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Review Article

Periodontitis as an Autoimmune Variant- A Systematic Review

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Abstract: Periodontitis is a multifactorial disease with microbial dental plaque as the initiator of periodontal disease. However, in 1965, Brandtzaeg and Kraus were the first to postulate the autoimmune basis in the pathogenesis of periodontal disease. Involvements of autoantibodies in the pathogenesis of chronic and aggressive periodontitis have been observed suggesting the role of autoimmunity in periodontitis. Few autoimmune diseases are known to coexist with periodontitis in humans such diseases include RA and, to a lesser extent, systemic lupus erythematosus (SLE). The aim of this review is to systematically study the various autoimmune concepts/immunological models that signifies their role in periodontitis.

Keywords: Autoimmunity, chronic periodontitis, Rheumatoid arthritis, periodontalmedicine.

INTRODUCTION

Autoimmune disease is defined as "a condition in which structural or functional damage is produced by the action of the immunologically competent cells or antibodies against normal components of the body". The concept of autoimmunity was first predicted by Nobel Laureate Paul Ehrlich at the start of the twentieth century, and he described it as 'horror autotoxicus' [1]. His experiments led him to conclude that the immune system is normally focused on responding to foreign materials and has an inbuilt tendency to avoid attacking self-tissues. But when this process goes wrong, the immune system can attack self-tissues resulting in autoimmune disease. The perplexing issue of what allows the immune system to attack self-tissues is a continuing focus of research [1].

Periodontitis is a chronic inflammatory disease characterized by mononuclear cell infiltration into the gingival tissues, leading to connective tissue destruction and alveolar bone resorption. Although periodontal bacteria are the causative agents in periodontitis, subsequent progression and disease severity are thought to be determined by the host immune responses[2]. The precise mechanisms of tissue destruction, however, have not been fully elucidated; nevertheless, a number of reports have implicated autoimmune responses in the disease process [2, 3]. Periodontitis like many other common diseases (e.g., Crohn's disease, cardiovascular diseases, diabetes) is considered to be a complex multifactorial disease. Apart from microbial etiology a number of factors viz environmental and genetic factors have been proposed to modulate a host microbial interaction that ultimately decides the clinical picture of periodontal disease [4].

In 1965, Brandtzaeg and Kraus were the first to postulate the autoimmune basis in the pathogenesis of periodontal disease [5]. Involvements of autoantibodies in the pathogenesis of aggressive periodontitis have been observed suggesting the role of autoimmunity in periodontitis [6]. Few autoimmune diseases are known to coexist with periodontitis in humans such diseases include RA and, to a lesser extent, systemic lupus erythematosus (SLE) [7]. The aim of this review is to systematically study the various autoimmune

concepts/immunological models that signifies their role in periodontitis

AUTOIMMUNE MECHANISMS IN THE PATHOGENESIS OF PERIODONTAL DISEASE

- Failure of Self tolerance and autoimmunity
- Single nucleotide polymorphisms
- Presence of Epithelial reactive antibodies
- Human Heat shock protein 60s (hsp60) antibodies
- Production of ANCAs (Anti-neutrophil cytoplasmic antibodies) in autoimmunity Role of Apoptosis in Autoimmunity
- Role of superantigens in Autoimmunity
- Involvement of autoimmune reactions to native and post-translationally modified extracellular matrix components.

1. Role of Self tolerance and autoimmunity

Self-tolerance refers to the mechanism in which all individuals are tolerant to their own potentially antigenic substances. Failure of self-tolerance is an elementary cause of autoimmune diseases. This process leads to functional unresponsiveness, deletion (apoptotic cell death), and suppression by regulatory T cells. In central tolerance, immature lymphocytes that happen to recognize self-antigens in generative lymphoid organs (the bone marrow for B cells and the thymus for T cells) die by apoptosis; in peripheral tolerance, mature self-reactive lymphocytes encounter self antigens in peripheral tissues and are killed or shut off[6]. Autoimmune diseases develop when self-reactive lymphocytes escape from tolerance and are activated. Similarly anti-cyclic citrullinated peptide (anti- CCP) autoantibody and citrullinated peptide have been determined in breaking the self tolerance in RA in presence of peptidylarginine deiminase (PAD) which is specific to P.gingivalis. PAD is involved in post-translational modification (citrullination) of protein- bound arginine of citullinated peptide[7].However PAD is specific to P.gingivalis and the researchers have estimated increased antibody titers to P. gingivalis correlating with anti- CCP antibody isotypes that are definite to RA. With this fact, it is also confirmed that bacterial PAD produced by P. gingivalis in periodontal lesion has the capacity of deiminating arginine in fibrin correlating with anti-CCP autoantibodies, recognizing the failure of self tolerance in autoimmunity [8].

2. Role of Genetics of single-gene disorder

To assess the contribution of genetic factors to disease susceptibility, genetic epidemiologists examine the extent of familial clustering; the degree to which monozygotic twins are more concordant for the presence of a disease compared with dizygotic twins; and the increased risk that family members of persons with disease will develop that disease compared with an individual from the general population [9]. Using such estimates of genetic risk, it becomes obvious that in single-gene disorders, the risk conferred on an individual by a given genetic variant is very high, but the overall impact on the population is minimal because these variants are rare. Evidence for the role of genetic component in chronic (adult) periodontitis has been conducted from twin and family studies. The twin model is probably the most powerful method to study genetic aspects of any disease, including periodontal disease [10]. In a study on 117 adult twin pairs [11] the analysis included the evaluation of the environmental factors like smoking and utilization of dental services. The results showed that chronic (adult) periodontitis was estimated to have approximately 50% heritability, which was unaltered following adjustments for behavioral variables including smoking. In contrast, there was no evidence of heritability for gingivitis after behavioral covariates such as utilization of dental care and smoking. Velden *et al*., [12] studied with a family study design the effect of sibling relationship on the periodontal condition in a group of young Indonesians deprived from regular dental care. The results of the analysis suggest that also in less severe forms of periodontitis there may be a genetic background for the disease. Also in a Dutch population epidemiological studies have suggested that chronic (adult) periodontitis aggregates in families [13].

From both the twin and family studies it can be concluded that the basis for familial aggregation of periodontitis appears not bacterial/ environmental/ behavioral in nature; rather, genetics seem to form the basis for the familial aggregation of periodontitis.

3. Polymorphisms in the IL1 Gene Cluster

Kornman *et al*., [14] reported on a composite genotype, composed of the IL1A 889 and IL1B 3953 polymorphisms both carrying an R-allele, in relation to periodontitis. To date, the following IL1 genetic polymorphisms have been studied in association with chronic periodontitis: IL1A 889 (in linkage disequilibrium with +4845), IL-1B 511 (in linkage disequilibrium with 31), IL1B +3954 (also mentioned in the literature as +3953), and IL1RN VNTR (in linkage disequilibrium with +2018). SNP IL1B +3954 (+3953) was initially proposed as risk factor for periodontitis among Caucasians. Among the Caucasian CP patients the IL1 composite genotype and/or IL1B +3953 genotype may be genetic risk factors. Results of the meta-analysis of Nikolopoulos *et al*., [15] also support an association between CP and IL1A 889 and IL1B +3953 R-allele

carriage as well separately as in composite genotype in Caucasians.

4. Epithelial reactive antibodies

Bacterial antigens perturbing the epithelial structure are the essential features of the destructive lesion of periodontitis. In a study it was found that the pathological lining epithelium of the periodontal pocket showed a marked reduction of epithelial cadherin, important in intercellular adhesion, of involucrin, a marker of terminal differentiation, and of the gap junction connexions that form intercellular communication channels. These changes were related with alterations of filamentous actin expression, collectively indicating profound perturbation of epithelial structure [16].

5. Role of Heat shock protein 60s (hsp60)

Despite being highly homologous between prokaryotic and eukaryotic cells, hsp60s are strongly immunogenic, and immune responses to microbial hsp60s are speculated to initiate chronic inflammatory diseases in which autoimmune responses to human hsp 60 may be central to pathogenesis [17]. It has also been reported that self-hsp60 can be recognized by T cells specific for mycobacterial hsp60, suggesting the presence of T cells with specificity for cross-reactive epitopes. These are remarkably immunogenic, and both T-cell and antibody responses to hsp60 have been reported in various inflammatory conditions. Periodontitis patients demonstrated significantly higher proliferative responses of peripheral blood mononuclear cells (PBMC) to human hsp60, but not to P. gingivalis GroEL, than control subjects[18]. The response was inhibited by anti-major histo-compatibility complex class II antibodies. Analysis of the nucleotide sequences of the TCR demonstrated that human hsp60-reactive T-cell clones and periodontitis lesion-infiltrating T cells have the same receptors, suggesting that hsp60-reactive T cells accumulate in periodontitis lesions [18].

6. Role of ANA in autoimmunity

Davies *et al*., [19] documented ANCAs for the subjects with acute necrotizing glomerulonephritis. ANCAs represent a heterogeneous group of antibodies also known as antinuclear factor (ANF) [20]. These factors target antigens that are primarily present in azurophil granules of polymorphonuclear leukocytes (PMNs).The role of ANCA are determined in several other known autoimmune diseases such as inflammatory conditions, infectious diseases, and neoplasms [20]. Few include systemic vasculitis, Wegener's granulomatosis, churg strauss syndrome, classic polyarteritis nodosa, microscopic polyarteritis, Rheumatoid arthritis, systemic lupus erythematosus, acute/chronic infection, HIV infection and Chronic periodontitis. Indirect immunofluorescence was advocated during the 1970s to demonstrate granulocyte specific antinuclear factors in synovial fluids and sera of rheumatoid arthritis (RA) patients [21].

Tendency for all the chronic inflammation to undergo dysfunction could be related to the immune specific genes such as alleles of human leukocyte antigens, and other genes that determine the level of the host immune response. Recently, microbial superantigens (SAgs) and mechanisms related to disturbed apoptosis or removal of apoptotic cells have been proposed for the induction of ANCA [22].

7. Role of ANA in periodontal pathogenesis

Studies are currently underway to study the potential pathogenic role of ANCA in periodontal tissue destruction. ANCA was first described by Parsons et al in a condition of localized hyperplastic ''strawberry'' gingival lesion, which was later diagnosed to be Wegener's granulomatosis [23]. A similar case was also reported by Manchanda *et al*., [24].

However, the first controlled study to explore the possible link between ANCA and periodontal disease was conducted by Novo and Viera [25]. The authors used ELISA (enzyme-linked immunosorbent assay) and IIF (indirect immunofluorescence) for various ANCA-associated antigens to determine the presence of ANCA in 12 chronic periodontitis patients. Their results demonstrated a statistically significant ($P < 0.001$) number of patients who were ANCA positive (pANCA) relative to healthy subjects**.** Although the mechanisms that trigger the development of ANCA are not completely understood, several hypotheses have been postulated, including immune specific genes, such as alleles of human leukocyte antigens, and other genes that determine the level of the host immune response [26]. Recently, microbial superantigens (SAgs) and mechanisms related to disturbed apoptosis or removal of apoptotic cells have been proposed for the induction of ANCA [27].

The autoimmune condition, rheumatoid arthritis, was shown to be associated with an increased incidence of periodontal disease [28]. However, in a study of periodontal disease in elderly individuals, no increase in rheumatoid factor or incidence of anti-nuclear antibodies was found to be associated with disease [28]. The authors did state that antinuclear antibody levels were higher in periodontal disease subjects than in controls, but no data were presented.

The mechanisms that trigger ANCA are:

1. Hyper primed neutrophils produce MPO and PR-3 trigger ANCA or
2. The exposure of the host to periodontal pathogens, along with a genetic susceptibility, could trigger ANCA by TNF-α.
3. Other known pathway is the ability of periodontal pathogens to possess a ‘‘superantigen’’ property, where they can directly activate the autoreactive B-lymphocytes in a T-cell–independent and –mediated pathway, which can also result in the production of ANCA.

Further these invoke an antigen antibody–dependent immune response, which results in the activation of neutrophils. The activated neutrophils release reactive oxygen radicals, enzymes, and various proinflammatory cytokines, all of which are known to mediate periodontal destruction [29]. ANCA activated neutrophils are also known to delay apoptosis, which can prolong the activity of neutrophils and thereby increase tissue destruction.

8. Role of Apoptosis in Autoimmunity

Autoimmune Apoptosis of neutrophils is essential for controlling the duration of early inflammatory response and thus limiting the local tissue damage that can result from prolonged activation of neutrophils. Utz and Anderson [30] suggested that defects in apoptosis or in the process of removal of apoptotic cells could lead to exposure of these cellular fragments to immune system and activating a humoral immune response. Also, studies have demonstrated the presence of ANCA during apoptosis of neutrophil. This could be an important stimulus that can drive the production of autoantibodies. Once the ANCA-mediated autoimmune response has been mounted, opsonization of apoptotic neutrophils by ANCA might accelerate inflammation and augment the autoimmune response.

9. Role of Apoptosis in Periodontitis

Apoptosis is induced in the periodontal tissue by host and microbial factors and support the hypothesis that apoptotic mechanisms could be implicated in the inflammatory process associated with gingival tissue destruction observed in adult periodontitis patients. Recent studies have reported association between hyper reactive neutrophils in the periodontal disease and an increased of the release of oxygen radicals in the periodontal damage tissue. Utz and Anderson [30] suggested that defects in apoptosis or in the process of removal of apoptotic cells could lead to exposure of these cellular fragments to immune system and activating a humoral immune response. Neutrophils activity would produce a delay in the death of cell by apoptosis, increasing the damage to periodontal tissue [30].

Presence of ANCA during apoptosis of neutrophil could be an important stimulus that can drive the production of autoantibodies. Immunodetection of caspase-3 protein, increase in procaspase- 3 levels than in healthy control neutrophils could indicate a possible protection of the neutrophils apoptosis in periodontitis. Delay in the apoptosis of neutrophils could participate in the pathogenesis of periodontitis [31, 32]. Gamonal *et al*., [33] demonstrated aberrant viz., accelerate or delayed neutrophil apoptosis with, a shift in the balance between the mammalian Bcl-2family of apoptosis-associated proteins, a reduction in cellular (neutrophil) expression of proapoptotic protein Bax, and elevated anti-apoptotic proteinBcl-2 [33]. In addition, they suggested that presence of elevated levels of GM-CSF and TNF-a in gingival crevicular fluid (GCF) from periodontitis sites relative to that of the healthy sites could also be attributed as the causative factor for the delay in neutrophil apoptosis [34]. Thus, the common link in the pathologic process involving ANCA- associated diseases and periodontal disease should be explored.

10. Role of superantigens in Autoimmunity

Superantigens are microbial or viral toxins that comprise a class of disease-associated, immunostimulatory molecules and act as Vβ-restricted extremely potent polyclonal T cell mitogens. They bind major histocompatibility complex (MHC) class-II molecules without any prior processing and stimulate large number of T cells (up to 20% of all T cells) on the basis of epitope specified by this receptor [35, 36]. These properties are attributable to their unique ability to cross-link MHC class II and the T cell receptor (TCR), forming a trimolecular complex The superantigens can be broadly classified into following families:

- Endogenous superantigens: These superantigens are encoded by various viruses integrated into the genome. Examples are superantigens produced by mouse mammary tumor virus (MMTV) and Epstein-Barr virus (EBV) associated superantigen [37, 38].
- Exogenous superantigens: These include the exotoxins secreted by microorganisms. Examples are staphylococcal enterotoxins (A, B, C1 to C3, etc.), streptococcal pyrogenic exotoxins (A1 to A4, C, etc) and others [37-39].
- B-cell superantigens: Those superantigens which stimulate predominantly B cells. Examples include staphylococcal protein A and protein Fv [40].

11. Role of superantigens in periodontitis

Immunological research studies in Periodontics have been directed towards determining the superantigenic periodontal pathogens. Immunomodulation by periodontopathic bacteria has been implicated in the pathogenesis of inflammatory periodontal diseases. A novel class of microbial-derived T cell mitogens, referred to as superantigens, has recently been described. Superantigens are unique in that they induce a tremendous activation and expansion of specific subsets of T cells in an antigen-independent manner; thereby causing immune dysfunction. The results of these studies suggest a role for the involvement of SAgs during periodontal diseases. Zadeh H [41] isolated leukocytes from gingival tissues obtained from 8 periodontitis and 4 non-periodontitis patients by collagenase digestion. Gingival cells demonstrated that in most periodontitis patients examined, patterns of V beta expression among T cells are characteristic of superantigen stimulation, i.e., there is an elevation in the proportion of one or a few V beta families [41]. Thus the study support the hypothesis that a large proportion of T cells in periodontitis sites have been stimulated and expanded by superantigens, presumably produced by periodontitis-associated bacteria. Mathur et al[42] studied the ability of Actinobacillus actinomycetemcomitans, Porphyromonas gingivalis, and Prevotella intermedia to determine SAg activity in vitro and reported that only P. intermedia has the capacity to increase the expression of T-cell Vab2, Vb5, and Vb6, thereby providing evidence for possible involvement of SAg in human periodontal diseases. Recently, a study by Leung and Torres demonstrated that P. intermediastrain[43], which is a clinical isolate, induced the strongest expansion of CD4+ T-cell subsets that express Vb8, Vb12, and Vb17 TCRs. Furthermore, to confirm the role of A. actinomycetemcomitans–derived SAg, Zadeh *et al*., [44] reported that the response to this bacterial stimulus was a large-scale T-cell activation in a Vb-specific manner demonstrating the superantigenic property by A.actinomycetemcomitans. Thus, these studies specify the possibility of role of superantigen in periodontitis. However, it may still be a possibility in some types of patients, for example, patients with refractory disease, who have low plaque scores, few suspected periodontal pathogens in that plaque, shallow gingival pockets, unremarkable levels of serum antibody against periodontal pathogens, and uncontrolled disease. Some mechanism(s) perpetuate the continued bone loss in these individuals. A.actinomycetemcomitans, P.gingivalis, and Intermedia activate T cells activation and expansion with TCR Vab2, Vb5, and Vb6, Vb8, Vb12, and Vb17 [44].

DISCUSSION

The understanding of pathogenesis in periodontal disease has been considered with the other chronic diseases viz RA and SLE. Studies in association with RA, SLE and periodontitis have a similar natural history, etiology, pathogenesis, immune potential and progression patterns of the disease. The confounding issue of what allows the immune system to attack self-tissues is a continuing focus of research. One of the most notable publications in this field is that of Ranney and Zander [45] who described an allergic reaction to crystalline ovalbumin that was produced in the gingiva of squirrel monkeys (Saimirisciureus). The initial lesion was acute destructive periodontitis. On repeated application of challenge antigen to the gingival crevice, chronic inflammation with infiltration of the gingiva by lymphocytes and plasma cells occurred. The reaction was remarkably similar to human chronic destructive periodontitis. With the supportive study by Dick and Trott [46] an arthus reaction was induced in the presence of nonspecific challenge antigen. Further a conceptual model given by Mergenhagen, Tempel, and Snyderman [47] showed gingival tissue destruction that follows chronic challenge by bacterial plaque. The authors of this study postulated that the bacteria of the dental plaque provide antigenic material that can induce antibody formation in regional lymph nodes and gingival tissues. The antibodies, reacting with bacterial antigens, might activate complement, releasing biologically active materials that induce vascular permeability and chemotaxis of neutrophils. Such a reaction induces edema and increased gingival permeability to bacterial antigens, with subsequent further stimulation of the host's immune system [48]. The host neutrophils, on phagocytizing bacterial products, release tissue- damaging enzymes, thereby causing further tissue destruction. With the ongoing challenge by bacterial antigens, the process would become chronic and lead to the changes recognized as chronic periodontitis.

Autoimmunity to specific citrullinated proteins gives the first clues to the etiology of rheumatoid arthritis. With this background research teams then focused on identifying antibody titers to P. gingivalis and found increased titers in patients with rheumatoid arthritis and are associated with disease-specific autoimmunity. Antibody responses to Porphyromonas gingivalis (P. gingivalis) in subjects with rheumatoid arthritis and periodontitis showed the similar responses [48].

Nitric oxide (NO) is not only important in host defense and homeostasis but it is also regarded as harmful and has been implicated in the pathogenesis of a wide variety of inflammatory and

autoimmune diseases [49]. The presence of NO in periodontal disease may reflect the participation of an additional mediator of bone resorption responsible for disease progression [50].

In recent time the research focus in periodontal medicine has tried to determine the interrelationship between RA and periodontitis. An imbalance in the immunoregulation, involvement of activated macrophages and dendritic cells, proinflammatory cytokine profiles such as IL-1, TNF-a, and prostaglandin E2 and a role for Reactive oxygen species (ROS) such as nitric oxide strengthen the link between the two conditions [51]. Various interventional and association studies have emphasized that periodontal infection could be a possible contributing factor for enhancing the severity of RA [52, 53]. However, there is only one study that evaluated the ANCA component levels in periodontitis and RA patients, the results was however not statistically significant. Novo *et al*., [54] found that ANCA was detectable in 10% of RA patients with periodontitis and 6.6% of RA patients without periodontitis.

FUTURE PERSPECTIVES

Estimation of ANCA in Periodontitis holds worthy for refractory disease with low plaque scores, with few suspected periopathogens in that plaque, shallow gingival pocket, unremarkable presence of serum antibodies against periopathogens, uncontrolled periodontal disease, generalised aggressive periodontitis and those with associated chronic conditions like RA, SLE and possibly HT. Diagnostic test like ANCA test, stress analysis, superantigens and gene test (HLA-antigens/MHC molecules) would also aid in establishing autoimmune etiology of periodontitis. Anti-nuclear antibodies are found to be associated with rheumatoid arthritis in genetically susceptible individuals and the same holds good with autoimmunity and periodontitis, but no data till today exists to show the correlation of autoimmune diseases and periodontitis. Hence future in periodontal medicine should be based upon autoimmune nature of these chronic conditions in relation to periodontitis. Gingival autoimmunization maybe initiated through a variety of mechanisms:

1. The tissue damage induced either by direct action of bacterial toxins or by the immune reaction postulated by Mergenhagen, Tempel and Snyderman [55] could give rise to an increased accessibility of normally inaccessible components of gingiva;
2. Bacterial or chemical modification of the gingival connective tissues might render them altered and therefore autoantigenic not recognizable as self [56];
3. Forbidden clones might develop within regions of gingival damage [57] and the products of tissue breakdown and/or bacterial metabolism might form protein-hapten complexes with the gingival components, with the end result that antibodies with gingival specificity would be formed [58].

CONCLUSION

Categorization of the diseases, potential evidence to establish etiologies, and possibly to diagnose and monitor disease activities is the goal of research conducts. This review article concentrates to determine the various mechanism models established for suggesting periodontitis as an autoimmune variant. We have made a sincere attempt with evidence-based studies to identify probable common mechanisms in the disease processes of RA (Rheumatoid Arthritis), SLE (Systemic Lupus Erythromatosis) and other chronic inflammatory conditions, and then compared with the periodontitis. Although future work in the form of cohort studies, controlled studies are required. The important role in assessing periodontal disease with autoimmunity should concentrate on the functional mechanisms of action of these autoantibodies, the critical immunogenic potential of ANAs and superantigens needs to be identified.

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