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REVIEW ARTICLE

ROLE OF RECEPTOR ACTIVATOR OF NUCLEAR FACTOR KAPPA B LIGAND (RANKL) AND OSTEOPROTEGERIN (OPG) IN PERIODONTAL BONE DESTRUCTION: A REVIEW

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ABSTRACT: Periodontal Disease also called as Periodontitis is a chronic inflammatory disease in which there is destruction of tooth supporting structures. Bacterial infection is the main etiologic factor. The Bacterial agents stimulate a cascade of local inflammatory reactions including activation of immune system which in turn leads to activation and release of pro-inflammatory cytokines apart from activation of phagocytes and lymphocytes. The tissue destruction which occurs is believed to a consequence of host response to various bacterial agents. In the present review we summarize the role of cytokine Receptor Activator of Nuclear Factor Kappa B Ligand (RANKL) and Osteoprotegerin (OPG) in periodontal bone destruction during periodontitis.
KEYWORDS: Periodontitis, RANKL, OPG.

INTRODUCTION: Periodontitis is a chronic inflammatory disease characterized by destruction of tooth-supporting tissues.[1] Among the bacterial species that colonizes oral cavity some of them cause periodontitis and are called as periodontopathogens, which includes Porphyromonas Gingivalis, Treponema Forsythia, Tannaerella denticola, Aggregatibacter Actinomycetemcomitans and Porpyromonas intermedia.[2, 3]

Complex cytokine network is synthesized as a result of activation of immune system and it plays an important role in periodontal disease. The cytokines are immunomodulating proteins that are categorized as signaling molecules. They are produced by immunocompetent cells such as T lymphocytes and Monocytes in local inflammatory tissue.[4]

A positive close relation between the occurrence of disease and elevated serum antibody response to the oral bacteria colonizing the gingival crevice has attracted more attention in recent times and it is now suggested that involvement of an immune response to the multiple bacteria in the onset and development of periodontal disease.[5-6]

Receptor Activator of Nuclear Factor-κB (RANKL): Receptor Activator of Nuclear factor Kappa B Ligand (RANKL) is a tumor necrosis factor related cytokine. RANKL is a type II homotrimetric trans membrane protein that is expressed as membrane bound protein that is derived from membrane as result of proteolytic cleavage.[7]

It is one of three members of the tumor necrosis factor (TNF) superfamily, (1) Osteoprotegerin (OPG), (2) Receptor Activator of Nuclear Factor kappa B ligand (RANKL), (3) Receptor Activator of Nuclear Factor kappa B (RANK).

RANKL expression is stimulated in osteoblast/stromal cells by most of the factors that are known to stimulate osteoclast formation and activity. It is highly expressed in lymph nodes, thymus

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and lung in other tissues including spleen and bone marrow.[8] RANKL is also expressed by osteoblasts, immune competent cells T and B lymphocytes and other cells including fibroblasts. It is in low concentrations in physiological conditions however under pathological conditions there is an increased expression of this cytokine, particularly in periodontal infections by A Actinomycetemcomitans and P gingivalis.[9,10]

Recent studies demonstrate that B cells produce RANKL in response to periodontal pathogen stimulation and that the majority of B cells in periodontal lesions are RANKL positive [11, 12]. Osteoblasts expresses Toll Like Receptor (TLR) 1, 2, 4 and 6 and they respond to TLR 2/6 and TLR 2/1 ligands by increasing RANKL expression.[13]

The RANKL receptors are RANK which is present on osteoclast precursors. The RANKL binds directly with RANK which are present on preosteoclasts and increases differentiation of osteoclast progenitors and mature osteoclasts.[14,15] RANK is a type I homotrimeric transmembrane protein whose expression was initially only detected on OCPs, mature osteoclasts, and dendritic cells [8].The (RANKL) that causes bone resorption processes is dependent on the osteoclast differentiation, activation, and survival factor.[16-18]

Involvement of immune cells in the course of bone resorption has been demonstrated by the expression of RANKL on activated T cells. RANKL is expressed by T cells as well as osteoblasts, bone marrow cells initiate signaling to the preosteoclasts which then differentiate into their mature form and express RANKL.[19, 20]

Osteoprotegerin (OPG): Osteoprotegerin is a soluble decoy receptor for RANKL and prevents the interaction with RANK. OPG is expressed by periodontal ligament cells, gingival fibroblasts, and epithelial cells, etc and it counter regulates the excessive bone loss by antagonizing the RANKL binding to its receptor RANK [21-23]. Its expression is regulated by most of the factors that induce RANKL expression including osteoblasts. There is an agreement that in general upregulation of RANKL is associated with down regulation of OPG, or at least lower induction of OPG, such that the ratio of RANKL to OPG changes in favor of osteoclastogenesis.

Many studies have confirmed that the RANKL/OPG ratio is a major determinant of bone mass.[24] With the background that RANKL/RANK signaling is essential for osteoclast formation, major studies have focused on the area to determine the full extent of the involvement of RANKL in osteoclast biology and common bone diseases. After RANKL binds to RANK, a key preliminary step in downstream signaling is binding of TRAFs to specific sites within the cytoplasmic domain of RANK, which is a transmembrane protein that - like the TNF receptors - has no intrinsic ability to activate protein kinases to mediate signaling. TRAF2, -5, and -6 all bind to RANK, but of these only TRAF6 appears to be essential in osteoclasts formation.[25, 26]

The levels of OPG have been found to low in periodontitis, which ultimately increases RANKL/OPG ratio. Immunohistochemical studies demonstrate significantly lower OPG staining in periodontitis-affected tissue compared to healthy gingival tissue, and gene expression studies report lower OPG expression levels in periodontitis compared to health controls.[27]

All the available studies collectively indicate that RANKL increases, whereas OPG decreases in periodontitis; however, no difference was reported in their ratios between patients with mild, moderate, or severe periodontitis.[28] Bostanci et al (2007) reported that there were no differences in RANKL and OPG levels between chronic and generalized aggressive periodontitis groups.[29]

The ratio of RANKL to OPG is normally increased in a bone resorptive lesion characterized by extensive osteoclastic activity.[30] Fatemeh S et al; study of the bone resorptive lesions of periodontal disease tissues demonstrated that, RANKL was expressed by both T cells as well as B cells. The concentrations of RANKL and IL-1 examined in the gingival tissue homogenates were significantly elevated in the diseased gingival tissues compared to healthy tissues, whereas OPG protein production was not significantly higher in diseased tissues than healthy tissues. In their study, in aggressive periodontitis patients group, 50% of the sites were having detectable levels of RANKL, compared with 46.4% of chronic periodontitis and 40% of healthy controls.[31]

Bostanci et al (2011) also reported that although the RANKL/OPG ratio has a potential diagnostic value for untreated periodontitis, however it may not be a suitable predictor of clinically successful treatment outcome.[32] Vernal et al. reported that RANKL was found in a higher proportion (85%) of samples from patients than from controls (46%). Their patients were adult patients with untreated chronic periodontitis. However, they did not determine any severity classification for the 20 study patient.[33]

CONCLUSIONS: it should be understood that the pathways involved in periodontal bone loss are complex. A network of cytokines, released by resident and migrating cells is involved in periodontal bone resorption. The RANKL and OPG are central in regulation of bone metabolism and contemporary research is focused on targeting this area in pharmacological treatments of pathological bone loss. Use of RANKL inhibitors in periodontitis has shown remarkable results in experimental models. Blocking the activity of proinflammatory cytokines may be a promising therapeutic modality for periodontitis. However long term studies in human population is yet to be done.

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