The Role of IL-6 and IGF-1 in Periodontitis Bone Destruction

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ABSTRACT

Background: *Periodontitis is an inflammatory condition affecting the tissues supporting the teeth, destroying the periodontal ligament and alveolar bone. This study aims to elucidate the roles of IL-6 and IGF-1 in periodontitis-induced bone resorption and explore their therapeutic implications for periodontal health. Periodontitis is initiated by periodontal pathogens, which trigger an immune response resulting in tissue damage.*
Methods: *Pro-inflammatory cytokines, particularly IL-6, have an important role in this process. IL-6, produced by various cells, including immune and periodontal ligament cells, enhances osteoclastogenesis by enhancing RANKL expression, thereby promoting bone resorption.*
Result: *Conversely, IGF-1, a hormone like insulin, is critical in bone homeostasis and regeneration. IGF-1, synthesised in the liver and locally in tissues, aids in the proliferation and differentiation of osteoblasts and osteoclasts, facilitating bone remodelling. IGF-1 also interacts with IL-6 to modulate inflammatory responses and osteoclast activity.*
Conclusion: *Understanding the interplay between IL-6 and IGF-1 offers insights into the mechanism of bone resorption in periodontitis and identifies potential therapeutic targets.*

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INTRODUCTION

Periodontitis is an inflammatory disease that impacts the tissues supporting the teeth and is triggered by a specific group of microorganisms. This condition causes the progressive destruction of the periodontal ligament and alveolar bone, leading to increased sulcus depth and recession both.(1) Key pathogens include *Porphyromonas gingivalis*, *Tannerella forsythia*, and *Aggregatibacter actinomycetemcomitans*. These bacterial products stimulate the production of pro-inflammatory cytokines that significantly contribute to bone destruction. In addition, immune cells and locally produced cytokines interact with these bacterial products, playing an important role in the pathogenesis of chronic periodontitis by perpetuating the inflammatory response and increasing tissue damage.[1] Chronic inflammation is influenced by various mediators, with a significant role played by interactions within cytokine networks. Cytokines are essential peptide mediators responsible for cell signalling and communication. Proinflammatory cytokines such as IL-6, IL-17, TNF-α, IL-1α, and IL-1β play a role in both acute and chronic inflammation in tissue damage. Conversely, certain cytokines, such as IL-10, have opposing effects that help to regulate inflammation.[2,3]

IL-6 is a cytokine with various functions in biological processes, including supporting B-cell differentiation, increasing T cell proliferation, and stimulating bone resorption. IL-6 production in tissues is part of the immune response when infection triggers B cells to produce antibodies.[4,5] IL-6 promotes the differentiation of osteoclasts, resulting in enlarged bone resorption, and it also inhibits bone formation in cases of periodontitis.[1,6] In periodontitis patients, IL-6 has been found in mononuclear cells isolated from inflamed gum tissue. The increase in IL-6 levels in resistant periodontitis sites compared to stable periodontitis sites suggests that IL-6 can be used as an active periodontitis marker.[7]

Growth factors are important peptides that promote various cellular mechanisms such as proliferation, differentiation, migration, adhesion and the deposition of the extracellular matrix throughout the wound healing process. Among these growth factors, Insulin-like Growth Factor-1 (IGF-1) serve as a crucial mitogen in wound healing that acts as a protective cytokine and is vital in various diseases.(9) IGF-1 is a hormone with a peptide sequence like insulin that is primarily synthesised in the liver as a growth hormone in an endocrine manner, but also locally in tissue organs in a paracrine or autocrine manner.[8,9] IGF-1 is important in regulating growth and development, metabolism, and maintaining bone homeostasis.[10] In oral tissue, IGF-1 contributes to homeostasis periodontal.[11] However, the expression of IGF-1 has been reported to significantly decrease the junctional epithelium of periodontal lesions in periodontitis patients.[12]

Periodontitis is caused by a complex process between bacterial products and the immune response, causing an inflammatory process that can lead to periodontal tissue destruction. IGF-1, a critical growth factor for maintaining bone homeostasis, has an unclear role in the immune response during periodontitis, particularly in its interaction with IL-6. This review focuses examines the molecular mechanisms by which IL-6 and IGF-1 contribute to bone resorption and considers their potential as therapeutic targets in periodontal disease.

IMMUNE RESPONSE IN PERIODONTITIS

Periodontitis is caused by biofilm bacteria on tooth surfaces that induce immune response. The role of the immune response is to eliminate pathogens but in periodontitis, it also causes tissue damage.

The immune response in periodontitis is both innate and adaptive immunity.[13] Initially, innate immunity is activated when pathogens invade the periodontium, leading to inflammation and destruction of periodontal tissues. The activation of the adaptive immune response follows this.[14]

In periodontitis, the immune system mechanisms become overactive, resulting in immune cell infiltration, excessive production of pro-inflammatory cytokines, stimulation of osteoclasts, and degradation of the gingiva and alveolar bone.[15] An imbalance in the local microbial community triggers local inflammation, and the excessive activation of the host immune response directly stimulates osteoclastic activity, leading to alveolar bone loss.[16] The persistent presence of bacteria within host tissues causes chronic inflammation and can be actively altered by pathogens that subvert the immune system.[17]

Dysbiosis in the oral microbial community leads to the systemic spread of oral bacteria through inflamed gingiva, impacting various systemic conditions. Bacterial components such as lipopolysaccharide (LPS) activate innate immune cells, including dendritic cells, macrophages, and periodontal ligament cells. In response, IL-6 is produced by periodontal ligament cells, which facilitates the increase of Th17 cells in the oral mucosa. Furthermore, Th17 cells generate IL-17, which can enhance the suppression of oral bacteria by stimulating the production of antibacterial peptides and neutrophil chemoattractants in gingival epithelial cells. Additionally, IL-17 induces receptor activators of nuclear factor-κB ligand (RANKL) expression on periodontal ligament cells and osteoblasts. Concurrently, bacterial proteases degrade osteoprotegerin (OPG). Macrophages and dendritic cells produce inflammatory cytokines such as TNF-α and IL-1, further stimulating RANKL production. The alteration of the RANKL/OPG ratio induces the formation of osteoclasts, which promotes osteoclastic bone erosion. [17,18]

BONE RESORPTION IN PERIODONTITIS

In periodontal disease, microbial and host-derived factors contribute to bone resorption and remodelling processes.[19] Periodontal disease results from a combination of innate and adaptive immune responses to an imbalance of oral bacteria. This immune response influences bone remodelling by osteoblasts, osteoclast and periodontal ligament fibroblasts, which in turn affects alveolar bone resorption and attachment. During bone resorption, the release of various factors from the bone matrix, together with the activity of osteoclasts and bone macrophages, plays a critical role in recruiting osteoblast precursors to form new bone. Several signalling pathways, such as IGF-1, FGF, Hedgehog, Wnt and Notch, regulate osteoblast differentiation and new bone formation.[20]

Pro-inflammatory cytokines are involved in osteoclast formation and activation. During periodontitis, immune cells produce cytokines, including TNF, IL-17, IL-11, IL-6, and IL-1, which actively promote osteoclastogenesis and stimulate bone resorption.[15] The regulation of these cytokines has the potential to increase RANKL expression, driving bone degradation. Additionally, cytokines from Th1 and Th17 cells stimulate chemokine production, which recruits macrophages and neutrophils to amplify the innate immune response. In contrast, Th2 and Treg lymphocytes release cytokines like IL-4, IL-10, IL-27, IL-35, and TGF-β that help in alleviating inflammation, which in turn reduces bone. [20] In advanced periodontitis, alveolar bone destruction by osteoclasts creates spaces that are invaded by connective

tissue and gingival epithelium. This invasion disrupts osteoblast activity, preventing the formation of new bone.[15]

IL-6

IL-6 is a four-helical cytokine 25 kDA molecule weight, consisting of 184 amino acids. [21,22] It is activated by type I interferons (IFNs) and is transcribed by the IL-6 gene.[23] The synthesis and secretion of IL-6 are induced during inflammatory conditions, such as when Toll-like receptor (TLR)-4 is stimulated by lipopolysaccharide, or when cells are regulated by IL-1 or tumour necrosis factor (TNF)-α.[21] IL-6 is released from various cell types, such as endothelial cells, immune cells, fibroblasts and keratinocytes. Specifically, it is generated by stimulated myeloid cells, B cells and T cells such as macrophages and dendritic cells. Additionally, IL-6 is also produced by other cells, including myocytes, myotubules, fibroblasts, osteoblasts, and osteocytes.[1]

IL-6 is a cytokine that affects specific immune responses and inflammatory reactions. This pro-inflammatory cytokine is primarily produced after acute inflammation caused by Th2 cells. IL-6 is crucial for stimulating B cells to differentiate into plasma cells and produce antibodies, thus playing a vital role in humoral immune responses. IL-6 activates hepatocytes, initiating acute phase responses that lead to the production of proteins associated with the acute phase, such as serum amyloid A (SAA), C-reactive protein (CRP), fibrinogen, and haptoglobin. Upon stimulation by IL-1 and TNF-α released from activated myeloid cells, endothelial cells and fibroblasts respond by increasing IL-6 production, thereby amplifying a positive feedback loop that sustains inflammation.[5,21,23]

IL-6 signalling occurs through a complex that includes either the transmembrane IL-6 receptor (mIL-6R) or its soluble variant of IL-6R (sIL-6R), along with the signal-transducing subunit molecule glycoprotein 130 (gp130) which expressed on all cell on the body.[22] IL-6 has three signalling pathways. The activation of the classic pathway relies on various cell types and is triggered by IL-6, which binds to mIL-6R.with receptor gp130.[22,24] The second pathway, trans-signalling can appear in all cells expressing gp130. As a result, IL-6 trans-signalling can significantly broaden the range of target cells affected by IL-6. The sIL6R extends the range of IL-6 activity, triggering trans-signalling with pro-inflammatory and pro-fibrotic effects. While classic signalling activation encourages anti-inflammatory responses, trans-signalling induction produces pro-inflammatory responses.[21,22,24] The third pathway involves the IL-6/IL-6R complex bound to dendritic cells, which then binds to gp130-expressing naïve T cells.[22] Upon binding to IL-6 receptors, IL-6 forms dimers with gp130 through disulfide bonds, activating the JAK/STAT pathway. This activation leads to the stimulation of STAT3, which subsequently triggers the expression of downstream genes, enabling a diverse array of physiological functions.[23]

IL-6 can indirectly stimulate osteoclastogenesis by upregulating the expression of the Receptor Activator of Nuclear Factor κB Ligand (RANKL) gene in osteoblasts. RANKL is a cytokine that promotes the differentiation and activation of osteoclasts. It is primarily produced by osteogenic cells, such as osteoblasts and periodontal ligament cells, particularly during periods of periodontitis.[25,26] IL-6 is important for maintaining homeostasis in periodontal tissue by regulating the host response. IL-6 plays a role in periodontal tissue homeostasis by regulating host response. During periodontitis, the

expression of IL-6 messenger RNA (mRNA) is significantly elevated in periodontal ligament cells. The production of IL-6 by fibroblasts in the periodontal ligament is stimulated by periodontal bacteria and pathogen-associated molecular patterns (PAMPs), including muramyl dipeptide (MDP), peptidoglycan (PGN) and lipopolysaccharide (LPS). At inflammatory sites, IL-6 will respond specifically by affecting myeloid cell differentiation and upregulating B lymphocytes and CD4+ effector T cells. Localized excessive release of IL-6 will determine tissue damage by enhancing the pro-inflammatory cascade by stimulating osteoclast activity and the growth of periopathogenic bacteria.[27,28]

Recent studies present a decreased risk of periodontitis by downregulating IL-6 signalling by inhibiting its receptor, IL-6R. Consequently, reducing IL-6 levels by blocking IL-6R can reduce serum levels of C-reactive protein (CRP) (Figure 1).[29]

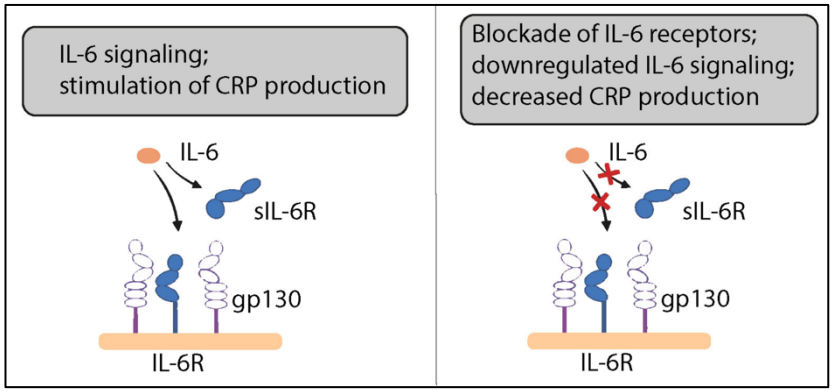

Figure 1. IL-6 activation of hepatocytes can trigger acute phase reactions that produce C-reactive protein (CRP), which can maintain inflammation. Decreasing IL-6 activation by blocking IL-6r can inhibit CRP production, giving potential drug targets for periodontitis therapy.[5,21,23,29]

IL-6R inhibition therapy using tocilizumab showed the effect of decreasing periodontal inflammatory mediators in periodontitis patients. This therapy significantly improved the gingival index, reduced probing bleeding, decreased probing depth, and enhanced clinical attachment levels in patients with chronic periodontitis.[30,31]

IGF-1

Growth Hormone (GH) is a protein produced by somatotropes cells in the anterior pituitary gland that is essential for human growth and development. Growth Hormone promotes growth and development by enhancing protein synthesis, encouraging lipolysis, stimulating IGF-1 secretion, facilitating cell proliferation, aiding cell differentiation, and inhibiting glucose metabolism. The release of growth hormone is controlled by an extended feedback mechanism involving indirect signals from the periphery. This includes negative feedback mediated by IGF-1 and positive feedback driven by ghrelin.[32,33] IGF-1 is 75% produced in the liver for release into the blood circulation, and 25% is produced in adipose tissue and muscle.[9]

IGF-1 is a peptide created by 70 amino acids and has a molecular weight of 7649 Da. It is produced under the control of GH through the action of the transcription factor Signal Transducer and Activator of Transcription 5b (STAT5B). In bone growth, IGF-1 can stimulate the proliferation of

mesenchymal stem cells and promote the differentiation of progenitor cells into osteoblast cells and chondrocytes.[9,34] Additionally, IGF-1, IGF-1 receptor (IGF-1R) and IGF-binding protein 1-6 (IGFBP-1-6) perform a function in the regeneration of tooth-supporting tissue cells, such as the periodontal ligament, osteoblasts in alveolar bone and jaw bone, and odontoclasts.[11]

IGF-1 facilitates the growth and development of mesenchymal and osteoprogenitor cells. Activation of IGF-1 and GH receptors on osteoblasts results in increased osteoblast proliferation and DNA synthesis. This activation also leads to osteoblast cell differentiation, which is associated with heightened collagen production and alkaline phosphatase activity. IGF-1 also impacts osteoclast cell development, fusion, and activity.[35] IGF-1 signalling can promote osteoclast differentiation by increasing the expression of RANKL and Macrophage Colony Stimulating Factor (MCSF) in osteoblasts. RANKL interacts with the RANK receptor located on the osteoclast cell membrane, with the regulation of tumour necrosis factor receptor-related factors (TRAF), facilitating signaling through the NF-κB and MAPK pathways. MCSF influences osteoclast function by binding to the c-FM receptor tyrosine kinase, which activates the downstream signalling molecule phosphatidylinositol 3 kinase (PI3K).).[20,36]

IGF-1 is one of the substrates widely found in the bone matrix and will be released during bone resorption, which couples with bone formation.[37,38] As a result, IGF-1 is essential for the mineralization of the bone matrix and for regulating the functions of osteoblasts and osteoclasts. During the process of bone resorption, osteoclasts release IGF-1 and TGF-β1 from the bone matrix, which encourages the migration of stem cells and the differentiation of osteoblasts. Therefore, new bone formation occurs through the differentiation of osteoblasts at the sites where osteoclasts have resorbed bone.[20,38,39] Recent studies show that therapy using TGF-β1 and IGF-1 at specific concentrations can enhance the osteogenic process and mineralisation of soft tissue in post-extraction sockets.[39] Moreover, the stimulation of IGF-1 and IL-1β in periodontal wound healing potentially enhances the proliferation of periodontal ligament cells, biomineralization, osteoblast differentiation, and p38 phosphorylation.[11] In addition, a study proved that calcined tooth powder (CTP) and silver nanoparticles (AgNPs) coupled with IGF-1 could induce PDLSCs into neuronal differentiation.[40] Further, studies of periodontitis in diabetic patients exposed that IGF-1R binding to SNA12 under high glucose conditions may inhibit osteogenic differentiation of PDLSCs, which may lead to alveolar bone destruction. Thus, IGF-1R can also be used as a molecular target in periodontitis therapy.[41]

CONCLUSION

The interaction between IL-6 and IGF-1 significantly affects the pathogenesis of periodontitis, especially in bone resorption. IL-6 is a pro-inflammatory cytokine that promotes osteoclastogenesis by upregulating RANKL, which exacerbates periodontal tissue destruction. In contrast, IGF-1 contributes to bone homeostasis by promoting osteoblast differentiation and bone matrix mineralisation, although its expression is reduced in periodontal lesions, suggesting impaired bone regeneration ability in periodontitis. Understanding these molecular processes provides insight into IL-6 and IGF-1 as potential therapeutic targets. Strategies to inhibit IL-6 signalling, such as IL-6 receptor antagonists, show promise in reducing inflammation and bone loss. Simultaneously, IGF-1-based therapies offer the prospect of promoting tissue regeneration and healing in periodontal disease. Future research should concentrate on optimising these therapeutic methods to effectively restore periodontal health and prevent the progression of disease.

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