Review Article

The role of interleukin-1 in syndromes: Periodontal manifestation of systemic diseases

D. Shruthi[1], Caroline Annette Jacob[1], Antonette Rhea[2]

ABSTRACT

Periodontal disease is caused by dental plaque biofilms. Periodontitis is a common disease that causes tooth loss, and chronic inflammation induced by bacterial infection which is the major cause of periodontium destruction. The treatment for periodontitis depends on removal of periodontopathogens and their toxic products. Interleukin-1 (IL-1) is the prototypic pro-inflammatory cytokine. There are two kinds of IL-1, IL-1alpha and IL-1beta, and in most research, their biological sports are indistinguishable. IL-1 affects nearly every cell type, frequently inflammatory cytokine, tumor necrosis factor. Since IL-1 can upregulate host defenses and feature as an immunoadjuvant, IL-1 is a tremendously inflammatory cytokine. The objective of this review is to understand and provide information about the role of IL-1 in syndromes periodontal manifestation of periodontal diseases and update knowledge for further advancement in future. The aim of this review is to provide comprehensive information about the role of IL-1 in syndromes periodontal manifestation of systemic diseases and to understand the role of IL-1 in syndromes periodontal manifestation of systemic diseases.

KEY WORDS: Cytokines, Fibroblast, Integrin, Leukocyte, Prostaglandins

INTRODUCTION

Periodontitis is a chronic bacterial infection of the supporting structures of the teeth as a result of dental plaque formation. The host response to infection has a major role in determining the extent and severity of periodontal disease. The host immune response to bacteria causes progression of the disease that leads to destruction of the connective tissue and alveolar bone.[1] Systemic factors modify periodontitis principally through their effects on the normal immune and inflammatory mechanisms.[2] The inflammatory process is regulated by an orchestrated network of cytokines and chemokines.[3] Interleukin 1 (IL-1) plays an important role in the pathogenesis of periodontitis through its involvement in the regulation of the host's inflammatory response. The genes that encode for IL-1 production have recently received most attention as potential predictors of periodontal disease progression.[4] IL-1 is a monokine that exerts biological effects on a variety of target cells *in vivo* and *in vitro*.[5] The subtypes of IL-1 are IL-1α and IL-1β. These subtypes upregulate prostaglandin E2 (PGE2) and matrix metalloproteinase (MMP) and also constitutively promote the loss of connective tissue and bone in periodontal disease. Vital functions such as immune cell recruitment, cell proliferation, tissue destruction, bone resorption, and vascular smooth muscle cell contraction are all affected by IL-1.[6] Several studies have also reported an association between IL-1 polymorphisms and periodontitis as well as cardiac disease.[7]

Access this article online	
Website: jprsolutions.info	ISSN: 0975-7619

Periodontitis in Syndromes

Periodontal involves inflammatory changes that result in bone loss and exfoliation of teeth. The histological change's reports show marked chronic inflammation of the lateral wall of the pocket with infiltration of predominantly plasma cell and altered cementum. Bacterial studies identified in dental plaque in a case of Papillon–Lefevre syndrome have revealed a similarity to the bacterial flora seen in chronic periodontitis.[8] Periodontal disease in Down syndrome (DS) is characterized by the rapid

[1]Department of Periodontics, Saveetha Dental College, Saveetha Institute of Medical and Technical Sciences, Saveetha University, Chennai, Tamil Nadu, India, [2]Department of Prosthodontics, Saveetha Dental College, Saveetha Institute of Medical and Technical Sciences, Saveetha University, Chennai, Tamil Nadu, India

***Corresponding author:** Antonette Rhea, Department of Prosthodontics, Saveetha Dental College, Saveetha Institute of Medical and Technical Sciences, Saveetha University, 162, Poonamallee High Road, Chennai – 600 077, Tamil Nadu, India. Phone: +91-9176645343. E-mail: arhea.a@gmail.com

Received on: 25-07-2018; Revised on: 26-08-2018; Accepted on: 28-09-2018

progression of periodontal with substantial plaque accumulation, frequently associated with acute necrotizing lesions.[8] In case of leukocyte adhesion deficiency (LAD), extremely acute inflammation and proliferation of the gingival tissues with rapid destruction of bone are seen which may be due to quantitative and qualitative defects in peripheral blood neutrophils and monocytes.[8]

IL-1 in DS

DS, a frequently encountered genetic disorder, has been associated with periodontal diseases and prolonged wound healing.[9] DS is the result of triplication of chromosome 21 (trisomy 21) causing various degrees of mental and physical defects including neuropathological and cognitive changes seen in Alzheimer's disease (AD).[10] Neuroinflammatory changes such as the rapid proliferation of activated glia overexpressing a chromosome 2 gene product: (IL-1) in developing human brains affected with DS indicates that early events in Alzheimer pathogenesis are driven by cytokines.[10] IL-1 has also been seen to be overexpressed up to 30 times in glial cells throughout the lifespan of individuals with DS, accelerating neurodegenerative in the pathogenesis of DS-related AD.[10] Subjects with DS have also demonstrated higher concentration of IL-1β, IL-4, IL-6, IL-10, IL-12, interferon gamma, and tumor necrosis factor alpha (TNF-α) in gingival crevicular fluid (GCF) compared to controls.[11] Learning defects could be the result of the lower levels of granulocyte macrophage colony-stimulating factor (GM-CSF), IL-1β, and macrophage inflammatory protein (MIP-1α) in the hippocampus when compared with the euploid (control) animals as the three cytokines interact with the N-methyl-D-aspartic acid receptors which are responsible for neuromodulatory functions.[12] In addition, DS thymuses also display cortical depletion and abnormal thymocyte differentiation. IL-4, without mitogen, induces a dose-dependent proliferation of both DS and control thymocytes comparable to that induced by IL-2 but greater than that mediated by IL-1β in the absence of mitogen.[13]

The DS candidate region-1 gene (DS Critical Region 1 [DSCR1] also known as regulator of calcineurin 1) situated close to DSCR contains genes responsible for many features of DS. Coimmunoprecipitation analyses of HEK293 cells, a cell line derived from human embryonic kidney cells grown in tissue culture, revealed that DSCR1-1S interacted with Tollip, an IL-1 receptor-associated kinase 1 (IRAK-1) inhibitor, leading to the dissociation of IRAK-1 from Tollip. Similarly, both DSCR1-1S and Tollip interacted with TNF receptor-associated factor 6 (TRAF6), with DSCR1 reducing interaction between Tollip and TRAF6. DSCR1-1S also stimulated IL-1 receptor-mediated signaling pathways, transforming growth factor beta-activated kinase-1 activation, nuclear factor kappa B (NF-κB) transactivation, and IL-8 production, all downstream consequences of IL-1R activation. DSCR1-1S isoform, therefore, positively modulates IL-1R-mediated signaling pathways by regulating Tollip/IRAK-1/TRAF6 complex formation.[14] However, the level of IL-1β was not seen to be significantly higher between DS individuals and a control group but displayed an increase of PGE2 when detected in GCF, which may be responsible for the pathogenesis of the periodontal disease frequently seen in these patients.[15]

Reactive oxygen species (ROS) have also been considered to mediate inflammation in DS. ROS have been demonstrated to activate NF-κB and IL-8 induction in DSCR1-transfected cells through a calcium-dependent pathway, which, in turn, is augmented by IL-1β. The reduction of ROS levels with antioxidant agents may be beneficial in preventing DS-associated inflammation by suppressing cytokine expression.[16] DS subjects were given antioxidant therapy over 6 months, after 12 months (i.e., after the interruption of antioxidant therapy for 6 months) (t2) and subsequently 6 months later with antioxidant supplementation (t3). At t2, DS patients showed increased glutathione peroxidase and gamma-glutamyltransferase activities along with elevated uric acid and thiobarbituric acid reactive substance levels. No changes were detected in the following enzymes: Superoxide dismutase, catalase, glutathione S-transferase, glucose-6-phosphate dehydrogenase, and myeloperoxidase. However, there was a reduction in the levels of the following levels: Glutathione (GSH), Vitamin E, PC, TNF-α, and IL-1β. These results indicated that the antioxidant intervention used increased the systemic oxidative damage in DS patients even after a relatively long period of the cessation of antioxidant therapy.[17]

IL-1 in Papillon–Lefevre Syndrome

Papillon–Lefevre syndrome (PLS) is an autosomal recessive genetic disorder caused by a deficiency in cathepsin C. Mutations in the cathepsin C gene (CTSC) have been identified as causal for the syndrome, which includes prepubertal periodontitis (PP) while some CTSC mutations are causal for PP without PLS.[18] Interestingly, no relationship has been demonstrated between CTSC mutations and other forms of periodontitis. Genetic polymorphism in a candidate gene approach has been explored as risk factors for periodontitis. There is limited evidence that some polymorphisms in the genes encoding for IL-1, Fc gamma receptors, IL-10, and the Vitamin D receptor may be associated with periodontitis in certain ethnic groups.[18] This may be because the studies available may be underpowered and do not adequately take into account other pertinent risk factors for periodontitis.

Recommendations include the use of larger cohorts, clearly define phenotypes and determination of confounders. In addition to the candidate gene approach, alternative strategies need to be considered to elucidate the gene variations that confer risk for periodontitis.[18]

Ullbro observed significantly higher levels of IL-1β ($P < 0.001$) and MMP-8 ($P < 0.05$) among PLS patients when compared with their controls, while the opposite was found for IL-8 ($P < 0.05$) and MMP-1 ($P < 0.001$), but individual variations were identified in both the groups. When comparing the expression of cytokines, MMPs, and tissue inhibitor of matrix metalloproteinase 1 in PLS patients with clinically active and non-active periodontitis, patients with non-active PLS showed significantly higher values of IL-1β than the patients with active periodontal disease (ANOVA, $P < 0.01$). The study was not able to demonstrate a clear-cut pathognomonic expression of cytokines or MMPs in patients with PLS, indicating the need for further studies on cytokine and MMP production in such individuals.[19]

IL-8 and IL-1α- and IL-1β-positive cells have also been detected from the gingival tissue of a PLS patient. However, there was no apparent dysfunction in the phagocytosis of the peripheral blood polymorphonuclear neutrophils that could be observed, suggesting that these cytokines may be responsible for modulating the process of rapidly progressive periodontitis for patient with PLS.[20]

IL-1 in Leukocyte Adhesion Deficiency

LAD, a rare autosomal recessive disorder, is characterized by immunodeficiency resulting in recurrent infections. The serum cytokine levels and their expression of mRNA on neutrophils from a bone marrow transplanted heifer with LAD were evaluated.[21] The concentration of IL-1β in serum ranged from 15.8 to 321.7 ng/ml, and the maximum concentration occurred at the time which coincided with a peak in IL-6. mRNAs for IL-1β, IL-6, IL-8, and GM-CSF were increased in neutrophils from the affected heifer were compared to the controls and was shown to have persistent hypergammaglobulinemia that was associated with enhanced mRNA expression for IL-6 and its serum levels. These findings suggest that humoral immunity in LAD is activated and the production of neutrophils appears to be enhanced under the incapability of β integrin-mediated functions of phagocytic cells.[21]

Neutrophil elastase (NE) remains a controversial player in the process of leukocyte transmigration and much of this controversy stems from conflicting reports on the effects of NE inhibitors. In a study, NE (-/-) mice were used to investigate the role of NE in leukocyte migration by intravital microscopy, induced by the particulate stimulus, zymosan.[22] Reductions in the levels of IL-1β and MIP-1α as well as an impairment in phagocytosis were observed in NE deficient mice which may also be responsible for impaired neutrophil function in LAD.

The CD11/CD18 complex of leukocyte adhesion molecules has been shown to bind LPS on the surface of Gram-negative bacteria and LPS-coated erythrocytes.[23] LPS stimulates leukocytes to secrete TNF-α and IL-1β, and enhances the release of oxygen radicals such as the superoxide anion. Surprisingly, monocytes and macrophages from CD18-deficient patients produce both normal amounts of IL-1β and TNF-α in response to LPS and display normal priming for enhanced release of superoxide anion in response to LPS.[23]

Neutrophil-dependent adherence induced by n-formylmethionyl-leucyl-phenylalanine occurred solely through the CD11/CD18-dependent mechanism, whereas endothelial-dependent adherence induced by a 4-h pretreatment with IL-1, TNF, or LPS involved both CD11/CD18-dependent and independent mechanisms. CD11/CD18-deficient neutrophils isolated from a patient with LAD maintained the ability to adhere to LPS-pretreated human umbilical vein endothelial cells (HEC) in the presence of Ca2+ only, indicating that this mechanism of adherence involves a receptor on the neutrophil different from that of CD11/CD18. Furthermore, the disappearance of the CD11/CD18 independent, but not of the CD11/CD18-dependent mechanism of adherence, in HEC treated with TNF for 24 h suggests that the two mechanisms of neutrophil adherence also involve distinct inducible endothelial-leukocyte adhesion molecules.[24]

IL-1 in Ehlers–Danlos Syndrome

In Ehlers–Danlos syndrome, gene mutations encode for fibrous proteins or enzymes. This causes an alteration in the collagen structure and function, leading to periodontal destruction, especially Type VIII collagen.[8] Decorin belongs to a family of small leucine-rich dermatan sulfate proteoglycans that are involved in the control of matrix organization and cell growth. The reduced decorin expression of fibroblasts patients with Ehlers–Danlos syndrome may be due to abnormalities in the regulatory regions, which is responsible for the IL-1beta stimulation.[25] Further studies may be required to elucidate the role of IL-1 in this syndrome.

CONCLUSION

It is well documented that DS individuals are more susceptible to periodontal disease than unaffected individuals and this may be largely attributed to the

interplay of the many cytokines involved including IL-1.[26] Severe periodontal disease is also a key finding in individuals with Papillon–Lefevre syndrome, but evidence seems contradictory when correlating the role of IL-1 in the pathogenesis of the inflammatory process. Data though limited in LAD and Ehlers–Danlos syndrome appear to indicate that IL-1 influences cellular and connective tissue function. Thus, the role of IL-1 in these syndromes may also be associated with the progression of periodontal disease seen in affected individuals.

REFERENCES

1. Mootha A, Malaiappan S, Jayakumar ND, Varghese SS, Thomas JT. The effect of periodontitis on expression of interleukin-21: A systematic review. Int J Inflamm 2016;2016:1-9.
2. Kinane DF, Marshall GJ. Periodontal manifestations of systemic disease. Aust Dent J 2001;46:2-12.
3. Lakshmanan R, Jayakumar ND, Sankari M, Padmalatha O, Varghese S. Estimation of pentraxin-3 levels in the gingival tissues of chronic and aggressive periodontitis participants: An *in vivo* study. J Periodontol 2014;85:290-7.
4. Grigoriadou ME, Koutayas SO, Madianos PN, Strub JR. Interleukin-1 as a genetic marker for periodontitis: Review of the literature. Quintessence Int 2010;41:517-25.
5. Hanazawa S, Nakada K, Ohmori Y, Miyoshi T, Amano S, Kitano S, *et al.* Functional role of interleukin 1 in periodontal disease: Induction of interleukin 1 production by *Bacteroides gingivalis* lipopolysaccharide in peritoneal macrophages from C3H/HeN and C3H/HeJ mice. Infect Immun 1985;50:262-70.
6. Kaarthikeyan G, Jayakumar ND, Padmalatha O, Sheeja V, Sankari M, Anandan B. Analysis of the association between interleukin -1β (+3954) gene polymorphism and chronic periodontitis in a sample of the South Indian population. Indian J Dent Res 2009;20:37-40.
7. Bashour L, Khattab R, Harfoush E. The role of interleukin-1 genotype in the association between coronary heart disease and periodontitis in a Syrian population. ISRN Dent 2013;2013:195678.
8. Carranza FA. Carranza's Clinical Periodontology. Vol. 9. St. Louis, Mo: Saunders Elsevier; 2002. p. 1033.
9. Iwamoto T, Yamada A, Yuasa K, Fukumoto E, Nakamura T, Fujiwara T, *et al.* Influences of interferon-gamma on cell proliferation and interleukin-6 production in down syndrome derived fibroblasts. Arch Oral Biol 2009;54:963-9.
10. Mrak RE, Griffin WS. Trisomy 21 and the brain. J Neuropathol Exp Neurol 2004;63:679-85.
11. Tsilingaridis G, Yucel-Lindberg T, Modéer T. T-helper-related cytokines in gingival crevicular fluid from adolescents with down syndrome. Clin Oral Investig 2012;16:267-73.
12. Roberson R, Kuddo T, Horowitz K, Caballero M, Spong CY. Cytokine and chemokine alterations in down syndrome. Am J Perinatol 2012;29:705-8.
13. Murphy M, Hyun W, Hunte B, Levine AD, Epstein LB. A role for tumor necrosis factor-alpha and interferon-gamma in the regulation of interleukin-4-induced human thymocyte proliferation *in vitro*. Heightened sensitivity in the down syndrome (trisomy 21) thymus. Pediatr Res 1992;32:269-76.
14. Lee JY, Lee HJ, Lee EJ, Jang SH, Kim H, Yoon JH, *et al.* Down syndrome candidate region-1 protein interacts with tollip and positively modulates interleukin-1 receptor-mediated signaling. Biochim Biophys Acta 2009;1790:1673-80.
15. Barr-Agholme M, Krekmanova L, Yucel-Lindberg T, Shinoda K, Modéer T. Prostaglandin E2 level in gingival crevicular fluid from patients with down syndrome. Acta Odontol Scand 1997;55:101-5.
16. Ko JW, Lim SY, Chung KC, Lim JW, Kim H. Reactive oxygen species mediate IL-8 expression in down syndrome candidate region-1-overexpressed cells. Int J Biochem Cell Biol 2014;55:164-70.
17. Parisotto EB, Giaretta AG, Zamoner A, Moreira EA, Fröde TS, Pedrosa RC, *et al.* Persistence of the benefit of an antioxidant therapy in children and teenagers with down syndrome. Res Dev Disabil 2015;45-46:14-20.
18. Loos BG, John RP, Laine ML. Identification of genetic risk factors for periodontitis and possible mechanisms of action. J Clin Periodontol 2005;32 Suppl 6:159-79.
19. Ullbro C, Crossner CG, Nederfors T, Parhar R, Al Mohanna F, Meikle MC, *et al.* Cytokines, matrix metalloproteinases and tissue inhibitor of metalloproteinases-1 in gingival crevicular fluid from patients with papillon-lefèvre syndrome. Acta Odontol Scand 2004;62:70-4.
20. Kabashima H, Yoneda M, Nagata K, Nonaka K, Hirofuji T, Maeda K, *et al.* The presence of cytokine (IL-8, IL-1alpha, IL-1beta)-producing cells in inflamed gingival tissue from a patient manifesting papillon-lefevre syndrome(PLS). Cytokine 2002;18:121-6.
21. Nagahata H, Hagiwara K, Higuchi H, Kirisawa R, Iwai H. Analysis of serum cytokine profile in a holstein heifer with leukocyte adhesion deficiency which survived for long period. J Vet Med Sci 2002;64:683-7.
22. Young RE, Thompson RD, Larbi KY, La M, Roberts CE, Shapiro SD, *et al.* Neutrophil elastase (NE)-deficient mice demonstrate a nonredundant role for NE in neutrophil migration, generation of proinflammatory mediators, and phagocytosis in response to zymosan particles *in vivo*. J Immunol 2004;172:4493-502.
23. Wright SD, Detmers PA, Aida Y, Adamowski R, Anderson DC, Chad Z, *et al.* CD18-deficient cells respond to lipopolysaccharide *in vitro*. J Immunol 1990;144:2566-71.
24. Dobrina A, Schwartz BR, Carlos TM, Ochs HD, Beatty PG, Harlan JM, *et al.* CD11/CD18-independent neutrophil adherence to inducible endothelial-leucocyte adhesion molecules (E-LAM) *in vitro*. Immunology 1989;67:502-8.
25. Wu J, Utani A, Endo H, Shinkai H. Deficiency of the decorin core protein in the variant form of ehlers-danlos syndrome with chronic skin ulcer. J Dermatol Sci 2001;27:95-103.
26. Khocht A, Heaney K, Janal M, Turner B. Association of interleukin-1 polymorphisms with periodontitis in down syndrome. J Oral Sci 2011;53:193-202.

Source of support: Nil; Conflict of interest: None Declared