Review Article

Role of Immunology in Periodontal Disease: A Brief Review

Vinoth Kumar B Na[1], Arvina R[2], Sivaranjani K S[3], Hema P[4], Arun Varghese R[5]

ABSTRACT

Periodontitis is a highly complex and multifactorial disease. In recent years, researchers began to focus on bacterial-host interactions. It had been recognized that though the bacteria present in plaque initiates the periodontal inflammation, the host response to these pathogens equally matters in the progression of the disease. Therefore, the severity of this disease is due to a variety of factors, including the presence of periodontopathic bacteria, high levels of proinflammatory mediators and low levels of antiinflammatory mediators. However, the immune response initiated by periodontal disease seems to be much broader. This review attempts to enlighten the various immune mechanisms involved in periodontal disease initiation and progression.

Key Words: Immunology, Periodontitis, Pathogens, Cytokines, Antibodies.

Introduction

Periodontitis is one of most common inflammatory diseases and it can be of inflammatory, traumatic, metabolic, developmental and/or genetic origin.[1] Till date, two principal forms of periodontitis have been recognized (chronic and aggressive periodontitis). Chronic periodontits is an inflammatory response in the periodontal tissue by the presence of microorganism in the dental plaque.[2] Aggressive periodontitis is a rapidly progressive form of periodontal disease, characterized by severe destruction of the hard tissue support of the dentition in early age and there is a high tendency for diseases to occur in families.[3]

Bacteria present in the plaque, are the primary etiological factor but the host immune response to these bacteria is the fundamental factor for the destruction of both soft and hard tissues in chronic and aggressive periodontitis.[4] Bacteria that colonize the subgingival plaque biofilm encounter both innate and acquired immunity. Host immune system response to the periodontopathic pathogens is believed to be the major part in periodontitis by the interaction between periodontopathic bacteria and host immune system.[5]

The paradigm of the pathogenesis of periodontitis is shifting. It is important to understand how oral bacteria alters the host immune responses and how periodontium is affected by the protective factors induced by host response. This review article highlights the major role of host immune system in chronic and aggressive periodontitis.

Innate Immunity

The epithelial tissues play a key role in innate response, because they are in constant contact with bacterial products. It is now recognized that epithelial cells also constitutively express a diverse range of antimicrobial peptides and their synthesis is upregulated in response to periodontal bacteria. These peptides belong to four families (α-defensins, β-defensins, cathelicidins, saposins) that have been found in humans.[6]

Innate recognition of bacteria and their products by the host involves a sophisticated array of receptors providing specificity to pathogen detection. Through these receptors, cells can directly respond to conserved pathogen-associated microbial patterns (PAMPs) and host danger-associated molecular patterns (DAMPs). These molecular motifs are recognized by pattern recognition receptors (PRRs) on immune cell surfaces.[7] PAMPs associated with periodontal disease are bacterial lipoproteins, lipopolysaccharide, peptidoglycan, fimbriae, flagellin, heat shock proteins, DNA. The toll-like receptor (TLR) family is the best characterized class of PRRs and detects multiple PAMPs.

In the context of periodontal disease, TLR-2 and TLR-4 play important roles in bacterial antigen sensing.[8,9] TLR signaling occurs in a manner that is dependent on the adaptor molecule myeloid differentiation primary response gene (MyD88) or occurs independently via TIR-domain-containing adapter inducing Interferon-β (TRIF). All TLRs with the exception of TLR-3 signal

via MyD88; however, TLR-4 engages both MyD88 and TRIF signaling pathways.[10]

Neutrophils are the first innate immune cells to migrate to the site of infection. Neutrophils utilize relevant Toll-like receptors to recognize and respond to different types of microbial challenge. Like neutrophils, macrophages/monocytes also play a key role in host defense by recognizing, engulfing and killing microorganisms.[11]

Role Of Neutrophils In Innate Host Defence

a) CHEMOTAXIS

Circulating neutrophils can be quickly mobilized to infection or inlammation sites through a systematically controlled process known as transendothelial migration.[12] This leukocyte adhesion cascade is positive regulated by tissue-derived cytokines and by tissue-derived chemokines. Once neutrophils move into tissues, they follow chemoatractant gradients to reach infection or inlammation sites through a process called chemotaxis. Some chemoatractants for neutrophils are activated by complement components, such as the anaphylatoxin C5a, and bacterial components, such as formyl-methionyl-leucyl-phenylalanine (fMLF).[13]

b) PHAGOCYTOSIS

Phagocytosis occurs when the neutrophil encounters the bacteria. Phagocytosis is greatly enhanced by coating of the bacteria with antibody or complement. These coating molecules (collectively called opsonins) facilitate binding and internalization via cell surface receptors including Fc receptors (receptors for the Fc fragment of IgG) and receptors for complement, specifically CR1and CR3.[14] During phagocytosis, the phagosome fuses with lysosomes to become phagolysosomes, within which bacteria are killed and fragmented by a variety of toxic substances, antimicrobial agents and enzymes. The bacteria are killed by a mechanism termed as intracellular killing which results in sequestration of the enzymes responsible for bacterial cell death. Killing can also occur through release of the granules into the tissues in the vicinity of the invading bacteria. This killing is termed as extracellular killing.[15]

Antigen Presentation

If the early lesion persists without resolution, bacterial antigens are processed and presented by lymphocytes, macrophages and dendritic cells. Broadly, two different subsets of lymphocytes have evolved to recognize extracellular and intracellular pathogens after being presented with antigens by the innate immune cells: T-lymphocytes and B-lymphocytes.[16] B-lymphocytes have immunoglobulin molecules on their surface, which function as antigen receptors. Activation of the T-cell receptor requires the major histocompatibility complex, which is also a member of the immunoglobulin superfamily.

Two classes of major histocompatibility complex molecules are required for the activation of distinct subsets of T-cells. Various T-cell subsets kill infected target cells and activate macrophages, B-cells and other T-cells. Thus, T-cells are essential for the regulation of both humoral and cell-mediated responses.[17] Classically, T-lymphocytes have been classified into subsets based on the cell-surface expression of CD4 or CD8 molecules. CD4+ T-cells (T-helper cells) were initially subdivided into two subsets, designated T-helper 1 and T-helper 2, on the basis of their pattern of cytokine production.[18]

Activation of B-cells is an important step in the maturation of the antibody response. This event is mediated mainly by the tumor necrosis factor family of proteins and their receptors.[19] In addition to their role in presenting antigen, B-cells also function as effectors, through cytokine secretion, lysosomal components, reduced oxygen metabolites, nitric oxide and antibodies. This is also important because in severe periodontal lesions, B-cells are the predominant antigen-presenting cells, suggesting that B-cell antigen presentation may allow further activation and clonal expansion of already activated T-cells.[20]

Adaptive Immunity

The adaptive immunity is activated when there is a breach in epithelial barrier, with its antimicrobial peptides and other components of innate systems. The immune response in periodontal disease is governed by the net effect of T-helper 1 (Th1) and T-helper 2 (Th2) cytokines.[21,22] The differentiation of Th1 and Th2 T cell subsets is determined by antigen, nature of the antigen-presenting cell and co-stimulatory molecules.[23] IL-18, as a cofactor with IL-12, is able to enhance the maturation of naive T cells to Th1 cells. Th1 cytokines include interleukin-2 and Interferon-γ and promote cell-mediated immunity, while the Th2 cytokine, interleukin-4, suppresses cell-mediated responses and enhances humoral immunity.[24]

However, there are controversial data about the Th1/Th2 immune response in periodontal disease. Studies over the past decade or so have supported the hypothesis

that Th1 cells are associated with the stable lesion and Th2 cells are associated with disease progression.[25-29] However, other studies have reported a predominance of Th1-type cells or reduced Th2 responses in diseased tissues.[30-32] Recently, a new subset of T-helper cells, Th17 cells, characterized by the production of interleukin-17, has been described. This subset may have both destructive and protective effects in periodontal diseases.[33,34]

On the other hand, the integrity of bone tissues depends on the interdependency between the osteoclasts and osteoblasts. The major regulatory mechanism of osteoclast activity is modulated by three novel members of TNF family of receptors, RANK (receptor activator of nuclear factor-β), osteoprotegerin (OPG) and the RANK ligand (RANKL).[35] RANK is expressed on osteoclasts and its precursors, while RANKL is expressed particularly on osteoblasts under homeostatic conditions. Interactions between RANK and RANKL are required for the differentiation and activation of osteoclast precursor cells to osteoclasts. OPG, a soluble decoy receptor produced by osteobalsts, marrow stromal cells and other cells, strongly inhibits bone resorption by preventing RANK-RANKL interaction.

RANKL also induces the production of some substances, such as MCP-1/CCL2, which could contribute to bone resorption.[36] Osteoblasts are found to express chemokine receptors during synthesis, which can modulate their function through the binding of chemokines. Additionally, an osteoclast can produce important chemokines which are involved in the recruitment of neutrophils and different lymphocyte subsets, suggesting a role for osteoblasts in the development of the inflammatory immune reaction.[37] Furthermore, the production of chemokines, with the consequent chemoattraction of inflammatory cells, may contribute to the disruption of bone homeostasis, resulting in bone resorption.

Conclusion

In this review, a brief introduction of periodontal disease, focusing on the participation of host immune system including both innate and adaptive systems, which may interfere in the development and progression of the periodontal disease, was described. The available data show that the host response is critical in protecting the periodontium from the pathological sequelae of bacterial colonization and invasion. However, till date no consensus regarding the pattern of the immune response in controlling the periodontal disease has been documented. Therefore, more researches are warranted to understand the intricacies of the immunological background of periodontal disease which will enable new treatment paradigms and prevention strategies.

References

1. Page RC, Schroder HE. Pathogenesis of inflammatory periodontal disease: A summary of current work. Lab Invest 1976; 4: 235-49
2. Lindhe J, Hamp SE, Loe H. Experimental periodontitis in the beagle dog. J Periodontal Res 1974: 8: 1-10.
3. Albandar JJ, Brown LJ, Loe H. Clinical features of early-onset periodontitis. J Am Dent Assoc 1997; 128: 1393-99.
4. Genco RJ. Host responses in periodontal diseases: Current concepts. J Periodontol 1992: 63: 338-58.
5. Page RC, Kornman KS. The pathogenesis of human periodontitis: An introduction. Periodontol 2000 1997: 14: 9-11.
6. Hancock RE, Scott MG. The role of antimicrobial peptides in animal defenses. J Clin Periodontol 2000; 97(16): 8856-61.
7. Lien E, Sellati TJ, Yoshimura A, Flo TH, Rawadi G, Finberg RW, et al. Toll-like receptor 2 functions as a pattern recognition receptor for diverse bacterial products. J Biol Chem 1999; 274(47): 33419-25.
8. Brightbill HD, Libraty DH, Krutzik SR, Yang RB, Belisle JT, Bleharski JR, et al. Host defense mechanisms triggered by microbial lipoproteins through toll-like receptors. J Immunol 1999; 285(5428): 732-6.
9. Takeda K, Kaisho T, Akira S. Toll-like receptors. J Immunol 2003; 21(1): 335-76
10. Sugawara Y, Uehara A, Fujimoto Y, Kusumoto S, Fukase K, Shibata K, et al. Toll-like receptors, NOD1, and NOD2 in oral epithelial cells. J Dent Res 2006; 85(6): 524-9.
11. Mocsai A: Diverse novel functions of neutrophils in immunity, inflammation and beyond. J Exp Med 2013; 210: 1283-99.
12. Amulic B, Cazalet C, Hayes GL, Mezler KD, Zychlinsky A. Neutrophil function: From mechanisms to disease. Annu Rev Immunol 2012; 30: 459-89.
13. Summers C, Rankin SM, Condlife AM, Singh N, Peters AM, Chilvers ER. Neutrophil kinetics in health and disease. Trends Immunol 2010; 31: 318-24.
14. Faurschou M, Borregaard N. Neutrophil granules and secretory vesicles in inflammation. Microbes Infect 2003; 5: 1317-27.
15. Sengelov H, Follin P, Kjeldsen L, Lollike K, Dahlgren CNB. Mobilization of granules and secretory vesicles during in vivo exudation of human neutrophils. J Immunol 1995; 154: 4157-65.
16. Gemmell E, Carter CL, Hart DN, Drysdale KE, Seymour GJ. Antigen-presenting cells in human periodontal disease tissues. Oral Microbiol Immunol 2002; 17(6): 388-93.
17. Cekici A, Kantarci A, Hasturk H, Van Dyke TE. Inflammatory and immune pathways in the pathogenesis of periodontal disease. Periodontol 2000. 2014; 64(1): 57-80.
18. Gemmell E, Yamazaki K, Seymour GJ. The role of T cells in periodontal disease: homeostasis and autoimmunity. Periodontol 2000. 2007; 43(1): 14-40.

19. Mackler BF, Frostad KB, Robertson PB, Levy BM. Immunoglobulin bearing lymphocytes and plasma cells in human periodontal disease. J Periodontal Res 1977; 12(1): 37-45.
20. Taubman MA, Valverde P, Han X, Kawai T. Immune response: The key to bone resorption in periodontal disease. Journal Periodontol. 2005; 76: 2033-41.
21. Taubman MA, Kawai T. Involvement of T-lymphocytes in periodontal disease and in direct and indirect induction of bone resorption. Crit Rev Oral Biol Med 200; 12(2): 125-35.
22. Nakajima T, Ueki-Maruyama K, Oda T, Ohsawa Y, Ito H, Seymour GJ, et al. Regulatory T-cells infiltrate periodontal disease tissues. J Dent Res 2005; 84(7): 639-43.
23. Eastcott JW, Yamashita K, Taubman MA, Harada Y, Smith DJ. Adoptive transfer of cloned T helper cells ameliorates periodontal disease in nude rats. Oral Microbiol Immunol 1994; 9(5): 284-9.
24. Yamashita K, Eastcott JW, Taubman MA, Smith DJ, Cox DS. Effect of adoptive transfer of cloned Actinobacillus actinomycetemcomitans-specific T helper cells on periodontal disease. Infect Immun 1991; 59(4): 1529-34.
25. Aoyagi T, Sugawara-Aoyagi M, Yamazaki K, Hara K. Interleukin 4 (IL-4) and IL-6-producing memory T-cells in peripheral blood and gingival tissues in periodontitis patients with high serum antibody titers to Porphyromonas gingivalis. Oral Microbiol Immunol 1995: 10: 304-10.
26. Bartova J, Kratka Opatrna Z, Prochazkova J, Krejsa O, Duskova J, Mrklas L, et al. T helper type 1 and Th2 cytokine profile in patients with early onset periodontitis and their healthy siblings. Mediators Inflamm 2000: 9: 115-20.
27. Manhart SS, Reinhardt RA, Payne JB, Seymour GJ, Gemmell E, Dyer JK, et al. Gingival cell IL-2 and IL-4 in early-onset periodontitis. J Periodontol 1994: 65: 807-13.
28. Gemmell E, Seymour GJ. Cytokines and T cell switching. Crit Rev Oral Biol Med 1994: 5: 249-79.
29. Lappin DF, MacLeod CP, Kerr A, Mitchell T, Kinane DF. Anti-inflammatory cytokine IL-10 and T cell cytokine profile in periodontitis granulation tissue. Clin Exp Immunol 2001: 123: 294-300.
30. Ebersole JL, Taubman MA. The protective nature of host responses in periodontal diseases. Periodontol 2000 1994: 5: 112-41
31. Salvi GE, Brown CE, Fujihashi K, Kiyono H, Smith FW, Beck JD, et al. Inflammatory mediators of the terminal dentition in adult and early onset periodontitis. J Periodontal Res 1998: 33: 212-25.
32. Takeichi O, Haber J, Kawai T, Smith DJ, Moro I, Taubman MA. Cytokine profiles of T-lymphocytes from gingival tissues with pathological pocketing. J Dent Res 2000: 79: 1548-55.
33. Gaffen SL, Hajishengallis G. A new inflammatory cytokine on the block: re-thinking periodontal disease and the Th1/Th2 paradigm in the context of Th17 cells and IL-17. J Dent Res 2008; 87(9): 817-28.
34. Adibrad M, Deyhimi P, Ganjalikhani Hakemi M, Behfarnia P, Shahabuei M, et al. Signs of the presence of Th17 cells in chronic periodontal disease. J Periodontal Res 2012; 47(4): 525-31.
35. Takahashi N, Udagawa N, Suda T. A new member of tumor necrosis factor ligand family, ODF/OPGL/TRANCE/RANKL, regulates osteoclast differentiation and function. Biochem Biophys Res Commun 1999: 256: 449-55.
36. Lorenzo J. Interactions between immune and bone cells: New insights with many remaining questions. J Clin Invest 2000: 106: 749-52.
37. Liu D, Xu JK, Figliomeni L, Huang L, Pavlos NJ, Rogers M, et al. Expression of RANKL and OPG mRNA in periodontal disease: Possible involvement in bone destruction. Int J Mol Med 2003: 11: 17-21.

Address of Correspondence

Dr. Vinoth Kumar. B.Na,
Department of Periodontology,
Indira Gandhi Institute of Dental Sciences,
Email id: vinothmessi@gmail.com
Phone no: 9843353089

Authors

[1]Final year post graduate student, Department of Periodontology, Indira Gandhi Institute of Dental Sciences.

[2]Senior Lecturer, Department of Periodontology, Saveetha Dental College and Hospitals, Chennai.

[3,4]Final year post graduate student, Department of Periodontology, Indira Gandhi Institute of Dental Sciences.

[5]Final year post graduate student, Department of Periodontology, Indira Gandhi Institute of Dental Sciences.

How to cite this article : Vinoth Kumar. B.Na, Arvina R, Sivaranjani. K S, Hema P, Arun Varghese R. Role of Immunology in Periodontal Disease: A Brief Review. Journal of Scientific Dentistry 2018;8(2):25-8

Source of support : Nil, **Conflicts of Interest :** None declared