoclasts and their precursors are derived from haematopoetic stem cells that also give rise to immune cells. Based on the discovery of such a close relationship between the immune and skeletal systems, an interdisciplinary field called ''osteoimmunology'' has developed. It is within this field that significant investigatory attention has been given to the emerging evidence that bone destruction can be caused by an inflammatory activation of the immune system in rheumatoid arthritis, as well as in periodontitis (Teng et al. 2000, Theill et al. 2002, Takayanagi 2005, Han et al. 2007). As a result of ''osteoimmunology'' studies, there are new changes in the periodontitis pathogenesis paradigm (Takayanagi 2005, Han et al. 2007). The most compelling evidence now indicates that periodontitis is not a conventional infectious disease, but is an inflammatory disease, triggered by host immune response to a constellation of periodontal biofilm-associated microorganisms. Intervening between the infection and the targets of the disease (bone, connective tissue) is a dense mononuclear inflammatory infiltrate containing all cellular components, including T and B lymphocytes, which are necessary to control immunological interactive networks (Stoufi et al. 1987). Previous studies have shown that these inflammatory cells can infiltrate gingival tissues in an antigen-specific manner (Kawai et al. 1998). Host response to bacteria can involve activated T lymphocytes in periodontitis pathogenesis and bone resorption. Antigen-specific T-cell clone (Kawai et al. 2000), and antigen-specific B lymphocyte (Han et al. 2006) adoptive transfer experiments firmly established a role for T and/or B cells in the induction of periodontal bone resorption in accordance with the presence of abundant osteoclasts on the alveolar bone crest of the animals receiving antigen-specific lymphocytes. It is also reported that the periodontal disease pathogen, *Porphyromonas gingivalis*, can cause osteoclastogenesis by induction of RANKL from the activation of mouse lymphocytes (Jiang et al. 2002). A key finding in these animal models is the dependence of RANKL production by activated lymphocytes on the induction of bone resorption and inhibition of such bone loss by OPG.

Basis of New Diagnostic Procedures and Therapeutic Methods for Periodontal Bone Loss

The specific hypothesis is that periodontal disease tissue destruction can be ameliorated by inhibition of activity and/or production of RANKL derived from immune effector cells. However, only a few contradictory studies currently report the RANKL-independent osteoclastogenesis mechanism by other cytokines, such as TNF-α (Kobayashi et al. 2000). Thus, it remains to be elucidated whether RANKL-mediated osteoclastogenesis is responsible for all periodontal bone loss events. Consequently, in order to establish sound methods for diagnosing those periodontal diseases in which bone loss develops in an RANKL-dependent manner, a more sophisticated evaluation is required to define the significance of the measurement of RANKL/OPG ratio in the GCF. The overall goal will be to develop and evaluate strategies aimed at the amelioration of tissue destruction of periodontal disease by regulating RANKL expression and/or the activity of immune effector cells.

Potential Intervention Strategies

Current treatment for periodontitis often relies on mechanical procedures and neglects the immune cells. New treatments for periodontal diseases must address the major immune cell contribution to periodontal bone resorption. Therefore, an important emphasis of new therapies should involve the development and evaluation of therapeutic strategies to treat immune cell-mediated periodontal disease. The focus of these treatments will be on RANKL. It has been demonstrated that OPG-Fc fusion protein is a potent inhibitor of T- or B-cell-mediated periodontal bone resorption. The strategy of physiological blockade of RANKL–RANK interaction and subsequent osteoclastogenesis with OPG-Fc is very powerful. Much remains to be determined before such strategy is capable of modulating the RANKL–RANK interaction and become effectively used in the management of bone resorptive diseases.

Therapeutic Implications in the Manipulation of Immune Responses

Both human and experimental animal studies support the hypothesis that there is considerable potential for amelioration of periodontitis tissue destruction by interference with the host immune system. Of particular interest in this regard, is Bostanci's finding in the current manuscript that immunosuppressed patients demonstrated lower RANKL and OPG levels than the untreated immunosuppressed group, indicating a tight linkage between immune response and level of RANKL expression in the gingival tissues. Evaluation of strategies aimed at interference with the detrimental effects of T- and B-cell activation are likely to affect periodontal bone resorption. Studies have suggested that excess RANKL shifts the balance of bone metabolism in the direction of catabolism and causes periodontal bone resorption. Therefore, RANKL inhibition offers the therapeutic possibility to treat periodontal bone resorption. This may include reduction of soluble RANKL release or interference with RANKL expression by T/B cells. Interference with these processes should contribute to abrogation of periodontal bone resorption and prevention of periodontal disease progression. It is now clear that multiple novel therapies may be implemented which more directly address the new periodontal disease pathogenesis concept (see Han et al. 2007 for an elaboration of therapeutic strategies).

To summarize, the findings by Bostanci et al. significantly impact our understanding of periodontal bone destruction mediated by the regulation of RANKL and OPG in connection with immune responses. Moreover, the method they have established by which to determine the RANKL/OPG ratio in the GCF provides a sound foundation on which to build novel diagnostic methodologies and therapeutic approaches targeting immune cell RANKL production in periodontal lesions.

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