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Immunomodulatory Effects of Novel Anti-Inflammatory Interleukins in Periodontitis

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Abstract: *This narrative review systematically synthesizes current preclinical and clinical evidence from PubMed-based electronic database searches to comprehensively elucidate the functional roles of interleukin (IL)-35, IL-37, and IL-38 in the pathogenesis of periodontitis and explore their translational potential for innovative periodontal therapeutic strategies. Existing studies demonstrate that these three cytokines exert crucial immunomodulatory effects on periodontal immune homeostasis with distinct expression patterns and functional characteristics. IL-35 is compensatorily upregulated in the local tissues and biofluids of periodontitis patients in a disease severity-dependent manner, and it protects periodontal tissues by remodeling the Th17/Treg/Breg immune balance, suppressing pro-inflammatory signaling pathways, and inhibiting osteoclastogenesis, while its local anti-inflammatory expression is markedly impaired by smoking and diabetes. IL-37 is elevated in periodontitis gingival lesions but downregulated in specific inflammatory models, serving as a vital anti-inflammatory mediator that blocks the NF-κB/NLRP3 signaling pathways, regulates macrophage polarization, and alleviates alveolar bone resorption and periodontal matrix degradation, with its biological function further modulated by genetic polymorphisms. Research on IL-38 remains in the preliminary stage, and available data indicate that its expression increases with inflammatory progression and is strongly correlated with clinical periodontal indicators, maintaining periodontal immune homeostasis mainly via antagonizing the IL-36 receptor, while inconsistent expression results in relevant studies are largely attributed to methodological heterogeneity. Collectively, IL-35, IL-37, and IL-38 act as key local immunomodulators that construct a complementary anti-inflammatory regulatory network together with IL-10, participating in the modulation of immune cell differentiation, inhibition of inflammatory cascade activation, and suppression of alveolar bone and connective tissue destruction during periodontitis development. Their aberrant expression profiles are closely associated with periodontitis progression, endowing them with great potential as non-invasive biomarkers for disease evaluation and therapeutic monitoring, as well as promising targets for periodontal immunotherapy. Nevertheless, current research still has inherent limitations including incomplete mechanistic exploration and insufficient clinical validation, and further translational studies are urgently needed to promote the clinical application of these cytokines and advance the development of precision periodontology.*

Keywords: *Periodontitis, IL-35, IL-37, IL-38, Immunomodulation, Biomarkers, Targeted therapy*

1. Introduction

Periodontitis is a chronic inflammatory disease initiated by dental plaque biofilms, primarily affecting the gingiva, periodontal ligament, alveolar bone, and cementum. Its hallmark pathological features include gingival inflammation, periodontal pocket formation, and progressive alveolar bone resorption. In its advanced stages, the disease leads to increased tooth mobility and loss, which not only impairs masticatory function and aesthetics but also contributes to systemic inflammation

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dissemination, posing a significant threat to general health[1,2]. Severe periodontitis, in particular, is characterized by extensive tissue destruction and a substantial disease burden, representing a major global public health challenge[3].

Epidemiological evidence underscores the widespread prevalence of this condition. In 2021, the age-standardized prevalence of severe periodontitis globally reached 12.50%, affecting more than 1.067 billion people, and it is estimated to increase to 1.566 billion by 2050, with an increase of 44.32%[3]. The peak incidence occurs in the 50–64 years old population, and the prevalence decreases with age due to tooth loss[3]; in the United States, the prevalence is particularly prominent among the elderly over 65 years old, which is the main threat to oral health in the elderly[4]. Geographically, the South Asian region has the highest prevalence (17.57%), while Denmark has the highest prevalence among high-income countries[3]. In addition, the prevalence of periodontitis in dentate populations in China showed a stable and high trend from 2011 to 2020, providing an important basis for disease prevention and control[5]. The progression of periodontitis is significantly exacerbated by risk factors such as smoking, diabetes, and betel quid chewing, which impair host immune responses[1]. Notably, studies on the prognostic effect of non-surgical treatment have confirmed that intervention on these risk factors is crucial for disease control[6], as risk factor-induced immune dysfunction is closely related to the progression of periodontitis. Immune imbalance is the core link in the progression of periodontitis[1]. Under physiological conditions, periodontal immunity maintains homeostasis; however, long-term plaque stimulation can break this balance, activate innate and adaptive immunity, and prompt macrophages and T cells to release a large number of pro-inflammatory factors (such as TNF-α, IL-6, and IL-1β), thereby triggering a cascade of tissue damage and bone resorption[1]. Periodontal tissues are often accompanied by immune cell infiltration and abnormal expression of inflammatory factors, and host regulatory therapy alleviates inflammation and delays disease progression by correcting immune imbalance[7]. Consistent with this, non-surgical treatment can regulate the periodontal immune microenvironment and inhibit excessive inflammation[6], which is in line with the modern periodontal treatment concept that focuses on etiological control and immune regulation[8].

The interleukin (IL) family constitutes a pivotal class of cytokines that orchestrate local immuno-inflammatory responses within the periodontium. Their functional dichotomy—categorized into pro-inflammatory and anti-inflammatory interleukins—establishes a dynamic equilibrium that dictates the clinical trajectory of periodontal destruction[9,10]. Specifically, pro-inflammatory mediators such as IL-1β, IL-6, IL-17, and IL-23 exhibit robust expression in response to pathogenic biofilms. These cytokines directly drive the degradation of periodontal connective tissues and promote alveolar bone resorption by upregulating RANKL expression and inducing osteoclastogenesis, while simultaneously amplifying the inflammatory cascade to exacerbate tissue lesions[9,11]. In contrast, the anti-inflammatory arm is traditionally centered on IL-10, which preserves periodontal homeostasis by post-transcriptionally inhibiting pro-inflammatory cytokine synthesis, arresting osteoclast formation, and modulating immune cell lineage commitment[9,12,13]. This cytokine plays a crucial protective role in preventing excessive inflammatory activation and the progression of gingivitis to periodontitis. Consequently, elucidating the complex interplay within the IL family is essential for identifying novel diagnostic biomarkers and therapeutic targets. Recent advancements have expanded this regulatory network to include novel anti-inflammatory interleukins—such as IL-35, IL-37, and IL-38. Similar to IL-10, these novel anti-inflammatory interleukins are involved in the regulation of periodontal immune homeostasis, and their discovery further enriches the understanding of the regulatory network of IL family in periodontal inflammation, providing more potential targets for the targeted treatment of periodontitis.

IL-35, a novel anti-inflammatory member of the IL-12 family identified in 2007, is a heterodimeric cytokine comprising the IL-12p35 and EBI3 subunits. It stands unique within its family for its specialized immunosuppressive capacity[14]. Primarily secreted by regulatory T and B cells (Tregs and Bregs), IL-35 directly curtails effector T-cell proliferation, inhibits Th17 differentiation, and facilitates the conversion of conventional T cells into iTr35 regulatory cells, thereby establishing a robust immunosuppressive positive feedback loop[14,15]. In autoimmune inflammatory diseases such as ankylosing spondylitis and systemic lupus erythematosus, the expression of IL-35 is significantly downregulated, which is negatively correlated with disease activity; exogenous IL-35 can promote Breg expansion and inhibit pro-inflammatory cellular responses[16,17]. In parallel, IL-37 serves as a critical immunomodulator within the IL-1 family. Distinguished by its lack of a murine homolog, IL-37 exerts dual inhibitory effects through distinct spatial pathways: intracellularly, it binds to Smad3 to modulate gene transcription, while extracellularly, it forms a functional receptor complex with IL-18Rα and IL-1R8[18-20]. Notably, IL-37 can be induced in human Bregs via the TLR9-HIF-1α axis independently of IL-10, providing a protective shield against excessive inflammation in conditions like

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psoriasis and colitis[18,19]. IL-37 plays a protective role in various inflammation-related diseases such as psoriasis and colitis by inhibiting the release of pro-inflammatory factors[18,19]. IL-38 (formerly IL-1F10), another pivotal IL-1 family member identified in 2001, shares significant structural homology with IL-1Ra and IL-36Ra[21,22]. Uniquely, IL-38 lacks a conventional signal peptide and requires N-terminal proteolytic processing to achieve full biological potency, where it primarily antagonizes the IL-36 receptor to arrest inflammatory signaling[21,22]. Dysregulated IL-38 expression is a hallmark of rheumatoid arthritis and gout, while its administration confers systemic protection in models of sepsis[21-23]. Collectively, these cytokines occupy distinct immunological niches: IL-35 orchestrates a self-sustaining suppressive loop, IL-37 utilizes dual-compartment signaling, and IL-38 establishes a protective anti-inflammatory network. Their mechanisms further diverge in their relationship with IL-10: IL-35 synergizes with IL-10 and promotes its secretion; IL-37 functions autonomously; and IL-38 upregulates IL-10 to achieve therapeutic synergy[14,16][18][24]. These nuanced distinctions suggest that IL-35, IL-37, and IL-38 act as complementary adjuncts to IL-10, offering a multifaceted toolkit for targeted immunotherapy. Given their unique regulatory profiles, these cytokines hold immense translational potential for the diagnosis and intervention of inflammatory diseases—particularly in periodontitis, where recalibrating the immuno-inflammatory balance is the cornerstone of effective therapy.

2. The Expression and Role of Novel Anti-Inflammatory Interleukins in Periodontitis

2.1. The Expression and Role of IL-35 in Periodontitis

As a cornerstone of the IL-12 family's anti-inflammatory and immunosuppressive repertoire, IL-35 exhibits a distinct temporal-spatial expression profile throughout the pathogenesis and progression of periodontitis. It serves a vital protective function in preserving periodontal homeostasis by modulating immune cell equilibrium, antagonizing pro-inflammatory signaling cascades, and curbing pathological alveolar bone resorption. A burgeoning body of clinical and preclinical research has further elucidated the expression dynamics, regulatory drivers, and molecular underpinnings of IL-35 within the periodontal microenvironment. These findings not only clarify its role in disease mitigation but also underscore its significant translational potential as a target for innovative therapeutic interventions.

Clinical investigations have revealed that IL-35 expression exhibits distinct tissue and biofluid specificity, closely mirroring the severity of the disease state. At the localized periodontal level, IL-35 levels in both gingival tissues and gingival crevicular fluid (GCF) are markedly elevated in patients with chronic and severe periodontitis compared to periodontally healthy controls. Furthermore, these levels exhibit a strong positive correlation with Probing Depth (PD) and Clinical Attachment Loss (CAL), suggesting a compensatory upregulation in response to advancing inflammatory destruction[25]. Of particular clinical relevance, GCF IL-35 levels in patients with Stage III and IV periodontitis are significantly increased, underscoring its potential as a localized biomarker for assessing disease severity[26]. However, a nuanced distinction exists regarding its quantification: while the total amount of IL-35 within the GCF reservoir increases, the volumetric concentration may appear diminished. This phenomenon is primarily attributed to the dilution effect resulting from the inflammatory surge in GCF volume, a critical factor to consider when interpreting humoral immune profiles in periodontal research[27].

Regarding extracellular biofluids, salivary IL-35 concentrations in periodontitis patients are significantly elevated compared to those in periodontally healthy individuals. Notably, tobacco smoking appears to exert a suppressive effect on this cytokine; smokers exhibit markedly attenuated IL-35 levels in both saliva and GCF relative to non-smokers, indicating that smoking may impair the local expression and anti-inflammatory potency of IL-35[25,28]. At the systemic level, serum IL-35 concentrations do not show significant variance between periodontitis patients and healthy controls, further underscoring its role as a primarily localized immunomodulator. However, in the context of systemic comorbidities, periodontitis patients with type 2 diabetes mellitus (T2DM) demonstrate diminished GCF IL-35 levels, which significantly rebound following non-surgical periodontal therapy (NSPT)[27]. This suggests that the dynamic fluctuations of IL-35 within the periodontal microenvironment can effectively reflect the host's response to treatment. A recent systematic review corroborates these findings, confirming that IL-35 is substantially upregulated in the saliva, GCF, and gingival tissues during active disease, followed by a significant decline in parallel with the resolution of inflammation post-therapy[29]. Consequently, IL-35 holds immense promise as a non-invasive diagnostic indicator for monitoring inflammatory activity and evaluating therapeutic outcomes in

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clinical practice.

Preclinical investigations have further substantiated the profound regulatory influence of the inflammatory microenvironment on endogenous IL-35 expression. In murine ligature-induced periodontitis models, IL-35 expression at lesion sites is upregulated in tandem with the kinetics of disease progression. Notably, the exogenous administration of IL-35 effectively augments the local cytokine pool, thereby alleviating gingival inflammation, reducing leucocyte infiltration, and significantly attenuating pathological alveolar bone resorption[30]. At the cellular level, stimulating human periodontal ligament cells (hPDLCs) with IL-17A serves to recapitulate the localized inflammatory milieu of periodontitis. In this microenvironment, endogenous IL-35 expression is markedly suppressed, whereas the introduction of recombinant IL-35 significantly mitigates the resulting inflammatory response[31]. Furthermore, in RANKL-induced osteoclastogenesis models, IL-35 displays dynamic expression shifts and exhibits a distinct bifunctional regulatory profile[32]. Additionally, expanded populations of CD25+ and CD1dhiCD5+ regulatory B cells (Bregs) in periodontitis models have been identified as a major cellular reservoir, orchestrating the robust secretion of IL-35 within the periodontal tissues[27,33].

The protective efficacy of IL-35 in periodontitis is primarily mediated through a triad of interconnected pathways: systemic immunomodulation, localized anti-inflammatory signaling, and potent osteoprotection. First, IL-35 recalibrates the Th17/Treg equilibrium by suppressing the expansion of pro-inflammatory Th17 populations while expanding the Treg compartment. Concurrently, it fosters a self-reinforcing anti-inflammatory circuit by stimulating Breg proliferation and augmenting the secretion of IL-10 and IL-35, thereby stabilizing the periodontal immune microenvironment[30,33]. Second, IL-35 directly abrogates the IL-17A-induced phosphorylation of ERK and NF-κB p65 signaling cascades. This molecular intervention inhibits the downstream release of key chemokines and cytokines (such as IL-6 and IL-8) from hPDLCs, effectively dampening the propagation of inflammatory signals[31]. Third, IL-35 exerts a direct inhibitory influence on osteoclastogenesis; by downregulating RANKL expression and concurrently upregulating OPG, it significantly lowers the RANKL/OPG ratio, thereby arresting osteoclast activation and curbing pathological bone resorptive activity[30].

Notably, IL-35 exhibits a striking context-dependent duality in its biological function. While it confers potent anti-inflammatory and osteoprotective effects in isolation, IL-35 can paradoxically facilitate osteoclastogenesis via the ERK/MAPK signaling pathway when acting synergistically with RANKL[32]. This suggests that the functional output of IL-35 is strictly governed by the local cytokine milieu, potentially explaining its divergent regulatory roles across varying inflammatory stages. Furthermore, IL-35 facilitates the induction of iTr35 regulatory T cells through the activation of the STAT1/STAT4 signaling axis, establishing a self-perpetuating immunosuppressive circuit. Of clinical significance, in patients where periodontitis is comorbid with rheumatoid arthritis, elevated IL-35 levels show a robust correlation with pro-inflammatory microbial signatures[27,34]. These multifaceted roles underscore the complexity of IL-35 as a pivotal immunomodulator that bridges local periodontal destruction with systemic autoimmune dynamics.

In aggregate, IL-35 is compensatorily upregulated within the localized periodontal tissues of affected patients, although its expression can be markedly attenuated by risk factors such as tobacco smoking and systemic comorbidities like type 2 diabetes. Evidence from both in vivo and in vitro models underscores that while endogenous IL-35 is modulated by the inflammatory milieu, exogenous supplementation can effectively mitigate periodontal inflammation and arrest pathological bone resorption. This protective efficacy is primarily underpinned by the cytokine's ability to recalibrate the Th17/Treg/Breg immunomodulatory axis, suppress pro-inflammatory signaling cascades, and antagonize osteoclastogenesis. Collectively, IL-35 emerges as a promising biomarker for disease assessment and a potent candidate for immune-targeted therapy, providing a robust theoretical framework for precision periodontology. Nonetheless, further investigations are warranted to elucidate the molecular intricacies governing its functional duality and to validate its clinical utility across diverse periodontitis phenotypes.

2.2. The Expression and Role of IL-37 in Periodontitis

As a paradigmatic anti-inflammatory mediator within the IL-1 family, IL-37 exhibits sophisticated temporal-spatial expression dynamics throughout the progression of periodontitis. It functions as a critical homeostatic regulator by modulating multi-targeted signaling pathways, thereby mitigating osteoclastic bone destruction and preserving periodontal tissue integrity. A synergistic body of clinical

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and mechanistic research has elucidated the expression profiles, regulatory triggers, and molecular underpinnings of IL-37, providing a robust foundation for its clinical translation.

Clinical investigations underscore distinct biofluid-specific profiles in IL-37 expression among periodontitis patients. Within the gingival architecture, IL-37 levels are significantly upregulated in lesions of both chronic and aggressive periodontitis compared to healthy tissues. Notably, IL-37b emerges as the predominant functional isoform, primarily orchestrated by gingival keratinocytes and infiltrating plasma cells[35,36]. In gingival crevicular fluid (GCF), the expression kinetics appear highly phenotype-dependent: in aggressive periodontitis, IL-37 levels are markedly elevated at baseline but decline in parallel with the resolution of inflammation post-therapy[37]. Conversely, a notable discrepancy exists in chronic periodontitis, where GCF IL-37 concentrations appear lower than in healthy individuals despite stable total amounts—a phenomenon primarily ascribed to the volumetric dilution effect of inflammatory GCF[38]. In saliva, the level of IL-37 in patients with unstable periodontitis (a subtype of chronic periodontitis) is significantly lower than that in healthy people[39]. Furthermore, the stability of serum IL-37 levels between patients and controls suggests that IL-37 acts as a localized immunomodulator with limited diagnostic utility as a systemic biomarker[10,38]. Crucially, the functional integrity of IL-37 is governed by genetic predisposition. Single nucleotide polymorphisms (SNPs), specifically the loss-of-function variant rs3811046, induce aberrant mRNA splicing and impaired protein secretion. This genetic defect results in a failure to suppress IL-1β expression within the GCF, significantly elevating the risk of severe periodontal destruction and long-term tooth loss[36].

Preclinical investigations have further substantiated the regulatory impact of the inflammatory microenvironment on IL-37 expression. Notably, an apparent paradox exists between the diminished IL-37 levels observed in fundamental models and the compensatory elevation seen in clinical tissues—a discrepancy likely ascribable to the absence of systemic compensatory feedback within simplified in vitro systems. In cellular models, such as LPS-stimulated human gingival epithelial cells and macrophages, endogenous IL-37 expression is significantly suppressed, indicating that acute inflammatory insults may initially impair IL-37 synthesis[40,41]. Conversely, in murine ligature-induced periodontitis, exogenous recombinant IL-37 administration effectively mitigates gingival inflammation, reduces leucocyte infiltration, and arrests pathological bone resorption[41,42]. Furthermore, IL-37 exhibits a dose-dependent inhibitory effect on osteoclastogenesis, effectively downregulating bone-resorption-related gene transcription[35,43].

Mechanistically, IL-37 exerts its periodontal protection through a bifaceted approach: multifaceted anti-inflammation and potent osteoprotection. The anti-inflammatory repertoire comprises a quadruple mechanism: First, it abrogates the activation of classic pro-inflammatory cascades, such as NF-κB and MAPK, thereby quenching the release of IL-1β, IL-6, and TNF-α[42,44]. Second, it directly antagonizes NLRP3 inflammasome activation, reducing Caspase-1-mediated maturation of IL-1β and interrupting the inflammatory cascade[41,42]. Third, it facilitates macrophage phenotypic switching, tilting the balance from pro-inflammatory M1 toward an anti-inflammatory M2 phenotype to restore immune homeostasis[41]. Fourth, it suppresses LPS-induced MMP-9 expression, preserving the integrity of the periodontal extracellular matrix[40].

The osteoprotective axis is characterized by the downregulation of RANKL and the suppression of master transcription factors for osteoclast differentiation[35,43]. Crucially, the functional potency of IL-37 is contingent upon Caspase-1-mediated proteolytic processing of its precursor; genetic variants that impair this cleavage efficiency effectively diminish its protective capacity—a finding that aligns with the increased risk of severe periodontitis observed in specific clinical cohorts[36].

In summary, while IL-37 expression patterns vary across clinical and experimental contexts, its role as a potent homeostatic rheostat is indisputable. IL-35, IL-37, and IL-38 collectively emerge as a novel immunoregulatory toolkit for the precision diagnosis and targeted intervention of periodontitis. Nevertheless, future research must prioritize elucidating the optimal therapeutic dosage and the precise molecular triggers governing the "clinico-basic" expression discrepancy.

2.3. The Expression and Role of IL-38 in Periodontitis

Compared to the extensive body of research on IL-35 and IL-37, investigations into interleukin-38 (IL-38) within the context of periodontitis remain relatively nascent. Current literature is predominantly characterized by descriptive analyses of expression profiles and clinical correlations, with a notable paucity of functional or mechanistic studies.

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Clinical evidence has substantiated the presence of IL-38 within the gingival tissues of periodontitis patients[45], implicating its involvement in the localized immunoregulatory network. Specifically, assessments of systemically healthy individuals—carefully screened to exclude comorbidities such as diabetes—revealed that IL-38 levels in both gingival crevicular fluid (GCF) and saliva were significantly elevated in Stage II-III periodontitis patients compared to healthy controls[46]. Furthermore, IL-38 concentrations exhibit robust positive correlations with hallmark clinical parameters, including Probing Depth (PD), Clinical Attachment Loss (CAL), and Gingival Index (GI). Notably, the progressive increase of IL-38 in GCF in tandem with advancing disease severity underscores its potential as a promising diagnostic biomarker for monitoring periodontal inflammatory activity[46].

Notwithstanding the aforementioned findings, a recent clinical investigation observed that salivary IL-38 levels were significantly lower in periodontitis patients compared to healthy controls[47]. These divergent outcomes may be ascribed to methodological heterogeneity, including the inclusion of systemic comorbidities (e.g., type 2 diabetes or hypertension), variations in periodontal staging and grading, and disparities in biofluid collection protocols (e.g., unstimulated whole saliva vs. stimulated samples) or analytical platforms (e.g., ELISA vs. qPCR)[47]. Furthermore, the finding that IL-38 expression is markedly diminished in the palatal mucosa of smokers suggests a critical nexus between this cytokine and oral mucosal immune homeostasis[48]. This observation indirectly corroborates the potential regulatory role of IL-38 in periodontitis, given the intrinsic link between mucosal barrier immunity and periodontal health. Preclinical evidence further supports this correlation; in murine ligature-induced periodontitis models, IL-38 expression in gingival tissues is significantly downregulated[49], a result that aligns with the protective role of IL-38 implied by some clinical cohorts.

In summary, the current understanding of IL-38 in oral inflammatory diseases remains fragmented. The primary research lacuna exists in the lack of functional validation, specifically regarding the molecular mechanisms by which IL-38 influences the pathogenesis and progression of periodontitis. Elucidating its regulatory effects on immune cell polarization, inflammatory signaling cascades, and its synergistic or antagonistic interplay with other anti-inflammatory cytokines represents a pivotal avenue for future inquiry and a cornerstone for developing novel immune-targeted therapies in periodontology.

3. Conclusion

Periodontitis is a chronic inflammatory disorder initiated by dysbiotic plaque biofilms, in which immuno-inflammatory dysregulation serves as the central pathological driver of tissue destruction. While canonical anti-inflammatory cytokines, such as IL-10, have been extensively characterized, their therapeutic translation is often hindered by their relatively narrow regulatory spectrum.

Consequently, a novel triad of anti-inflammatory interleukins—IL-35, IL-37, and IL-38—has garnered significant attention due to their unique immunosuppressive architectures and multifaceted regulatory repertoires. This review provides a systematic synthesis of their temporal-spatial expression profiles and molecular mechanisms during the pathogenesis and progression of periodontitis. Furthermore, it evaluates their potential as diagnostic biomarkers and therapeutic candidates, aiming to furnish a robust theoretical framework for the advancement of Host Modulatory Therapy (HMT) strategies. Collectively, these insights strive to bridge the gap between basic immunobiology and the implementation of precision periodontology.

As the only member of the IL-12 family with specific anti-inflammatory activity, IL-35 exhibits a compensatory elevation in the gingival tissue, gingival crevicular fluid (GCF), and saliva of patients with periodontitis, compared with healthy individuals. Importantly, its expression level is positively correlated with the severity of periodontitis, suggesting that IL-35 is expected to be a non-invasive biological marker for evaluating the activity of periodontal inflammation and therapeutic efficacy. At the mechanistic level, IL-35 exerts anti-inflammatory and bone-protective effects through multiple pathways: remodeling the Th17/Treg/Breg immune balance, blocking the activation of NF-κB and ERK pro-inflammatory signaling pathways, and regulating the activity of the RANKL/OPG axis to inhibit bone resorption. Notably, the biological effects of IL-35 are microenvironment-dependent: it exerts a protective effect on periodontal tissues when used alone, but may promote osteoclast formation when acting synergistically with RANKL. This characteristic indicates that precise control of local concentration and cytokine microenvironment is required when conducting IL-35-related interventions in clinical practice. Risk factors for periodontitis, such as smoking and type 2 diabetes, can significantly downregulate the expression level of IL-35 in local tissues, thereby impairing its anti-inflammatory and bone-protective biological efficacy—this finding provides a new research

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direction for combining risk factor intervention with immune regulation therapy.

Different from IL-35, IL-37 exerts its biological functions through dual anti-inflammatory signaling pathways and targeted regulation of inflammasomes. Clinically, IL-35 is compensatory elevated in periodontal lesion tissues; however, its expression is downregulated in inflammatory cell models and animal models of periodontitis. Exogenous administration of recombinant IL-37 can effectively alleviate local periodontal inflammatory responses and inhibit bone resorption damage. Its core regulatory mechanisms include multiple aspects: on the one hand, it inhibits the activation of the NF-κB/MAPK signaling pathway; on the other hand, it blocks the activation of the NLRP3 inflammasome; meanwhile, it regulates the polarization state of M1/M2 macrophages, ultimately inhibiting osteoclast differentiation and MMP-9-mediated extracellular matrix degradation. Polymorphisms of the IL-37 gene can directly affect the shearing, processing, and secretion efficiency of its protein, significantly increasing an individual's susceptibility to severe periodontitis and the risk of tooth loss. This result suggests that individual differences at the genetic level are important entry points for achieving precise diagnosis and treatment of periodontitis in the future. In addition, the anti-inflammatory effect of IL-37 is independent of IL-10 mediation, and it can form a complementary immune regulatory network with traditional anti-inflammatory factors.

As an antagonist of the IL-36 receptor belonging to the IL-1 family (IL-36 subfamily), research on IL-38 in periodontitis is still in the preliminary exploration stage, and existing research conclusions remain controversial. Most clinical studies have shown that with the aggravation of periodontal inflammation, the expression level of IL-38 in GCF, saliva, and gingival tissue tends to increase, and it has a strong correlation with clinical periodontal parameters (e.g., probing depth [PD], clinical attachment loss [CAL], and gingival index [GI]). However, some studies have observed a decrease in IL-38 expression level in saliva, which may be related to various factors such as the selection of study population (e.g., whether combined with systemic diseases), disease staging, sample types (e.g., whole saliva vs. unstimulated saliva), and detection methods (e.g., ELISA vs. qRT-PCR). Notably, the controversial results may also be attributed to the small sample size and lack of unified detection standards in existing studies. Animal experiment results have confirmed that the expression of IL-38 at periodontitis lesion sites is decreased, suggesting that it is involved in the maintenance of oral mucosal immune homeostasis and can exert anti-inflammatory effects by antagonizing the IL-36 inflammatory signaling pathway and synergistically upregulating IL-10 expression. Although the complete functional mechanism of IL-38 has not been fully clarified, it has shown potential value as a non-invasive monitoring marker for periodontitis, and is a core focus direction for subsequent mechanistic and translational medical research.

There are complex synergistic effects and functional division of labor between IL-35, IL-37, IL-38, and the traditional anti-inflammatory factor IL-10: IL-35 can induce B cells to secrete IL-10, IL-38 can upregulate the expression level of IL-10, while the functional exertion of IL-37 is independent of IL-10. These three interleukins together form a multi-level and multi-pathway anti-inflammatory immune regulatory network in the periodontium. In contrast to the overactivation of pro-inflammatory factors (e.g., IL-1β, IL-6, IL-17), novel anti-inflammatory interleukins mainly exhibit a compensatory expression response in periodontitis; their insufficient expression or functional defects will accelerate the amplification of inflammatory responses and the destruction of periodontal tissues, which further confirms that "immune imbalance" is the core pathological link driving the progression of periodontitis.

Despite the significant progress made in the research on these three novel anti-inflammatory interleukins, there are still several limitations in current studies. First, the expression trend of IL-38 in different body fluids and tissues remains controversial, and its specific functional mechanism and downstream signaling pathways have not been fully clarified, requiring more in-depth studies to confirm. Second, most existing studies are based on small sample sizes and lack the support of long-term follow-up clinical evidence, making it difficult to fully verify the actual clinical value of these factors as indicators for the diagnosis and prognosis evaluation of periodontitis. Third, relevant targeted therapy studies are currently limited to cell and animal model levels and have not advanced to the clinical transformation stage; in addition, the interactive regulatory network between the three factors and the effect of combined intervention have not been systematically analyzed. Fourth, the comparative study between these three novel anti-inflammatory interleukins and other anti-inflammatory factors (e.g., IL-4, IL-13) in periodontitis is lacking, and their unique advantages in clinical application have not been fully clarified.

Future research should focus on the following perspectives to overcome current research limitations. First, multi-center clinical studies with unified detection protocols and standardized disease staging and grading criteria are required to determine the cut-off value, sensitivity, and specificity of IL-35, IL-37,

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and IL-38 as promising biomarkers for periodontitis diagnosis, severity grading, and therapeutic monitoring. Second, further investigations are needed to elaborate the activation, modification, cellular source, and receptor signaling pathways of IL-38, thereby improving the current understanding of its mechanisms in periodontitis. On this basis, novel targeted therapeutic strategies, including combined cytokine delivery and genetic modification techniques, should be explored. Integrative microbiomic and genomic analyses are also warranted to clarify the interactive regulatory network among oral flora, host genetic background, and these anti-inflammatory cytokines. Third, future studies should evaluate the regulatory effects of these cytokines in periodontitis patients with systemic comorbidities, such as diabetes, rheumatoid arthritis, and cardiovascular diseases, and clarify their differential expression and functional characteristics under different comorbid conditions. Fourth, preclinical targeted intervention studies should be performed to determine the optimal dosage, administration route, and biosafety of IL-35, IL-37, and IL-38, so as to accelerate the translational progression from preclinical exploration to clinical application.

In summary, as key regulatory molecules of periodontal immune homeostasis, IL-35, IL-37, and IL-38 can delay the progression of periodontitis through multiple pathways, including inhibiting excessive inflammatory responses, regulating immune cell differentiation, and blocking bone resorption and extracellular matrix degradation. These three interleukins have dual potential as biological markers and therapeutic targets, which provides a new research path for the transformation of periodontitis treatment mode from traditional mechanical treatment to precise treatment of "anti-infection + immune regulation". This review not only summarizes the latest research progress of the three novel anti-inflammatory interleukins in periodontitis but also points out the existing limitations and future research directions, which has important theoretical research significance and clinical application value for reducing the global disease burden of periodontal diseases.

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