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INFLUENCE OF INTERLEUKIN-17 IN PERIODONTITIS

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ABSTRACT

Cytokines are protein cells that are involved in a variety of physiological responses. They have a picomolar concentration of action and are exceedingly powerful. Physiological and pathological tissue remodelling, haematopoiesis, angiogenesis, and wound healing are all regulated by individual cytokines. It binds to cell surface receptors with a high affinity for them. The type of cell, local concentrations, and other cell regulatory factors to which it is constantly exposed determine a cell's response to a given cytokine. The IL-17A isoform (also known as IL-17) is involved in nearly all IL-17-related studies in the field of periodontal disease. To comprehend the significance of IL-17 in periodontitis, it is necessary to first review the cytokines basic biology and the cells that form it. Because of its role in inflammatory disease, IL-17 is one of the most well studied cytokines in immunology. The aim of this review is to know the role of IL-17 in periodontal disease.

KEYWORDS: Cytokine, Basics biology of Interleukin-17, Periodontal disease, Complement and IL-17, Neutrophil homeostasis.

INTRODUCTION

Periodontitis is a persistent inflammatory infection marked by a large lymphocyte infiltrate into the periodontal lesions, resulting in periodontal disease which leads to release of various cytokines. This eventually results in the breakdown of periodontal tissues, including the Alveolar bone (Williams 1990). variations in CD4/CD8 T-cell ratios (Kinane et al. 1989). Reactions of autologous mixed lymphocytes (Kimura et al. 1991). Activation of polyclonal B cells (Tew et al. 1989). T cell role in the pathogenesis of Periodontal disease has been examined from a variety of perspectives, such as transformation of T-cell lesions to B-cell lesions (Seymour et al. 1979). Profiles of Th1/Th2 cytokines (Taubman et Al. 2001). Antigen-restricted immune responses (Ohyama et al. 1998). Berglundh et al. 2002).

Interleukin-2 (IL-2) is produced by Th1 cells and interferon (IFN)- gamma, which cause cellular immunity and generation of pro-inflammatory cytokines. (Yamamura et al. 1991). Cytokines regulate cellular connections and hence play a vital role. At the site of inflammation, cells such as macrophages/monocytes, neutrophils, dendritic cells, lymphocytes, fibroblasts and endothelial cells produce cytokines. Other names for cytokines are monokine (cytokines produced by monocytes), lymphokine (cytokines produced by lymphocytes), chemokine (cytokines with chemotactic activity), and interleukin (cytokines produced by interleukin) (cytokines made by one leukocyte and acting on other leukocytes).

Mechanism of action of cytokines

Cytokines communicate in a network, first activating one another, then transmodulating cell surface receptors, and eventually interacting with cells in synergistic, additive, or antagonistic ways.[2] Cytokines have the ability to act on the neighbouring cells (paracrine action), in some cases, distant cells (endocrine action) and on cells that release them (autocrine action). Pleiotropic cytokines are those that evoke diverse biological activity in distinct cells. Cytokines are significant components in the pathogenesis of any inflammatory disease, including periodontal inflammation. They play a critical role in the onset, progression, and alternation in host modulation of any inflammatory disease, including periodontal inflammation. Bacterial toxins such as lipopolysaccharide and other toxin products stimulate host cells, causing them to release cytokines. To initiate or repress tissue reactions, the cytokine network takes control of the inflammatory mechanism. Because of their involvement in leukocyte communication, the name "interleukins" has substituted the term "cytokines".[4]

The Concept of Anti-Inflammatory and Pro-Inflammatiory Cytokines

Proinflammatory and anti-inflammatory cytokines are two types of cytokines, and the balance between them is critical in determining disease onset and progression.[6] Any change in the balance between proinflammatory and anti-inflammatory cytokines affects the degree, extent, and resolution of any inflammation.[3] The idea that some cytokines are primarily responsible for inducing inflammation while others are responsible for suppressing inflammation is crucial to both cytokine biology and clinical practice. The hypothesis is based on the up-regulation of genes that code for the creation of tiny mediator molecules during inflammation. Type II phospholipase (PL) A2, cyclooxygenase (COX)-2, and inducible NO synthase are examples of proinflammatory genes. These genes code for enzymes that boost

the production of platelet-activating factor, leukotrienes, prostanoids, and nitric oxide (NO). Chemokines, which are short peptides (8,000 d) that enhance the transit of leukocytes from the circulation into the tissues, are another class of proinflammatory genes. The neutrophil chemoattractant IL-8 is the archetypal chemokine. Neutrophils are also activated by IL-8, causing them to degranulate and cause tissue injury.

Cytokine response to Inflammation and Infection

Interleukin (IL) is a term given to 18 different cytokines. Other cytokines, such as tumour necrosis factor (TNF), have preserved their original biological descriptions. IL-4, IL-10, and IL-13, for example, are powerful B cell activators. IL-4, IL-10, and IL-13, on the other hand, are also strong anti-inflammatory agents. They are anti-inflammatory cytokines because they decrease the genes that produce proinflammatory cytokines like IL-1, TNF, and chemokines. Another example of cytokines pleiotropic nature is interferon (IFN)-ϒ. IFN-ϒ, like IFN-α and IFN-β, has antiviral properties. IFN-ϒ also activates the pathway that leads to the production of cytotoxic T cells. IFN-ϒ, on the other hand, is classified as a proinflammatory cytokine since it increases TNF activity and produces nitric oxide (NO). As a result, categorizing cytokines should be done with an open mind, as each cytokine may operate differently depending on the biological process.

Interleukin 17: Basic biology and its role in immunity and inflammation

Interleukin-17(IL-17, also known as IL-17A) is a critical cytokine that connects T-cell activation to neutrophil recruitment, mobilization and activation. Innate immune cells and lymphocytes that produce Interleukin-17 are emerging as potential participants in the pathogenesis of rheumatoid arthritis, psoriasis and periodontal disease. The IL-17 gene was cloned from a mouse cytotoxic T lymphocyte hybridoma cDNA library in 1993[38] and the involvement of human IL-17 in inflammation was quickly established. However, after discovery of a developmentally differentiated CD4+ T helper subset that express IL-17 and drives tissue inflammation, IL-17 became the focus of immunological attention. Interleukin-17A is the first member of the cytokine family that encompasses IL-17B through IL-17F.[27]

Complement and IL-17

Both complement and IL-17 are involved in the regulation of neutrophil recruitment, which is necessary for maintaining periodontal tissue homeostasis, albeit both excessive and inadequate recruitment can lead to periodontitis.[22] For neutrophil extravasation into gingival tissues, CXCR2 is necessary. Transmigrating neutrophils use CXCR2 to follow the

chemokine gradient deposited by the endothelium at first, but they must then move towards a gradient present in infected or inflamed tissue. Chemoattractants obtained from bacteria (e.g., N-formyl-methionylleucyl-phenylalanine) or complement C5a fragments formed from local complement activation could be used in such gradients.[31] C5aR is widely expressed on neutrophils and has been proven to aid their migration to peripheral tissues in this regard.[39] Atleast in acute forms of inflammation, C5a-induced activation of C5aR also leads to the induction of granulocyte colony-stimulating factor, though it's unclear if this role includes collaboration with IL-17. Due to a continual input of microbial inflammatory chemicals and the presence of periodontal bacteria that can subvert complement function, the complement system might become unregulated in a particular niche, such as the gingival crevices.[11] Complement has been found to boost IL-17 synthesis in the mouse periodontal tissue in collaboration with Toll-like receptors[5], despite the fact that complement has complicated effects on IL-17 expression that include both positive and negative regulation. In a rat model of periodontal disease, C5a-induced activation of C5aR synergizes with Toll-like receptor-2 to produce copious elevations in IL-17, IL-1, IL-6, and tumour necrosis factor, resulting in considerable bone loss. Mice lacking either C5aR or Toll-like receptor-2, on the other hand, are protected from experimental periodontitis.

Interleukin-17 and T-cells

T helper (Th) cells are classified as Th1 or Th2 subtypes based on their cytokine profiles and functional properties. Th1 cells stimulate cellular immunity and cytokine synthesis in the body. Th2 cells stimulate humoral immunity and anti-inflammatory cytokine patterns in B cells.[8] Th17, a subset of CD4+ T-cells, has recently been identified as an IL17-producing cell. Th17 cells play a critical function in the host's protective antibacterial response.[9] IL17 is a proinflammatory cytokine that was first discovered in 1993 as a T-cell product.[19] The six structurally related members of the family are IL17A, B, C, D, E (IL25), and IL17F. The IL17A and IL17F genes are found on chromosome 6q. On chromosome 5q, the IL17B gene is found. The IL17C, IL17D, and IL17E genes are found on chromosome arm 16q, 13q, and 14q, respectively.[8]

Role of Interleukin-17 on systemic diseases

Different types of systemic inflammatory conditions, such as rheumatoid arthritis, systemic sclerosis, psoriasis, bowel disease and systemic lupus erythematosus have been linked to IL17.[13] The level of IL17 has been found to be higher in people with systemic lupus

erythematosus. By stimulating the local release of neutrophil mobilisation factors in resident cells, IL17 plays a critical role in host defence within the lungs.

Neutrophil homeostasis and interleukin-17

IL-17 is critical for neutrophil homeostasis and, as a result, periodontal health, because any deviation from normal neutrophil activity (numbers or activation status) can lead to periodontitis.[22] In fact, IL-17 plays an important role in the monitoring of neutrophil rheostat (neutrostat) feedback mechanism that keeps neutrophil numbers at a constant condition. IL-23, which is generated by innate immune cells during infection or inflammation, generates IL-17, which increases granulopoiesis and mobilisation of mature neutrophils from the bone marrow by upregulating granulocyte colony stimulating factor. Transmigrated neutrophils become apoptotic and are phagocytosed by tissue phagocytes as they age, resulting in IL-23 production being suppressed and the IL-17–granulocyte colony-stimulating factor axis being downregulated, allowing steady-state neutrophil levels to be maintained. While granulocyte colony-stimulating factor is crucial for granulopoiesis, neutrophil recruitment into local tissues is also critical for maintaining the neutrostat regulatory circuit and, as a result, neutrophil homeostasis. This is best exemplified in illnesses that affect neutrophil recruitment to peripheral organs, obliterating the regulatory signals for IL-23 and IL-17 production, which are typically linked to apoptotic neutrophil phagocytosis. For example, mice lacking adhesion molecules (e.g., lacking 2 [CD18] integrins) have blood neutrophilia and are unable to recruit neutrophils in peripheral tissues (such as the lungs and gut) where IL-17 production is unrestrained. In mouse models and humans, this homeostatic failure has recently been linked to IL-17–driven disease. In mice lacking either the LFA-1 (CD11a/CD18) integrin or CXCR2, defective neutrophil recruitment to the periodontal tissue leads to severe periodontal bone loss and overexpression of IL-17, whereas local anti-IL-17 therapy restores the disease phenotype.[33] Periodontal bacteria rely on inflammation to acquire vital resources including tissue breakdown products (peptides) and heme-containing substances. Patients with Type I leukocyte adhesion deficit have IL-17 upregulation in their gingival tissue (LAD-I).[33] LAD-I is a disease syndrome characterised by mutations in the CD18 subunit of 2 integrins that is linked to recurrent microbial infections and early-onset severe periodontitis.[14] Lack of neutrophil surveillance of the periodontal infection has been linked to LAD-I periodontitis in the past. However, recent evidence shows that IL-17 is abnormally upregulated in this condition, as well as evidence that neutralising IL-17 in relevant mouse models reverses both destructive inflammation and bacterial dysbiosis, suggests that LAD-I–associated

periodontitis is primarily caused by a dysregulated host response characterised by IL-17 overproduction. Additional disorders related with deficiencies in processes that regulate the generation and life cycle of neutrophils (e.g., congenital neutropenia, Chediak-Higashi syndrome, and Papillon-Lefevre syndrome) highlight the relevance of neutrophil homeostasis for periodontal health.[21] Although the underlying molecular pathways causing severe periodontitis in these patients are unknown, we anticipate that an IL-17–driven mechanism could be applicable to any disorders involving weak or no neutrophil accumulation in extravascular locations, such as the Chediak-Higashi syndrome.

IL-17 and periodontal bacteria

CXCR2 has been demonstrated to modulate the IL-17–granulocyte colony-stimulating factor axis in the intestine in a bacteria-dependent manner in the context of the neutrostat mechanism outlined above. Despite the fact that CXCL5 has been identified as the CXCR2 ligand that regulates the IL-17–granulocyte colony-stimulating factor axis in the intestine, CXCL5 has yet to be studied in gingival tissues. However, commensal bacteria have been demonstrated to promote neutrophil recruitment to gingival tissues by inducing CXCL2. At this time, it is unknown whether CXCL2 serves a comparable role in the periodontium as CXCL5 does in the intestine. Little is known about the processes by which periodontal bacteria govern IL-17 or IL-17–producing cells, and more research could shed light on neutrophil recruitment and activation mechanisms. Th17 cells can contribute to neutrophil recruitment not only through the production of IL-17, but also through the expression of CXCL8.[36] Recruited neutrophils, on the other hand, can boost Th17 cell recruitment by producing CCL2 and CCL20 chemokines, which are ligands for the chemokines CC-receptor -2 (CCR2) and -6 (CCR6), which are both expressed by Th17 cells.[36] This apparent reciprocal link between neutrophils and Th17 could have significant ramifications in periodontal health and illness, either supporting a protective immune response to manage periodontal bacteria or magnifying a destructive inflammatory response. IL-17 is a critical molecule in the defence against extracellular bacterial and fungal infections, as previously described.[34] The ability of IL-17 to not only organise neutrophil recruitment but also induce the generation of antimicrobial peptides from epithelial and other cell types, such as -defensin-2, S100 proteins, and cathelicidin, are among the defensive mechanisms involved.[34] In a mouse model of periodontitis caused by implantation of a human periodontal pathogen, IL-17 receptor activation was linked to protection (P. gingivalis).[43] IL-17 receptor signalling, on the other hand, was linked to protection against naturally

occurring chronic bone loss in mice. Deficiency of Del-1, an endothelial cell-secreted glycoprotein that antagonises the LFA-1 integrin, leads to unrestricted neutrophil infiltration and IL-17-dependent bone loss in the latter model. This apparent disparity could be due to the two models' differing natures (chronic versus a relatively acute periodontitis model). Chronic IL-17 receptor signalling has the ability to transform an acute inflammatory response into chronic immunopathology, as seen in rheumatoid arthritis.[32] Although it is unknown how periodontal bacteria regulate IL-17 synthesis, there is evidence that P. gingivalis fosters an IL-17 environment, ostensibly to take advantage of the resultant inflammatory response in the form of tissue breakdown products and heme-containing molecules. P. gingivalis stimulation of healthy volunteers' peripheral blood mononuclear cells resulted in increased IL-17 production in CD3+ T cells and increased IL-23 production in macrophages. Furthermore, P. gingivalis lipopolysaccharide was found to trigger IL-17 and IL-23 production in human periodontal ligament cells, and its outer membrane proteins could stimulate IL-17 mRNA expression in gingivitis and periodontal disease patients' peripheral blood mononuclear cells. P. gingivalis, surprisingly, appears to skew a Th1 response toward Th17, allegedly to avoid Th1 cell-mediated immunity, which the organism appears to be vulnerable to.[25] P. gingivalis ability to decrease gingival epithelial cell synthesis of Th1-recruiting chemokines, as well as T cell production of interferon-, may contribute to its suppression of Th1 cell-mediated immunity.[25] P. gingivalis possesses a virulence factor arsenal that allows it to control innate and adaptive immune cells to trigger a nutrient-rich inflammatory response orchestrated by IL-17. In human periodontitis, the presence of P. gingivalis in the subgingival biofilm was linked to higher levels of IL-17 in gingival crevice fluid.[40]

IL-17 in Relation to Periodontitis

Periodontitis is characterised by an inflammatory process that leads to periodontal damage, which is caused by mediators derived from the adaptive and innate immune responses to microorganisms in biofilms. Cytokines are soluble proteins that bind to cell surfaces via particular receptors, influencing cell activity and mediating complicated cell interactions in periodontal disease. The most thoroughly studied cytokines in periodontitis are interleukin-1 (IL-1), tumour necrosis factor (TNF-), and IL-17, which trigger intracellular cascades and phenotypic alterations that govern the amplitude and severity of the host response. A number of proinflammatory cytokines are generated in response to periodontal bacteria and their toxin products, according to studies. Andrukhov et al. proposed that periodontitis can be related with distinct cytokine profiles due to changes in the bacterial profile. Controlling the

Th1/Th2 balance is widely regarded as crucial to periodontal disease immunoregulation. The pathogenesis of periodontitis is clinically considered to involve a Th1/Th2 pattern, with stable periodontal lesions mediated by Th1 cells and progression of periodontitis reflecting a shift towards Th2 cells.[15] As a result, the pathogenesis of periodontitis is clinically considered to involve a Th1/Th2 pattern. However, current research has discovered a considerable increase in the level of IL17 in periodontitis patients. In periodontal disease, significant levels of IL-17 are detected. By activating gingival fibroblasts to create inflammatory cytokines, IL17 exacerbates periodontal disease. There is a lot of evidence that substantial tissue degradation occurs in periodontitis as a result of the recruitment of host cells via the activation of monocytes/macrophages, lymphocytes, and fibroblasts.[15] Periodontitis patients had higher levels of IL17 than gingivitis patients.[16] Takahashi et al. hypothesised that IL17 is produced in periodontitis, and that it is engaged in Th1 regulation and increases inflammatory reactions via gingival fibroblast-derived mediators, suggesting that IL17 may play a role in periodontal disease pathogenesis. Alveolar bone cells are affected by IL17. T cells have been shown to play a direct role in bone metabolism via cytokines generated from T cells, including IL17. IL17 stimulates osteoclast cells and activates the synthesis of receptor activator of nuclear factor kappaB ligand by osteoblasts.[17]

Role of Interleukin-17 in inflammatory bone loss

The triad of proteins of the tumour necrosis factor/tumor necrosis factor receptor family, receptor activator of nuclear factor-B ligand (RANKL), its functional receptor RANK, and its decoy receptor osteoprotegerin, are required for bone homeostasis.[19] These proteins are important for the differentiation and function of osteoclasts: The contact of RANKL (expressed by osteoblasts as well as activated T cells and B cells) with RANK on osteoclast precursors promotes osteoclastogenesis, whereas osteoprotegerin inhibits the interaction of RANKL with RANK. However, because the osteoprotegerin/RANKL ratio falls with increased periodontal inflammation, the bone-protective action of osteoprotegerin is decreased in periodontitis.[18]

Because of its ability to induce RANKL production by osteoblasts and other stromal cells, IL-17 has significant osteoclastogenic capabilities and is thus a main topic of interest in bone-related illnesses such as rheumatoid arthritis, osteoporosis, and periodontal disease. In addition, IL-17 can stimulate the expression of matrix metalloproteinases in fibroblasts, endothelial cells, and epithelial cells, potentially causing connective tissue and bone

degradation. Th17 cells can behave as a specialised osteoclastogenic subset that links T-cell activation to inflammatory bone degradation by expressing both IL-17 and RANKL. The majority of what we know about Th17 and IL-17 in bone loss control comes from rheumatoid arthritis research. In that they both involve chronic inflammatory bone loss, periodontal disease and rheumatoid arthritis have certain commonalities.[23] Human B cells survival and proliferation, as well as their differentiation into antibody-secreting plasma cells, have been demonstrated to be enhanced by interleukin-17.[24] B cells/plasma cells are a key source of RANKL in chronic periodontitis bone resorption lesions. This raises the idea that IL-17's influence on B cells and plasma cells may have bone-destructive effects, contributing to periodontal disease progression. It might be suggested that IL-17-mediated antibody response augmentation could counteract such negative effects. The relevance of the antibody response in periodontitis, however, is unknown, despite the fact that naturally produced antibodies against periodontal bacteria are assumed to have low affinity and poor functioning. Chronic inflammatory illnesses appear to become more common as people get older. Mice also have a higher risk of periodontal disease as they become older, which is linked to greater IL-17 production and a higher number of periodontal neutrophils.[44] It's interesting to note that neutrophils can cause osteoclastic bone resorption by expressing membrane-bound RANKL[20], however it's unclear if this occurs in periodontal tissue. In the periodontal tissue of aged mice, increasing IL-17 production is negatively associated to a drop in Del-1 expression.[44] Human gingiva has an inverse association between IL-17 and Del-1, with IL-17 and Del-1 predominant in inflamed and healthy gingiva, respectively.[44] In human endothelial cells, IL-17 reduces Del-1 expression[41]; similarly, neutralisation of IL-17 in murine periodontal tissue results in enhanced Del-1 expression, reduced neutrophil infiltration, and decreased periodontal bone loss.[44] These data show that IL-17 biologics could be useful in the treatment of periodontal disease in humans.

Clinical studies on interleukin-17 in periodontal disease

Human periodontitis has been linked to higher amounts of locally generated IL-17 in comparison to healthy periodontal tissue in numerous investigations. Furthermore, a single nucleotide polymorphism linked to elevated IL-17 expression was shown to be more common in chronic periodontitis patients than in control subjects. When compared to people with the GG genotype, people with the IL-17 G197A allele had higher IL-17 and CXCL8 expression, which was associated with worse clinical periodontal metrics but higher myeloperoxidase activity. Despite their importance, these studies do not formally demonstrate IL-17 as a cause

of periodontitis. However, given IL-17's pro-inflammatory and osteoclastogenic capabilities, as well as the above-mentioned intervention studies in mice models, it's plausible to believe that IL-17 is a key participant in periodontal immunopathology. It is still unclear if periodontitis is a continuous pathologic process or a series of transient acute bursts.[26] It's tempting to infer that IL-17–producing cells with inflammatory or regulatory activities are engaged in the mechanisms that cause "inflammatory bursts" in the context of the burst model. In light of Tregs' ability to transform into IL-17-producing (Th17) cells, a recent study found IL-17+/Foxp3+ double-positive cells in human periodontal lesions, implying an intermediate T cell stage in the process.[35] The presence of IL-23 in periodontal tissue, which has been demonstrated to suppress Treg formation in favour of effector Th17 cells, may aid this conversion.[37] Furthermore, IL-23 can cause Th17 cell clonal growth and promote IL-17 production.[42] In this context, a recent study found that the amount of IL-23–producing macrophages was strongly linked with both inflammation and the abundance of IL-17–producing T cells, which was the main T cell subset in the lesions.

The outcome of Periodontal Therapy on IL-17 Levels

The effect of nonsurgical periodontal therapy on Th 17 associated cytokines (IL-17 and IL-21) in gingival crevicular fluid and Th 17 cells in peripheral blood in 30 systemically healthy adult subjects with chronic periodontitis was studied by Lu Zhao and colleagues (2008). Six weeks following treatment, IL-17 levels were found to be significantly lower. In another study from Vishnu Jayakumar Sunandhakumari et al. (2018), effect of conventional nonsurgical periodontal therapy on plasma levels of IL-17 in twenty chronic periodontitis patients with well controlled Type-II Diabetes Mellitus and in twenty systemically healthy patients with chronic periodontitis. One month following treatment Th17 related cytokine (IL-17) in plasma both in chronic periodontitis with well-controlled Type 2 Diabetes mellitus patients and systemically healthy chronic periodontitis patients were reduced.

Effect of Interleukin-17 on Other Cytokines

Through stimulation of epithelial, endothelial, and fibroblastic cells, IL17 also stimulates other proinflammatory cytokines such as IL1, IL6, IL8, prostaglandin E2, and matrix metalloproteinases.[11] IL17 appears to be insufficient to create a powerful inflammatory response on its own, but it enhances inflammation when it collaborates and/or synergizes with other inflammatory cytokines. By boosting the expression of target genes, IL17 can trigger a powerful inflammatory cascade. The release of IL8 is crucial for neutrophil

recruitment. In vitro, IL6 stimulates the release of elastase from human neutrophils. IL17, like IL1 and tumour necrosis factor alpha, uses the same transcriptional pathways. The transcriptional factors p38 and nuclear factor kB are required for IL17 function. The generation and release of colony stimulating factors (CSFs) granulocytes and granulocyte-macrophage is induced by IL17. For neutrophils, both CSFs are potent antiapoptotic survival agents.[12]

CONCLUSION

Based on the following studies, there is substantial evidence that IL-17 plays a major role in the immunological and inflammatory response as well as bone resorption in periodontitis.

- In vitro studies show that IL-17, a mediator for inflammation, host response, and bone degradation, can be produced by a variety of periodontal cells in the periodontium.
- IL-17 levels are upregulated locally in periodontal tissues, GCF, and definitively in saliva in periodontitis patients, with the potential to spread to the systemic circulation, as seen by elevated IL-17 serum levels in periodontitis patient.

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