Review Article

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Dentistry Section

# Role of Interleukin-33 in Immunity and Periodontal Inflammation- A Literature Review

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## ABSTRACT

The Interleukin-33 (IL-33) is a member of IL-1 family discovered in the year of 2005. The Interleukin-1 (IL-1) family of cytokines is commonly encountered in chronic inflammatory diseases such as rheumatoid arthritis and periodontitis. IL-33 regulates the innate and adaptive immunity and it also participates in initiation and progression of periodontal diseases. The aim of this review was to analyse the biological and immunological role of IL-33 in progression of periodontal diseases. This review also deals with the IL-33 signaling pathway in the periodontal inflammation.

**Keywords:** Biological role, Inflammatory, Periodontitis

## INTRODUCTION

Chronic periodontitis is a bacterially induced inflammatory condition that destroys the soft and hard tissue components of the periodontium. It is a complex disease in which disease expression involves interaction of the biofilm with host immune inflammatory response and subsequent alteration in homeostasis [1]. The basic fundamental of defense mechanism has been documented as either innate or adaptive immunity. Various virulent factors such as destructive enzymes and toxins are secreted by microbial organism which in turn induces the secretion of inflammatory mediators by the host cells, as a part of homeostasis. These inflammatory mediators are enzymes, cytokines and prostaglandins and other cellular products [2]. The defense mechanisms could either be production of appropriate cytokine with protective immunity or inappropriate cytokine production with destruction and progression of diseases [3].

The IL-1 family of cytokines is commonly encountered in chronic inflammatory diseases such as rheumatoid arthritis and periodontitis [4]. The IL-1 family members are able to change the host response into an inflammatory reactions or immunological alterations. The IL-33 is most recently detected member of IL-1 family. IL-33 has been identified to regulate the innate and adaptive immunity and suggested to participate in initiation and progression of periodontal diseases. It is constitutively expressed as a nuclear factor mRNA in many cell types including fibroblasts, keratinocytes, activated macrophages, smooth muscle cells, epithelial cells and dendritic cells [5]. IL-33 plays an important role in initiation and progression of chronic periodontitis in different pathway and through activation of Receptor Activator of Nuclear factor Kappa-B Ligand (RANK-L), Osteoprotegerin (OPG) and Nuclear Factor Kappa-light chain enhancer of activated B cells (NFκB) [6]. IL-33 is present in both intra and extra cellular environment. It is considered as an endogenous molecule and it actively participates in normal homeostasis mechanism [7].

The mature form of IL-33 has two important functions. The prime function is that it is a strong inducer of T helper immune response and secondly it is an important mediator for mucosal healing and hence it plays a central role in fibrosis and wound repair [8]. It is released extracellularly due to cell damage or stress thereby inducing the secretion of pro-inflammatory mediators through intracellular cyclic mechanisms. The potential role of IL-33 in periodontal diseases is considered as destructive pro-inflammatory action [9]. The periodontal pathogen induces the production of cytokines when it contacts the first line of cell population in gingival epithelium. In periodontal diseases, Th2 (T helper Type-2 cells) and mast cells have important role in progression of periodontal diseases [10]. The Th2 cell stimulated by IL-33 leads to secretion of IL-4, IL-5 and IL-13 cytokines. The IL-33 also triggers the release of inflammatory mediators such as TNF-α, IL-6, and IL-1β. IL-33 initiates and regulates the events in mast cells including expression of chemokines, cytokines and lipid mediators. The adhesion of mast cells during inflammation, its maturation and survival is activated by IL-33 [11]. Buduneli N et al., compared the levels of IL-33 in Gingival Crevicular Fluid (GCF), saliva, plasma and concluded that there was no significant difference between chronic periodontitis and periodontally healthy group [12]. On the other hand, IL-33 stimulated by TNF-α leads to protective anti-inflammatory and reparative immune responses in human gingival fibroblasts. The IL-33 levels has over expressed in gingival epithelial cells of chronic periodontitis induced by *Porphyromonas gingivalis*.

The signaling pathways of IL-33 have been described through several mechanisms. It can form a complex with orphan IL-1 receptor ST2. IL-33 signaling through ST2 binding suggested that this receptor is a part of a functional IL-33 receptor complex [5]. IL-33 induces NFκB phosphorylation and activates the Mitogen Activated Protein Kinases (MAPKs) and it may trigger RANK-L expression in addition to direct effect on *P. gingivalis*.

The aim of this review is to analyse the biological and immunological role of IL-33 in progression of periodontal diseases and also deals with the IL-33 signaling pathway in the periodontal inflammation.

### History and its Structure

IL-33 is an eleventh member of IL-1 family and broadly expressed in inflammatory conditions [13]. It was identified and recognised in the year of 2005 as a ligand for an orphan receptor ST2. Lopetuso LR et al., first identified IL-33 in endothelial cells, venules, payer's patches and lymph nodes. IL-1 family has a common beta-trefoil structure and has high pro-inflammatory properties [14]. IL- 33 arises as a 30 kD acid protein and it undergoes caspase-1 cleavage to form an active component of 18 kD acid protein, and it also functions as nuclear factor.

### Signaling Pathway

The signaling is induced through the cytoplasmic Toll-interleukin-1 Receptor (T1R) domain of IL-1RAcP. This leads to recruitment of the adapter protein MyD88 and activation of transcription factors such as NFκB via TRAF6 and MAPKs. IL-33 has elicited cell signaling on

target tissues similar to that of IL-1 family. ST2 is the ligand binding chain of the IL-33R complex receptor which is expressed on the surface of Th2 cells and mast cells [15]. It is one of the components of IL-33R complex. First IL-33 receptor ST2 has formed the signaling complex with IL-R complex protein. These activates NFκB, Activator Protein-1 (AP-1), c-Jun-N-terminal Kinase (JNK), ERK1/2 and p38 signals and phosphorylation of c-Jun, IL-33 other way of activation through MyD88 [16].

## IL-33R Complex

The most common members of the IL-I family are IL-1 and IL-18. These cytokines have individual receptors and they do not share their receptors with other members of the family. It means that IL-18 receptor is only suitable for IL-18 induced cytokines. However, some members of IL-1 (IL-1F6, IL-1F8 and IL-F9) and IL-33 have been shown to use second component of the IL-1R complex i.e., IL-1R Accessory Protein (IL-1 RAcP) [17]. The ST2 receptor is a stable receptor present and expressed on Th2 cells but not on Th1 cells. IL-33 receptor complex binds with a ST2 receptor. ST2 has two isoforms that is Transmembrane (ST2L) and soluble (sST2). IL-33/ST2 receptor system was more commonly involved in cardiovascular diseases, asthma and rheumatoid arthritis. The recent study carried out proved that IL-33 act through IL-1RAcP thereby initiating signal transaction same as IL-1 cytokines and IL-1R associated kinase 4, MyD88, TNRR-associated factor 6 [5]. It then leads to the activation of NFκB and MAPKs. In final stage ST2 was found to be a primary ligand-binding receptor in the initial activation of IL-33. The IL-1 (α and β), IL-1F6, IL-1F8, IL-1F8 and IL-1RAcP are second component of its signaling receptor complex. Recent studies also found that PAP2 signaling pathway is also involved in the mechanism [18].

## Biological Role of IL-33

IL-33 has a dual role and acts as pro-inflammatory extracellular cytokine and as an anti-inflammatory intracellular cytokine. IL-33 has an important role in rheumatoid arthritis, ulcerative colitis, anaphylactic shock, cardiac hypertrophy, atherosclerosis and psoriatic skin diseases. IL-33 is found to induce the differentiation of osteoblast precursors and matrix formation which does not involve in mineralisation [12]. Protective function of IL-33 is that, it acts through intracellular mechanism. The previous study revealed that circulating IL-33 in patient with allergies polliniques sufferers were 550 pg/mL in control and 360 pg/mL in test group. The results also analysed that IL-33 concentration varied from 0 to 2000 pg/mL in the health and control group. The mean values of IL-33 were suggested to be 43.2 pg/mL in test group and 3.3 pg/mL in control group [16].

Expression and regulations of IL-33 in bone cells reveal the initiation of osteoclast differentiation through RANK-L, Macrophage-Colony Stimulating Factor (M-CSF). In contrast to this study, IL-33 has very weak or indirect action similar to IL-6 and TGF β on this cell population. They also act through indirect mechanism of inducing the osteoclast formation by T cells, macrophages and osteoclasts [16]. The osteoclast expressed ST2L mRNA on response by IL-33 and affects osteoclast-dependent formation of osteoclasts [14]. Contrary to the previous studies, the present study suggested that IL-33 negatively affect osteoclast cell by inhibiting their action on spleen and bone marrow cell populations [19]. IL-33 known to elicit the release of Th2 cytokines thereby induces the secretion of IL-4, IL-13 and IL-10. This leads to inhibition of osteoclast which promotes the anti-inflammatory effects [20].

## IL-33 in Periodontal Disease

The IL-33 cytokine is a family of cytokines and involved in regulation of innate and adaptive immunity. The previous studies also suggest that IL-33 is involved in initiation and progression of periodontal diseases. The commonly involved bacteria in chronic periodontitis are *Porphyromonas gingivalis*, *Prevotella intermedia*, *Tannerella forsythia*, and *Neisseria gonorrhoeae* [21]. The most abundant organism in progression of periodontitis is *P. gingivalis*. The presence of these pathogens, IL-33 cytokine level was increased in chronic stage of periodontal diseases. The host cells (recruited inflammatory cells) have the ability to recognise the pathogen as "danger signals", in addition to its direct effect on *P. gingivalis*, IL-33 influences the secretion of anti-inflammatory cytokines through IL-33 pathway and it is over expressed in gingival tissues which trigger the RANK-L. IL-33 is expressed as a nuclear factor in epithelial cells, fibroblast and endothelial cells [15]. IL-33 also induces the expression of gene encoding for pro-inflammatory cytokines, as an endogenous molecule. It occurs through crucial transcription factors NFκB. This leads to regulation of normal tissue homeostasis by processing and secretion of anti-inflammatory cytokines. An anaerobic bacterium, *Porphyromonas gingivalis* (Pg) infection suggested to regulate an over expression of RANK-L mRNA however, it is a weak inducer of IL-33 mRNA in human oral epithelial cells. IL-33 has been act as secondary factors to promote bone resorption through RANK-L after infection with *P. gingivalis* [15].

IL-33 was commonly involved in chronic stage of periodontal inflammation. It acts as a chemoattractant for Th2 cells and also binds with these cells. Th2 cells released the cytokines such as IL-4, IL-5, IL-6 and IL-13 which activate B cells. Activated B cells were differentiated into plasma cells. B cells and plasma cells were major components of inflammatory cells in advanced periodontitis lesions [14]. Previous studies have showed that GCF level of IL-33 significantly increased in patients with chronic periodontitis and also suggested that *P. gingivalis* upregulates the IL-33 mRNA expression in gingival epithelium through PAR-2 signaling pathway [13]. IL-33 has a negative effect that inhibits the osteoclast differentiation thereby (protective effect) preventing the bone loss. In periodontitis progression, TNF-α act as a crucial cellular marker during inflammation and revealed that it can affect its target cells through both auto and paracellular mechanism [16]. The TNF-α positive producer cells suggested co-regulating with IL-33 in gingival fibroblasts in chronic periodontitis. TNF-α regulation was found to be specific to the cell and/or pathway type [14].

Previous investigation showed that induction of mRNA of IL-33 was expressed by NFκB/AP-1 and p38. The natural killer cells with ST2-positive responds well to IL-33 and releases large amount of Th2 cytokines. Fluctuations in the cytokines may induce the inflammation during periodontitis.

ST2 may serve as reservoir for IL-33 soluble IL- 6 receptor. IL-33 reported to be correlated with levels of OPG and RANKL and mast cells and Inflammation cell numbers [22]. Literature reviews suggested that the experimental periodontitis significantly increased the expression of IL-33 and RANK-L on mast cells. IL-33 enhanced the expression of RANK-L and few studies have proved that the correlation significantly exist between IL-33 and IL-6. The signaling pathway of IL-33 expression on RANK-L production depends on T helper cells through direct (chemotactic for Th2) and indirect (mast cells) mechanism. Mun SH et al., added that, IL-33 and RANK-L act as counterpart to under certain physiological conditions. It also has significant correlation between genome-wide signal of periodontal pathogen colonization (red complex) and IL-33 single nucleotide polymorphism (rsl16924631) [23].

# CONCLUSION

Understanding the function of IL-33 at various stages of inflammation is very difficult and hence the exact role of the cytokine namely protective or destructive is still not elucidated. Studies suggest that IL-33 plays an important role in chronic stage of periodontal disease progression. It could induce the inflammation directly through the IL-33 dependent Th2 cytokine producing cells and it also participates in mast cell degranulation, destruction of fibroblasts and epithelial

cells by necrosis. IL-33 produces several pro-inflammatory cytokines and chemokines, especially TNF-α is overexpressed in the gingival tissues. Though it acts as chemoattractant and as a systemic cytokine, elaborate studies are needed to understand the biological and immune functions of IL-33 in periodontal diseases.

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