



UDC: 616.31-002:612.017.1

GRNTI: 76.29.55

REGULATORY ROLE OF INFLAMMATORY MEDIATORS IN THE PATHOGENESIS OF ORAL INFLAMMATORY DISEASES: A REVIEW

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Abstract: Inflammatory diseases of the oral cavity are increasingly recognized as immune-mediated disorders in which disease progression is largely determined by dysregulated host inflammatory responses rather than by microbial factors alone. This review aimed to analyze the regulatory role of inflammatory mediators in the pathogenesis of periodontitis and pulpitis and to evaluate their diagnostic and therapeutic significance.

A structured literature search was conducted using PubMed, Scopus, Web of Science, and Google Scholar databases for publications published between 2000 and 2025. Relevant studies addressing cytokines, chemokines, matrix metalloproteinases, oxidative stress, lipid mediators, osteoimmunology, and host-modulation therapy in oral inflammatory diseases were included.

The analysis demonstrated that IL-1 β , TNF- α , IL-6, IL-17, reactive oxygen species, matrix metalloproteinases, and the RANKL/OPG axis play central roles in inflammatory tissue destruction and chronicity. In addition, increasing evidence supports the concept of defective inflammation resolution associated with impaired specialized pro-resolving mediator pathways. Biomarker analysis of saliva and gingival crevicular fluid appears promising for disease monitoring and personalized therapeutic strategies.

Inflammatory mediator regulation represents a key pathogenetic mechanism in oral inflammatory diseases and may serve as a promising target for biomarker-guided diagnostics and host-modulation therapy in personalized dental medicine.

Keywords: pathophysiology, etiology, pathogenesis, inflammatory mediators, oral diseases, therapeutic control of mediators.



1. Relevance

Periodontitis and pulpitis are among the most common inflammatory diseases of the oral cavity and remain leading causes of tooth loss and endodontic interventions in the adult population. Modern understanding of their pathogenesis has evolved substantially: whereas the “infectious” paradigm previously prevailed, viewing disease as a direct consequence of microbial action, the currently accepted model is that of a dysregulated host inflammatory response. In this model, the microbial biofilm serves as a necessary trigger, but the severity, rate of progression, and outcome of the disease process, including reversibility of inflammation, chronicity, and the extent of tissue destruction, are determined by which mediator networks are activated and how effectively the body initiates mechanisms that limit and resolve inflammation [1].

This concept is especially productive with regard to periodontitis, as it explains a clinical paradox: comparable bacterial burden in different patients may be associated with fundamentally different outcomes, ranging from localized gingivitis to rapidly progressive attachment loss and alveolar bone destruction. Large-scale reviews and clinical syntheses demonstrate that periodontitis is a chronic immunoinflammatory disease in which tissue destruction is caused not so much by the direct action of bacteria as by persistent activation of innate and adaptive immune mechanisms [39], including cytokine cascades, chemokine-mediated leukocyte recruitment, complement activation, and osteoimmunological pathways [2,3]. Within this framework, the concept of “inflammatory mediators” becomes central: it is these mediators that shape the trajectory of the process, from protective, localized inflammation to self-sustaining chronicity.

Pulpitis, although anatomically and clinically distinct, also fits well within the mediator paradigm. In the dental pulp, inflammation develops within a “rigid compartment” (the pulp chamber), and therefore even a moderate vascular reaction accompanied by edema may lead to compression of the microcirculation, ischemia, and necrosis. Accordingly, pain intensity, irreversibility of the lesion, and the likelihood of preserving pulp vitality depend not only on the degree of microbial invasion but also on the mediator profile (IL-1 β , TNF- α , IL-6, chemokines), as well as on the balance between pro-inflammatory and reparative signals within the tissues [4]. This is of fundamental clinical importance: for the pulp, approaches aimed not at the “complete suppression” of inflammation but at the precise modulation of mediator pathways may prove especially promising, limiting tissue damage while preserving reparative potential.

Thus, in both diseases, periodontitis and pulpitis, mediators act as pivotal regulators: they connect the microbial stimulus with cellular infiltration, vascular reactions, extracellular matrix degradation, pain mechanisms, and ultimately the clinical outcome. Therefore, focusing this review on mediator networks is justified from both pathogenetic and applied perspectives, as it provides a basis for (i) biomarker-based diagnostics (saliva, gingival crevicular fluid), (ii) prognostic models of disease progression, and (iii) host-modulation and pro-resolution therapeutic strategies.

The aim of this review is to analyze the influence of key mediators, including cytokines, chemokines, lipid mediators, metalloproteinases, oxidative factors, and neuroimmune signals, on the course of inflammatory diseases of the oral cavity, primarily periodontitis and pulpitis, and to discuss the prospects for therapeutic control of these mediator pathways.

2. Host-Microbe Interaction and Innate Immunity: PRRs, TLRs, NF- κ B, and the Inflammasome

2.1 Microbial Biofilm as a Trigger of Innate Immunity

The microbial biofilm of the periodontal pocket is a structured microbial community that includes Gram-negative anaerobes such as *Porphyromonas gingivalis*, *Tannerella forsythia*, and *Treponema denticola*. These microorganisms possess pronounced immunomodulatory potential and are capable of disrupting the physiological balance between the microbiota and the host [5].

The key molecular triggers of inflammation are microbial cell components, including:

- lipopolysaccharide (LPS),
- lipoproteins,
- flagellin,



- peptidoglycan,
- bacterial DNA (CpG motifs).

These structures are recognized by innate immune receptors, namely pattern recognition receptors (PRRs), primarily Toll-like receptors (TLR2, TLR4) and NOD-like receptors (NLRs) [6].

Thus, inflammation begins not with “tissue destruction” itself, but with receptor-mediated recognition of microbial patterns by epithelial cells, fibroblasts, macrophages, and dendritic cells.

2.2 Toll-Like Receptors and NF- κ B Activation

TLR2 and TLR4 play a central role in the recognition of bacterial components in periodontal tissues. Their activation initiates intracellular signaling cascades through the adaptor molecules MyD88 and TRIF, leading to activation of the transcription factor NF- κ B and MAPK pathways [7].

NF- κ B regulates the transcription of the following genes:

- IL-1 β ,
- TNF- α ,
- IL-6,
- IL-8 (CXCL8),
- COX-2• iNOS.

In periodontal tissues, persistent NF- κ B activation has been shown to be one of the key mechanisms underlying chronic inflammation [8]. Moreover, *P. gingivalis* is capable of modifying TLR signaling pathways, thereby altering the intensity and nature of the immune response, which contributes to the persistence of inflammation.

Thus, TLR signaling forms the primary wave of mediators that determines the дальнейший ход воспалительного процесса. Thus, TLR signaling forms the primary mediator wave that determines the subsequent course of the inflammatory process.

2.3 Inflammasome and IL-1 β Maturation

The NLRP3 inflammasome complex is of particular importance in the pathogenesis of periodontitis and pulpitis. In contrast to TLR signaling, which induces the synthesis of pro-IL-1 β , the inflammasome is responsible for its proteolytic maturation through caspase-1 activation [9].

Activation of the NLRP3 inflammasome may occur under the influence of:

- bacterial toxins,
- ROS,
- extracellular ATP,
- crystalline structures.

In periodontal tissues, increased expression of inflammasome components has been demonstrated during active inflammation [10]. IL-1 β released after inflammasome activation enhances:

- RANKL expression,
- MMP production,
- vascular permeability,
- neutrophil recruitment.

Thus, the inflammasome amplifies the mediator cascade and promotes transition to the destructive phase.

2.4 Complement and Amplification of the Inflammatory Response

The complement system actively participates in the pathogenesis of periodontitis. *P. gingivalis* has the ability to modulate the C5a receptor and interact with TLR2, thereby generating a “dysregulated” inflammatory response [11].

Cross-activation of TLRs and complement receptors enhances the production of pro-inflammatory cytokines and promotes persistent neutrophilic infiltration.

Thus, the inflammatory response becomes self-sustaining, which is a key characteristic of chronic periodontitis.



2.5 Features of the Innate Response in the Dental Pulp

The dental pulp also expresses TLR2 and TLR4. In carious lesions, when bacterial products penetrate through the dentinal tubules, a TLR-dependent cascade is activated, leading to the expression of IL-1 β , IL-6, and TNF- α [12].

However, the anatomical confinement of the pulp creates unique conditions:

- limited outflow of exudate,
- increased intrapulpal pressure,
- vascular compression.

Therefore, mediator activation, which is physiologically aimed at protection, may rapidly transform into ischemic injury.

2.6 Transition from Protective Inflammation to Tissue Destruction

Under normal conditions, the innate immune response should remain limited and be accompanied by activation of resolution mechanisms. However, with persistent microbial stimulation, the following occur:

1. sustained NF- κ B activation;
2. increased production of IL-1 β and TNF- α ;
3. enhanced RANKL-dependent osteoclastogenesis;
4. damage to the extracellular matrix.

It is at this stage that mediator regulation becomes the determining factor in disease progression.

3. Cytokine Network in Periodontitis and Pulpitis: IL-1 β , TNF- α , IL-6, IL-17, and the RANKL/OPG Axis

3.1 Principles of the “Cytokine Network”: Not a Single Mediator, but a Cascade and Amplification

Inflammation in oral tissues is rarely determined by one “main” cytokine. In practice, a cytokine network is formed in which individual mediators enhance each other’s expression, activate common transcriptional pathways, and switch cellular programs such as migration, survival, protease secretion, and osteoclastogenesis. IL-1 β and TNF- α are traditionally regarded as the most potent pro-inflammatory mediators that elevate the overall inflammatory burden; IL-6 contributes to chronicity and systemic reactivity; IL-17 sustains neutrophil dominance and links inflammation with bone resorption via RANKL [5,13,14].

From the clinical perspective, this is crucial: the severity of tissue destruction, including attachment loss, matrix degradation, and bone resorption, correlates not only with the presence of microbial stimulation but also with the persistence of activation of these mediator circuits.

3.2 IL-1 β : Amplification of Inflammation, MMPs, and Bone Resorption

IL-1 β is one of the key mediators shaping the destructive phenotype of periodontitis. Its effects include:

1. activation of the endothelium and enhancement of leukocyte recruitment;
2. induction of matrix metalloproteinases (MMP-1, MMP-8, MMP-9) involved in collagen degradation;
3. stimulation of RANKL-dependent osteoclastogenesis, which directly links inflammation with alveolar bone loss [8,15].

Classic studies in periodontology emphasize the contribution of IL-1 and TNF to periodontal tissue destruction; in particular, IL-1 β is regarded as a potential target for host-modulation approaches, especially in patients with high inflammatory reactivity. An additional aspect is genetic predisposition: polymorphisms in IL-1 genes have been associated with an increased risk of more severe disease in some patients, supporting the concept of host-dependent variability in disease progression [16].

3.3 TNF- α : Vascular Reactivity, Cellular Infiltration, and Interaction with IL-1 β

TNF- α enhances inflammation through:

- increased expression of adhesion molecules,
- increased vascular permeability,
- activation of macrophages and enhanced production of other cytokines,
- stimulation of MMPs and synergism with IL-1 β .



TNF- α and IL-1 β often act as a “pair,” forming a persistent pro-inflammatory background. Experimental models of inflammatory bone loss have shown that these cytokines do not merely accompany tissue destruction but function as its drivers. For this reason, therapeutic concepts borrowed from rheumatology, such as anti-TNF and anti-IL-1 approaches, are periodically discussed in the context of severe forms of periodontitis, although their direct clinical application remains limited by safety and feasibility considerations.

3.4 IL-6: A “Bridge” Between Local Inflammation and Systemic Inflammatory Burden

IL-6 is of particular importance because it participates both in local regulation of inflammation and in the systemic acute-phase response through hepatic production of CRP and other proteins. In the context of periodontitis, IL-6 is regarded as both a marker and a mediator of chronic activity, as well as a possible explanation for the association between periodontitis and certain systemic diseases through increased overall inflammatory burden [17,18].

In practical terms, this means that:

- in patients with active periodontitis, IL-6 may be elevated not only in gingival crevicular fluid but also in saliva and/or serum;
- IL-6-dependent circuits sustain the persistence of inflammation even when bacterial pressure is partially reduced.

This is particularly relevant in patients with metabolic disorders, such as diabetes mellitus, in whom inflammatory regulatory pathways are already impaired and a more pronounced pro-inflammatory profile is observed [19].

3.5 IL-17/Th17: Neutrophil Dominance and Coupling with Osteoimmunology

IL-17 is a key product of Th17 cells and plays an important role in maintaining chronic inflammation in periodontitis. Its main effects include:

- enhancement of neutrophil chemoattractant production and maintenance of neutrophilic infiltration;
- induction of pro-inflammatory cytokines and MMPs;
- enhancement of RANKL expression in osteoblastic and immune cells, thereby promoting osteoclastogenesis [5,14,20].

Thus, IL-17 links adaptive immunity with bone resorption. The concept of osteoimmunology emphasizes that bone tissue is not a passive “victim” of inflammation but an active participant in immune interactions, and that RANKL is the key molecular “node” in this connection [22].

3.6 The RANKL/OPG Axis as an Integrator of Cytokine Signals

RANKL (receptor activator of nuclear factor κ B ligand) is the principal factor driving osteoclast differentiation. Pro-inflammatory cytokines such as IL-1 β , TNF- α , and IL-17 increase RANKL expression and/or decrease the level of OPG (osteoprotegerin), shifting bone remodeling toward resorption [4,21].

In periodontitis, this means that:

- even with moderate bacterial stimulation, but high cytokine activity, bone resorption may continue to progress;
- the clinical activity of the disease is closely associated with mediator profiles rather than solely with microbial characteristics.

3.7 Cytokines and Pulpitis: Mediator Profile and Clinical Irreversibility

In the dental pulp, IL-1 β , TNF- α , and IL-6 are significant inflammatory mediators, but the clinical dynamics differ due to anatomy. Increased vascular permeability and edema within the confined pulp chamber lead to compression of microvessels, development of hypoxia, and intensification of pain. Therefore, pro-inflammatory cytokines influence not only tissue destruction but also the “mechanical” component of the pathological process, namely intrapulpal pressure and ischemia.

Systematic reviews of biomarkers of pulpal inflammation emphasize that cytokine profiles may have diagnostic value, including in differentiating reversible from irreversible inflammation, although standardization of sampling and interpretation of biomaterials remains a challenge [4].



3.8 Section Conclusions: Clinical Significance of the Cytokine Network

1. IL-1 β and TNF- α form the “core” of pro-inflammatory activity and initiate tissue destruction through MMPs and RANKL.
2. IL-6 contributes to chronicity and links local inflammation with systemic inflammatory burden.
3. IL-17 maintains neutrophil dominance and enhances osteoclastogenesis.
4. The RANKL/OPG axis integrates cytokine signals into the final phenotype: alveolar bone resorption.

4. Neutrophils, NETs, ROS/NO, and Matrix Metalloproteinases: The Effector Arm of Inflammatory Destruction

4.1 Neutrophils as Central Cells of the Innate Response in the Periodontium

Neutrophils are the most abundant leukocyte population in the gingival sulcus and play a key role in maintaining the barrier between the biofilm and the underlying tissues. Under physiological conditions, they provide controlled antimicrobial defense through:

- phagocytosis,
- degranulation,
- production of reactive oxygen species (ROS),
- secretion of antimicrobial peptides.

However, in chronic periodontitis, the neutrophil response becomes quantitatively and functionally dysregulated. It has been shown that in patients with active disease, neutrophils are characterized by hyperreactivity, increased ROS production, and enhanced degranulation [22,23].

This leads to a paradoxical situation: cells intended to protect tissues become the main source of their injury.

4.2 Neutrophil Extracellular Traps (NETs)

One of the mechanisms enhancing antimicrobial defense is the formation of neutrophil extracellular traps (NETs), networks of DNA, histones, and proteases capable of capturing and neutralizing bacteria.

However, under chronic inflammatory conditions, excessive NET formation is accompanied by:

- extracellular matrix damage,
- macrophage activation,
- amplification of pro-inflammatory signaling,
- increased cytokine expression.

Studies show that in periodontitis, the balance between NET formation and clearance is disrupted, contributing to the maintenance of chronic inflammation [23].

Thus, NETs are not only a defense mechanism but also a factor that amplifies tissue destruction.

4.3 Reactive Oxygen Species (ROS) and Nitric Oxide (NO)

ROS, including superoxide anion and hydrogen peroxide, as well as reactive nitrogen species, play a key role in the microbicidal activity of neutrophils and macrophages. However, their excessive production leads to:

- oxidative damage to lipids and proteins,
- NF- κ B activation,
- inflammasome enhancement,
- vascular endothelial injury.

In periodontal tissues, signs of pronounced oxidative stress have been identified, correlating with disease severity [24].

In the pulp, the situation is aggravated by anatomical peculiarities: increased vascular permeability and edema combined with hypoxia enhance ROS production, which may accelerate necrotic changes.

4.4 Matrix Metalloproteinases (MMPs): Destruction of the Extracellular Matrix

Matrix metalloproteinases are key enzymes involved in the degradation of collagen and extracellular matrix components. The most extensively studied in the context of periodontitis are:

- MMP-8 (collagenase-2),
- MMP-9 (gelatinase B).



Sources of MMPs include:

- neutrophils,
- macrophages,
- fibroblasts,
- epithelial cells.

Under the influence of IL-1 β and TNF- α , MMP expression increases substantially. MMPs are responsible for the destruction of collagen fibers of the periodontal ligament and progressive attachment loss [24].

Particular attention has been paid to the active form of MMP-8 as a biomarker of disease activity; its detection in gingival crevicular fluid is regarded as a promising diagnostic tool [25].

4.5 Interrelationship Between ROS, MMPs, and Cytokines

ROS enhance MMP expression and activate pro-forms of metalloproteinases. At the same time, IL-1 β and TNF- α induce MMP synthesis in fibroblasts and macrophages.

Thus, a self-amplifying loop is formed: cytokines \rightarrow ROS \rightarrow MMPs \rightarrow matrix destruction \rightarrow release of DAMPs \rightarrow additional activation of inflammation.

It is this loop that determines the transition from reversible gingivitis to irreversible tissue destruction in periodontitis.

4.6 Effector Mechanisms in Pulpitis

In the dental pulp, neutrophilic infiltration is characteristic of acute forms of inflammation. The release of proteases and ROS in a confined space enhances:

- vascular collapse,
- ischemia,
- tissue necrosis.

Unlike the periodontium, where tissue is capable of partial adaptation, the pulp is less resistant to mediator overload. Therefore, the balance between protection and injury is especially fragile here.

4.7 Clinical Significance of the Effector Arm

Effector mechanisms, including neutrophils, NETs, ROS, and MMPs, represent the point at which cytokine regulatory signals are translated into actual tissue destruction.

Accordingly:

- controlling the cytokine network without controlling MMPs may be insufficient;
- antioxidant strategies may complement anti-inflammatory therapy;
- monitoring MMP-8 and MMP-9 may have prognostic value.

5. Lipid Mediators and Active Resolution of Inflammation: The Concept of “Defective Resolution” in Periodontitis and Pulpitis

5.1 From Suppression of Inflammation to Its Active Resolution

The traditional model of anti-inflammatory therapy was long based on suppression of pro-inflammatory mediators, such as COX inhibition and cytokine blockade. However, modern immunology views the termination of inflammation not as a passive fading of the signal, but as an active, tightly regulated process governed by specialized pro-resolving mediators (SPMs) [26].

These molecules include:

- lipoxins (LXA₄),
- resolvins (RvE, RvD),
- protectins,
- maresins.

SPMs are synthesized from polyunsaturated fatty acids, including arachidonic, eicosapentaenoic, and docosahexaenoic acids, and perform the following functions:

- limiting neutrophil infiltration,
- enhancing efferocytosis,
- switching macrophages toward the M2 phenotype,
- restoring tissue homeostasis.



Thus, resolution of inflammation is not simply “anti-inflammation,” but a programmed biological phase.

5.2 Pro-Inflammatory Eicosanoids: PGE₂ and LTB₄

Before SPM pathways are activated, pro-inflammatory lipid mediators predominate:

- prostaglandin E₂ (PGE₂),
- leukotriene B₄ (LTB₄).

PGE₂, synthesized via COX-2, enhances:

- vasodilation,
- pain,
- RANKL expression,
- osteoclast differentiation.

LTB₄ enhances neutrophil chemotaxis and maintains the inflammatory infiltrate [27].

Elevated levels of PGE₂ have been detected in gingival crevicular fluid in active periodontitis and correlate with the severity of tissue destruction [27]. This explains the clinical effect of NSAIDs; however, simple COX inhibition does not restore resolution mechanisms.

5.3 Lipoxins and Resolvins: Limiting Inflammatory Escalation

Lipoxin A₄ (LXA₄) was the first described pro-resolving lipid mediator. It:

- suppresses neutrophil migration,
- reduces IL-1 β and TNF- α production,
- enhances macrophage clearance of apoptotic cells [28].

Resolvins, particularly RvE1, have demonstrated in experimental models of periodontitis the ability to:

- reduce inflammatory infiltration,
- inhibit alveolar bone loss,
- alter the microbial composition of the biofilm toward a healthier profile.

This is a highly important observation: SPMs do not merely suppress inflammation, but restore immune balance, making them a promising host-modulation strategy.

5.4 The Concept of “Defective Resolution” in Periodontitis

Current evidence indicates that in chronic periodontitis, not only the regulation of pro-inflammatory signals is impaired, but also the phase of active resolution [29].

This is manifested by:

- reduced SPM production,
- impaired receptor signaling,
- predominance of a PGE₂-dependent profile,
- persistent neutrophil activation.

Thus, periodontitis may be regarded as a disease not only of excessive inflammation, but also of insufficient resolution.

This concept explains why mechanical removal of the biofilm does not always completely halt disease progression in patients with marked mediator dysregulation.

5.5 Lipid Mediators in Pulpitis

Data on SPMs in the pulp are less extensive; however, it is known that in acute forms of pulpitis, PGE₂ production is increased, which is associated with pain and enhanced vascular reactivity [30].

Theoretically, activation of resolution pathways could:

- reduce neutrophil infiltration,
- decrease intrapulpal pressure,
- promote preservation of vitality.

However, clinical studies in this field remain limited, and the use of SPMs in endodontics remains a promising future direction.

5.6 Interaction Between SPMs and Osteoimmunology

SPMs not only suppress cytokine escalation but also influence bone remodeling:

- they decrease RANKL expression,



- enhance OPG,
- limit osteoclast differentiation.

Thus, resolution of inflammation is directly linked to restoration of bone homeostasis.

5.7 Therapeutic Prospects

Approaches aimed at enhancing SPM pathways may include:

- local application of resolvins,
- dietary modulation with omega-3 fatty acids,
- pharmacological stimulation of lipoxygenase pathways.

Unlike classical anti-inflammatory agents, SPMs do not suppress immunity but return it to physiological balance.

5.8 Section Conclusions

1. Chronic periodontitis is characterized not only by excessive production of pro-inflammatory mediators but also by impairment of the resolution phase.
2. SPMs represent a key link in the restoration of homeostasis.
3. Future therapy will likely be based on modulation of resolution rather than solely on blockade of inflammation.

6. Biomarkers of Inflammation in Periodontitis and Pulpitis: Saliva, Gingival Crevicular Fluid, and the Pulpal Environment

6.1 Biomarkers as a Tool for Clinical Stratification

The modern concept of mediator-driven inflammation raises an important question: is it possible to quantitatively assess disease activity through analysis of local mediators? Inflammatory biomarkers may potentially allow:

- identification of the active phase of disease;
- prediction of progression;
- monitoring of response to therapy;
- differentiation between reversible and irreversible forms of inflammation, especially in the pulp.

In dentistry, the greatest attention is paid to three biological media:

1. gingival crevicular fluid (GCF);
2. saliva;
3. pulpal tissue/exudative environment.

6.2 Gingival Crevicular Fluid (GCF): Local Mediator Profile

GCF reflects the condition of periodontal tissues directly at the site of inflammation. In active periodontitis, increased levels of the following are detected in GCF:

- IL-1 β
- TNF- α
- IL-6
- IL-17
- PGE₂
- active MMP-8

MMP-8, in particular, has been extensively studied as a marker of collagen destruction. Clinical studies show that active MMP-8 levels correlate with periodontal pocket depth and attachment loss [31]. This makes it a promising chairside diagnostic tool.

IL-1 β in GCF is also regarded as a marker of disease activity and may decrease after successful therapy [32].

Thus, GCF is the most sensitive medium for assessing local mediator activity.

6.3 Saliva: A Systemically Integrative Indicator of Inflammation

Saliva is more accessible and convenient for large-scale screening. The following can be detected in saliva:

- IL-6
- IL-1 β



- TNF- α
- CRP
- MMP-8
- oxidative markers

Studies show that salivary levels of IL-6 and MMP-8 can distinguish patients with active periodontitis from healthy individuals [32,33].

However, saliva has certain limitations:

- dilution of mediators;
- influence of systemic conditions;
- variability in composition depending on time of day and stimulation.

Nevertheless, salivary diagnostics remains a promising platform for personalized dentistry.

6.4 Pulpal Biomarkers: The Challenge of Differentiating Reversible and Irreversible Pulpitis

Diagnosing the reversibility of pulpal inflammation remains one of the most difficult tasks in clinical endodontics. Biomarkers may assist in differentiating:

- reversible inflammation with regenerative potential;
- irreversible pulpitis;
- necrosis.

Systematic reviews demonstrate increased levels of:

- IL-1 β ,
- IL-6,
- TNF- α ,
- PGE₂,

in pulp tissue in irreversible forms of inflammation [4].

However, practical application is limited by the difficulty of standardizing sample collection. At present, pulpal biomarker analysis remains primarily a research tool.

6.5 Oxidative Markers and Antioxidant Status

Elevated levels of malondialdehyde (MDA) and other lipid peroxidation markers in periodontitis confirm the role of oxidative stress in disease pathogenesis [24].

Changes in the antioxidant status of saliva may correlate with inflammatory activity and decrease after therapy.

6.6 Prospects for Multiplex Panels

Modern technologies such as Luminex and proteomics make it possible to analyze dozens of mediators simultaneously. This opens the possibility of generating:

- prognostic profiles,
- individual mediator “signatures,”
- patient stratification according to the risk of rapid progression.

The future of diagnosis in periodontology will likely depend not on a single marker, but on a combination of cytokines, MMPs, and SPM profiles.

6.7 Limitations and Challenges

Despite their promise, biomarker diagnostics face several problems:

- interindividual variability,
- influence of systemic diseases,
- lack of unified threshold values,
- methodological differences among studies.

Therefore, clinical interpretation must always consider the overall disease context.

6.8 Section Conclusions

1. GCF is the most specific medium for assessing local activity.
2. MMP-8 and IL-1 β are the most validated biomarkers of periodontitis activity.
3. Saliva is promising for screening but is less specific.
4. Pulpal biomarkers have diagnostic potential but require further standardization.



7. Therapeutic Modulation of Mediator Pathways in Periodontitis and Pulpitis

7.1 From Antibacterial Therapy to Host-Modulation Therapy

Classical therapy for periodontitis is primarily aimed at controlling the microbial biofilm through mechanical debridement, antiseptics, and antibiotics. However, taking into account the mediator-based model of the disease, it becomes clear that microbial reduction alone is not always sufficient to stabilize the process. This is why the concept of host-modulation therapy (HMT) was developed — a targeted intervention directed at the host's inflammatory and tissue-destructive mechanisms [34].

HMT does not replace mechanical therapy, but complements it by reducing the destructive potential of mediator cascades.

7.2 NSAIDs and Inhibition of the Prostaglandin Pathway

Nonsteroidal anti-inflammatory drugs (NSAIDs) suppress COX-1/COX-2 activity and reduce PGE₂ synthesis. Clinical studies have shown that prolonged NSAID use may slow the rate of alveolar bone loss [34].

However, their use is limited by:

- the risk of gastrointestinal and cardiovascular complications,
- lack of effect on inflammation-resolution mechanisms,
- the need for prolonged administration.

Thus, NSAIDs act mainly on the pro-inflammatory arm but do not restore homeostatic balance.

7.3 Inhibition of Matrix Metalloproteinases

One of the most extensively studied directions of HMT is the use of subantibacterial-dose doxycycline (SDD), which is capable of inhibiting MMP-8 and MMP-9 activity without a pronounced antibacterial effect [35].

Clinical data show that adding SDD to mechanical therapy may:

- reduce periodontal pocket depth,
- decrease attachment loss,
- reduce MMP activity in GCF.

This is one of the first examples of the clinical implementation of the mediator concept in periodontology [36].

7.4 Anti-Cytokine Strategies

In theory, blockade of IL-1 β or TNF- α could reduce tissue destruction. Experimental models confirm that inhibition of these cytokines decreases inflammatory bone loss [37].

However, systemic anti-cytokine therapy, as used in rheumatology, is associated with a risk of immunosuppression and has not yet found widespread application in dental practice.

A promising direction is the local modulation of cytokine activity.

7.5 Omega-3 Fatty Acids and Stimulation of SPM Pathways

Dietary modulation with omega-3 polyunsaturated fatty acids is considered a means of enhancing the production of resolvins and other SPMs. Clinical studies show that omega-3 supplementation, especially in combination with low-dose aspirin, may improve the outcomes of periodontal therapy [38].

This supports the concept that therapy should not only suppress inflammation but also enhance its resolution.

7.6 Antioxidant Approaches

Given the role of ROS in tissue destruction, antioxidants are being considered as an adjunctive strategy. Some studies demonstrate a reduction in oxidative stress markers after antioxidant support, although the evidence base remains limited.

7.7 Pulpitis: The Principle of “Vitality Preservation”

In endodontics, therapeutic modulation is aimed at:

- reducing pro-inflammatory activity,
- pain control through PGE₂-related pathways,
- preserving pulp viability.



Biological methods such as vital pulp therapy, the use of calcium-containing materials, and MTA may partially influence the local mediator environment, promoting reparative dentinogenesis.

In the future, local agents regulating the balance of cytokines and SPMs in the pulp may be developed.

7.8 Personalized Mediator Therapy

The future of periodontology is likely to be associated with:

- stratification of patients according to mediator profile,
- the use of multiplex biomarker panels,
- individualized host-modulation therapy.

Patients with pronounced pro-inflammatory reactivity may require more aggressive mediator correction.

7.9 Section Conclusions

1. Host-modulation therapy is a logical continuation of the mediator model of inflammation.
2. Simple blockade of pro-inflammatory mediators is insufficient without restoration of resolution mechanisms.
3. A personalized approach may improve therapeutic effectiveness.

8. Discussion: Integration of the Mediator Model, Clinical Implications, and Future Research Directions

8.1 From the Microbial to the Mediator-Regulatory Paradigm

Current evidence convincingly demonstrates that periodontitis and pulpitis cannot be regarded exclusively as infectious diseases. The microbial biofilm is a necessary, but not sufficient, factor. Clinical variability, different rates of progression, and unequal responses to therapy are explained primarily by the specific features of the host immune response's mediator regulation.

Integration of the mechanisms discussed above allows three key regulatory levels to be distinguished:

1. **Initiation** — PRR/TLR signaling and NF- κ B activation;
2. **Escalation** — the cytokine network (IL-1 β , TNF- α , IL-6, IL-17), activation of RANKL, MMPs, and ROS;
3. **Resolution or chronicity** — the balance between SPMs and pro-inflammatory eicosanoids.

The transition from reversible inflammation to chronic tissue destruction occurs precisely at the level of disturbed balance between these phases.

8.2 The Mediator Network as a Self-Amplifying System

- One of the central conclusions is the presence of self-sustaining loops:
- IL-1 β /TNF- α \rightarrow MMPs \rightarrow matrix destruction \rightarrow DAMP signaling \rightarrow amplification of inflammation;
 - ROS \rightarrow NF- κ B activation \rightarrow enhanced cytokine production;
 - IL-17 \rightarrow RANKL \rightarrow osteoclastogenesis \rightarrow release of bone resorption factors.

These loops explain why inflammation may persist even after bacterial load is reduced. Thus, mediator dysregulation is an independent driver of disease.

8.3 The Concept of "Defective Resolution" as the Key to Chronicity

Traditional therapeutic approaches have focused on suppressing inflammation. However, current evidence indicates the fundamental role of impaired active resolution. Insufficient production of SPMs or disruption of their receptor signaling creates conditions for persistent neutrophilic infiltration and maintenance of a pro-inflammatory profile.

Accordingly, periodontitis may be interpreted as a disease not only of hyperinflammation but also of an insufficient resolution phase. This concept is of fundamental importance for the development of new therapeutic strategies.

8.4 Periodontitis as a Systemic Inflammatory Modifier

The presence of persistent mediator activity, including IL-6, TNF- α , and CRP, links periodontitis to systemic diseases, including:

- type 2 diabetes mellitus,
- cardiovascular diseases,
- metabolic syndrome.



An increased systemic inflammatory burden may enhance local mediator reactions and create a vicious cycle. Thus, periodontitis should be regarded as part of the body's broader immunoinflammatory network.

8.5 Features of the Pulp: Confined Space and Rapid Escalation

Unlike the periodontium, the pulp functions under conditions of anatomical confinement. Even moderate mediator activation may lead to:

- increased intrapulpal pressure,
- vascular compression,
- ischemia,
- necrosis.

Therefore, the clinical window for “optimal regulation” of inflammation in the pulp is significantly narrower than in the periodontium. This explains the rapid transition to irreversible forms of inflammation.

8.6 Limitations of Existing Studies

Despite substantial progress, unresolved issues remain:

- variability of biomarker data;
- lack of unified diagnostic thresholds;
- difficulty in assessing local SPM profiles;
- limited clinical studies on active stimulation of inflammation resolution.

In addition, most data are based on cross-sectional studies, whereas long-term prospective models of disease progression remain limited.

8.7 Promising Research Directions

Promising directions include:

1. Multiplex mediator panels for predicting the risk of disease progression.
2. Local delivery of SPMs and resolvins.
3. Genetic and epigenetic stratification of patients.
4. Integration of microbiome data with mediator profiles.
5. Development of biomaterials with immunomodulatory properties in endodontics.

8.8 Clinical Implications

The mediator model of inflammation implies:

- transition to personalized therapy;
- combination of mechanical biofilm control and host-modulation;
- biomarker monitoring to assess disease activity;
- emphasis on restoration of the inflammation/resolution balance.

Thus, the treatment strategy should be aimed not only at eliminating the trigger, but also at normalizing immune regulation.

9. Conclusion

Inflammatory diseases of the oral cavity are complex immune-mediated processes in which the outcome is determined by the quality of the host mediator response. IL-1 β , TNF- α , IL-6, and IL-17 form the core of the pro-inflammatory network, ensuring cell recruitment, MMP activation, and osteoclastogenesis through RANKL. Effector mechanisms, including neutrophils, ROS, and MMPs, mediate tissue destruction.

The key conceptual conclusion is the role of active resolution of inflammation. Defects in SPM pathways contribute to chronicity and disease progression. Therapeutic prospects are associated with a shift from simple suppression of inflammation toward restoration of immune balance.

Thus, mediator regulation is the central mechanism determining the course of periodontitis and pulpitis and represents a promising target for personalized dental medicine.

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