Review Article

Role of Interleukin-17 in Immunopathology of Chronic and Aggressive Periodontitis

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ABSTRACT

Interleukin-17 (IL-17) is a pro-inflammatory cytokine which is derived from T-cells. It is a strong agent of inflammation in inflammatory condition including the periodontitis. Several studies have focused on finding the role of IL-17 in the initiation and progression of chronic periodontitis and aggressive periodontitis (AgP). The aim of this review is to analyze the role of IL-17 in immunopathology of chronic periodontitis and AgP. An electronic literature search was conducted in the PubMed database using keywords aggressive, chronic, cytokine, IL-17, and periodontitis. A total of 152 publications were identified, wherein 43 studies fulfilled the inclusion criteria which were included and data extraction was done. Findings of these studies indicate that IL-17 is the important cytokine which plays a crucial role in the initiation and progression of periodontitis. More studies in all ethnic groups are necessary and hence that the predictive value (cutoff) of IL-17 levels in chronic and AgP can be determined.

KEYWORDS: *Aggressive, chronic, cytokine, interleukin-17, periodontitis*

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INTRODUCTION

Cytokines are protein cells which play an important role in many physiological responses. Individual cytokine regulates physiological and pathological tissue reorganization, hematopoiesis, angiogenesis, and wound healing. They are extremely potent and act at picomolar concentration. It interacts with high-affinity-specific cell surface receptors. The response of a cell to a given cytokine depends on the type of cell, local concentrations, and other cell regulatory factors to which it is constantly exposed. Cytokines play an important role by controlling cellular interactions. Cytokines are produced by the cells such as macrophages/monocytes, dendritic cells, lymphocytes, neutrophils, endothelial cells and fibroblasts at the site of inflammation.[1,2]

Periodontitis is a chronic inflammatory condition which leads to the release of cytokines. It is further classified into chronic and aggressive periodontitis (AgP). AgP differs from chronic periodontitis in microbiological, immunological aspect, rate of disease progression and has been proven to have genetic and hereditary pattern.[3]

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It has been found that IL-17 plays a vital role in the progression of the periodontitis, but the role of the IL-17 is same in aggressive as well as chronic periodontitis. Therefore, the aim of this review is to analyze the role of IL-17 in the immunopathology of these two conditions.

METHODOLOGY

An electronic literature search was conducted in PubMed database using keywords aggressive, chronic, cytokine, interleukin-17 (IL-17), and periodontitis were done. A total of 152 publications were identified, wherein 43 studies fulfilled the inclusion criteria which were included, and data extraction was done. (a) Studies which were performed in AgP patients, chronic periodontitis patients using gingival crevicular fluid

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and periodontal tissues, (b) studies performed on the periodontal microorganism, inflammatory systemic condition in relation with IL-17, and (c) Effect of periodontal therapy on IL-17 were included to write review. Exclusion criteria included studies performed on smokers, diabetes mellitus, and saliva [Flow chart I].

Mechanism of Action of Cytokines

Cytokines communicate in network, first by activating each other followed by transmodulating cell surface receptors and finally by synergistic, additive, or antagonistic interactions on cell action.[4,5] The intensity, extent, and resolution of any inflammation depend on the shift in balance between the action of pro-inflammatory and anti-inflammatory cytokines.[6] The term "interleukins" have been replaced the term "cytokines" due to their role in communication between leukocytes.[7]

Some cytokines exhibit autocrine function (binding to the cell that produced them) or paracrine (binding to nearby cells) or endocrine (binding to distant cells). Cytokines may be pleiotropic, i.e., eliciting different biological activities on different cells.[7,8] Different cytokines are grouped into families with respect to genome location, gene, and protein structure. It is important to note that members of the same family do not necessarily exhibit similar biological effects.[9]

Cytokines are further classified into pro-inflammatory and anti-inflammatory cytokines and balance between them is crucial for determining disease initiation and progression.[10] Cytokines are considered as a key component to the pathogenesis of any inflammatory diseases and play an important role in the initiation, progression, and alternation in host modulation of any inflammatory disease including periodontal inflammation.[11-13] Lipopolysaccharide and other toxin products released by bacteria lead to the stimulation of host cells resulting in the release of cytokines. Cytokine network takes control over inflammatory mechanism to trigger or suppress tissue reactions.[14]

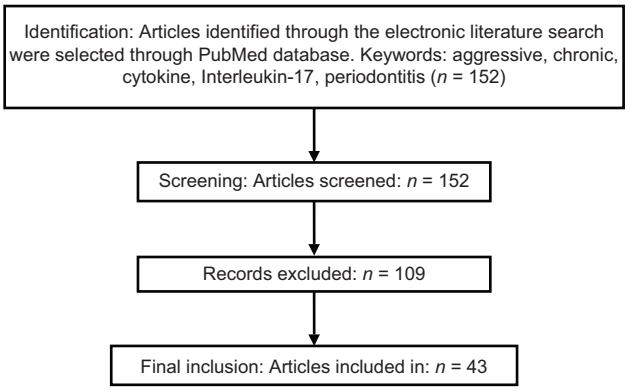
T-Cells and Interleukin-17

T helper (Th) cells are divided into Th1 and Th2 subtypes according to their cytokine profiles and have different functional properties.[15,16] Th1 cells activate cellular immunity and the production of pro-inflammatory cytokines. Th2 cells induce B-cell-mediated humoral immunity and anti-inflammatory cytokine patterns.[16,17] Recently, IL-17-producing cell named as Th17 was identified which is a subset of $CD4^+$ T-cells. Th-17 cell plays an important role in protective antibacterial host response.[18]

IL-17 is a pro-inflammatory cytokine and was first described as T-cell product in 1993.[19,20] The family consists of the following six members: IL-17A, B, C, D, E (IL-25), and IL-17F which are structurally associated. The genes for IL-17A and IL-17F are located on chromosome 6q. IL-17B gene is located on chromosome 5q. Genes for IL-17C, IL-17D, and IL-17E are located on chromosome 16q, 13q, and 14q arm, respectively.[17,21-24] IL-17 is 17-kd protein that is secreted as a dimer. IL-17 shares no sequence homology with other known mammalian proteins, and therefore, constitute as a specific cytokine family. IL-17 acts through cell-membrane receptors.[25,26] Various effects of interleukin -17 on cell populations in human body are mention in Table 1.

Role of Interleukin-17 on Other Cytokines

IL-17 is also responsible to stimulate other pro-inflammatory cytokines such as IL-1 β, IL-6, IL-8, prostaglandin E_2, and matrix metalloproteinases through the stimulation of epithelial, endothelial, and fibroblastic cells.[27,28] IL-17 appears to be inadequate to mount a potent inflammatory response by itself, but in



Flow Chart 1: Protocol for the identification of studies for review writing

Table 1: Effects of interleukin-17 on cell populations present in the human body[25]

IL-17 and its effects on cell populations:

- Monocytes/macrophages: Production of cytokine-TNF-α, IL-1, NO, PGE_2
- T-cells: IL-17 production
- Neutrophils: Progenitor differentiation, cytokine and chemokine production, maturation, activation
- Osteoblasts/osteoclasts: Cytokine production, differentiation, induction of RANKL, activation and maturation, matrix destruction, and matrix synthesis inhibition

TNF-α=Tumor necrosis factor alpha; IL-1=Interleukin-1; NO=Nitric oxide; PGE2=Prostaglandin E2; IL-17=Interleukin-17; RANKL=Receptor activator of nuclear factor kappa-B ligand

collaboration and/or synergism with other inflammatory cytokines, it accelerates the inflammation. IL-17 can induce a potent inflammatory cascade by increasing the expression of target genes.[29] IL-8 release is functionally important for neutrophil recruitment. IL-6 increases the release of elastase from human neutrophils *in vitro*.[30,31] IL-17 shares transcriptional pathways with IL-1 and tumor necrosis factor alpha. p38 and nuclear factor κB are the key transcriptional factors for IL-17 function.[25,26] IL-17 induces the production and release of colony-stimulating factors (CSFs) granulocyte and granulocyte-macrophage CSFs. Both CSFs are powerful anti-apoptotic survival factors for neutrophils.[32-35]

Effect of Interleukin-17 on Systemic Diseases

IL-17 has been associated with the pathogenesis of different types of systemic inflammatory disorders such as rheumatoid arthritis, psoriasis, systemic sclerosis, systemic lupus erythematosus and bowel disease.[36-38] It has been observed that the IL-17 level is increased in systemic lupus erythematosus patients. IL-17 plays a crucial role in host defense within the lungs by the stimulation of local release of neutrophil-mobilizing factors in resident cells.

Role of Interleukin-17 in Periodontitis

The initiation and progression of periodontal disease depends on complex interactions between periodontal bacteria and cells of immune system.[39-41] Studies have demonstrated that a number of pro-inflammatory cytokines are released in response to periodontal bacteria and their toxin products.[42,43] Andrukhov *et al*. suggested that due to differences in the bacterial profile in periodontitis can be associated with different cytokine profiles.[44]

It is generally acknowledged that control of the Th1/Th2 balance is central to the immunoregulation of periodontal disease.[45] It has been suggested that stable periodontal lesions are mediated by Th1 cells and progression of periodontitis reflects a shift towards Th2 cells,[46,47] and therefore, the pathogenesis of periodontitis is clinically considered as involving Th1/Th2 pattern. However, recently, studies have found that significantly increase in the level of IL-17 in periodontitis condition.

IL-17 is found in high amounts in periodontal disease.[48] IL-17 aggravates periodontal disease by activating gingival fibroblasts to produce inflammatory cytokines. There is abundant documentation that suggests major tissue destruction in periodontitis which results from the recruitment of host cells through the activation of monocytes/macrophages, lymphocytes, and fibroblasts cell.[47-49] IL-17 is more frequently detected in periodontitis patients than in gingivitis patients.[50] Takahashi *et al*. have suggested that IL-17 is produced in periodontitis, which may be involved in Th1 modulation and which increase inflammatory reactions through gingival fibroblast-derived mediators and thus, IL-17 has a potential role in the pathogenesis of the periodontal disease.[51] IL-17 has an action on alveolar bone cells. It has been documented that T-cells can be directly involved in bone metabolism through T-cell-derived cytokines which includes IL-17.[52,53] IL-17 has the ability to stimulate osteoclast cells and activate receptor activator of nuclear factor kappa-B ligand production by osteoblasts.[54,55]

AgP is generally seen in teenagers and young adult. It is the most severe form of periodontitis which can lead to significant periodontal inflammation and premature tooth loss in maximum number of cases at early age.[56] There is abundant literature suggesting aberrant polymorphonuclear leukocytes (PMN) function as a key pathogenic mechanism in AgP exhibiting defective *in vitro* PMN chemotactic response and enhanced oxidative metabolic responses.[56] Evidence suggest that the rate of bone destruction is about the three to four times faster than in chronic periodontitis. Early age of onset is one of the main characteristics features of AgP; however, patients with AgP are clinically healthy.[42] The amount of microbial deposits is inconsistent with disease severity and the presence of familial aggregation has been reported.[57]

IL-17 may play a significant role in AgP because of the functional impairment of PMN and because of the association of IL-17 pathways with the recruitment of neutrophils which results in enhanced inflammation and bone resorption.[58] It has been hypothesized that IL-17 has a key role in regulating neutrophils *in vivo* and neutrophils play a crucial role in controlling periodontal infection. Neutrophils are considered as the first line of defense against a broad range of periodontal pathogens. Functionally intact neutrophils are necessary for defense in any inflammatory condition. Patients suffering from defects in neutrophils function suffer from recurrent and severe infection including AgP. Neutrophils are also potentially harmful if turned against host tissue.[38] The constant phases of neutrophil mobilization are key components of innate immunity contributing to host defense.[59-62] Fossiez *et al*. have suggested that IL-17 activates the mobilization and *de novo* generation of neutrophils by granulocyte-CSFs, thereby bridging innate and adaptive immunity.[63] IL-17 is important for neutrophil homeostasis and therefore for periodontal health. Any alteration from normal neutrophil activity (in

terms of numbers or activation status) can potentially cause periodontitis.[64,65] The functional pathways of the IL-17 cells in periodontitis are still not sufficiently understood, and thus, more research is required.

There is abundance literature available with IL-17 levels in chronic periodontitis but miniscule information with IL-17 in relation to AgP cases. More studies in all ethnic groups are necessary which can be used in the development of individualized diagnostic and treatment plans of periodontitis, especially in case of AgP.

Conclusion

Periodontitis is multifactorial in nature. It is initiated by microorganisms and perhaps viruses and further affected by factors such as diet, smoking, stress, and environmental factors. It is also influenced by acquired systemic diseases which reduce or alter host response. Apart from this, the genetic factor can also be responsible for susceptibility to periodontitis.[3]

IL-17 plays an important role in periodontitis, but it shows some variations in the levels with respect to chronic periodontitis and AgP. This may be due to different microbiological profiles in periodontitis and defects in neutrophil actions in AgP. Further investigations with larger populations are needed to clarify the specific contribution of IL-17 in the immunopathology of AgP and chronic periodontitis. This will help for anti-IL-17 intervention in periodontitis cases and also to determine the predictive value (cutoff) of IL-17 levels in periodontitis for the diagnostic purpose. Anti-IL-17 intervention for systemic inflammatory conditions such as for rheumatoid arthritis, psoriasis, and ankylosing spondylitis as have already been performed.[66-70]

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Conflicts of interest

There are no conflicts of interest.

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