Interleukin-1β is a potential therapeutic target for periodontitis: a narrative review

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Interleukin (IL)-1β, a pro-inflammatory cytokine, was elevated and participates in periodontitis. Not only the link between IL-1β and periodontitis was proved by clinical evidence, but also the increased IL-1β triggers a series of inflammatory reactions and promotes bone resorption. Currently, IL-1β blockade has been therapeutic strategies for autoimmune and autoinflammatory diseases such as rheumatoid arthritis, cryopyrin-associated periodic syndromes, gout, and type II diabetes mellitus. It is speculated that IL-1β be a potential therapeutic target for periodontitis. The review focuses on the production, mechanism, present treatments and future potential strategies for IL-1β in periodontitis.

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THE PRODUCTION OF IL-1B IN PERIODONTITIS
IL-1β is gingival fibroblasts, periodontal ligament cells, and osteoblasts can also secrete IL-1β. The secretion of IL-1β is unique. The cytokine is first produced as a proprotein, which is subsequently proteolyzed into its active form by caspase-1. The inactive precursor, pro-IL-1β, is produced in response to pathogen-associated molecular patterns (PAMPs, e.g., lipopolysaccharide (LPS)) or damage-associated molecular patterns (DAMPs, e.g., HMGB1, ATP). PAMPs and DAMPs function through pattern recognition receptors (PRRs), e.g., Toll-like receptors (TLRs), to activate the signalling adaptor myeloid differentiation primary response 88 (MyD88). MyD88 activation results in the degradation of IkB as a prerequisite for the release of NF-κB dimers and hence promotes pro-IL-1β expression.

Pro-IL-1β is produced as biologically inactive forms that must be proteolytically cleaved to acquire functional activity. Caspase-1, originally recognised as an IL-1-converting enzyme, is able to cleave pro-IL-1β into active IL-1β, leading to the final secretion. Caspase-1 undergoes activation by a multi-molecular assembly known as the inflammasome. Inflammasomes are composed of the sensor (PRRs including NLRP1, NLRP3, NLRC4, Pyrin and AIM2), the adaptor ASC (apoptosis-associated speck-like protein containing a CARD), and caspase-1. To date, most investigations have focused on the NLRP3 inflammasome, which is involved in various inflammatory diseases. The NLRP3 inflammasome is activated in response to a variety of PAMPs and DAMPs. In macrophages, NLRP3 inflammasome activation is proposed to be a two-signal pathway. The first signal is priming, which is induced by microbial or endogenous stimuli that promote NLRP3 and pro-IL-1β expression through the activation of NF-κB. The second signal is activation, which is triggered by exogenous ATP (eATP), pore-forming toxins and particulate matter sensors, which activate the NLRP3 inflammasome and caspase-1 and cleave pro-IL-1β into its mature form. The protein gasdermin is another substrate of active caspase-1. Active caspase-1 cleaves gasdermin at the N terminus and C terminus. The N terminus of gasdermin forms pores on cell membranes and subsequently induces pyroptosis.

In recent decades, the production of IL-1β and pyroptotic processes has been studied in the field of periodontitis. The periodontal pathogens belong to PAMPs that initiate IL-1β production. In macrophages, leucocytes and gingival fibroblasts, Porphyromonas gingivalis (P. gingivalis) is able to activate caspase-1, IL-1β and IL-18. P. gingivalis fimbriae, LPS and DNA act as PAMPs and are recognised by several surface and cytosolic PRRs, e.g., TLRs. However, different cell types vary in their priming and activating pathways. Macrophages and gingival epithelial cells participate in two signalling pathways. They first promote NLRP3 and pro-IL-1β expression in response to P. gingivalis. Subsequently, the binding of eATP to the P2X7 receptor, an ion-gated channel, is required for the maturation of IL-1β and final secretion. However, human monocytes require only one signal for secreting IL-1β after stimulation with TLR2 or TLR4 receptors due to the endogenous release of ATP and the activation of the P2X7 receptor. Human gingival fibroblasts are special in their response to P. gingivalis for the maturation of IL-1β. Supragingival biofilms could enhance caspase-1 activation and the expression of IL-1β and IL-18 in gingival fibroblasts. It was suggested that hypoxic conditions were essential in the maturation of IL-1β.

Actinobacillus actinomycetemcomitans (A. actinomycetemcomitans), the pathogen of aggressive periodontitis, upregulates IL-1β expression in human mononuclear leucocytes and macrophages. Leukotoxin, an important virulence factor that targets leucocytes, rapidly activates caspase-1 and thus induces a massive secretion of IL-1β in human monocytes and macrophages. The NLRP3 and AIM2 inflammasomes, reactive oxygen species and cathepsin B might be involved in the process. However, the exact signalling pathways are not clear and require further investigation.

THE ROLE OF IL-1B IN PERIODONTITIS
After secretion, the accumulated IL-1β triggers a series of inflammatory reactions and participates in the pathology of periodontal disease.
in the periodontium produce pro-inflammatory mediators, e.g., IL-6, IL-8, which are reported to stimulate bone resorption. In brief, IL-1β has a long-lasting effect on osteoclastogenesis, which leads to bone resorption.

THE INFLUENCE OF CURRENT THERAPIES ON IL-1β

The treatments for periodontitis consist of scaling and root planing (SRP), surgery and some adjunctive therapies, e.g., antibiotics, laser therapy or antimicrobial photodynamic therapy (aPDT). The therapies not only improve clinical parameters but also influence the levels of cytokines. However, conventional SRP and surgery are not efficient in reducing the IL-1 levels. Some adjunctive therapies have unexpected effects.

SRP and surgery
SRP is a cost-effective, minimally invasive and non-surgical treatment to prevent and/or control periodontal diseases. However, the mechanical treatment may be incomplete in eliminating the pathogenic microorganisms. The levels of pro-inflammatory cytokines may be continuously high after treatment. Previous studies found that SRP did not significantly reduce the IL-1 levels. Some recent studies also show that the IL-1β level is decreased after SRP treatment. SRP results in a decrease in the level of IL-1β in GCF or saliva. However, the amounts are still higher than in the healthy group. Furthermore, an obvious increase in the IL-1β level is detected even after papillary flap debridement, which suggests that trauma and wound healing result in prolonged production of IL-1β.

Due to the difficult access by SRP, the removal of plaque and infectious cells can be impaired in some sites. Although SRP treatment is effective in reducing clinical parameters, it is insufficient in the anti-inflammatory treatment for increased mediators. Thus, some adjuvant therapies have been analysed for this purpose.

Antibiotics
The local and systemic administration of antibiotics is an adjunctive treatment for periodontitis. Drugs such as minocycline, doxycycline, roxithromycin, amoxicillin and metronidazole are typically used. Clinical studies have shown that antibiotics promote clinical parameters. However, its effect on IL-1β is limited.

The local administration of minocycline microspheres in periodontal pockets during periodontal maintenance significantly reduces IL-1β in GCF at 6 months. However, there are no changes over 24 months. The systemic administration of amoxicillin and metronidazole is an adjunctive treatment for aggressive periodontitis. This treatment reduces the IL-1β level in GCF at 3 months, but it has no effect at the 6-month follow-up. Roxithromycin therapy is applied in cyclosporine-A-induced gingival overgrowth. However, there is no effect on the level of IL-1β. Furthermore, antibiotics at or below minimal inhibitory concentrations increase IL-1β secretion in macrophages by inducing the shedding of LPS by P. gingivalis.

Laser therapy
Lasers could be used as a monotherapy, as an adjunct to SRP, or in a surgery for incision. Laser therapy provided minimally invasive soft tissue and biostimulatory effects on tissue regeneration. Laser therapy significantly improved clinical parameters, including the plaque index, gingival index, probing depth, clinical attachment level and BOP. The biochemical parameters IL-1β and TNF-α were reduced as well.

For the treatment of periodontal inflammation, Nd:YAG therapy combined with SRP was more effective than SRP alone in reducing GCF IL-1β levels at the 1-week, 3-month and 6-month follow-ups. Nd:YAG laser therapy was also effective in reducing serum IL-1β in patients with periodontal diseases. Er,Cr:YSGG
laser therapy decreased IL-1β in both aggressive periodontitis and chronic periodontitis.107 However, SRP plus the adjunctive use of diode laser therapy did not reduce GCF IL-1β levels compared to SRP alone,108 nor did it reduce inflammation in sites with ≥5 mm PD.109 Er:YAG laser irradiation had little effect on GCF IL-1β levels, both in the SRP+laser group and in the laser-only group.110

Different types of lasers are more effective in some specific clinical areas. For example, the Nd:YAG laser could be used to remove gingival tissue and was the only laser for possible periodontal regeneration.111 The present evidence showed that the Nd:YAG laser was also effective in reducing IL-1β. However, more evidence about the types of lasers, different wavelengths and the best exposure protocol is needed to assess laser therapy.

Antimicrobial photodynamic therapy (aPDT)
aPDT is an antimicrobial treatment. The therapy is an oxygen-dependent photochemical reaction that occurs upon light-triggered activation of a certain photosensitisising compound. The reaction finally leads to the production of cytotoxic reactive oxygen species, predominantly singlet oxygen, which kills microorganisms including viruses, bacteria and fungi.112 Due to its antibacterial effects, aPDT along with SRP is advantageous and effective in the treatment of periodontitis.113 aPDT plus SRP resulted in a significant reduction in probing depth and a suppression of IL-1β and MMP-8 in GCF when compared with SRP alone.114 aPDT plus SRP also decreased the amount of periodontal pathogens (red and orange complexes) and lowered the IL-1β/IL-10 ratio in GCF compared to SRP alone.115 Compared with the systemic use of metronidazole, aPDT significantly lowered the bacterial load and IL-1β level of the gingival sulcus of rats with periodontitis.116 These results suggest that aPDT has an anti-inflammatory effect on IL-1β.

Overall, conventional treatment, including SRP, surgery and antibiotics, has limited effects on IL-1β. Some new adjunctive treatments, including laser therapy and antimicrobial photodynamic therapy, are comparably more efficient than conventional treatment. Some potential adjunctive treatments might be new strategies to target IL-1β.

THERAPEUTIC STRATEGIES FOR THE POTENTIAL USE OF IL-1 BLOCKAGE IN PERIODONTITIS

Other than the current therapies for IL-1β, are there any potential strategies to target IL-1β in periodontitis?2

The pathological role of IL-1 is being discovered in a broadening list of diseases in which blocking strategies of IL-1 could be effective. These diseases include classic autoimmune diseases and autoinflammatory diseases. The classic autoinflammatory diseases are rare, including neonatal-onset multisystem inflammatory disease, Muckle-Wells syndrome, familial cold-induced autoinflammatory syndrome, hyperimmunoglobulin D syndrome, etc. Recently, the benefit of IL-1 blockade has expanded to rare conditions, such as gout, diabetes mellitus and even myeloma. These conditions share the common feature that IL-1 is involved in their pathogenesis.112 Urate crystals promote IL-1β secretion and thus induce joint inflammation in gout.118 Type II diabetes mellitus is a chronic inflammatory disease in which β cells are continuously destroyed by IL-1119 and is improved by treatment with an IL-1 receptor antagonist.120 IL-1β produced by myeloma cells stimulates the secretion of IL-6 by adjacent stromal cells. The excess IL-6 in turn promotes the proliferation of the pre-myeloma cells.121

The effect of IL-1β in periodontitis is discussed above. Studies early in 1998 showed that blocking IL-1β resulted in reduced progression of periodontal bone loss and attachment loss in a non-human primate model of periodontitis,2,122 suggesting that IL-1 blockage is potentially effective in periodontitis. With the current development of IL-1 blocking agents, the strategy of blocking IL-1β may have new prospects.

Fig. 3 The agents that block IL-1β activity, including IL-1β inhibitors, IL-1 receptor antagonist, NLRP3 inflammasome inhibitors and P2X7 antagonists. IL-1R1, subunit of IL-1 receptor; IL-1RAcP, IL-1R accessory protein.

Since the first blocking agent, anakinra (Kineret; Amgen) was introduced in 1993,124 a variety of agents have been produced for IL-1 blockage, including IL-1β receptor antagonists, inflammasome inhibitors and P2X7 antagonists. These antagonists/antibodies are shown in Fig. 3.

IL-1β receptor antagonists/antibodies
Anakinra (Kineret). Anakinra is a recombinant homologue of the IL-1 receptor antagonist. It competes with IL-1α and IL-1β to bind to the IL-1 receptor and thus reduces the activity. Anakinra was first approved in the US in 2001 and in Europe in 2001 for the treatment of rheumatoid arthritis. It has been proven to be effective in a variety of inflammatory diseases.124,125 In 2018, the National Health Service (England) published a Clinical Commissioning Policy for anakinra to treat periodic fevers and autoinflammatory diseases at all ages. However, anakinra has a short half-life of 4–6 h; therefore, daily subcutaneous injections were required.126

Rilonacept (Arcalyst). Rilonacept is a recombinant IL-1 antagonist consisting of the extracellular portion of the human IL-1 receptor and the IL-1 receptor accessory protein fused with the Fc portion of human IgG1. The extracellular portion has a strong affinity for both IL-1α and IL-1β, thereby neutralising their activities and functioning as an “IL-1 trap”.127,128 It was approved by the FDA in 2008 for the treatment of cryopyrin-associated periodic syndromes (CAPS). Presently, a number of clinical trials are being developed for chronic inflammatory diseases, including type I diabetes (NCT00962026), atherosclerosis (NCT00174177), hepatitis (NCT01903798) and chronic kidney disease (NCT01663103).129 Furthermore, rilonacept has a longer half-life of 6–8 days; therefore, the interval of injections can be extended to a week.126

Canakinumab (Ilaris). Canakinumab is a high-affinity, fully human monoclonal anti-IL-1β antibody designed to exclusively bind and neutralise human IL-1β. Canakinumab was approved by the FDA in 2009 for the treatment of CAPS. Some more clinical trials for diseases such as osteoarthritis (NCT01160822), chronic obstructive pulmonary disease (NCT00581945), type II diabetes (NCT00605475), atherosclerosis (NCT00995930) and rheumatoid arthritis (NCT00504595, NCT00424346) are undergoing. The half-life of canakinumab is as long as 26 days, which ensures that the
injection can be administered bimonthly, a substantial advantage over anakinra and rilonacept.126

Inflammasome inhibitors
The NLRP3 inflammasome contributes to the maturation of IL-1β. The inflammasome inhibitors include the targets caspase-1 and NLRP3.

Caspase 1 inhibitor. Belnacasan (VX-765, Vertex Pharmaceuticals) is a selective inhibitor of caspase-1. It is an orally absorbed prodrug that is converted to VRT-043198 under the action of plasma and liver esterase.123 Currently, Belnacasan is used to suppress caspase-1 activity in inflammatory diseases. It inhibits collagen-induced arthritis and lung inflammation in mouse models.130,131 It partly decreases bone resorption in the periapical lesion of rat experimental apical periodontitis.80 In addition to its anti-inflammatory effect, VX-765 also has a protective role against cell death. It combines with a P2Y12 antagonist, cangrelor, to reduce myocardial infarct size and preserve ventricular function.132 VX-765 is well tolerated in phase II clinical trials in patients with epilepsy and133 also possesses neuroprotective activity in multiple system atrophy in a mouse model.134

NLRP3 inflammasome activation inhibitors. MCC950 and β-hydroxybutyrate are two small-molecule inhibitors of the NLRP3 inflammasome. MCC950 is a diarylsulfonlfurea-containing compound that selectively inhibits the activation of the NLRP3 inflammasome. MCC950 acts specifically on the NLRP3 inflammasome but not on NLRP1, AIM2 or NLRC4 inflammasomes. MCC950 blocks ASC oligomerization and the activation of caspase-1 and IL-1β in mouse and human macrophages.135 Thus, MCC950 reduces IL-1β production and may serve as a potential target for inflammatory diseases.136–138 It also provides protection against injury. MCC950 significantly reduces the development of atherosclerotic lesions, cardiac infarction and brain injury after intracerebral haemorrhage in mice.139–141

β-Hydroxybutyrate (BHB) is a ketone body that is produced as an adaptive starvation response during a negative energy balance.142 BHB inhibits the NLRP3 inflammasome in macrophages and neutrophils.143,144 Although IL-1β or IL-1 receptor antagonists have been approved by the FDA and have been shown to be effective in some clinical trials, the high costs and potential risk may limit their use. BHB, an endogenous ketone, may function as a regulatory metabolite to regulate inflammation. It has an anti-inflammatory effect on retinal damage.143 BHB prevents NLRP3 inflammasome activation in both mouse and human neutrophils and reduces urate-crystal-induced inflammation in individuals with gout.144

Compared with the currently used IL-1β or IL-1 receptor antagonists, MCC950 and BHB are less expensive to produce. Due to their specificity, MCC950 and BHB will benefit NLRP3-targeted therapies for both acute and chronic inflammatory diseases.146

P2X7 antagonists
The P2X7 receptor is an ionotropic ATP-gated cation channel. DAMPs, such as eATP, which is released from damaged cells, activate the purinergic receptor and function as a second signal for assembly of the NLRP3 inflammasome. The NLRP3 inflammasome in turn initiates and amplifies the innate immune and IL-1β-dependent pro-inflammatory responses.147,148 The P2X7 receptor antagonist has potential in the treatment of chronic pain, inflammation and cancer.149,150 The P2X7 receptor antagonists inhibit eATP-induced IL-1β secretion in P. gingivalis-infected macrophages.38 An antagonist of the P2X7 receptor, AZ106006120, reduces neutrophil infiltration and the secretion of pro-inflammatory cytokines in a mouse model of acute lung injury.151 Several P2X7 antagonists are in clinical trials for inflammatory or pain-related diseases. Unfortunately, AstraZeneca’s AZD-9056 and Pfizer’s CE-224,535 failed in phase II clinical trials. Evotec’s EVT 401 is in phase II clinical trials. GSK’s GS1482160 and Afectex’s Pharmaceutical’s AFC-5128 are currently in phase I clinical trials.149

OTHER POTENTIAL AGENTS THAT INFLUENCE IL-1B IN PERIODONTITIS
Some in vitro and in vivo experiments showed that some other agents have anti-inflammatory properties against IL-1β. They might be candidates for future adjuvant treatments.

Plant-derived substances
Plant-derived substances are largely utilised in immunomodulatory therapy. Some of them have anti-inflammatory effects that modulate the host response in inflammation.152 Resveratrol and curcumin are produced by several plants and belong to polyphenols. They are capable of reducing IL-1β and bone loss in animal models of experimental periodontitis.153 The anti-inflammatory properties of curcumin are similar to those of chlorhexidine-metronidazole.154 Curcumin attenuates the production of IL-1β and TNF-α stimulated by LPS in rat gingival fibroblasts in vitro.154 Piperine isolated from black and long peppers exhibits anti-inflammatory activity. It inhibits alveolar bone loss and downregulates the expression of IL-1β in rat periodontitis.155 Plumbagin is extracted from the roots of Plumbago zeylanica L. It significantly decreases the expression of TNF-α, IL-1β and IL-6 and decelerates bone destruction in rats with chronic periodontitis.156 Compared to the systemic antimicrobial agents or the chemical agent chlorhexidine gluconate, plant-derived substances partly avoid the problems of drug resistance, overdoses and a number of adverse effects.157,158 Plant-derived substances have great potential as adjuvant therapy for periodontal diseases.

Anti-inflammatory agents
Some anti-inflammatory or antioxidant agents are beneficial for reducing IL-1β. Metformin is an agent for the treatment of type II diabetes. Metformin activates AMP-activated protein kinase, which has been shown to exert significant anti-inflammatory and immunosuppressive effects.159,160 Metformin reduces the concentrations of IL-1β and bone loss in a rat model of experimental periodontitis.161 In vitro, metformin inhibits LPS-induced IL-1β production in human gingival fibroblast cells.162

Vitamin E, a potent antioxidant, is important to the host’s antioxidant defence and immune functions.163 Vitamin E decreases the secretion of IL-1β in human gingival fibroblasts stimulated with P. gingivalis LPS. As a result, vitamin E may have anti-inflammatory effects against P. gingivalis.164

Antibodies or antagonists
There are also some antibodies or antagonists that indirectly influence IL-1β. Infliximab is a monoclonal antibody against TNF-α. It reduces the expression of IL-1β in gingiva and has significant anti-inflammatory and bone-protective effects in Wistar rats with experimental periodontitis.165 Bortezomib, a proteasome inhibitor, is used as an anticancer drug. Bortezomib interrupts the breaking-down process of the proteasome and promotes the death of cancer cells. The anticancer activity is accompanied by an anti-inflammatory effect. It has been reported that bortezomib inhibits the expression of IL-1β and prevents alveolar bone absorption in experimental periodontitis.166

CONCLUSION
IL-1β is an important pro-inflammatory cytokine and participates in periodontitis. As a strong stimulator of bone resorption, continuous bone loss may be induced by IL-1β. Conventional
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therapies, SRP, surgery and antibiotics have limited effects on IL-1β. IL-1β blockage by receptor antagonists, antibodies, inhibitors, plant-derived substances and anti-inflammatory agents is benefi-
cial for reducing IL-1β. More investigation is necessary for IL-1β blockage to be used in periodontal treatment or as an adjunctive treatment in the future.

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T.H. and R.C. jointly designed the theme and content structure. R.C. and Z.W. wrote the manuscript. M.L. contributed to the figures. M.S. contributed to the revision. T.H. conducted the editing and critical revision.

ADDITIONAL INFORMATION
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