Immune Regulation in Periodontal Disease: A Review

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Abstract

It is an established fact that dental plaque as a biofilm is responsible for various types of gingival and periodontal diseases. It is a multifactorial disease in which one of the important components is the host defense mechanism. Through many years of research, it has now been established that the bacteria alone are not sufficient to cause the disease, it's only when they evade the host defense, and in the course of protecting the host, its immune system acts against the tissues resulting in native periodontal tissue damage. This review tries to gain insight into the complex immune mechanisms which take place during the pathogenesis of periodontal diseases.

Keywords: *Plaque biofilm, Humoral immunity, Innate immunity, antibody.*

Introduction

It has been very well known over the last thirty years that while plaque is the cause of periodontal disease, it is the inherent vulnerability of the host that decides the end stage of the disease. Innate susceptibility, in turn, is governed by the type of the feedback provided by one's immunity to the specific periopathogenic bacteria residing in the plaque biofilm.[1]

The washing action of saliva, gingival crevicular fluid, phagocytes, non-specific antibodies, complements, epithelium and defensinsseem to prevent the bacterial attachment and subsequent colonization in the gingival sulcus. However, the role of defensins in arresting the growth of bacteria in the plaque biofilm has yet to be ascertained.[2]

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Many often low virulent pathogens clear out by scavenger receptor of phagocytes or Innate cells without evoking further adaptive immune responses.[3] However, the highly pathogenic bacteria with strong antigenicity infect the sulcus, TLR mediated cytokines from resident leukocytes, activate Innate cell (PMN, Mo) homing to expedite bacterial Killing. If innate cell is unable to destroy periopathogens, they enter the periodontal tissues because Aggregatibacter actinomycetemcomitans (A.a) and red-complex bacteria are unyielding to phagocytosis.[4]

Role of Host Immune Defense Against Periopathogens: "Virulence factors of these periopathogens induce TLR dependent APC activation results in upregulation of MHC-II and Co-stimulatory molecules as well as cytokine release." With strong innate response against periopathogen, antigen-presenting cells (APC'S) liberate IL-1, IL-12 and NK cell liberates INF-γ. In presence of IL-12 and INF-γ, short term, high-affinity APC-TCR binding between naïve T cells and APC leads to Th-1 response.[5] A continued strong Thl response produces INF-γ (i.e., CD4 cells) that would pool the PMNs, macrophages, Natural killer cells (NK) and CD8 T-cells to the siteof infection, that may contain the disease (i.e., containment of infection in chronic gingivitis) by exerting anti-bacterial activity,

intracellular and/or direct contact killing mechanism. The disease might not be eliminated rather persists due to continuous supply of microorganisms from other niches and plaque biofilm.[5]

Atypical LPS of P. gingivalis induces poor innate response for a protracted course. P.gingivalis LPS inhibits IL-12 release from DC and INF-γ from activated Th0 cells (i.e., increased IL-4, IL-5 secretion). Therefore, Th1 to Th2 shift mainly depended on nature of the antigen, antigen dose, cytokine environment and nature of APC.[5] In presence of IL-4, IL-13 and low level of IL-12, prolonged, low-affinity APC- TCR binding leads to Th-2 response (Figure-5).[5] Exaggerated Th2 response induces B cell proliferation (i.e., Polyclonal B cell activation), class switching of plasma cells and antibody-mediated humoral immune response in periodontal lesion.[5,6]

Increased counts of plasma cells suggest enhanced Th2 action in severe periodontal disease. Increased protective anti-bacterial antibody could removeperiopathogens, but if the secreted antibodies become nondefensive for the host (i.e., Low Ab affinity and avidity) or are unable to kill the periopathogens, periodontal disease may ameliorate to an advanced stage.[5] The presence of both Th 1 and Th2 in periodontitis[7,8]points out the importance of both in the pathogenesis of periodontal disease. Hence, the difference between "protective" and "destructive" antibody synthesis would be the most important determinant in the progression of the disease.[5]Alteration of the Thl/Th2 balance may be a direct outcome of the "super antigenic" actionof the notorious periodontal pathogens.

"Although there was no direct evidence for a role in periodontal disease pathogenesis but IL-10 from Th2 cells would promote T-regulator cell activity with concomitant suppression of cell-mediated immune responses." $CD4^+CD25^+$ cell also play a beneficial part in regulating autoreactive T cells mobilized as a part of the host response to periopathogens.[9]

"High titers of anti-collagen type 1 antibody and specific t-cell clones have been identified in inflamed gingival tissues of periodontitis patients."[10] It has been pointed out that human hsp60-reactive T-cell clones and T cells occupying the periodontitis affected areas had the same receptors and cytokines profile (INF-γ) suggestive of the fact the anaerobic bacteria causing periodontitis may activate the self hsp60-reactive T-cells with similar cytokine form.[11] On the contrary, Petit et al. believed that a higher level of anti HSP antibodies were protective of destructive periodontal diseases.[12] The conflict between the two studies might be due to racial variation, the difference in the extent of the disease and variations in the age of the various study groups.[11]

It was found that expression of Vβ was quite increased in the circulating blood mononuclear cells of individuals with Prevotella intermedia infection in comparison to healthy subjects raising suspicion towards the role of superantigens in periodontitis.[13] But other study results failed to show super antigenic activation of T-cells suggested that role of a superantigen in the periodontal disease was variable and inconsistent.[14] The conflicting reports regarding the role ofsuperantigens in periodontitis is yet to be confirmed.

"Although few if any NK cells are seen in healthy tissues, their numbers increase from health to gingivitis to periodontitis."[15] Besides their cytotoxic nature, NK cells can monitor B-cell movement and propagation, which is the pathognomonic histopathological feature of severe periodontal disease.[16] The cell-killing action of NK cells is potentiated by IFN-γ. "Surface lipopolysaccharides (LPS) from Gram-negative periodontal bacteria appear to provide the major activation signal for NK-cell-mediated cytotoxicity."[9]

"The peripheral and local immune cell profiles in patients with disease differ substantially, which suggests that the immunological response to periodontal pathogens is primarily a local phenomenon with mild to moderate systemic involvement."[17]

RANKL expression by T-cell was not critical for bone resorption rather other mechanisms (i.e., hormones, Calcium ion signaling) also have an effective role in osteoclast differentiation in the absence of RANKL. Several studies suggested that T-cell is only indirectly involved in osteoclastogenesis. Moreover, activated T-cells not only positively regulate osteoclastogenesis by RANKL expression but also negatively affect it by secreting IFN-γ. This counterbalancing action of IFN-γ suppresses boneresorption in normal T-cell response as well as in many chronic periodontitis patients. Thus, the detrimental effects of T-cells onosteoclastogenesis revolve around the compelling balance of RANKL expression and cytokine profile.

There arises the need of added studies to find out the components of alveolar bone loss and pathogenic T-cell phenotype associated with periodontal bone loss.[18]

B-cells secrete high amounts of IL10 and IFN-γ, which are inhibitory cytokines but these seemed to be outrun by stimulatory factors such as macrophage inflammatory protein-alpha (MIP-α), monocyte chemotactic protein-3 (MCP-3), and M-CSF.[19] Although it has been demonstrated both in vitro and in vivo that activated B -cells enhance osteoclastogenesis and bone resorption it is still inconclusive if B- cells are more responsible for bone loss than T-cells.

"Periodontal Antibody (Ab) producing B cells may be inadequate or of insufficient longevity to deal with the continuous assault from biofilm and/or chronicity of the infectious disease. Meanwhile, memory B-cells and Ab-producing plasma cells may eventually become "crippled" or "degenerated" and thus trigger further immune/inflammatory responses by invading pathogens resulted in progressive tissue destruction."[20] Therefore, "Ab-mediated protection is incapable of achieving total or sterile eradication of the invading periodontal pathogens and, hence, is sub-optimal."Contrary to that,"activated" B-cells in the form of antigen-presenting cells totrigger memory T-cells for cellular immunity.[21] This is precisely why antibody-mediated immune response anticipates periodontal pathogens first but fails to curb the advancing form of periodontitis.[22] The B-cells localized in the periodontal tissues also deposit IL-1β that is crucial for alveolar bone loss. It has to be seen in the future as to why the humoral immunity fails to arrest the periodontal disease progression before a definitive attempt to prevent periodontal disease in the form of a vaccine can be thought of.

Conclusion and Future Directions: "Host immune-pathogen interaction is a complex interplay, which is intimately regulated by the innate and acquired immunity to deal with immediate and long-lasting assaults imposed by invading micro-organisms in periodontal pockets." Pathogen-specific $CD4^+$ T cells are both protective, and destructive whereas $CD8^+$ T-lymphocytes are not responsible for periodontal disease. We have sufficient evidence pointing towards the role of $CD4^+$ T cells in the development of the host's antibacterial resistance and maintenance of harmony of the periodontium.

With the basic understanding of the interplay of the immune cells and cytokines in the process of bone resorption, would help to develop novel methodto treat periodontitis and other systemic disease associated with bone loss. Therapeutic approaches such as potassium channel blockers to block the calcium signaling for RANKL expression and gene therapy to reduce IL-1 or TNF-α production are being investigated. In periodontitis host modulation using chemically modified tetracycline (CMT) or low dose doxycycline have shown to reduce the periodontal disease by suppression of matrix metalloproteinases (MMP) activity.

A clear understanding of the immunopathogenesis of periodontal disease is essentially required to develop diagnostic aids for prediction of disease activity reliably, vaccine preparation and to differentiate between a healthy and periodontally affected site.

Currently the relationship between periodontal disease and systemic health is considered as a two-way road. Immunity in most individuals establishes a 'China wall' between the two. Moreover, epidemiological findings suggest that even in the absence of oral hygiene maintenance rapid periodontal breakdown occurs occasionally. Considering the relationship between periodontal disease and systemic health it can be stated that even tooth loss in some individuals as a consequence of chronic infectious periodontal disease represents a protective role of host immune response by essentially exfoliating the infective source (i.e., tooth associated plaque and calculus) that could create a greater danger to systemic health.

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References

1. Ohlrich EJ, Cullinan MP, Seymour GJ. The immunopathogenesis of periodontal disease.Aust Dent J. 2009 Sep;54 Suppl1:S2-10.
2. Marshall RI. Gingival defensins: linking the innate and adaptive immune responses to dental plaque. Periodontol 2000 2004; 35:14-20.
3. Peiser L, Mukhopadhyay S, Gordon S. Scavenger receptors in innate immunity. CurrOpinImmunol 2002; 14:123-128.
4. Hyun SJ, Park E et al. Susceptibility of various oral bacteria to antimicrobial peptides and phagocytosis by neutrophils. J Periodontal Res 2007; 42:410-419.
5. Gammell E, Seymour GJ. Immunoregulatory control of Th1/Th2 cytokine profiles in periodontal

disease. Periodontol 2000 2004; 35:21-41.

6. Teng YT. Mixed periodontal Th1-Th2 cytokine profile in Actinobacillusactinomycetemcomita ns-specific osteoprotegerin ligand (or RANK-L)-mediated alveolar bone destruction in vivo. Infect Immun. 2002 Sep;70(9):5269-73.
7. Taubman MA, Eastcott JW, Shimauchi H, et al. Modulatory role of T lymphocytes in periodontal inflammation. In: Genco RJ, Hamada S, Lehner T, McGhee J, Mergenhagen SE, eds: Molecular pathogenesis of periodontal disease. Washington DC: American Society of Microbiology, 1994:147-157.
8. Prabhu A, Michalowicz BS, Mathur A. Detection of local and systemic cytokines in adult periodontitis. J Periodontol. 1996 May;67(5):515-22.
9. Yamazaki K, Nakajima T. Antigen specificity and T-cell clonality in periodontal disease. Periodontol 2000 2004; 35:75-100.
10. Wassenaar A, Reinhardus C, Thepen T, et al. Cloning, characterization, and antigen specificity of T-lymphocyte subsets extracted from gingival tissue of chronic adult periodontitis patients. Infect Immun1995; 63:2147-2153.
11. Yamazaki K, Ohsawa Y, Yoshie H. Elevated proportion of Natural Killer T-cells in periodontitis lesions: a common feature of chronic inflammatory diseases. Am J Pathol2001; 158:1391-1398.
12. Petit MDA, Wassenaar A, Van Eden W, et al. Depressed responsiveness of peripheral blood mononuclear cells to heat shock proteins in the periodontitis patients, J Dent Res 1999;78:1393-1400.
13. Mathur A, Yang C, Aeppli D, et al. Influence of periodontal bacteria and disease status on Vβ expression in T-cell. J Periodontal Res 1995; 30:369-373.
14. Petit MDA, Stashenko P. Extracts of periodontopathicmicroorganismss lack functional superantigenic activity for murine T-cells. J Periodontal Res 1996; 31:517-524.
15. Fong TA, Mosmann TR. Alloreactive murine CD8+ T-cell clones secrete the Th1 pattern of cytokines. J Immunol1990; 144:1744-1752.
16. Wassenaar A, Reinhardus C, Abraham Inpijn L, Kievits F. Type-1 and type-2 CD8+ T-cell subsets isolated from chronic adult periodontitis tissue differ in surface phenotype and biological functions. Immunology 1996; 87:113-118.
17. Reinhardt RA, Mc Donald TL, Bolton RW, DuBois LM, et al. In situ activated T-lymphocytes inactive versus stable periodontal lesions. J 1988; 23:295-302.
18. Takayanagi H. Inflammatory bone destruction and Osteoimmunology. J Periodont Res 2005; 40; 287-293.
19. Choi Y, Woo KM, Ko S H et al. Osteoclastogenesis is enhanced by activated B cells but suppressed by activated CD8+ T cells. Eur. J. Immunol; 2001: 2179-2188.
20. Ebersole JL, Cappelli D, Holt SC. Periodontal diseases: to protect or not to protect is the question? Acta Odontol Scand 2001;59: 161-166.
21. Jotwani R, Palucka AK, Al-Quotub M, Nouri-Shirazi M, Kim J, Bell D, et al. Mature dendritic cells infiltrate the T cell-rich region of oral mucosa in chronic periodontitis: in situ, in vivo,and in vitro studies. J Immunol 2001; 167:4693-4700.
22. Baker PJ, Carter S, Dixon M, Evans RT, Roopenian DC.Serum antibody response to oral infection precedes but doesnot prevent Porphyromonasgingivalis-induced alveolar bone lossin mice. Oral Microbiol Immunol1999; 14:194-196.