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An immunological approach to treat chronic periodontitis

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Introduction

Periodontal health of an individiual is usually affected by various conditions which may vary from gingivitis to more serious and threatening chronic generalized and aggressive forms which not only affect the dental health but also the overall health of an individual.[1] Periodontitis is mainly characterized by the inflammation of tissue and bone resorption by osteoclasts.[2] There is a physiological equilibrium maintained between the process of bone formation and bone resorption. Whenever this equilibrium is disturbed, it may result in development of various bone related disorders including periodontal diseases.

Previously most of the treatment modalities of periodontitis aimed at treatment of gingival inflammation but in modern times advanced researches in the field of osteoclast functions and their differentiation have given more understanding of the process of pathologic bone loss and thus providing new concepts for diagnosis and treatment of periodontitis. Thus for the treatment of periodontitis it is necessary to understand the mechanism of bone resorption, their mediators and their potential role in the diagnosis and treatment of pathologic bone loss found in periodontitis.

Under physiological as well as pathological conditions, osteoclastogenesis and bone resorption are mainly controlled by a bimolecular system of receptor activator of NF-κB ligand-osteoprotegerin (RANKL-OPG).[3]This bimolecular system of RANKL and OPG is related to TNF ligand and receptor superfamilies respectively. Various studies have shown that conditions, such as bacterial arthritis, rheumatoid arthritis, and periodontitis have shown that both RANKL and OPG are equally important in the process of osteoclastogenesis.[4-5]

Several studies conducted for localization and expression of RANKL and OPG in healthy individuals and individuals with periodontitis have shown that RANKL-OPG system has significant role in the pathogenesis of periodontitis. Immunohistochemical studies have shown that periodontitis affected tissues have higher RANKL and lower OPG staining than healthy gingival tissue.[6]Many clinical studies have shown that RANKL and OPG is also present in the human GCF. In case of periodontitis RANKL is increased while OPG is decreased in GCF resulting in net increase in RANKL/OPG ratio.Thus, increased RANKL/OPG ratio in GCF is an indicator of periodontitis and can be used as a diagnostic biomarker of the disease.

The main objective of periodontal treatment should be reducing the RANKL/OPG ratio and associated bone destruction by targeting RANK-RANKL-OPG axis.The main objective of this review is to provide a better understanding of diagnostic and therapeutic process of pathologic bone loss as seen in periodontitis by targeting RANK-RANKL-OPG axis.

The origin of RANKL and OPG occurs in the periodontium both under physiological and pathological conditions but both originate from different cells under the two conditions. In healthy periodontium RANKL is produced by mesenchymal cells mainly osteoblasts and PDL cells while in periodontitis it is produced by Th1 or Th17 cells, as well as B-cells[7-8] along with resident mesenchymal cells.The source of origin of OPG remain the same under both physiological as well as pathological conditions. It is resident periodontal connective tissue fibroblasts and potentially endothelial cells which produces OPG.[9]

The importance of RANKL and OPG to the periodontium can be evaluated by the fact that PDL cells not only produce RANKL and OPG but also regulate osteoclastogenesis by instructing RANKL action.[10] RANKL is found in membrane bound (mRANKL) and secreted / soluble forms (sRANKL). There are certain evidences suggesting that osteoclastogenesis is more potentially induced by sRANKL than mRANKL.There are 3 isoforms of RANKL with different osteoclastogenic potential.[11] These are RANKL1, RANKL2 and RANKL3 with RANKL 1 being the most potent inducer while RANKL 3 being the potent attenuator.[12] RANKL 3 is thought to act as soluble ligand.

RANKL belongs to the Tumor Necrosis Factor ligand superfamily. It is mainly found on the surface of the cells of monocytes /macrophage lineage including pre-osteoclasts , B and T cells, dendritic cells ,fibroblasts and mature osteoclastsRANK belongs to the TNF receptor superfamily. It is present mainly on the surface of the cells of monocytes /macrophage lineage including pre-osteoclasts , B and T cells, dendritic cells ,fibroblasts and mature osteoclasts.

When RANKL binds to its allied RANK receptor on the surface of pre-osteoclasts, triggers a cascade of events leading to differentiation into mature osteoclasts and ultimately resulting in bone resorption.[13] OPG, a lure receptor possessing structural homology to RANK can inhibit this RANKL mediated bone resorption.[14] OPG exhibits competitive inhibition with RANK for the RANKL. OPG binding to RANKL results in failure of RANK-RANKL interaction and ultimately all the downstream molecular events that lead to osteoclast differentiation and bone resorption.

Osteoimmunology: A novel concept in periodontal pathogenesis paradigm

Many studies done approximately 6-7 yrs ago have shown a strong relationship between the immune and skeletal systems. Such interdependency between the two biological systems can be reflected by the fact that

RANKL is produced not only by skeletal cells but also by activated T and B cells[15] and immune cells are produced by haematopoetic stem cells that also give rise to osteoclasts. Both the immune and the skeletal system share a number of regulatory cytokines and other molecules. Based on the above recognition between the immune and skeletal system an ambidextrous field "osteoimmunology" has been investigated.[16]

Various Investigations done to demonstrate the pathogenesis of Periodontal diseases are now considered under the frame of ''osteoimmunology.''[17-18] This field based on the accumulated evidences elucidate that Periodontal disease results from an inflammatory activation of immune system.The studies of osteoimmunology has led to a novel concept in periodontitis pathogenesis paradigm [19] i.e periodontitis is not a typical infectious disease but host immune mediated inflammatory disease in response to a group of periodontal biofilm associated microorganisms. Several studies done in animal models have shown that RANKL production is dependent on activated lymphocytes for inducing bone resorption and such bone destruction is inhibited by OPG.

It has been elucidated that knowledge of osteoimmunology is important to develop new methodology for preventing and managing pathologic bone destruction in periodontal diseases. The key regulatory molecules involved in osteoclastic bone resorption have been found to be associated with receptor activator of nuclear factor kappaβ ligand (RANKL), its receptor, receptor activator of nuclear factor kappaβ (RANK) as well as associated signaling molecules and transcription factors.[20].

Various studies done so far clearly indicate the presence of both RANKL and OPG in gingival tissues and biological fluids i.e GCF, saliva and serum.

Studies done in the past on gene expression and tissue localization have confirmed the RANKL and OPG involvement in periodontal disease pathogenesis. But due to the invasive nature of the procedure as tissue biopsy is required, such perspective cannot practically support the diagnosis of periodontal status .This necessitate the development of a non-invasive diagnostic approach i.e GCF sampling for the analysis of periodontal conditions. GCF is considered to be the "window" to the periodontium.[21]As GCF contains a rich array of numerous pro-inflammatory mediators associated with osteoclastic activity it provides a sound basis for detecting RANKL and OPG as well. Mogi and coworkers in 2004 first demonstrated RANKL and OPG in GCF by conventional enzyme-linked immunosorbent assay (ELISA).[22]

Osteoclastic bone resorption occurring in periodontal diseases can be either entirely RANKL mediated or RANKL – independent, i.e mediated by other cytokines i.e TNF-α etc.[23] If RANKL is the cause of this pathologic bone loss in periodontitis, it can be rectified either by inhibiting the action of RANKL or reducing RANKL production from immune cells. Thus to diagnose RANKL –dependent osteoclastic bone resorption in periodontal diseases a debonair assessment needs to define the significance of RANKL/OPG ratio in GCF.

Numerous clinical studies have analysed the concentrations of RANKL and OPG in gingival tissues and GCF of patient with periodontitis to determine RANKL/OPG ratio. Wide variations in the studies exist regarding the relation between RANKL and OPG with periodontitis. Some studies have shown an increase in sRANKL concentrations without any change in OPG levels in periodontitis patients as compared to healthy controls. Other studies demonstrated a reciprocal relationship between the levels of RANKL and OPG in GCF of periodontitis patients;[24] i.e an increase in RANKL

levels and decrease in OPG levels were found in GCF of periodontitis patients in comparison to healthy controls. The final outcome of several studies done so far have been a net increase in RANKL/OPG ratio in periodontitis patients compared to healthy subjects. This outcome clearly demonstrate the principal role of RANKL in regulating osteoclastogenesis in periodontitis. Though this ratio is increased at inflammatory periodontal sites but no correlation appears to exist between RANKL/OPG ratio and gingival inflammation suggesting specificity of this parameter for pathologic bone loss seen in periodontitis. Increased RANKL/OPG ratio is also indicative of on-going active osteoclastic bone resorptive phenomema leading to increased risk of disease recurrence at corresponding periodontal sites.

Relationship between RANKL, OPG and clinical parameters have also been studied demonstrating wide variations among them.

While RANKL exhibits a positive correlation with periodontal pocket depth, clinical attachment level and plaque index but not with papilla bleeding index, OPG exhibits negative correlation with all the mentioned clinical parameters. Ultimately, a positive correlation existed between the net RANKL/OPG ratio in GCF and periodontal pocket depth, clinical attachment level, but not with papilla bleeding index in patients of periodontitis.

Thus inflammatory status cannot be be judged by RANKL/OPG ratio but the same has potential implications on periodontal disease progression rate and its severity. Though periodontitis is associated with an elevated RANKL/OPG ratio, the ratio may not necessarily differentiate between the different grades of periodontitis i.e the mild ,moderate and severe forms of periodontitis.

Increased RANKL/OPG ratio may also indicate the continuous on going activity of osteoclastic bone resorption at active sites in periodontitis thus increasing the risk of further relapse of the disease at relative periodontal sites in future.

Discussion

Current management of periodontitis usually deals with the inflammation mediated periodontal pathogenesis by mechanical procedures including surgical and non-surgical therapy while neglecting immune cell mediated pathogenesis for the same. Though such therapy may have been successful in reducing the inflammatory component but failed to have any direct effect on controlling or reversing the pathologic bone loss in periodontitis. Several human and experimental studies have demonstrated significant reduction in periodontal tissue destruction by judicial modulation of host immune response. Therefore, new treatment strategies should deal with management of immune cell mediated periodontitis.

A number of studies have shown that either an increase in RANKL concentration or decrease in OPG levels results in an increase in RANKL/OPG ratio in periodontitis. Therefore inhibition of RANK/RANKL /OPG axis should be the target of newer therapies.

Several mechanisms have been proposed for achieving this target in various conditions associated with bone resorption including periodontitis.

This can be achieved either by reducing the release of soluble RANKL ,interrupting RANKL binding with RANK , inhibiting its expression by activated T or B cells or by enhancing overexpression of OPG.

OPG-Fc fusion protein reported to be a potent inhibitor of T- or B- cell -mediated periodontal bone destruction can be considered as a successful strategy for treating immune mediated bone resorption in periodontitis.[25-27] However clinical application of such strategy for physiological blockade of RANKL-RANK interaction require more sound knowledge and skillful technique.

Another treatment modality that can be adopted in bone resorptive diseases including Periodontitis is development of antibody against RANKL. This RANKL antibody specifically binds to human RANKL and does not appear to produce antibodies. Denosumab is a fully human monoclonal antibody against RANKL which has been investigated in osteoporotic women and rheumatoid arthritis patients.[28] Alongwith inhibiting pathological bone resorption it also inhibits physiological bone resorption resulting in adverse systemic effect. Its use has been restricted to experimental periodontitis in animal interventional studies.[29]

Increased RANKL /OPG ratio play an important role in clinical periodontology by virtue of its diagnostic potential for the disease. It is important to understand whether conventional periodontal treatments can actually reduce this ratio to the normal healthy range and thus predict the successful outcome of periodontal treatment. But studies demonstrated that initial non-surgical phase of periodontal therapy i.e oral hygiene instructions and scaling and root planning actually does not do so.

A study using semiquantitative PCR technique was performed in a group of periodontitis patients receiving periodontal surgical therapy 4-6 weeks following the initial phase of periodontal treatment to investigate RANKL and OPG gene expressions in gingival tissues. Surgically treated sites demonstrated decreased expressions of both genes than healthy sites without significant changes in RANKL/OPG ratio.[30]

Later on the effect of periodontal treatment on the RANKL-OPG system in GCF was investigated by several studies. One such study performed 4weeks following initial phase of periodontal treatment showed a decrease in OPG concentration with no change in RANKL levels but a possible increase in RANKL/OPG ratio.

A recent study demonstrated that there is no change in RANKL/OPG ratio following the initial periodontal treatment in a group of chronic periodontitis and aggressive periodontitis patients in spite of improved clinical response.

Thus accumulated evidences suggest that though RANKL /OPG ratio may be a potential biomarker for untreated periodontitis but it cannot genuinely predict the outcome of clinically successful periodontal treatment.Thus, an additional adjunctive treatment approach needs to be followed for the increased RANKL/OPG ratio after initial periodontal therapy.

Future Protocols

It has been a challenge to the periodontist to treat the pathologic bone loss associated with periodontal diseases. Various studies done so far have shown considerable variation in the levels of RANKL, OPG or RANKL/OPG ratio levels. RANKL/OPG ratio can be used as a risk indicator for periodontal disease progression and /or predictor of ongoing disease activity but for that this ratio needs to be defined more accurately. Due to lack of any defined values for RANK, RANKL and OPG it is hard to differentiate a healthy periodontium from diseased one. Various protocols need to be followed prior to apply RANKL-OPG system in clinical periodontology. These include the global standardization of the sample collection techniques and detection assays. Biological fluids should contain a defined physiological concentration of RANKL and OPG so that healthy range or periodontal range RANKL/OPG ratio can be determined.

Though many cross-sectional studies have been carried out, there is a need for longitudinal studies to evaluate simultaneously disease progression rates as well as RANKL/OPG levels. Latest adjunctive treatment modalities need to be tested by performing Interventional studies to evaluate a proportional relationship between

RANKL/OPG ratio reduction and long term maintenance of successful clinical outcome

Conclusion

It can be concluded from the accumulated evidences that RANKL and OPG are definetely present in the GCF. It has been elucidated that periodontal diseases express higher RANKL and lower OPG levels leading to net increase in RANKL/OPG ratio. It makes no sense in studying RANKL and OPG separately in clinical periodontology due to their inability to assess disease state.

Therefore, it is wise to study them simultaneously as their relative ratio because it is the RANKL/OPG ratio which is steadily raised in all forms of periodontitis. Clinically successful periodontal therapy may neither reduce nor ceases RANKL/OPG ratio . Thus, success of a periodontal therapy cannot be judged by RANKL/OPG ratio.

Thus, overall need is to use host response modulation therapies as an adjunctive therapy targeting specifically RANKL-OPG host response for the management of periodontal diseases. This act of targeting RANKL-RANK-OPG axis leads to betterment of osteoclastic bone resorption in periodontitis. Such a judicious approach can form the future basis for drug therapy in periodontal disease.

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