Biochemical Genetics
https://doi.org/10.1007/s10528-026-11435-w

REVIEW

Influence of Genetic and Epigenetic Factors on Periodontitis Susceptibility and Treatment Outcomes

Maryam Jalili Sadrabad[1] · Parham Mohammadian Semnani[2] · Farid Ghadyani[3] · Nika Moghadamnia[2] · Sahar Maleki[2] · Mohammad Amin Hemmati[4] · Majid Eslami[5,6]

Received: 29 January 2026 / Accepted: 11 July 2026

Abstract

Periodontitis (PD) is a complex inflammatory condition driven by the interplay of microbial, genetic, epigenetic, and environmental factors. While bacterial biofilms are regarded as the primary cause, growing evidence underscores the significant role of genetic predisposition in determining susceptibility to the disease, its progression, and treatment outcomes. This review explores the genetic polymorphisms of PD, focusing on genes related to inflammatory mediators, immune responses, antimicrobial peptides, matrix metalloproteinases, and vitamin D receptor pathways. Key epigenetic mechanisms including DNA methylation, histone modifications, non-coding RNAs, and emerging RNA methylation pathways are explored in their roles in modulating inflammation, tissue destruction, bone metabolism, and interactions between the host and microbes. Advances in transcriptomic technologies, particularly RNA sequencing, have enhanced our ability to identify molecular biomarkers and cell-specific gene expression profiles associated with disease severity and responses to treatment. The potential for leveraging genetic and epigenetic profiling presents an exciting avenue for personalized periodontal care, including the use of epigenetic therapies targeting pathways involved in inflammation and tissue regeneration. Nonetheless, the current body of evidence has limitations. These include significant variability across studies, inconsistent disease classification systems, small sample sizes, and a predominance of preclinical or exploratory research. Many biomarkers and therapeutic targets proposed to date require further validation before they can be routinely applied in clinical practice. While integrating genetic, epigenetic, transcriptomic, and clinical data holds promise for advancing precision periodontology, rigorous large-scale, and multicenter studies are essential to confirm clinical applicability, validate biomarkers, and facilitate their incorporation into evidence-based treatment protocols.

Extended author information available on the last page of the article

Published online: 20 July 2026

Highlights

- Genetic polymorphisms in immune and inflammatory genes contribute to periodontal disease susceptibility.
- Epigenetic mechanisms, including DNA methylation and histone modifications, regulate gene expression in periodontal tissues.
- Epigenetic changes act as both biomarkers and therapeutic targets in periodontal disease.
- Novel epigenetic therapies show potential in reducing inflammation and enhancing tissue regeneration.
- Integrating genetic and epigenetic profiling supports personalized diagnosis and treatment strategies for periodontal disease.

Keywords Epigenetic · Genetic variation · MicroRNA · Periodontitis · Treatment outcome

The Role of Genetic Predisposition in Periodontitis (PD)

Individuals indicate a wide variety of susceptibility to PD; some are highly susceptible, while others demonstrate more resistance. Microbial biofilm is acknowledged as the main cause of periodontitis; however, significant evidence highlights the role of genetic and epigenetic factors in shaping individual susceptibility to the disease. These factors also impact its severity, progression, and response to treatment by altering host immune and inflammatory mechanisms (Shaddox et al. 2021). Moreover, lifestyle factors, such as smoking habits, nutrition and oral hygiene can lead to PD and increase its predisposition (Gao et al. 2024). Studies have shown that the effect of heritability on incidence of PD in specific populations with constant environmental factors was high. If significant environmental factors, like smoking, become prevalent within the population, the impact of genetics and heritability on the progression of PD will lessen (Shaddox et al. 2021).

According to a systematic review investigating animal models, over one-third of phenotypic-associated bone loss is attributed to genetic factors (Nibali et al. 2020). Based on a systematic review of human studies, heritability is significantly higher for aggressive PD. Heritability of PD has been examined on twins and other familial groups. The results showed heritability in approximately 0.38 of twins, 0.15 of other families, and 0.29 of combined familial relationships (Nibali et al. 2019). This review aims to critically analyze the genetic factors influencing susceptibility to periodontitis and its treatment outcomes, focusing on conditions previously categorized as chronic and aggressive periodontitis. Rather than treating all reported polymorphisms as equally valid evidence, the discussion prioritizes distinctions between biological plausibility, statistical significance, functional evidence, and clinical relevance. Genes associated with antimicrobial defenses, inflammatory signaling, innate immune recognition, antigen presentation, connective tissue remodeling, and bone metabolism have been examined as potential susceptibility loci. These include antimicrobial peptide and defensin-related genes, cytokine genes like IL-1, IL-6, IL-10, and IL-17, pathways involving TNF, vitamin D receptor (VDR), matrix metallopro-

teinases (MMPs), Toll-like receptors (TLRs), CD14, and human leukocyte antigen (HLA) loci. The biological relevance of these pathways is evident because they are integral to host-microbial interactions, the regulation of inflammation, extracellular matrix turnover, and alveolar bone remodeling (Brodzikowska and Górski 2022).

The majority of evidence linking these loci to periodontitis stems from candidate-gene case–control studies. As a result, the robustness of the evidence varies significantly across genes and populations. Among cytokine-related genes such as IL-1, IL-6, IL-10, and TNF-related pathways, there is a relatively extensive body of literature supporting their association with periodontitis, including some meta-analytic findings. Nonetheless, the strength and consistency of these associations fluctuate depending on factors like ancestry, smoking status, diabetes presence, periodontal disease definitions, and analytical approaches (Loos et al. 2015). Consequently, these variants are better viewed as indicators of susceptibility rather than confirmed causal determinants. For genes related to antimicrobial peptides, VDR, MMPs, CD14/TLRs, and HLA loci, the broader biological plausibility at the pathway level often outweighs the specific clinical evidence for individual variants. For instance, TLRs and CD14 are essential for microbial recognition, MMPs are involved in matrix degradation, VDR influences immune response and bone homeostasis, and HLA molecules regulate antigen presentation. However, replication of associations between specific polymorphisms and periodontitis remains limited, and functional validation in human periodontal tissues is rare. As a result, these genetic markers should not yet be regarded as reliable diagnostic tools or determinants for tailoring treatment strategies (Dommisch et al. 2025).

A key limitation of most available genetic studies is their cross-sectional nature, which makes it difficult to separate the genetic factors contributing to disease onset from those affecting progression or stemming from chronic inflammation. Research on the utility of genetic data for predicting periodontal treatment responses is notably lacking. To consider a genetic marker clinically actionable, it must meet rigorous criteria: replication in large and diverse populations; assessment using standardized periodontitis definitions; evidence of mechanistic relevance in periodontal tissues or cells; and demonstrable enhancement of prediction accuracy beyond traditional clinical risk factors. In conclusion, while current evidence supports a polygenic basis for periodontitis susceptibility, no single polymorphism whether linked to cytokines like IL-1 or IL-6, VDR, MMPs, CD14/TLRs, HLA, or antimicrobial peptides has been validated to the extent required for routine clinical application or for guiding periodontal treatment based on genotype (Dommisch et al. 2025). Figure 1.

Epigenetic Modifications and Their Impact on PD Susceptibility

As previously discussed, the development of PD involves a complex interplay of numerous molecules and pathways. Genetic research on PD may result in controversial findings, influenced by the sample size and other limitations (Ustianowska et al. 2024). Gene expression is significantly influenced by epigenetic modifications, such as DNA methylation, post-translational modification of histones, histone variants, ATP-dependent chromatin remodeling, and non-coding RNA. MicroRNA-mediated

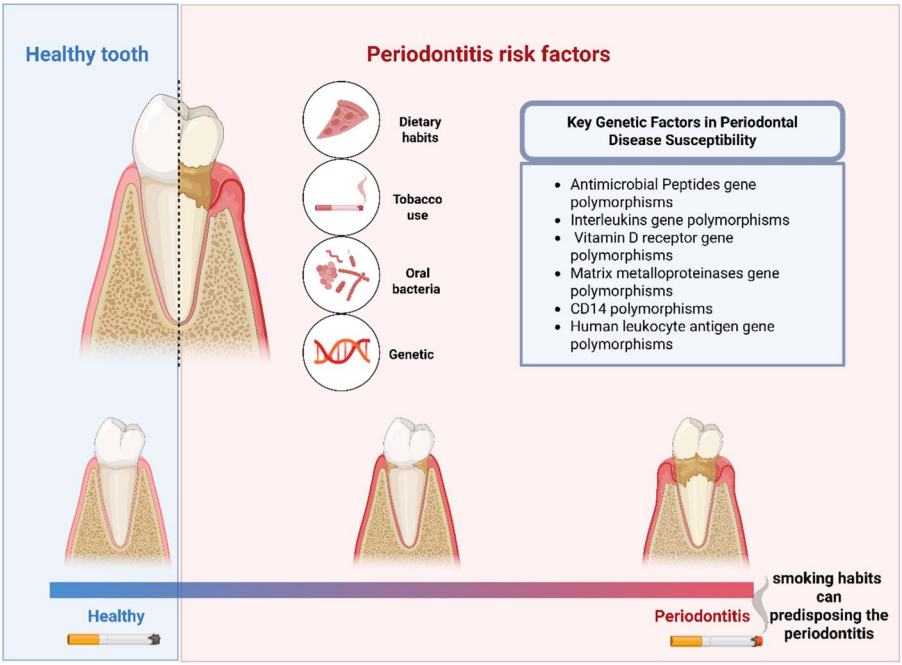

Fig. 1 The shift from periodontal health to periodontitis results from the synergy between bacterial biofilm and host-modifying factors. Inherited susceptibility arises from polymorphisms in genes encoding antimicrobial peptides, interleukins, the vitamin D receptor, matrix metalloproteinases, CD14, and human leukocyte antigens. Modifiable lifestyle influences including smoking, dietary habits, and dysbiotic oral microbiota exacerbate this genetic liability and hasten destruction of the tooth-supporting tissues

regulatory networks are now widely acknowledged as critical modulators of gene expression linked to diseases. They offer valuable insights into intricate gene-disease relationships and the regulation of inflammatory pathways. Recent research has been focused on assessing the role of epigenetics in managing a range of inflammatory diseases, including PD (Chen et al. 2023). MicroRNA-mediated regulatory networks have become powerful tools to identify disease-associated molecular interactions and novel therapeutic targets in complex inflammatory diseases (Li et al. 2022). Recent research has emphasized the regulatory influence of long non-coding RNAs (lncRNAs) on immune modulation and disease development, underscoring their potential as biomarkers and therapeutic targets in inflammation-related oral conditions (Gong et al. 2024).

DNA Methylation

DNA methylation significantly impacts gene expression, and pathogens associated with PD can alter these methylation patterns. Studies indicate that individuals with PD exhibit a unique methylation profile compared to those in the control group (Ustianowska et al. 2024). *Porphyromonas gingivalis* (*P. gingivalis*), a bacterium which is linked to PD, has been shown to have key interactions with epigenetics.

These bacteria synthesize outer membrane vesicles (OMVs) which contain various bacterial components and products that can influence host immune responses and contribute to the development of PD. According to the study by Fan et al. these OMVs could be absorbed by human periodontal ligament cells (hPDLCs). In addition, small RNA (sRNA45033) in the *P. gingivalis* OMVs could lead to cell death and inflammatory reactions. The sRNA45033 in OMVs will target chromobox 5 (CBX5). CBX5 controls the methylation and expression of p53 DNA and this leads to apoptosis of hPDLCs. These findings indicate a possible mechanism by which *P. gingivalis*-derived OMVs might drive the inflammatory responses linked to periodontitis. Nonetheless, the majority of the evidence stems from experimental studies and necessitates additional confirmation in human subjects (Ustianowska et al. 2024).

A recent study found that inflamed gingival tissues exhibit hypomethylated signal transducer and activator of transcription 5 (STAT5) genes compared to healthy gingival tissues. This finding suggests that methylation loss in the STAT5 gene promoter could play a role in the development of PD (Liaw et al. 2022). Also some studies on DNA methylation in PD, have focused on genes related to cellular signaling. These 12 genes have been compared between PD-affected tissue and clinically healthy ones: DCC, KCNA3, KCNA2, RIMS2, HOXB7, PNOC, IRX1, JSRP1, TBX1, OPCML, CECR1, and SCN4B. These indicated different DNA methylation patterns at the promoter regions (Liaw et al. 2022). Altered DNA methylation patterns have been suggested as potential biomarkers; however, their diagnostic value remains unclear due to the exploratory nature of most studies and the absence of extensive clinical validation (Ustianowska et al. 2024). DNA methyltransferases (DNMTs) play a crucial role in regulating epigenetic gene silencing via DNA methylation. Their dysregulation has been found to profoundly impact inflammatory responses and contribute to the development of various human diseases (Yang et al. 2024).

Histone Modifications

Histone modifications, such as acetylation, phosphorylation, and methylation, regulate gene expression by altering chromatin structure, which can control the epigenetic state of gene promoters. Histone acetylation typically activates gene expression, while histone methylation can either activate or repress it, based on the specific site and extent of methylation (Ustianowska et al. 2024). Studies confirm that epigenetic mechanisms, particularly histone methylation and modification enzymes, play a crucial role in the inflammatory response to LPS bacterial toxins and the function of periodontal stem cells (Huang and Zhou 2022). Periodontal ligament cells (PDLCs) exhibited increased expression of the histone methyltransferase SETD1B when treated with *P. gingivalis* LPS SETD1B is involved in regulating inflammatory cytokines in LPS-treated PDLCs (Huang and Zhou 2022).

Dysregulated histone demethylases (KDMs) play a significant role in inflammatory responses, including in cancer, viral infections, and PD. Increased levels of KDM4B and KDM4E are found in diseased periodontal tissues, while other KDMs, such as KDM3C and PHF8, have anti-inflammatory effects, which are suppressed by *P. gingivalis* LPS exposure (Liaw et al. 2022). The positive effects of chemical epigenetic modulators on alveolar bone loss and PDL cells with osteogenic abil-

ity suggest that the epigenetic status of periodontal tissue has significant influences on PD susceptibility, onset and progression. Environmental factors, such as smoking, also play a crucial role in this process and interact with epigenetics. Modulating epigenetic pathways has demonstrated encouraging results in experimental models. However, its potential for clinical use remains uncertain, primarily because human intervention studies are still limited (Suzuki and Yamada 2022). Figure 2.

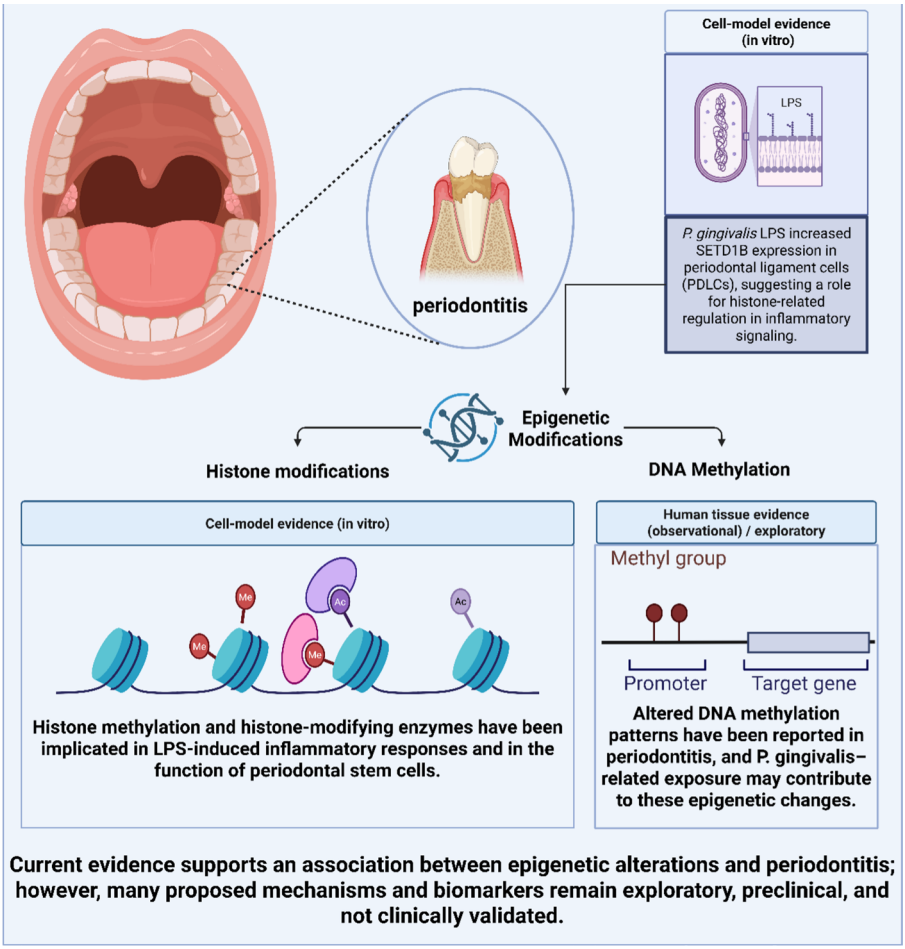

Fig. 2 Evidence map of selected epigenetic mechanisms implicated in periodontitis. Differential DNA methylation patterns have been reported in periodontitis-affected tissues, representing primarily observational human-tissue evidence. In vitro studies have shown that *P. gingivalis* LPS can alter histone-related regulators, including SETD1B, in periodontal ligament cells. Histone-related enzymes have also been implicated in inflammatory responses and periodontal stem-cell function in cell-based models. Overall, the evidence supporting epigenetic involvement in periodontitis is heterogeneous, and many proposed mechanisms, biomarkers, and therapeutic targets remain exploratory, preclinical, or not clinically validated

What has Changed in the Field?

The landscape of periodontal epigenetic research is evolving rapidly, shifting focus from simply identifying new molecular markers to distinguishing disease-related signals from cell-specific and potentially functional mechanisms. Initially, studies relied heavily on bulk gingival tissue samples, targeted DNA methylation assays, microarray analyses, and bulk transcriptomic datasets. While these efforts uncovered numerous differences between healthy and periodontitis-affected tissues, they were inherently limited (Dommisch et al. 2025). Bulk gingival tissues comprise diverse cell populations, such as epithelial cells, fibroblasts, endothelial cells, neutrophils, macrophages, lymphocytes, osteoblasts, and periodontal ligament cells. Since the cellular composition of inflamed tissues differs significantly from healthy counterparts, bulk-tissue datasets cannot clarify whether identified epigenetic changes stem from intrinsic cellular regulation or are merely artifacts of immune-cell infiltration and altered tissue composition. Consequently, many findings from these studies remain at the level of associations rather than definitive causal links (Dommisch et al. 2025).

Recent advances in single-cell and spatial transcriptomic approaches have elevated the precision of periodontal research. These methods delineate cell-specific transcriptional programs and map potential intercellular communication within periodontal tissues. They have enabled researchers to pinpoint inflammatory, osteogenic, epithelial, fibroblast, and immune-cell responses with much finer detail. However, the majority of these studies are cross-sectional, involve relatively small patient cohorts, and focus on RNA expression rather than directly demonstrating causal epigenetic changes. This limits their capacity to determine whether molecular alterations drive disease onset, are consequences of inflammation, or can predict therapeutic outcomes (Razzouk 2024). Instead, they provide valuable insights to shape hypotheses for future research. In vitro studies using isolated cell types such as gingival fibroblasts, gingival epithelial cells, periodontal ligament cells, and macrophage or osteoclast models offer more robust mechanistic evidence. Experiments exposing these cells to bacterial components, inflammatory cytokines, or epigenetic modulators have shown impacts on processes like cytokine production, osteogenic differentiation, apoptosis, extracellular matrix remodeling, and osteoclastogenesis. Yet these models cannot fully replicate the intricate dynamics of host–microbiome interactions, immune-cell diversity, mechanical forces, or structural complexities found in human periodontal lesions (Dommisch et al. 2025).

Animal models provide a complementary perspective by enabling direct testing of pharmacological inhibitors, gene perturbations, or localized delivery systems on inflammation and bone loss. These studies are instrumental in exploring causality and therapeutic interventions but face challenges in translating findings to humans due to species-specific immune responses, variations in disease progression, and discrepancies in drug metabolism (Graves et al. 2012). The study of RNA methylation such as m6A and m6Am illustrates the current trajectory of periodontal epigenetics. Existing findings largely stem from computational analyses, expression profiling of RNA methylation regulators, and a few cell-based or animal experiments. Preliminary evidence suggests a role for RNA methylation in inflammatory signaling, osteoclast differentiation, and bone remodeling (Zhang et al. 2021). However, com-

prehensive mapping of RNA methylation in well-characterized human periodontal cells remains scarce. Studies that replicate findings across multiple cohorts or conduct longitudinal observations before and after treatment are still limited. Similarly, functional rescue experiments have been rare. As a result, RNA methylation should be considered an intriguing but still nascent hypothesis rather than a proven diagnostic biomarker or therapeutic target. The field is evolving beyond descriptive gene and epigenetic marker catalogs toward integrative approaches incorporating multi-omics data, single-cell analysis, longitudinal tracking, and experimental perturbations. Achieving clinical translation will require a cohesive body of evidence derived from independent human studies, functionally relevant periodontal tissues, mechanistic cell research, and preclinical animal models, as well as rigorous clinical validation (Mongan et al. 2019).

Critical Synthesis of Current Evidence

A growing body of research underscores the role of epigenetic mechanisms in periodontitis, although the strength of evidence varies significantly across different regulatory pathways. Among these, DNA methylation and histone modifications emerge as the most consistently supported mechanisms, backed by experimental studies and analyses of human periodontal tissues. These modifications are suggested to influence critical biological processes such as inflammatory signaling, immune responses, and alveolar bone remodeling. However, a substantial portion of this understanding comes from in vitro experiments and animal models, with limited data demonstrating causal relationships in humans. Similarly, non-coding RNAs appear to play a role in regulating periodontal inflammation; yet, their clinical relevance and reproducibility across diverse populations remain areas requiring further investigation. Emerging epitranscriptomic modifications like m6A RNA methylation also show potential, but current findings are mostly exploratory and insufficient to justify clinical applications at this stage. Consequently, although epigenetic dysregulation is increasingly recognized as a factor in PD, its translation into clinically useful biomarkers or therapies remains challenging. Rigorous validation through large-scale longitudinal and interventional studies will be crucial in advancing this research field.

Genetic Variations and Their Influence on Treatment Outcomes (TO) in PD

Genetic factors, while influencing periodontal conditions and potentially exacerbating them, also play a significant role in determining the prognosis and outcomes of periodontal treatment. In the context of genetic variations and their periodontal implications, certain risk factors simultaneously serve as prognostic markers. This duality arises because some genes share mechanisms that impact both periodontal health and the efficacy of treatment. However, not all genes exhibit such dual functionality; some exclusively affect disease susceptibility and progression. These genetic influences stem from the role of the gene's final product often a protein in maintaining periodontal health or contributing to pathogenesis. Consequently, polymorphisms in

these critical genes may result in varying levels of disease susceptibility or treatment success. In light of this, researchers have proposed strategies addressing these genetic variations to achieve three key objectives: (a) developing chairside genotypic tests to assess clinically relevant genetic variations prior to treatment planning; (b) implementing targeted and personalized therapeutic approaches, particularly for complex or syndromic cases; and (c) utilizing genetic backgrounds to predict tissue responses and refine prognostic evaluations. The impact of genetic polymorphism (GP) on periodontal TO can manifest as variations in long-term prognosis or alterations in the efficacy of specific therapeutic phases. GP may influence TO at three critical stages: pharmacotherapy, Phase I therapy, and Phase II therapy. While not all identified genetic variations have demonstrated clinical utility in periodontal therapy or suitability for targeted treatment approaches, certain polymorphisms have shown promising potential.

Pharmacotherapy

The administration of local or systemic medications in periodontal therapy is justified only when the tissue demonstrates a desirable response, ideally with minimal adverse effects. This response is influenced by the biological characteristics of cells, which are governed by their genetic and allelic profiles. Consequently, the impact of genetic background on the efficacy of pharmacotherapy has been extensively studied in various medical conditions, including inflammatory diseases, with promising outcomes (CYP2C19 2023). However, such investigations remain limited in the field of periodontics, likely due to the specific role of pharmacotherapy in PD. Commonly prescribed medications include antibiotics, anti-inflammatory agents, and oral rinses. While the genetic and genotypic factors of biofilms and pathogens have been explored in relation to drug resistance and PD susceptibility (Nabil 2024), there are relatively few studies focusing on the GP of the host in this context. Although some researchers have examined the effects of host GP on adjuvant pharmacotherapy in Phase IV periodontal treatment the currently available data and published evidence are insufficient to draw definitive conclusions (Kay-Arne 2022).

Non-surgical Periodontal Treatment (NSPT)

The primary goal of NSPT is to leverage the periodontium's inherent self-healing capacity by eliminating pathological factors. Consequently, the success of Phase I treatment is heavily reliant on the biological properties and behavior of the periodontal tissues. Research has demonstrated that periodontal healing and susceptibility are influenced by specific genetic factors. Based on this evidence, some researchers have proposed that GP in periodontium-related genes, particularly those associated with disease susceptibility, may impact the outcomes of Phase I therapy. Among the most extensively studied genetic factors are interleukins-encoding genes, which play critical roles in the inflammatory response and tissue repair.

Genetic markers associated with treatment response:

- **IL-1**: IL-1 is among the most extensively studied genes in relation to various aspects of PD. IL-1 influences innate immune activity by promoting the secretion of cytokines involved in tissue destruction. As such, genotypes associated with heightened IL-1 activity are expected to contribute significantly to the pathological mechanisms of PD and potentially influence the healing process following NSPT. Although IL-1 polymorphisms are predominantly linked to PD susceptibility, their role in TO remains less conclusive. For example, Brodzikowska et al. investigated the IL-1 A−889 and IL-1B+3954 gene loci in a Polish population, reporting reduced PD susceptibility associated with IL-1 A−889 and IL-1B+3954 C/C homozygosity (Association 2022). Conversely, Walther et al. studied the same loci in a Caucasian population and found no significant differences in NSPT outcomes between genotype groups. Similar inconsistencies are evident across other studies. Consequently, many researchers suggest that IL-1 GP primarily affect PD susceptibility rather than TO. A commonly accepted explanation for these discrepancies is the impact of ethnic and geographic factors on the populations being studied (Brodzikowska et al. 2019).
- **IL-6 and IL-10**: These interleukins, due to their established roles in immune response and involvement in PD, have been investigated more extensively than most others, with the exception of IL-1. IL-6 is a polymorphic cytokine whose levels are associated with periodontal conditions and exhibit changes following periodontal therapy (Shinji Matsuda et al. 2023). Certain alleles, such as IL-6−174 G, which are linked to increased gene expression, are hypothesized to influence inflammation and tissue response, thereby potentially affecting TO. While the role of these alleles in PD susceptibility is well-supported, their impact on TO remains less clear. A study noted that carriers of the IL-6−572 GG genotype or IL-10–592 A allele showed comparable TO after NSPT to those without these alleles (Georgios and Chatzopoulos 1 2020). Although these cytokines appear to have limited direct effects on TO, they remain promising targets for genetic prevention and adjunctive therapies. For instance, Nolde et al. demonstrated that genetically proxied downregulation of IL-6 signaling is a viable drug target for reducing PD risk (Nolde et al. 2023). However, further studies are needed to evaluate the effects of various alleles and to validate these findings. Additionally, differences in susceptibility and TO between allele carriers and non-carriers vary across populations, highlighting the necessity of studying unexamined demographic groups before definitively ruling out associations between these genes and TO.
- **IL-8**: IL-8 contributes to PD primarily through its chemoattractive properties. Similarly, while other research has noted an association between IL-8 levels and PD, the aforementioned study did not identify any such relationship. Another investigation examining the IL-8 ATC/TTC and AGT/TTC haplotypes reported no significant differences in pathogen reduction or clinical TO following NSPT (Finoti et al. 2013). These findings suggest that the effects of IL-8 GP may vary by allele. In other words, regardless of ethnic and geographic background, certain alleles of IL-8 may influence disease susceptibility, while others might have no effect or could influence both susceptibility and TO. However, the current evidence is insufficient to draw definitive conclusions regarding these relationships. Despite this, IL-8 has shown potential as a target for therapy and as a predictor of

TO. For instance, Huang et al. demonstrated that inhibiting IL-8 in vitro reduced inflammatory activity, suggesting its potential for targeted therapy in chronic PD (Huang et al. 2021). Additionally, Bumm et al. reported that IL-8 levels could predict tissue responsiveness during Phase 1 and 2 of NSPT (Bumm et al. 2024). These findings raise two hypotheses: the potential to genetically target IL-8 as part of future NSPT strategies and the possibility that lower-expressing genotypes may be associated with improved treatment responses.

- **GATA-3**, **COX-2 and IL-4**: These genes are recognized for their roles in mediating the inflammatory response and contributing to the pathological mechanisms of PD. Previous efforts to target these cytokines in periodontal therapy, such as the use of non-steroidal anti-inflammatory drugs (NSAIDs), yielded limited success. However, following the discovery of their GP and their association with PD susceptibility, researchers began exploring their potential as therapeutic targets and their influence on TO. A multicenter study by Walther et al. investigated the relationship between the GP of IL-1, IL-4, COX-2, and GATA-3 and the TO of NSPT. While all these genes were associated with PD susceptibility, only the GP of GATA-3 demonstrated a potential influence on TO, suggesting its role as a predictor of future clinical attachment loss. However, this association was modest, and GATA-3 was considered a contributory rather than a definitive factor in predicting TO. Although GATA-3 has been successfully used as a prognostic and diagnostic marker in other medical fields, such as oncology and as a therapeutic target for certain inflammatory diseases, However, its role in periodontal therapy remains a topic of debate and requires further investigation (Yoo et al. 2023) The majority of studies do not support a significant influence of GP on TO in NSPT. However, several critical points warrant consideration:
- **Population-Specific Influences**: Ethnic, genetic, and geographic backgrounds of the studied populations have been shown to impact results. Therefore, generalizing findings across diverse populations requires further investigation in underrepresented groups.
- **Allelic Variability**: Different alleles of the same gene may exert varying levels or types of influence on PD susceptibility and treatment response. Future research should aim to encompass a broader range of alleles to provide a more comprehensive understanding.
- **Limited Role of GP Post-NSPT**: While genotypes seem to influence periodontal conditions, the healing process and inflammation reduction following effective NSPT appear largely unaffected by GP, provided that oral hygiene is maintained. Notably, some studies have linked GP with elevated inflammatory cytokine levels before treatment, but these associations diminish after modifiable factors such as plaque and calculus are addressed. This highlights the non-modifiable nature of GP as a less critical factor in periodontal health maintenance once other predisposing factors are controlled. Additionally, the common methodology of comparing affected patients to unaffected individuals in susceptibility studies raises questions about the broader implications of GP in the absence of other risk factors.
- **Targeting GP in Advanced Therapy**: Current evidence does not strongly support the notion that GP significantly alters the TO of NSPT. Consequently, target-

ing GP in Phase IV periodontal therapy may lean toward overtreatment rather than a practical future direction.

- **Disease Class Distinctions**: The connection between genetic polymorphisms and periodontitis can differ depending on the disease's phenotype and severity. Previous studies have highlighted distinct associations in what were once categorized as chronic and aggressive periodontitis.
- **Surgical Periodontal Treatment (SPT)**: The GP background plays a significant role in influencing TO in SPTs, primarily through three key mechanisms: tissue healing and bone metabolism, inflammation regulation, and immune response modulation. Given that healing and regenerative processes are integral to many SPTs, GP is likely to affect the success of these procedures. However, certain specific treatments have been more extensively studied in the literature regarding their interaction with GP, warranting further exploration to better understand the broader implications.
- **Dental Implants**: The influence of genetics on implant dentistry is a multifaceted area that warrants a dedicated review. The primary mechanisms through which GP may affect implant success involve bone metabolism and the inflammatory response around dental implants. In this context, the failure rate during the surgical phase is linked to the patient's GP and subsequent host response. A recent meta-analysis revealed that the IL-1B-511 (2/2) genotype is associated with increased early crestal bone loss (Agrawal et al. 2021). However, this association is conditionally dependent on other factors, as demonstrated by Agarwal et al. (2022), who found that early crestal bone loss was higher in individuals with IL-1B-511 AA and/or IL-6–572 GG genotypes, but only when bone mineral density was below normal (Agrawal et al. 2024). Interestingly, certain genetic factors appear to influence implant TO without affecting PD susceptibility. For example, a recent meta-analysis found no significant association between MMP-3 GP and PD susceptibility, but some studies indicated a relationship between MMP-3 variants and a higher risk of osseointegration failure (Hu et al. 2024). The most common causes of implant failure identified in the literature include peri-implantitis, osseointegration problems, and inflammatory reactions. A study on Basque patients suggested that individuals with peri-implantitis may carry alleles related to GBP1 and BRINP3 proteins, which modulate the osseointegration process by altering immune responses to pathogens (Lafuente-Ibáñez-de-Mendoza et al. 2024). Consequently, one of the emerging trends in implant therapy is the development of personalized treatment strategies and targeted therapies to enhance the success rate of implants.
- **Regenerative Therapies and Augmentation**: Genetic and epigenetic factors influencing the metabolism and remodeling of intra- and extra-oral bones in maxillofacial structures have been extensively studied. These processes are well recognized for their role in regenerative medicine. Leveraging the genetic characteristics of cells has shown promise in advancing periodontal tissue engineering, with innovative approaches such as gene-activated bone grafts and gene delivery being introduced (Bozo et al. 2021). Furthermore, genetic manipulation and gene expression control are actively being explored for soft tissue regeneration. As a result, GP are expected to significantly impact tissue response, potentially

enhancing regenerative outcomes. However, there is limited data on their direct effect on the TO of regenerative SPT. However, it is also crucial to consider non-surgical factors that may influence gene expression. In this context, gene expression levels can be affected by factors unrelated to SPT, as gene expression is intrinsically linked to the natural biological conditions of the tissue prior to any intervention. For example, studies have shown that BMP2 expression, a key gene for osteogenesis regulation, is influenced by the craniofacial growth pattern of the jaw (Olsson et al. 2021). Furthermore, animal studies have demonstrated that gene expression profiles can vary depending on the materials used in regenerative surgeries. Therefore, further research is needed to address the current gap in data and to isolate the specific effects of GP on the TO of regenerative SPT (Suleimenova et al. 2017).

- **Long-term Success**: While most studies have assessed the impact of GP based on short-term evaluations of TO, it has been shown that GP may exert a different or even opposite influence over long-term follow-ups. This could be explained by considering the long-term success of regenerated tissues as being similar to the predisposition of natural, unaltered tissues. In other words, after successful treatments, patients whose genotype predisposes them to PD may remain susceptible to the same condition, which could subsequently affect regenerated or healed tissues. Although this rationale appears plausible, it is not sufficiently supported by evidence. Moreover, there is a lack of comprehensive data establishing a clear relationship between the TO of regenerative therapies and IL-1 GP. A systematic review by Chatzopoulos found the available data to be limited and inconclusive regarding this relationship (Nolde et al. 2023). Since then, a few recent studies have been published with conflicting results, underscoring the need for further targeted research to draw definitive conclusions.

Epigenetic Therapy as a Novel Approach for PD Management

As the epigenetic factors have been shown to be related to PD susceptibility they are suggested to be potential targets for novel PTs. Here, we briefly review the rationale, efficacy, history, and new horizons of epigenetic therapies (ETs) for the future of clinical periodontics.

1. History, rationale, and potential of epigenetic interventions for PTs.

The term "epigenetic" was invented by Waddington in 1942 as the connection between genetics and phenotype. Through the evolution of epigenetic concepts, ET was introduced as it was found that non-sequence-based mechanisms may alter the phenotype. It means that modifying the genetic trait is possible without manipulating the sequence of alleles, which is not easily feasible. This attitude follows the scheme of phenotype alternation but is based on the options to regulate the expression level of the natural alleles instead of revising its sequence or managing their consequences with conventional drugs. Accordingly, the first attempts were conducted in the 1960 s, and the first approved drug was introduced in the

2000 s (Feehley et al. 2023). ET drug evolution records could be divided into four waves (Ganesan et al. 2019). Accordingly, nowadays, the main epigenetic approaches are direct epigenetic reprogramming (epigenetic editing) and interfering with natural gene expression (GE) processes by epigenetic drugs (epidrugs). Not to be missed, there are also non-epigenetic approaches that affect GE as well. However, despite extra-oral conditions the dental problems are not well studies and hence still passing older waves. Regarding the PDs, growing documents indicate ET's potential as a future solution. The philosophy of this approach originates from the fact that taking control over the genes related to inflammation and immunologic reactions can be beneficial by reducing destructive host responses and improving the healing process. It relies on epigenetic targeting strategies for therapeutic purposes, diagnosis, or personalizing treatments based on the patient's epigenetic profile. The affirmative evidence emphasizes various grounds, which all are founded on the role of epigenetics on PD pathogenesis and its effects compared to conventional PTs:

- **Epigenetics aspects of periodontal risk factors**: Several studies demonstrate that some environmental risk factors are contributing via epigenetic changes. For instance, smoking is shown to be effective in the cellular expression of epigenetic markers of periodontal lesions. The fundamental of this relation is also investigated as the DNA methylation modification after smoking in gingival tissue is reported (Cho et al. 2017). Some other risk factors like nutrition, are also supported to interact with epigenetic regulation of periodontal tissues. Also, some other environmental factors are shown to at least relate to epigenetic changes. Hence in brief, it suggests that epigenetics is a possible course of action either for preventive or therapeutic interventions by mimicking and following the natural course of environmental influence.
- **Epigenetic aspects of PD pathogenesis**: Epigenetics are shown to contribute to the mechanism of periodontal health. It is shown that different epigenetic patterns can lead to different PD susceptibility. Also, PD makes localized and systemic epigenetic changes by altering expressions of some genes like the SOCS family which are responsible for some undesirable consequences(Ghafouri-Fard et al. 2022). On the other hand, dysbiosis may lead to cellular epigenetic changes. Hence, a reciprocal relation between epigenetics and the periodontal condition is suggested which indicates its potential for therapeutic purposes for reestablishing symbiosis or improving periodontal health.
- **Epigenetic aspects of current PTs**: Asa'ad et al. conducted a case study evaluating epigenetic alternations following NSPT in patients suffering from chronic PD. They concluded that NSPT resets the DNA methylation status of inflammatory genes. Also, some conventional drugs have an epigenetic side. For instance, Shi et al. successfully utilized an aspirin drug delivery system in the PD model with significant results on macrophage metabolic phenotype modification and inflammation inhibition (Shi et al. 2023). Besides, though not for PD for some medical conditions, it is shown that aspirin efficacy is dependent on the patient's epigenetic profile (Wang et al. 2019). Hence,

there are growing numbers of evidence demonstrating a reciprocal relation between epigenetics and the efficacy of conventional treatments. It exhibits ET's potential to improve TO as a combination therapy or distinctly.

- **Epigenetic aspects of systemic conditions**: It has been discussed for a long time that some systemic diseases may impact periodontal conditions and vice versa. However, with the emergence of epigenetic investigations, some epigenetic mechanisms are also revealed in this matter. Li et al. indicated that DNA methylation patterns are influenced in diabetic patients which overshadows their PD susceptibility. On the other hand, diabetes can also be associated with the periodontal microbial population of periodontal patients shifts in the amount and type (Qin et al. 2022). Interestingly, systemic and localized microbial infections are demonstrated to Hence, epigenetic targets are proper points to direct as a part of PTs in systemic conditions.
- **Epigenetics superiority**: ET also suggests advantages over conventional PTs or other biomolecule-targeting therapies. Though the genetic background affects the patient's susceptibility and treatment efficacy, reversing inherited gene-related traits is usually arduous. Thus, despite a few genetic diseases, it is practically difficult to cure the patient by eradicating such etiologic factors. That is why most interventions are designed to manage these situations at the non-genomic level. The epigenetic condition is inheritable but shown to be reversible. Also, it is suggested that in some conditions like tissue aging the pathologic epigenetic events are reversible (Ruden and Rappolee 2023). These are advantages of ET in the case of a patient's genetic predisposition or even as a treatment option. In general, the current trend of research supports that the epigenetic-periodontic relation has the potential for therapeutic intervention. Epigenetic interventions have sparked significant interest as potential therapeutic approaches, but their use in periodontology is still predominantly in the preclinical stage. Currently, there is a lack of robust clinical evidence to endorse epigenetic therapies as replacements for traditional periodontal treatments. As such, these strategies should be viewed as experimental rather than clinically validated.

2. **Efficacy of ET as a PT**: Evidence for epigenetic therapies in periodontitis must be considered within the context of the specific experimental models employed. The majority of existing data comes from in vitro studies involving gingival fibroblasts, periodontal ligament cells, macrophages, or models related to osteoblast and osteoclast activity, as well as animal studies focused on inflammatory bone loss. While these investigations provide important mechanistic insights and preclinical proof-of-concept support, they do not confirm clinical efficacy or safety in humans. Human-based evidence is still scarce, primarily derived from observational studies on gingival tissues and small-scale exploratory research. As a result, epigenetic therapies are best viewed as experimental at this stage rather than established treatments for periodontal conditions (Dommisch et al. 2025). Referring to the available studies, the most investigated target points for epigenetic regulations in periodontal tissues are GPs, micro-RNAs, histone modifications, and DNA methylation. Based on that, some novel PTs are designed and examined with

promising results. Recent studies have shown that inhibiting NF-κB is a promising molecular approach to suppress pathological cell proliferation and inflammatory signaling in oral diseases (Cheng et al. 2025).

1. DNA Methylation (DM): DM is a major epigenetic mechanism that regulates GE in various ways. As the methylated site shows an altered affinity for biochemical reactions, when it occurs in critical segments, it leads to regulation of GE. In that matter, there are direct and indirect mechanisms depending on the affected site. Accordingly, different trials are conducted to reprogram cells for an improved tissue response as a part of PT.

    1.1. Promoter methylation: It is the main direct mechanism in which DM occurs on the site of a gene promoter and results in inhibiting transformative factors to bind DNA. thus a decreased level of GE is expected for the neighbor gene due to silencing. In this regard, an examined intervention is the application of DM inhibitors concerning the genes that are essential for an appropriate periodontal response such as TLR2. However, recent studies suggest more complicated effects of large-scale promoter methylation on the downstream, which must be considered for genomic engineering and ET (Mendoza et al. 2022).
    1.2. Epidrugs and Transcription-related proteins: Currently, there are several available FDA-approved epidrugs for different conditions and mostly cancer therapy. However, some researcher explored their influence for other conditions including PD. for instance, Decitabine is a DN inhibitor focusing on methyltransferase first introduced for hematologic cancer treatment which was recently examined for other purposes like improving cancer vaccine efficacy and other types of cancers (Tatman et al. 2022). Tanaka et al. tried that for periodontal bone loss inhibitions in an in-vivo model. They found that its application inhibits bone loss and upregulates inflammatory cytokines (Tanaka et al. 2021). Decitabine is also able to decrease methylation level of osteogenesis related genes promoters in gingival fibroblast (Cho et al. 2017). There are also other epidrugs with similar potential; however, the available data in this regard is limited and needs further investigation.
    1.3. Contributing to other strategies: it is shown that DN can indirectly play a role by means of other strategies including histone modification and micro-RNA involvement Besides, some DN inhibitor epidrugs has a dual effects that alter epigenetic situation relying on other mechanism. For example Decitabine is shown to have histone code effects as well (Dalvand et al. 2021). Hence, its application in combination with other strategies or as an adjuvant is suggested.

2. Histone modification (HM): Besides DM, HM is the most investigated epigenetic mechanism in periodontics. HM is able to modify bone metabolism and consequently periodontal condition and implant success. Hence, HM epidrugs, which are mainly Histone deacetylase inhibitors (HDACi) were investigated

for multiple situations including PD. There are multiple generations of HM drugs according to the type of targeted enzyme and features. Algate et al. studied two types of HDACi for HDAC I and II in an in-vitro study and showed decreased osteoclastic activity and cytokine suppression. These drugs also differ in selectivity and tolerability. Lagosz et al. combined selective class I and II for pre and post-exposure treatment and showed similar successful results (Lagosz et al. 2020). It worth noting that broad-spectrum HDACis are one of the most challenging epidrugs due to their side effects.

3. Micro RNA (mi-RNA): mi-RNA is more investigated for their role in PD susceptibility rather than treatment. However, it is promising ground as its application on other medical field has been successful and its dental application is just recently started to be investigated.
4. GP: Although major epigenetic mechanisms in PDs are those mentioned above, some minor operations like GP are also suggested. It is more beneficial by playing role where it's beyond the impacts of major mechanisms.

    4.1. Despite GP reports about translatable genes, there is evidence that promoters GP is also effective in the case of PD. Such a phenomenon appears in the same way that the promoter DM or RNA does. The concept that a gene like SOCS1 may contribute due to its DM but not its promoter methylation is also reported for non-periodontic disease as well (Emamgholipour et al. 2023).
    4.2. Similarly, Asa'ad et al., there was no influence on TNF-α, IFN-γ and LINE-1 after NSPT but significantly on COX-2 DM level (Asa'ad et al. 2017). It suggests that epigenetic-periodontic relation is not generalized to all genes related to PD Though addressing them to treat some diseases has been attempted, there are not enough studies for periodontal purposes. Also, as mentioned before, GP is shown to be involved in the development risk of PD but not the TO of PTs. However, promoter GP is indicated to impact TO of some other conditions like IL-10 in HCV patients (Dhaouadi et al.).
    4.3. On the other hand, some genes like COX-2 influence PD susceptibility by GP but they don't show any impact on TO (shan 2018). However, its DM level is shown to be related to PD susceptibility and influenced by PT (Asa'ad et al. 2017). These facts suggest that epigenetic-periodontic relation mechanisms do not generally affect all related genes. As a result, epigenetic profiling, personalized treatment planning, and targeted therapy by various strategies must be considered a future direction of ET. However, limited information is available about targeting GP as an epigenetic treatment strategy for PD, which needs more investigation.

5. Tissue engineering and regenerative therapies (RT): Though RT is not an epigenetic mechanism but a kind of treatment, it is revolutionary changing by merging ET with that. Despite newly introduced horizons, some previous attempts are shown to pose epigenetic effects as well. in brief ET are investigated for improving GE of desirable genes, enhancing host response for better adaption to implants or tissue healing. For instance, Decitabine is shown to be effective for differentiating

gingival fibroblast to osteoblasts in combination with BMP-2 (Cho et al. 2017). Additionally some researchers focused on manipulating epigenetic features of bone metabolism for nonregenerative therapies like integrating with titanium implants (Zhang et al. 2021). Hence, the future of RT seems to be strongly related to progress in ETs. Figure 3. Epigenetic therapeutic strategies investigated for periodontitis shown in Table 1.

Future Directions and Pitfalls

Despite all the advantages of ET, there are some risks as well. The results of regulating GE are not restricted to therapeutics but to pathological processes as well. There are concerns about possible adverse effects of ET in PT with some oncologic consequences (Barros et al. 2020). Additionally, epidrugs are not yet as developed as they could specifically target a particular tissue, and consequently, they could affect

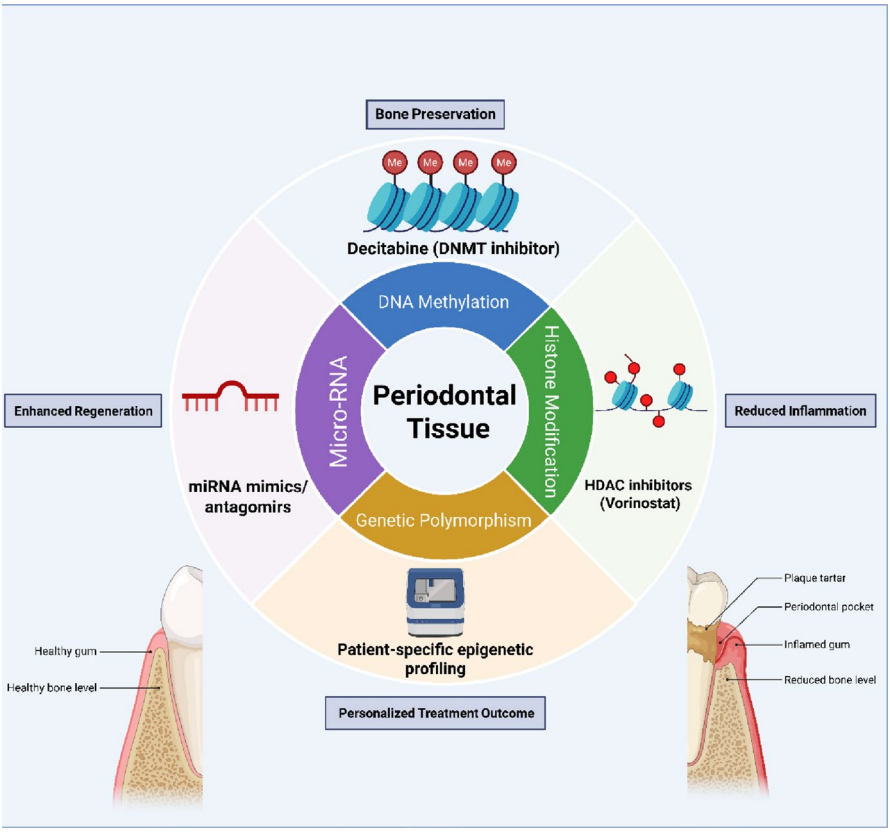

Fig. 3 Emerging ET for periodontitis target DNA methylation (e.g., the DNMT-inhibitor decitabine), histone modifications (HDAC inhibitors such as vorinostat), and micro-RNA networks (mimics or antagomirs), while patient-specific genetic/epigenetic profiling guides their personalized application. By reprogramming periodontal-tissue gene expression, these strategies converge on three clinical goals—bone preservation, inflammation reduction, and enhanced regeneration—paving the way for precision periodontal therapy

Table 1 Epigenetic therapeutic strategies investigated for periodontitis

Target mechanism	Example intervention	Model system	Effect on inflammation	Effect on bone loss/regeneration	Delivery method	Safety concerns	Human evidence	Translational stage
DNA methylation inhibition	Decitabine (DNMT inhibitor)	Cell culture, animal models	↓ Pro-inflammatory cytokines	↓ Bone loss; ↑ osteogenic differentiation	Local/systemic experimental delivery	Off-target effects, cytotoxicity	Very limited	Preclinical
Histone modification (HDAC inhibition)	HDAC inhibitors (e.g., TSA, MS-275)	Cell culture, animal models	↓ Inflammatory signaling	↓ Osteoclast activity; ↑ bone formation	Experimental local/systemic	Broad epigenetic effects, toxicity	None	Preclinical
microRNA modulation	miRNA mimics/inhibitors (e.g., miR-146a, miR-155)	Cell culture, animal models	Modulates immune response	Promotes tissue repair; reduces bone resorption	Nanoparticles, viral vectors, local delivery	Delivery efficiency, off-target effects	Very limited	Early preclinical
Glycosylation-related modulation	Experimental glycosylation-targeting approaches	Experimental studies	Potential anti-inflammatory effects	Uncertain	Experimental	Limited evidence	None	Exploratory
Epigenetic-assisted regenerative therapy	Decitabine + BMP-2; epigenetic modulation of stem cells	Cell culture, animal models	Indirect reduction of inflammation	↑ Osteogenic differentiation and periodontal regeneration	Biomaterials/scaffolds/local delivery	Long-term safety unknown	None	Early preclinical

DNMT, DNA methyltransferase; HDAC, histone deacetylase; BMP-2, bone morphogenetic protein-2

the whole body. Additionally, drug tolerability, dose-limiting problems, and adverse effects of broad-spectrum epidrugs limited the administration for non-life threatening conditions like PD. Some side effects are nausea, cardiac abnormalities, thrombocytopenia, diarrhea, etc. However, higher specifies and tolerability are potentially possible and hoped for in the next generations of ET. Additionally, there are some concerns about the ethical aspects of epigenetic research and personalized ET (Santaló 2022). Though the potential of ET is leading the trend of PTs for a paradigm shift, its application in other medical branches is more developed. The history of first attempts for extraoral disease returns to older times and there are FDA-approved epidrugs and ETs for those conditions nowadays. Currently, the mainstream epigenetic-periodontic investigations are focused on the diagnosis and pathogenesis of PD, in which ET possesses a minor but upgrowing share. Recent evidence indicates that, while a variety of epigenetic signatures have been identified, only a limited number have shown adequate reproducibility and clinical relevance to warrant integration into routine periodontal care. The majority of these findings are still in the exploratory phase and require further validation through independent studies conducted on larger and more ethnically diverse populations (Dommisch et al. 2025). Additionally, not all the potential epigenetic targets mentioned are investigated for therapeutic purposes. Epigenetic research is advancing quickly, offering significant insights into the mechanisms underlying PD. However, the clinical use of epigenetic therapies is still in its early experimental phase. Currently, the available evidence does not yet justify their routine implementation in periodontal care, as numerous biological, safety, and translational barriers remain to be addressed.

Epigenetic interventions hold significant therapeutic promise for PD; however, their clinical application faces several methodological and translational hurdles. Periodontal tissues are composed of diverse cell populations, such as epithelial cells, fibroblasts, immune cells, osteoblasts, osteoclasts, and periodontal ligament stem cells, each with unique epigenetic profiles and biological responses. This cellular diversity complicates the identification of specific epigenetic targets linked to the disease and may lead to variability in treatment outcomes. Moreover, many epigenetic drugs exert broad-spectrum effects, potentially altering non-target genes or signaling pathways, raising safety concerns and introducing biological unpredictability. Tissue-specific delivery also remains a significant obstacle, as systemic administration risks unintended effects on organs and tissues beyond the periodontal region. Additional challenges include the absence of standardized dosing protocols, uncertainties regarding the duration of treatment, and potential long-term cumulative effects of epigenetic modulation. Notably, much of the supporting evidence for these therapies in periodontology comes from in vitro studies and animal models, with human clinical trials still being limited. Greater research is essential to confirm their efficacy, safety, optimal delivery methods, and long-term outcomes before these interventions can be adopted into standard periodontal care (Dommisch et al. 2025).

Many of the challenges associated with epigenetic therapies go beyond mere gaps in research, reflecting deeper translational barriers that currently hinder their clinical implementation. Epigenetic regulators often influence multiple biological pathways concurrently, complicating precise therapeutic targeting and increasing the likelihood of unintended off-target effects. Additionally, several epigenetic mechanisms crucial

for processes such as inflammation and tissue regeneration are closely linked to cellular proliferation, differentiation, and oncogenesis. As a result, prolonged manipulation of these pathways raises concerns about tumorigenicity and biological unpredictability. Another significant obstacle lies in the lack of reliable tissue-specific delivery systems. Epigenetic agents administered systemically may impact various organs and cell populations outside the targeted periodontal environment, heightening the risk of systemic toxicity and adverse effects. Furthermore, the periodontal tissue itself is a highly heterogeneous cellular ecosystem, encompassing epithelial cells, fibroblasts, immune cells, osteoblasts, osteoclasts, and periodontal ligament stem cells, all of which possess distinct epigenetic profiles. This complexity complicates the identification of broadly effective therapeutic targets and can lead to variability in treatment outcomes across patients.

Therefore, despite promising findings from preclinical studies, the development of epigenetic therapies for periodontitis remains largely in the experimental phase. Bridging the gap to routine clinical application will require not only further research but also the resolution of critical biological and technological hurdles to enhance safety, predictability, and therapeutic precision.

How Genetic and Epigenetic Factors Interact in the Development of PD

Since the 1960 s, many studies have explored how genetic factors influence periodontitis susceptibility and progression, showing that genetic susceptibility makes certain individuals more prone to these conditions. In recent years, epigenetic research has aimed to clarify how gene-environment interactions influence both the development of PD and treatment responses (Loos 2020). Periodontitis is a multifaceted inflammatory condition arising from interactions among microbial, genetic, epigenetic, environmental, and host immune factors. Although genetic susceptibility has been acknowledged for years as a key factor influencing disease risk, growing emphasis is now being placed on epigenetic mechanisms that bridge environmental exposures and host biological reactions. Gaining a deeper understanding of how genetic and epigenetic elements interplay could offer valuable perspectives on the disease's variability, progression, and response to treatment.

Gingivitis commonly coexists with PD, with the host immune response playing a regulatory role in this progression. Acquired immunity shapes the host's response, but individual genetic profiles significantly influence it, determining responses to specific antigens (Kozak et al. 2020). Epigenetic alterations in PD include DNA methylation and histone modifications, which may either amplify or reduce inflammation in response to bacterial challenges. The evolving field of epigenetic regulation has sparked considerable interest in its potential for diagnostic and therapeutic use. Despite this enthusiasm, the majority of epigenetic biomarkers and therapeutic targets under consideration are still experimental. While some studies have identified links between specific epigenetic patterns and aspects such as disease activity, progression, or response to treatment, most of these findings lack sufficient validation across diverse populations and clinical contexts. As a result, their application

in routine diagnosis, prognosis, patient stratification, or treatment planning remains uncertain. Robust longitudinal, multicenter research, along with mechanistic investigations, is essential before epigenetic biomarkers and therapies can be incorporated into evidence-based approaches for periodontal care. When interpreting epigenetic findings in periodontitis, reverse causality is an important factor to consider. While many studies indicate that epigenetic changes might play a role in disease susceptibility and progression by affecting inflammatory and immune pathways, it is equally plausible that these changes result from chronic periodontal inflammation rather than serving as primary causative factors. Prolonged exposure to inflammatory cytokines, oxidative stress, microbial products, and tissue damage can lead to modifications in DNA methylation, histone structure, and non-coding RNA expression. As a result, the relationship between periodontitis and epigenetic regulation is increasingly seen as bidirectional, where epigenetic alterations can both shape and be shaped by the inflammatory environment. This intricate interplay complicates efforts to establish clear causal relationships, underscoring the importance of longitudinal studies to differentiate between initiating mechanisms and secondary biological processes.

Genetic and epigenetic factors operate within a complex interplay involving the host, microbes, and environmental influences, rather than functioning as isolated contributors to periodontitis. Candidate-gene studies have identified potential links with cytokine-associated genes such as IL-1, IL-6, IL-10, IL-17, and TNF pathways, alongside variants related to VDR, TLRs, CD14, MMPs, HLA loci, and genes tied to epithelial defense or bone metabolism. However, these findings should not all be considered equally robust. Many stem from cross-sectional case–control studies that often suffer from small sample sizes, varied disease definitions, and population-specific biases (Cho et al. 2021). Genes coding for inflammatory cytokines provide the clearest biological rationale due to their role in regulating inflammatory responses and tissue destruction. Yet, the associations identified for specific gene variants remain inconsistent across different populations, potentially influenced by factors such as genetic ancestry, smoking habits, diabetes, microbial exposure, or variations in clinical presentations. Similarly, findings involving genes like VDR, TLR4, Fcγ receptor genes, IL-17-related loci, and other inflammatory polymorphisms lack the consistency needed to classify them as reliable markers for disease progression, severity, or treatment outcomes (Zhao et al. 2023).

From an epigenetic perspective, mechanisms such as DNA methylation, histone modifications, non-coding RNAs, and RNA-modification pathways are thought to affect processes like inflammatory signaling, osteoclast activity, tissue remodeling, and bone metabolism. However, the interpretation of these observations depends on the type of evidence presented. While studies based on gingival tissue expression and methylation can reveal molecular patterns associated with disease, they cannot confirm causality as these patterns may simply reflect changes in cell composition or ongoing chronic inflammation (Raut et al. 2019). Cell-based experiments may offer mechanistic insights, and animal models can assess intervention effects; however, neither approach fully establishes direct clinical relevance for humans. Consequently, longitudinal studies in human populations, alongside independent replication and functional validation, are essential before genetic or epigenetic biomarkers can be

reliably integrated into risk assessment models or tailored periodontal therapies (Raut et al. 2019).

Candidate-Gene Studies versus GWAS and Mendelian Randomization Approaches

The study of the genetic underpinnings of periodontitis has traditionally focused on candidate-gene approaches, targeting biologically significant genes implicated in inflammation, immune regulation, and tissue remodeling. Genes such as IL-1, IL-6, TNF-α, VDR, and members of the TLR family have been central to these investigations. While these studies have identified numerous potential susceptibility loci, the reproducibility of their findings across various ethnic groups and research settings has often been limited. Factors such as variation in environmental exposures, disease classification criteria, sample sizes, and genetic diversity have contributed to these inconsistencies. In recent years, genome-wide association studies (GWAS) have introduced a hypothesis-free methodology to discover genetic variants associated with periodontitis across the entire genome. Unlike candidate-gene studies, GWAS offers enhanced statistical precision and minimizes selection bias, enabling the identification of novel susceptibility loci. Moreover, Mendelian randomization (MR) has emerged as a complementary approach to explore causal relationships between genetic factors, systemic traits, and PD. By using genetic variants as instrumental variables, MR provides valuable insights into the biological connections underlying disease mechanisms (Gao et al. 2024). Mendelian randomization studies have shown that circulating immune cell profiles could play a causal role in disease susceptibility. This underscores the value of using genetic instrumental variable methods to better understand immune-related pathological conditions (Li et al. 2024).

Despite their advantages, GWAS and MR approaches have notable limitations. The genetic variants identified often account for only a modest fraction of the heritability of periodontitis, and the biological pathways they implicate typically require further functional validation. Current evidence suggests that combining findings from candidate-gene research with data from GWAS, MR, transcriptomic, and epigenomics analyses could offer the most robust strategy for deciphering the complex genetic architecture of periodontitis and uncovering actionable therapeutic targets (Gao et al. 2024). GWAS and Mendelian randomization findings should primarily be viewed as tools for prioritization rather than definitive evidence of clinical applicability. Their translation into practice demands validation through replication, molecular correlations specific to periodontal tissue, and functional perturbation experiments conducted in appropriate cellular systems or models (Omidiran et al. 2024). The following tables provide an overview of the latest evidence regarding genetic and epigenetic contributors to periodontitis. Evidence levels were determined based on factors such as the consistency of replication, the size and diversity of study samples, the use of standardized periodontal classifications, the availability of functional validation, and the potential for clinical application. “Strong” evidence refers to findings that show consistent replication across independent studies, are supported by functional validation, and hold potential clinical significance. “Moderate” evidence corresponds to associations that have been observed repeatedly but exhibit some heterogeneity, along with partial functional support. “Weak” evidence signifies findings

with limited or inconsistent replication. "Exploratory" evidence mainly stems from smaller-scale, cross-sectional, bioinformatic, in vitro, or preclinical studies, lacking established clinical relevance. Table 2 compares the principal experimental and analytical approaches currently used to investigate the genetic and epigenetic basis of periodontitis.

Table 3 Critical appraisal of genetic evidence in periodontitis and Table 4 Critical appraisal of epigenetic evidence in periodontitis. The tables indicate that the majority of genetic and epigenetic candidates mainly demonstrate biological plausibility or links to disease, rather than serving as validated tools for clinical prediction. Currently, no single genetic polymorphism or epigenetic marker has been proven reliable enough to routinely predict the outcomes of periodontal treatment. To facilitate the interpretation of the available evidence, Table 5 summarizes the principal genetic and epigenetic biomarkers investigated in periodontitis, together with their sample sources, level of evidence, replication status, clinical relevance, and current translational readiness.

Personalized Periodontal Care: The Role of Genetic and Epigenetic Profiling

PD is a complex multifactorial disease, where a person's genetic makeup and environmental factors together shape susceptibility and disease progression. Gene polymorphisms, which can vary by race, influence individual susceptibility to PD and responsiveness to treatment. While maintaining oral hygiene through flossing and

Table 2 Comparison of molecular approaches used to investigate genetic and epigenetic mechanisms in periodontitis

Approach	Can prove	Cannot prove	Major confounders	Best use
Candidate-gene studies	Gene–disease associations	Causality	Population stratification, small cohorts	Hypothesis testing
GWAS	Novel susceptibility loci	Mechanism or causality	Multiple testing, ancestry	Gene discovery
MR	Potential causal relationships	Cellular mechanisms	Pleiotropy, weak instruments	Causal inference
Bulk methylation	Disease-associated methylation	Cell-specific effects	Tissue heterogeneity	Epigenetic biomarker discovery
Bulk RNA-seq	Differential gene expression	Cell-specific regulation	Mixed cell populations	Pathway analysis
scRNA-seq	Cell-specific expression	Causality	Technical variability, cost	Cell-type identification
Spatial transcriptomics	Spatial gene expression	Functional validation	Resolution, tissue quality	Tissue architecture
In vitro perturbation	Molecular mechanisms	Clinical relevance	Artificial conditions	Functional validation
Animal models	In vivo functional effects	Direct human translation	Species differences	Preclinical testing
Longitudinal human studies	Biomarker dynamics, prognosis	Molecular mechanisms	Treatment and environmental variability	Clinical validation

Table 3 Critical appraisal of genetic evidence in periodontitis

Gene/pathway	Evidence grade	Main evidence source	Replication	Clinical implication
IL-1, IL-6, TNF, IL-10	Moderate	Candidate-gene studies; meta-analyses	Partial; population-dependent	Possible susceptibility association; no validated treatment prediction
IL-17 pathway	Weak–moderate	Candidate-gene studies	Limited	Exploratory susceptibility marker
VDR	Moderate	Candidate-gene studies; meta-analyses	Inconsistent across populations	Possible susceptibility association; no validated treatment prediction
MMPs	Weak–moderate	Candidate-gene studies; tissue-expression studies	Limited	Biological relevance stronger than genetic prediction
CD14/TLRs	Weak–moderate	Candidate-gene studies; selected tissue/cell studies	Limited and population-specific	Exploratory susceptibility association
HLA loci	Weak	Small population-specific association studies	Poor	Exploratory only
Antimicrobial peptides/defensins	Exploratory	Small association and tissue studies	Very limited	No established clinical utility
GWAS loci	Moderate	GWAS and replication studies	Selected loci replicated	Susceptibility signals; not treatment predictors

interdental brushing is essential for gum health, these practices mainly helps reduce periodontal pocket depth and bleeding on probing (BOP) rather than directly eliminating gingival inflammation. Yet, patients tend to forget nearly half of the provided health recommendations (Toy 2019). Understanding how genetic variations interact with environmental factors is crucial for tailoring effective periodontal treatment. Personalized medicine focuses on customizing healthcare and treatment plans for each individual. Despite having attracted considerable attention in periodontology, its application in routine clinical practice is still limited owing to methodological, economic and logistical limitations. This approach relies on laboratory tests that analyze genetic, molecular, epidemiological, physiological, and social factors to provide precise diagnoses and optimize treatment for each patient (PM 2018).

The IL-1 A (−889 C/T) polymorphism has been linked to an increased risk of developing periodontitis in various populations. Previous research highlighted this connection specifically in individuals previously grouped under the now-outdated PD classification. In South India, the rs4647602 GG genotype of CASP3 is prevalent among Tamils with PD, while in Koreans, high-risk genetic markers include IL-1β + 3954 and TNF-α −863 variants. Research in Chinese populations has identified FOSB (rs708905 G/G and rs8105114 A/A) and SOCS3 (rs7207782 G/G) genotypes as risk factors for PD and osteopenia. Among Iraqi patients, IKKβ polymorphisms intensify responses to PD, especially the GT genotype at rs17875746, which is associated with tooth mobility, family history, CAL, and gingival recession

Table 4 Critical appraisal of epigenetic evidence in periodontitis

Mechanism	Evidence grade	Main evidence source	Replication	Clinical implication
DNA methylation	Moderate	Bulk gingival tissue studies; selected cell models	Partial at pathway level	Potential disease-activity marker; not validated for treatment prediction
Histone modifications/HDACs	Moderate	Gingival tissue, cell models, animal studies	Limited human replication	Preclinical therapeutic target
microRNAs	Moderate	Gingival tissue, GCF, saliva, cell and animal studies	Partial; heterogeneous	Potential biomarker; treatment prediction remains exploratory
Long non-coding RNAs	Weak–moderate	Small tissue datasets and cell models	Limited	Exploratory biomarker/target
Circular RNAs	Weak	Transcriptomic datasets and cell models	Very limited	Exploratory only
m6A RNA methylation	Exploratory	Bioinformatic datasets; cell and animal studies	Very limited	Emerging mechanistic target; no clinical utility
m6Am RNA methylation	Exploratory	Indirect evidence; limited periodontal data	Absent	No current clinical utility
scRNA-seq/spatial transcriptomics	Exploratory–moderate	Small cross-sectional human gingival datasets	Early replication	Research tools for cell-state and inflammatory-niche mapping; not routine diagnostics

Table 5 Genetic and epigenetic biomarkers in periodontitis: current evidence and clinical translation

Marker/pathway	Sample type	Evidence source	Typical cohort size	Replication status	Association with staging	Treatment-response evidence	Functional validation	Clinical-readiness level	Key limitations
IL-1 (IL1A, IL1B polymorphisms)	Blood DNA, saliva	Candidate-gene studies, meta-analyses	100–1000+	Moderate; population-dependent	Moderate association with disease severity; inconsistent under 2018 classification	Limited and inconsistent for NSPT outcomes	Moderate (cytokine biology well established)	Research use only	Ethnic heterogeneity; inconsistent replication
IL-6 polymorphisms	Blood DNA	Candidate-gene studies, Mendelian randomization	100–1000	Moderate	Associated with inflammatory burden rather than staging	Weak evidence	Moderate	Research use only	Small cohorts; inconsistent findings
IL-10 polymorphisms	Blood DNA	Candidate-gene studies	100–500	Limited	Weak association	Limited	Moderate	Research use only	Poor reproducibility
TNF-α polymorphisms	Blood DNA	Candidate-gene studies, meta-analyses	100–1000	Moderate	Variable association	Minimal evidence	Moderate	Research use only	Population-specific effects
VDR polymorphisms	Blood DNA	Candidate-gene studies	100–500	Limited	Possible influence on bone metabolism	Insufficient	Moderate	Exploratory	Inconsistent replication
MMP family (MMP-8, MMP-3, MMP-9)	Saliva, GCF, blood DNA	Clinical studies, meta-analyses	100–1000	Moderate (protein); limited (genetics)	MMP-8 strongly correlates with disease activity	MMP-8 decreases after treatment	Strong for MMP biology	genetic variants exploratory	Genetic findings inconsistent
TLR2/TLR4, CD14	Blood DNA	Candidate-gene studies	100–500	Limited	Weak-to-moderate	Very limited	Moderate	Exploratory	Lack of large validation studies
HLA loci	Blood DNA	Association studies	Variable	Limited	Population-specific	None	Moderate	Exploratory	High genetic diversity
DNA methylation (e.g., STAT5, SOCS, COX-2)	Gingival tissue, GCF	Human tissue studies, experimental models	20–200	Limited	Potential association with disease severity	Preliminary evidence of reversal after NSPT	Moderate	Exploratory	Mostly cross-sectional; causality uncertain

Table 5 (continued)

Marker/pathway	Sample type	Evidence source	Typical cohort size	Replication status	Association with staging	Treatment-response evidence	Functional validation	Clinical-readiness level	Key limitations
Histone modifications (HDACs, SETD1B, KDMs)	Gingival tissue, cultured cells	Cell culture, animal models	Mostly preclinical	Limited	Not established	Preclinical evidence only	Strong experimental evidence	Preclinical	Few human studies
microRNAs (miR-146a, miR-155, miR-21, miR-203, etc.)	Saliva, GCF, gingival tissue	Clinical observational studies	30–300	Moderate for selected miRNAs	Associated with inflammatory activity and severity	Emerging evidence	Moderate	Early translational	Lack of standardized assays
Long non-coding RNAs (lncRNAs)	Gingival tissue	Transcriptomic studies	20–100	Limited	Potential association	None	Moderate	Exploratory	Early-stage research
RNA methylation (m6A regulators)	Gingival tissue	Bioinformatics, transcriptomics, experimental studies	Mostly < 100	Very limited	Unknown	None	Limited	Discovery stage	Few human validation studies

Table 5 (continued)

Marker/pathway	Sample type	Evidence source	Typical cohort size	Replication status	Association with staging	Treatment-response evidence	Functional validation	Clinical-readiness level	Key limitations
Transcriptomic signatures (RNA-seq, single-cell RNA-seq)	Gingival tissue	Omics studies	20–200	Emerging	Strong biological association with disease activity	Potential predictive value	Strong mechanistic evidence	Discovery stage	Expensive; lack of clinical validation
Multi-omics biomarker panels	Blood, saliva, GCF, gingival tissue	Integrative omics studies	Variable	Limited	Potential for future staging and precision medicine	Preliminary	Limited	Discovery stage	No standardized clinical pipeline

GCF, gingival crevicular fluid; NSPT, non-surgical periodontal therapy; VDR, vitamin D receptor; MMP, matrix metalloproteinase; TLR, Toll-like receptor; HDAC, histone deacetylase

(GR). The GA genotype at rs12676482 also indicates higher susceptibility (Toy 2019, Mahmood and Hussein 2023). In Brazil, the DNMT3B (rs2424913) polymorphism has been associated with increased PD risk in a specific population group. Notably, IL1A/rs1800587 and IL1B/rs1143634 polymorphisms have emerged as potential biomarkers of periodontitis susceptibility, although the original studies were conducted using the former PD classification (Silva et al. 2021). Distinguishing genetic variants linked to periodontitis susceptibility from those that affect treatment response is essential. While numerous polymorphisms have been associated with disease risk, the evidence for their potential as predictors of treatment outcomes in periodontitis remains sparse and varies inconsistently between studies.

Recent advancements in gene therapy offer new treatment avenues for PD by introducing specific genes into periodontal cells to promote tissue repair and regeneration. This approach targets genetic and cellular pathways essential for tissue healing, offering a promising long-term solution for maintaining periodontal health. Gene therapy enables the modulation of proteins involved in tissue regeneration, potentially transforming periodontal treatment into a more targeted and personalized approach. One diagnostic application in PD is measuring MMP8 enzyme levels in gingival fluid and saliva, as elevated concentrations are common in affected patients, aiding diagnosis and monitoring treatment effectiveness (Zalewska et al. 2024). Genetic profiles might play a role in risk stratification for specific populations, but their effectiveness in predicting periodontal treatment outcomes remains unclear. This uncertainty arises from the limited evidence available and the lack of consistent validation across independent study groups. Gene therapy shows potential to not only regenerate damaged periodontal tissues but also provide comprehensive treatment by targeting multiple genetic factors simultaneously. Gene therapy represents a significant advancement in personalized dental care, enabling clinicians to tailor interventions based on each patient's genetic predispositions and treatment needs (Barhate et al. 2023). Recently, immunomodulators and microbial therapies have been introduced in dentistry to enable personalized, targeted interventions. These strategies address the complex interactions among the immune system, oral microbiome, and overall oral health. Immunomodulators, in particular, offer a novel approach by adjusting immune responses to control inflammation and promote tissue regeneration. This integration of immune and microbial therapies marks a shift toward more precise, individualized treatment options in oral health care. The predictive reliability of most currently suggested genetic and epigenetic markers is still inadequate for routine clinical use, underscoring the importance of further validation and standardization efforts (Dommisch et al. 2025). Current research indicates that numerous genetic variants linked to periodontitis susceptibility may not reliably forecast treatment responses. Although polymorphisms in genes related to inflammation and immune regulation have been explored as potential influences on treatment outcomes, the findings often vary widely and lack reproducibility. Differences in study methodologies, disease categorization, treatment approaches, and population demographics further weaken the reliability of existing evidence. As a result, genetic testing cannot yet be routinely employed to predict periodontal treatment outcomes. More robust prospective clinical studies are necessary before genotype-based periodontal therapy can be adopted into standard clinical practice.

Despite the growing interest in personalized periodontal care, there are several important barriers that remain to limit its translation into routine clinical practice. One of the major challenges is the lack of standardization of the proposed genetic and epigenetic biomarkers. Differences in sample collection, laboratory methods, analytical platforms and disease classification systems have led to inconsistent results between studies, limiting reproducibility and clinical translation. Ethnic and population heterogeneity is another important consideration. Several genetic variants associated with periodontitis susceptibility in specific populations have been identified, but these variants have not been consistently shown to have similar associations in other ethnic groups. Hence, biomarkers identified in one population may not be directly translatable to another, underscoring the importance of validation in heterogeneous cohorts.

Economic and technological factors are also substantial barriers. Large-scale genetic, epigenetic, transcriptomic, and multi-omics analyses are still relatively expensive and often require specialized laboratory infrastructure, advanced sequencing technologies, and bioinformatics expertise that are not widely available in routine dental practice. These limitations may further exacerbate disparities in access to precision-based periodontal care. Finally, the clinical utility of many proposed biomarkers is still unclear. While a plethora of genetic and epigenetic markers have been associated with disease susceptibility and progression, only a few have demonstrated enough predictive value to guide treatment decisions or improve clinical outcomes beyond traditional periodontal assessment methods. Further efforts are therefore needed to establish standardized methodologies, validate biomarkers in diverse populations, demonstrate cost-effectiveness, and confirm clinically meaningful benefit in prospective studies before personalized periodontal care can be widely implemented.

Biomarker Translation: From Discovery to Clinical Application

The expanding body of research on genetic, epigenetic, transcriptomic, and proteomic factors in periodontology has resulted in a substantial list of potential biomarkers. However, the strength of evidence supporting these biomarkers varies widely, and not all are viable for clinical application. To better understand their potential, periodontal biomarkers can be categorized into three main groups: discovery biomarkers, validated biomarkers, and clinically deployable biomarkers (Dommisch et al. 2025).

Discovery Biomarkers

These include genetic polymorphisms, DNA methylation patterns, histone modifications, RNA methylation markers, transcriptomic data, microRNAs, and other molecular features identified through high-throughput omics studies. Recent progress in nanoscale biosensing technologies capable of detecting single-molecule proteins, presents promising opportunities for highly sensitive biomarker identification in intricate inflammatory diseases (Cheng et al. 2026). Although they provide critical insights into disease susceptibility, progression, and responses to treatment, most are

still in the exploratory phase. They are primarily derived from relatively small study cohorts and lack validation across diverse populations (Dommisch et al. 2025).

Validated Biomarkers

Validated biomarkers are those that have demonstrated consistent associations in multiple independent studies and across varied populations. Examples include specific inflammatory cytokines, certain genetic variants, and consistent methylation patterns linked to disease progression or treatment outcomes. Despite their potential, these biomarkers require additional standardization and prospective studies before they can be widely integrated into clinical practice (Gao et al. 2024, Razzouk 2024).

Clinically Deployable and Near-Clinical Biomarkers

At present, only a few periodontal biomarkers have reached the level of practical clinical application. Active matrix metalloproteinase-8 (aMMP-8) stands out as one of the most extensively studied markers and has already been incorporated into commercially available chairside diagnostic tools. While research into salivary and gingival crevicular fluid biomarkers continues to show promise, most genetic, epigenetic, transcriptomic, and multi-omics markers remain confined to the research stage. They have yet to achieve the necessary clinical validation for routine usage. As a result, the primary obstacle in contemporary periodontal biomarker research lies not in discovering new markers but in effectively translating laboratory findings into reliable diagnostic and prognostic tools for clinical practice (Gao et al. 2024, Razzouk 2024). Comparison of biomarker development stages in periodontitis: from discovery to clinical application shown in Table 6.

Influence of Genetic and Epigenetic Factors on Disease Susceptibility and TO

Changes in Gene Expression Associated with the Severity of PD

Recent research has deepened our understanding of the genetic and molecular mechanisms contributing to PD severity, highlighting how specific genetic and environmental factors, such as smoking, influence disease progression. Smoking has been shown to increase the expression of IL-6 and TNF-α (Dosseva-Panova and Mlachkova 2022). Single-cell RNA sequencing of human gingival tissue reveals that several genes linked to periodontitis, such as IL1B, PTGS2, and IL10, are primarily expressed within immune-cell populations like macrophages. These findings highlight the significance of innate immune-cell states in driving periodontal inflammation. However, since most of the current datasets are cross-sectional in nature, they mainly identify cellular programs associated with the disease rather than providing direct evidence that macrophage dysfunction serves as a primary causal factor for increased susceptibility to periodontitis (Caetano et al. 2022). Understanding gene-expression and epigenetic findings in periodontitis requires careful differentiation

Table 6 Comparison of biomarker development stages in periodontitis: from discovery to clinical application

Feature	Discovery biomarkers	Validated biomarkers	Clinically deployable biomarkers
Purpose	Identify novel molecular candidates	Confirm reproducibility and biological relevance	Support clinical diagnosis, prognosis, or treatment decisions
Evidence level	Exploratory	Moderate	High
Typical examples	DNA methylation signatures, miRNAs, lncRNAs, transcriptomic profiles	Replicated methylation/gene-expression markers	Active MMP-8 (aMMP-8)
Clinical validation	Limited	Moderate	Extensive
Standardization	Not established	Partial	Established
Routine clinical use	No	Not yet	Yes (selected biomarkers only)
Main limitations	Lack of replication	Limited multicenter validation	Few biomarkers currently available

between biological markers indicative of disease activity and the molecular mechanisms that directly drive its progression. Many genes and regulatory molecules, such as inflammatory cytokines and microRNAs, identified as differentially expressed in periodontitis might represent downstream responses to chronic inflammation rather than the initial causes. This raises the issue of reverse causality, as prolonged periodontal inflammation can itself influence gene expression and epigenetic profiles. While certain molecular changes may actively contribute to disease progression, others might primarily function as indicators of ongoing tissue damage or immune system activation. To untangle these complexities and establish causal links, longitudinal and mechanistic research remains essential. Additionally (miRNAs) from periodontal tissue cells and herpesviruses serve as regulators of tissue homeostasis, playing a role in disease pathogenesis (Naqvi 2021). Further, specifications in PD offer insights into disease progression. For example, early-stage PD is marked by hypermethylation in TLR regulatory genes, including MAP3K7, MYD88, and IL6R, while advanced stages show hypomethylation of these genes, reflecting changes in immune responses over time. In patients with poorly diabetes, dyslipidemia, and PD, genes like TGFB1I1, VNN1, HLADRB4, and CXCL8 are differentially expressed in lymphocytes and monocytes, linking systemic health factors to PD. The DAB2 gene is particularly overexpressed in cases of both dyslipidemia and PD (Cárdenas et al. 2022).

A study by Caetano et al. identified 20 out of 26 candidate risk genes, including MT-ND1, VAMP-8, PKN2, CAMTA1, and PTGS2/COX2, as being prominently

expressed in specific gingival cell populations. Differentially methylated genes with differential expression between health and PD include DCC, KCNA3, and RIMS2, suggesting these genes' promoter regions play a role in gene expression and disease onset (Kim et al. 2021). Additionally, 27 immune-related differentially expressed genes (iRDEGs) were identified, involved in granulocyte and leukocyte chemotaxis, cytokine receptor binding, and immune response pathways. IFNG and TLR2 were highlighted as core genes within the protein-protein interaction network, presenting potential therapeutic targets for modulating immune responses in PD (Ban et al. 2022). MicroRNA (miRNA) regulation also plays a critical PD. Studies demonstrate that miR-142-3p is downregulated in inflamed gingiva. Notably, miR-146 levels are significantly increased in PD as a critical mediator of inflammation. miR-223, specific to hematopoietic cells, contributes to alveolar bone resorption, promoting neutrophil differentiation and recruitment while encouraging osteoclastogenesis and inhibiting osteoblast differentiation through targeting NF1-A. In contrast, miR-26a-5p is downregulated in inflamed gingiva, while its target upregulated, showing a functional interplay between miRNA and mRNA expression in inflammation control. Furthermore, CST3 and its protein product, Cystatin C, are elevated in severe PD associating this gene with disease progression (Valverde et al. 2024). These findings underscore the complex interaction between genetic expression and environmental factors, with significant implications for personalized treatment approaches and potential therapeutic targets in periodontal care. Genetic and epigenetic factors, beyond their link to disease susceptibility and severity, may play a role in shaping treatment outcomes for periodontitis. Research suggests that interindividual differences in healing responses following nonsurgical periodontal therapy could be influenced by variations in inflammatory cytokine genes, immune-response pathways, and epigenetic regulatory mechanisms. Additionally, specific methylation patterns and microRNA expression profiles have been identified as potential markers for treatment responsiveness, likelihood of disease recurrence, and long-term periodontal stability. Despite these promising insights, current evidence remains limited and inconsistent, with no genetic or epigenetic marker yet achieving the predictive reliability needed for routine clinical application in treatment planning. As a result, further validation through large-scale prospective clinical studies is essential before these findings can be effectively integrated into prognostic assessments or therapeutic strategies.

Use of Technologies Like RNA-Seq to Analyze Gene Expression Patterns

RNA sequencing (RNA-seq) has proven instrumental in identifying biomarkers and potential drug targets for inflammation in periodontal tissues affected by PD. Through both traditional RNA-seq and advanced single-cell RNA sequencing (scRNA-seq), researchers can pinpoint cell-type-specific gene expression changes linked to disease susceptibility. This approach has uncovered diverse cell subtypes within gingival tissue, revealing distinct gene expression profiles associated with PD severity. Such insights could lead to improved diagnostics and treatments tailored to specific cellular responses within periodontal tissues (Moreno et al. 2022). Omics technologies, including RNA-seq, have enabled researchers to assess the pathogenic effects of *P. gingivalis*, a primary bacterium implicated in PD. Using metatranscriptomics, studies

on gene expression changes in both the host and its microbiome during disease progression have been conducted in experimental models, revealing how host-microbe interactions contribute to inflammation and tissue breakdown. Additionally, scRNA-seq of human gingival samples from both healthy and affected individuals has provided insights into the cellular heterogeneity and gene expression shifts associated with PD (Nuñez-Belmar et al. 2022).

scRNA-seq has transformed our understanding of periodontitis by providing a detailed, cell-level perspective on the biological processes underlying the disease. It has been instrumental in identifying cellular populations involved in epithelial barrier disruption, inflammatory amplification, vascular activation, immune-cell recruitment, connective tissue remodeling, and alveolar bone loss. Junctional epithelial cells play a critical role, as they form the interface between the subgingival biofilm and the host tissues. These cells contribute to maintaining the barrier function, antimicrobial defense, chemokine production, and communication with both immune and stromal cells (Shah et al. 2025). In periodontitis, dysregulated epithelial processes may enable microbial invasion and perpetuate inflammatory signaling. Gingival fibroblasts should no longer be viewed as a homogeneous stromal cell population. Single-cell analyses reveal distinct fibroblast subsets that specialize in roles such as extracellular matrix production, collagen turnover, release of inflammatory mediators, wound healing, and interactions with immune cells. Certain fibroblast states associated with disease may drive chronic inflammation and tissue destruction through their cytokine, chemokine, and matrix-remodeling activities. Similarly, endothelial cells are significant players in the disease process; their activation facilitates leukocyte adhesion, transendothelial migration, and recruitment of inflammatory cells into periodontal tissues. This endothelial inflammatory response contributes to the establishment of localized inflammatory niches (Wielento et al. 2023).

Within the immune cell populations, macrophages and neutrophils are pivotal for innate host defense and are key mediators of periodontal tissue injury. Macrophages are involved in cytokine secretion, antigen presentation, phagocytosis, and promoting osteoclastogenesis. Neutrophils, on the other hand, play essential roles in bacterial clearance, protease release, reactive oxygen species production, and the formation of neutrophil extracellular traps (NETs) (Yin et al. 2022). However, prolonged or dysregulated activation of these immune cells can exacerbate tissue damage. Chronic inflammation in periodontitis is further influenced by adaptive immune components such as plasma cells and T-cell subsets. These cells contribute to antibody production, cytokine-mediated signaling, and regulation of osteoclast activity, which may shape the progression from acute inflammation to more persistent lesions. Bone-related cell types such as osteoclasts and osteoblast-lineage cells are integral to understanding alveolar bone loss mechanisms. An imbalance between increased osteoclast activity and impaired osteoblast-driven bone synthesis directly drives periodontal bone destruction. Additionally, periodontal ligament stem cells play a vital role in maintaining tissue homeostasis, facilitating repair, and promoting osteogenic differentiation; however, their regenerative potential may be compromised by the inflammatory and microbial challenges associated with diseased periodontal tissues (Zhu et al. 2026).

By integrating scRNA-seq and spatial transcriptomics, researchers can elucidate how epithelial, stromal, immune, vascular, and bone-related cellular states interact within specific microenvironments during periodontitis. This approach offers critical insights into the cellular mechanisms that sustain inflammation and tissue damage in the disease. RNA-seq combined with DNA methylation analysis has further refined our understanding by identifying genes with altered expression and methylation patterns across health states periodontal health, gingivitis, and PD. For example, studies have shown that methylation changes in inflammatory response genes correlate with disease progression, suggesting potential avenues for future mechanistic investigations and therapeutic development (Chen et al. 2022). In research settings, methods such as real-time polymerase chain reaction (RT-PCR) and enzyme-linked immunosorbent assay (ELISA) are frequently used alongside RNA-seq to validate gene-expression findings and quantify protein levels of key inflammatory mediators, including IL-1β, IL-6, TNF-α, IL-10, and NF-κB. Together, these technologies have substantially improved our understanding of the molecular pathways involved in periodontal inflammation and tissue destruction and have facilitated the discovery of candidate biomarkers and therapeutic targets. However, the clinical utility of these molecular signatures remains under investigation, and their role in guiding individualized periodontal treatment has not yet been established (Camargo GAdCG et al. 2022).

RNA-seq and single-cell transcriptomic techniques have advanced our knowledge of periodontal pathobiology. However, many of the identified expression patterns are still primarily research tools and need further validation through larger, independent cohorts before they can be translated into clinical practice. RNA-seq, scRNA-seq, and spatial transcriptomics have significantly deepened our understanding of the biological mechanisms underpinning periodontitis. However, these methods are better suited as research tools at this stage, rather than routine diagnostic approaches. Among them, scRNA-seq are effective in identifying various gingival cell states such as epithelial, fibroblast, endothelial, myeloid, lymphoid, and bone-related populations while spatial transcriptomics adds the capability to pinpoint the localization of these cell states and their molecular interactions within the structural context of tissue. When used together, these methodologies provide valuable insights into inflammatory niches, revealing coordinated processes such as epithelial dysfunction, stromal activation, vascular changes, immune-cell infiltration, and osteoclastogenic signaling (Ma et al. 2024).

Despite this potential, their application in routine periodontal diagnosis remains limited. Current studies frequently rely on cross-sectional designs, involve relatively small sample sizes, and often vary in aspects such as disease classification criteria, tissue sampling methods, cell isolation protocols, sequencing technologies, and bioinformatics workflows (Dommisch et al. 2025). Additionally, transcriptomic profiles may capture variations in cellular composition, levels of inflammation, smoking habits, diabetes status, microbial exposure, or prior treatments, rather than identifying robust disease-specific biomarkers. To date, no marker derived from scRNA-seq or spatial transcriptomics has demonstrated sufficient sensitivity, specificity, reproducibility, cost-efficiency, or clinical relevance to be used for diagnosis, risk assessment, or personalized treatment planning. For now, these advanced techniques are most

impactful in identifying gingival cell states, mapping inflammatory microenvironments, generating new mechanistic hypotheses, and highlighting targets for future validation efforts rather than serving as tools for immediate clinical application (Razzouk 2024).

Nevertheless, several hurdles need to be addressed. Transcriptomic signatures often show variability across studies due to differences in disease definitions, sampling methods, sequencing platforms, bioinformatics workflows, and patient demographics. Additionally, the inherent cellular complexity of gingival tissues complicates the task of distinguishing disease-specific molecular patterns from broader context-dependent inflammatory responses. Despite the promise of spatial transcriptomics and single-cell technologies in mapping key inflammatory niches in diseased periodontal tissues, no universally validated transcriptomic marker has so far achieved the sensitivity, specificity, and reproducibility necessary for widespread clinical use in diagnosis or patient stratification. As a result, the current transcriptomic insights should be viewed primarily as tools for generating hypotheses and understanding mechanisms rather than as immediately actionable clinical resources. Moving forward, integrating transcriptomic data with epigenomics, proteomic, and microbiome profiles in large, multicenter studies will be critical for transforming these discoveries into clinically viable biomarkers and therapeutic strategies (Razzouk 2024). Future research should combine scRNA-seq and spatial transcriptomics with longitudinal clinical phenotyping, data on periodontal treatment responses, epigenomics profiling, proteomics, and microbiome analyses across large, multicenter cohorts. This approach aims to identify cell-state signatures that are consistent, biologically relevant, and clinically applicable.

Targeting Epigenetic Pathways for Improved PD Treatment Outcomes

Identifying Epigenetic Pathways that Could be Targeted for Therapy

Epigenetic modifications, including DNA methylation and histone modifications, play a pivotal role in the development and progression of PD. These changes have been observed in periodontal tissues. They are associated with alterations in gene expression that contribute to inflammation and increased disease severity. Specifically, DNA methylation patterns in key immune-related genes, such as cytokines and matrix metalloproteinases, regulate the production of inflammatory mediators and tissue degradation during PD. These epigenetic changes are sensitive to environmental factors like microbial infections and systemic diseases, which can influence the progression of the disease. Targeting these epigenetic pathways offers a promising approach for therapy. Small molecule inhibitors that modulate DNA methylation and histone modifications have been proposed as potential treatments, aiming to reduce the excessive inflammatory response associated with PD. Additionally, research into the role of non-coding RNAs and m6A RNA methylation in PD has opened new avenues for diagnostic and therapeutic strategies. By manipulating these pathways, future therapeutic strategies may potentially support more personalized approaches to periodontal treatment (Barros et al. 2020).

The current evidence supporting epigenetic therapies in periodontology is largely preclinical. Most research involving DNA methylation modifiers, histone deacetylase inhibitors, microRNA-based interventions, and epigenome-targeting strategies has been conducted on cellular models or in animals. While these studies have shown encouraging results in areas such as inflammation control, tissue regeneration, and bone metabolism, comprehensive evidence from large-scale human clinical trials is still absent. Therefore, the therapeutic effectiveness, long-term safety, and clinical feasibility of these methods have yet to be validated.

Epigenetic-Based Therapeutic Strategies

Therapeutic strategies aimed at targeting epigenetic mechanisms can be broadly classified into two categories: anti-resorptive therapies and immunomodulatory therapies. Anti-resorptive therapies focus on preventing bone loss and include bisphosphonates, RANKL inhibitors, OPG-FC, and strontium ranelate. These agents work by inhibiting the activity of osteoclasts, which are responsible for bone resorption during PD progression. Immunomodulatory therapies seek to modulate the immune response to reduce inflammation and promote tissue healing. These therapies include the use of CTSK inhibitors, specialized pro-resolving mediators (SPMs), biological therapies (e.g., growth factors), non-coding RNAs, and antimicrobial photodynamic therapy (aPDT). These strategies are designed to regulate inflammatory cytokine release, prevent tissue destruction, and enhance tissue regeneration in affected periodontal areas. Emerging therapies also include the use of probiotics, statins, vitamins, and omega-3 fatty acids, which have demonstrated anti-inflammatory effects and the potential to modify disease progression by influencing epigenetic pathways. These compounds are thought to exert their effects through immune modulation, reducing the inflammatory response that contributes to tissue damage in PD (Yousefi et al. 2019, Ghasemian et al. 2018).

Role of MicroRNAs (miRNAs) in PD

MicroRNAs (miRNAs) have gained significant attention in recent studies due to their ability to regulate gene expression at the post-transcriptional level. miRNAs modulate the expression of various target genes, influencing both inflammatory responses and tissue remodeling in PD. Several miRNAs have been identified as key regulators in the pathogenesis of PD, making them attractive targets for therapeutic intervention (Arif et al. 2020).

- **miR-146**: This miRNA has been shown to play a central role in periodontal inflammation by targeting NF-κB, a key regulator of the inflammatory response. Overexpression of miR-146 in inflamed gingival tissues is associated with reduced levels of pro-inflammatory cytokines such as IL-1β, IL-6, IL-8, and TNFα, which can help mitigate the inflammatory environment in PD. Given its function as a negative feedback regulator of inflammation, miR-146 holds promise as a therapeutic agent for controlling periodontal inflammation and promoting tissue repair.

- **miR-21 and miR-200c**: Both of these miRNAs exhibit anti-inflammatory and anti-osteoclastic properties. miR-21, for example, has been shown to suppress the NF-κB signaling pathway, while miR-200c can inhibit the RANKL/OPG signaling pathway, both of which are involved in the bone resorption process during PD. These miRNAs help regulate the immune response and bone remodeling, making them potential targets for the treatment of PD-related bone loss (Arif et al. 2020).
- **miR-142-3p**: This miRNA has been identified as a modulator of cytoskeletal rearrangement and cell migration. In a murine model of PD, the in vivo delivery of miR-142-3p resulted in a reduction in pro-inflammatory cytokines (such as IL-6 and TNFα), decreased neutrophil infiltration, and a shift in immune cell polarization towards a less inflammatory phenotype. These effects suggest that miR-142-3p may have therapeutic potential in controlling inflammation and promoting tissue repair in PD (Valverde and Naqvi 2020).
- **miR-26a-5p**: miR-26a-5p plays a critical role in host defense and wound healing, both of which are essential for the resolution of PD. By targeting pathways involved in inflammation and tissue repair, miR-26a-5p could potentially facilitate healing and regeneration in periodontal tissues (Uttamani et al. 2023).

Targeting epigenetic pathways and microRNAs offers a promising strategy for improving the TO of PD. By modulating key genes involved in inflammation, tissue degradation, and bone resorption, these therapies can reduce the severity of PD and promote tissue regeneration. Further research into the precise molecular mechanisms of miRNAs and epigenetic modifications in PD will be critical for the development of personalized, effective treatments for this chronic inflammatory disease. Recent research has highlighted the promising potential of combining genetic and epigenetic interventions to treat PD. Epigenetic mechanisms, including DNA methylation and histone modifications, play a crucial role in regulating immune responses and inflammation associated with PD. Aberrant methylation profiles of inflammatory genes and dysregulation of histone-modifying enzymes have been observed in patients with PD, making these epigenetic alterations important therapeutic targets. By combining these epigenetic interventions with genetic approaches, it may be possible to enhance therapeutic responses and reduce the progression of PD (Santonocito et al. 2022). Further studies are needed to refine these combination therapies and translate them into clinical practice. Understanding how genetic factors, epigenetic mechanisms, and microbial interactions work together will be essential to developing optimized, targeted treatments for PD.

Recent Advances in Epigenetic Drugs and Their Effects on TO

Recent advances in epigenetic research have highlighted the importance of epigenetic modifications in the pathogenesis of PD, as well as their potential to improve TO. The ENCODE project has provided valuable insights into the role of DNA methylation in both oral and systemic health, highlighting how epigenetic dysregulation contributes to the development of PD (Cho et al. 2021) In patients with PD, epigenetic changes can lead to oxidative stress, immune system imbalances, and inflammation,

which can exacerbate the disease and increase the risk of systemic conditions like cardiovascular disease and diabetes (Patel et al. 2019). Additionally, research has shown that epigenetic dysregulation in PD may contribute to an environment conducive to cancer development. This highlights the need for precision health approaches in managing PD to not only improve oral health but also prevent the onset of systemic conditions (Isola et al. 2021). Several adjuvant treatments have emerged from epigenetic research to complement traditional periodontal therapies. Notable therapeutic agents include:

- **Anti-inflammatory drugs**: Doxycycline and NSAIDs have been studied for their ability to reduce inflammation in periodontal tissues.
- **Bisphosphonates**: These drugs inhibit bone resorption and have shown promise in preventing bone loss in PD patients.
- **Statins**: Known for their anti-inflammatory properties, statins may help modulate immune responses in periodontal tissues.
- **Metformin**: This drug, commonly used in diabetes management, stimulates bone formation and reduces inflammation in periodontal tissues.
- **Omega-3 fatty acids**: These have demonstrated anti-inflammatory effects and may help in reducing the severity of PD.

These treatments, when combined with epigenetic approaches, may offer potential opportunities for improving periodontal management; however, further clinical validation is required.

The combination of genetic and epigenetic insights has deepened our understanding of the diverse nature of PD and sparked significant interest in personalized treatment strategies. Despite this progress, such approaches are still primarily in the experimental phase when it comes to clinical application. Many potential biomarkers and therapeutic targets lack adequate validation across varied populations, leaving their reliability in guiding treatment choices and predicting long-term outcomes uncertain. Advancing in this field will necessitate standardized methods, large-scale longitudinal studies, robust clinical trials, and cross-population validations before these integrated approaches can become a standard part of periodontal care.

Epigenetic Modifications in PD and Their Therapeutic Implications

The infection of gingival epithelial cells, gingival fibroblasts, and periodontal ligament cells by oral pathogens such as *P. gingivalis* or *Treponema denticola* leads to significant alterations in the expression and activity of chromatin-modifying enzymes. These changes, which affect DNA methylation and histone modifications, are integral to the development and progression of PD. Epigenetic modifications, such as site-specific changes in DNA methylation profiles and alterations in histone acetylation and methylation, play a critical role in the regulation of inflammatory responses, tissue remodeling, and immune cell activation within periodontal tissues. These modifications not only contribute to the pathogenesis of PD but also represent potential targets for the development of novel diagnostic tools and targeted epigenetic therapies.

Epigenetic Drugs and Their Role in PD Treatment

Bromodomain and Extra-Terminal (BET) Inhibitors: BET inhibitors, such as I-BET151 and JQ1, have shown promise in suppressing inflammatory gene expression and mitigating alveolar bone loss in both in vitro and in vivo models of PD. These drugs target the BET family of proteins, which are involved in the regulation of gene expression by influencing histone acetylation. By modulating the epigenetic regulation of inflammatory pathways, these inhibitors help reduce the pro-inflammatory cytokines and osteoclastogenic factors associated with periodontal tissue destruction. They have demonstrated potential as effective therapeutics to alleviate bone loss in PD.

HDAC Inhibitors: HDAC inhibitors are another promising class of epigenetic drugs for PD treatment. Selective HDAC inhibitors targeting HDAC1 and HDAC2 have been shown to exert anti-inflammatory and anti-osteoclastogenic effects in cell culture models. Broad-spectrum HDAC inhibitors, such as 1179.4b, have been found to reduce osteoclast formation and prevent alveolar bone loss in animal models of PD. These drugs work by preventing the deacetylation of histones, which can activate inflammatory pathways and lead to tissue destruction in PD. By inhibiting HDACs, these drugs help restore normal immune function and suppress the inflammatory response, offering a potential therapeutic strategy for managing PD.

Alternative and Adjunctive Therapies for PD

While the following approaches are not classified as direct epigenetic therapies, they are included due to emerging evidence indicating their potential influence on inflammatory and immune pathways that interact with epigenetic regulatory mechanisms. However, their possible epigenetic effects are not yet fully understood, and existing evidence does not justify categorizing them as recognized epigenetic interventions. Beyond traditional antibiotics and anti-inflammatory agents, recent research has explored various alternative therapies aimed at enhancing PD treatment, focusing on mechanisms like biofilm disruption and microbiome modulation (Haque et al. 2022).

1. **Biofilm Disruption and Quorum Sensing Inhibitors**: One of the challenges in treating PD is the persistence of microbial biofilms, which protect bacteria from both the host immune system and antimicrobial treatments. Quorum sensing (QS), a bacterial communication system, plays a key role in the formation and stability of these biofilms. Quorum sensing inhibitors (QSIs) aim to disrupt bacterial communication, preventing biofilm formation and potentially enhancing the efficacy of conventional treatments. This strategy can help reduce the microbial load and inflammation associated with PD (Haque et al. 2022).
2. **Microbiome Modulation**: The oral microbiome plays a critical role in the development of PD, with dysbiosis contributing to disease progression. Recent advancements have focused on microbiome modulation through oral microbiota replacement therapy and probiotic therapy. These treatments aim to restore the natural microbial balance in the oral cavity, potentially reducing the pathogenic burden and improving periodontal health. By promoting the growth of beneficial

bacteria, these therapies may help prevent the onset of PD or reduce the severity of disease in conjunction with other treatments (Haque et al. 2022, Karbalaei et al. 2021).

3. **Targeting the Inflammasome**: The inflammasome, a multiprotein complex involved in the innate immune response, has been identified as a key player in the inflammatory processes of PD. Drugs targeting specific inflammasomes, such as the NLR, ALR, and Pyrin inflammasomes, can help reduce the excessive inflammatory response seen in periodontal tissues. By inhibiting these pathways, these drugs can mitigate the inflammatory cascade that leads to tissue damage, thus providing a potential therapeutic option for controlling periodontal inflammation (Haque et al. 2022).
4. **Anabolic Agents for Bone Regeneration**: Anabolic agents, such as teriparatide and sclerostin antibodies, hold promise in promoting alveolar bone regeneration in patients with advanced PD. Teriparatide, a recombinant form of parathyroid hormone, has been shown to stimulate bone formation, while sclerostin antibodies work by inhibiting the sclerostin protein, which negatively regulates bone formation. These agents can be used to support bone regeneration in periodontal tissues and enhance the outcomes of periodontal treatments, especially in patients with significant alveolar bone loss (Haque et al. 2022).
5. **Enamel Matrix Derivatives (EMDs) and Platelet-Rich Plasma (PRP)**: Enamel matrix derivatives have been widely used to promote periodontal tissue regeneration by stimulating the growth of periodontal ligament cells and enhancing new bone formation. Similarly, PRP, which contains growth factors, has shown efficacy in enhancing tissue healing and regeneration following periodontal procedures.

While there is growing evidence linking genetic and epigenetic changes to susceptibility, progression, and treatment response in periodontitis, several challenges presently limit their clinical application. Systematic reviews highlight that many of the associations reported show limited reproducibility across different populations and are often influenced by factors such as ethnicity, environmental conditions, disease classification standards, and study design. Additionally, numerous omics-based studies including those focusing on transcriptomics and epigenomics are constrained by small sample sizes and the use of mixed tissue types comprising diverse cell populations, which complicates biological interpretation. Though many potential biomarkers and therapeutic targets have been identified, only a few have undergone thorough validation in large-scale, prospective studies. As a result, most genetic, epigenetic, and RNA-based markers currently identified remain exploratory and hypothesis-driven rather than ready for clinical application. To advance personalized periodontal care, future research must concentrate on multicenter studies, standardized protocols, analyses at the specific cell-type level, longitudinal validation, and an evaluation of their clinical relevance before widespread implementation.

Conclusion

PD is a complex and evolving condition influenced by genetic and epigenetic factors that play vital roles in its development, progression, and treatment response. Microbial biofilms are the main causative factor behind periodontitis, while variations in host genetics could influence individual susceptibility. Nevertheless, the majority of reported links with cytokines, immune receptors, and regulatory molecules are inconsistent across different populations and should not yet be regarded as established clinical indicators. Epigenetic processes, such as DNA methylation, histone modifications, and non-coding RNAs, are critical in modulating gene expression within periodontal tissues. These processes are linked to inflammatory signaling, tissue remodeling, and bone resorption. Nonetheless, for numerous suggested epigenetic markers, it remains unclear whether the observed changes serve as causal factors driving the disease or merely arise as secondary effects of prolonged periodontal inflammation. As research continues to uncover the influence of these factors, it not only enriches our understanding of PD but also covers the way for personalized diagnostics and treatments. Recent advancements in genetic and epigenetic research have significantly enhanced our understanding of the biological mechanisms driving PD, uncovering numerous potential biomarkers and therapeutic targets. These breakthroughs have sparked growing interest in precision periodontology and personalized treatment approaches. Nonetheless, it is important to acknowledge that most the current evidence remains at the preclinical or translational stage of research. While many genetic and epigenetic markers show encouraging associations with disease susceptibility, progression, and treatment outcomes, their clinical applicability has not yet been sufficiently validated for widespread use. Future developments will require standardized methodologies, multi-center longitudinal studies, robust clinical trials, and validation across diverse populations. Until such comprehensive evidence is available, genetic and epigenetic precision-based strategies should be considered promising investigational tools rather than established components of standard periodontal practice.

Acknowledgements We would like to thank the Clinical Research Development Unit of Kowsar Educational and Research and Therapeutic Center of Semnan University of Medical Sciences for providing facilities to this work.

Author Contributions All authors contributed to the study conception and design. Material preparation, data collection and analysis, P. M., and F. Gh.; the first draft of the manuscript, M. E., and M. J.; Writing—original draft preparation, P. M., N. M, and S. M.; Software, M. H.; Data Curation, Writing - Review & Editing, M. E.; Supervision and project administration, M.E.; All authors read and approved the final manuscript.

Funding This research received no external funding.

Data Availability No datasets were generated or analysed during the current study.

Declarations

Competing Interests The authors declare no competing interests.

References

Agrawal A KK, M, Gupta, C, Chand P, SV Singh (2021) Association of interleukin-1 gene polymorphism and early crestal bone loss around submerged dental implants: A systematic review and meta-analysis. Indian Prosthodont Soc 2021 Apr–Jun(212):116–124

Agrawal KK, Chand SN, Singh P, Solanki SV, Garg N, Chaurasia RK (2024) A., *Associations among gene polymorphisms, crestal bone loss, and bone mineral density in patients receiving dental implants.* J Taibah Univ Med Sci., 2023;19(2):313–320

Arif KMT, Haupt EE, Griffiths LM (2020) Regulatory Mechanisms of Epigenetic miRNA Relationships in Human Cancer and Potential as Therapeutic Targets. Cancers (Basel) 12(10):2922

Asa'ad F, Pagni BV, Castilho G, Rossi RM, Pomingi E, Tarantini F, Consonni L, Giannobile D, Rasperini WV (2017) Evaluation of DNA methylation of inflammatory genes following treatment of chronic periodontitis: A pilot case-control study. J Clin Periodontol 44(9):905–914

Association between IL-1 gene polymorphisms and stage III Grade B periodontitis in polish population. (2022)

Ban Q, Ding LX, Meng H, Li J, Zhang Y, Zhu J (2022) Screening of periodontitis-related genes and immune cells based on an integrated bioinformatics analysis. Ann Transl Med 10(10):558

Barhate A, Shirbhate BP, Reche U, Pahade A, Agrawal A (2023) Implications of Gene Therapy in Dentistry and Periodontics: A Narrative Review. Cureus 15(11):e49437. https://doi.org/10.7759/cureus.49437. PMID: 38149156; PMCID: PMC10750132

Barros SP, Tarran FF, Kim R, Scarel-Caminaga S, Justice RM, North A (2020) Epigenetic reprogramming in periodontal disease: Dynamic crosstalk with potential impact in oncogenesis. Periodontol 2000 82(1):157–172

Bozo IY, Redko DA, Komlev NA, Isaev VS, Deev AA (2021) RV., *Bringing a Gene-Activated Bone Substitute Into Clinical Practice: From Bench to Bedside.* Front Bioeng Biotechnol., 2021;9:599300

Bumm CV, Heck SF, Frasheri K, Summer I, Ern B, Heym C, Werner R, Folwaczny N (2024) M., *The Role of Interleukin-8 in the Estimation of Responsiveness to Steps 1 and 2 of Periodontal Therapy.* J Clin Periodontol, 2024;51(11):1433–1442

Brodzikowska A, GR, Kowalski J (2019) Interleukin-1 Genotype in Periodontitis. Arch Immunol Ther Exp (Warsz) 2019(676):367–373

Brodzikowska A, Górski B (2022) Polymorphisms in genes involved in inflammation and periodontitis: a narrative review. Biomolecules. https://doi.org/10.3390/biom12040552

Caetano AJ, Sharpe DAE, Nibali P (2022) Expression of periodontitis susceptibility genes in human gingiva using single-cell RNA sequencing. J Periodontal Res 57(6):1210–1218. https://doi.org/10.1111/jre.13057. Epub 2022 Sep 28. PMID: 36170299

Camargo GAdCG dSRJ, de Amorim CS, de Farias Wenderoscky L, Pascoal VDB, Souza ACA, Duque C (2022) Gene expression of inflammatory immune factors and clinical parameters in diabetes and nondiabetes patients with periodontal disease. Res Soc Dev 11:e17711124185–e

Cárdenas AM, Vernal AL, Melgar-Rodríguez R, Hernández S (2022) Biomarkers of Periodontitis and Its Differential DNA Methylation and Gene Expression in Immune Cells: A Systematic Review. Int J Mol Sci 23(19):12042. https://doi.org/10.3390/ijms231912042. PMID: 36233348; PMCID: PMC9570497

Chen Y et al (2023) Epigenetic regulation of chemokine (CC-motif) ligand 2 in inflammatory diseases. Cell Prolif 56(7):e13428

Chen Y, Yang WH, Zhao Q, Chen W, Ni Y, Li Q, Shi W, Zhang J, Li W, Xu L, Zhang Y, Miao H, Xing D, Sun L (2022) Single-cell RNA landscape of the osteoimmunology microenvironment in periodontitis. Theranostics 12(3):1074–1096

Cheng Y et al (2025) The Investigation of Nfκb Inhibitors to Block Cell Proliferation in OSCC Cells Lines. Curr Med Chem 32(33):7314–7326

Cheng L et al (2026) *Sub-10 nm Silicon-Based Pyramidal Nanopore Enabling High Performance Single Protein Molecule Detection.* Advanced Functional Materials, n/a(n/a): p. e76232

Cho Y, Bae KB, Kim H, Baek W, Woo J, Lee K, Seol G, Lee Y, Ku Y, Rhyu Y, Ryoo I (2017) H Direct Gingival Fibroblast/Osteoblast Transdifferentiation via Epigenetics J Dent Res 96(5):555–561

Cho YD, Kim KP, Seol HG, Lee YJ, Ku YM, Rhyu Y, Ryoo IC (2017) HM., *Transcriptomics and methylomics in chronic periodontitis with tobacco use: a pilot study.* Clin Epigenetics., 2017;9:81

Cho YD et al (2021) Current advances of epigenetics in periodontology from ENCODE project: a review and future perspectives. Clin Epigenetics 13(1):92

Cho YD, Ryoo KW, Kim HM, Kim HG, Ku KH, Seol Y (2021) Current advances of epigenetics in periodontology from ENCODE project: a review and future perspectives. Clin Epigenetics 13(1):92. https://doi.org/10.1186/s13148-021-01074-w. PMID: 33902683; PMCID: PMC8077755

da Silva FRP, Shin PL, Alves JI, Koga EHP, Smith RS, Vasconcelos CV, Pereira DFP (2021) Polymorphisms in the interleukin genes and chronic periodontitis: A field synopsis and revaluation by Bayesian approaches. Cytokine 138:155361. https://doi.org/10.1016/j.cyto.2020.155361. Epub 2020 Nov 19. PMID: 33223448

Dalvand S, Sepahvand NA, Meshkibaf F, Ahmadpour MH (2021) Investigation of Decitabine Effects on HDAC3 and HDAC7 mRNA Expression in NALM-6 and HL-60 Cancer Cell Lines. Rep Biochem Mol Biol 10(3):420–428

de Mendoza A, Ford NT, Poppe E, Buckberry D, Pflueger S, Grimmer J, Stolzenburg MR, Bogdanovic S, Oshlack O, Farnham A, Blancafort PJ, Lister P (2022) Large-scale manipulation of promoter DNA methylation reveals context-specific transcriptional responses and stability. Genome Biol 23(1):163

Dhaouadi T, Ben Abdallah RA, Gorgi T, Sfar Y (2024 Jan Dec) Impact of IL-10 gene promoter polymorphisms on treatment response in HCV patients: A systematic review, a meta-analysis, and a meta-regression. Int J Immunopathol Pharmacol 38:3946320241240705

Dommisch H et al (2025) Genetic Biomarkers for Periodontal Diseases: A Systematic Review. J Clin Periodontol 52(Suppl 29):182–210

Dommisch H et al (2025) Epigenetic regulation in the pathogenesis of periodontitis. J Periodontal Res. https://doi.org/10.1111/jre.70036

Dosseva-Panova V, Mlachkova P-TZ (2022) A., *Relationship between smoking and periodontal clinical findings and gene expression of IL-6 and TNF-α in severe periodontitis (clinical and laboratory data).* Biotechnology & Biotechnological Equipment ; 36: 662-7

Emamgholipour S, Shabani EF, Hasanpour M, Pilehvari SZ, Zabihi-Mahmoudabadi M, Motevasseli H, Shanaki M (2023) Alterations of SOCS1 and SOCS3 transcript levels, but not promoter methylation levels in subcutaneous adipose tissues in obese women. BMC Endocr Disord 23(1):7

Feehley T, Mendlein ODC, Karande J, McCauley M (2023) T., *Drugging the epigenome in the age of precision medicine.* Clin Epigenetics., 2023;15(1):6

Finoti CS LS, Anovazzi G, Teixeira SR, Capela MV, Tanaka MH, Kim YJ, Orrico SR, Cirelli JA, Mayer MP, Scarel-Caminaga RM (2013) Pathogen levels and clinical response to periodontal treatment in patients with Interleukin 8 haplotypes. Pathog Dis 2013(691):21–28

Ganesan A, Rots AP, Jeronimo MG, Berdasco C (2019) M., *The timeline of epigenetic drug discovery: from reality to dreams.* Clin Epigenetics., 2019;11(1):174

Gao C et al (2024) Genome-wide association studies on periodontitis: a systematic review. PLoS One 19(9):e0306983

Georgios S, Chatzopoulos 1 A-ED (2020) Sofia Zarenti 3, Menelaos Anastasopoulos 3, Anastasia Kouvatsi 4, *Interleukin-6 and Interleukin-10 Gene Polymorphisms in Patients with Chronic Periodontitis and Response to Treatment after 3 Years.* Acta Stomatol Croat, 2020;54(3):238–249

Ghafouri-Fard S, Sadeghpour GL, Nazer S, Hussen N, Sayad BM, Taheri A (2022) M., *Altered expression of SOCS genes periodontitis.* BMC Oral Health., 2022;22(1):551

Ghasemian A et al (2018) Probiotics and their increasing importance in human health and infection control. Reviews Res Med Microbiol 29(4):153–158

Gong H et al (2024) Identification of cuproptosis-related lncRNAs with the significance in prognosis and immunotherapy of oral squamous cell carcinoma. Comput Biol Med 171:108198

Graves DT et al (2012) Animal models to study host-bacteria interactions involved in periodontitis. Front Oral Biol 15:117–132

Haque MM, Kelekis-Cholakis YK, Duan A (2022) Advances in novel therapeutic approaches for periodontal diseases. BMC Oral Health 22(1):492

Hu A et al (2024) Association between matrix metalloproteinase-3 gene polymorphism and susceptibility to chronic periodontitis: a systematic review and meta-analysis. J Med Biochem. https://doi.org/10.5937/jomb0-49044

Huang J, Zhou Y (2022) Emerging role of epigenetic regulations in periodontitis: a literature review. Am J Transl Res 14(4):2162–2183

Huang YK, Tsai TK, Wang PH, Lee JS, Shen CY (2021) MY., *IL-8 as a Potential Therapeutic Target for Periodontitis and Its Inhibition by Caffeic Acid Phenethyl Ester In Vitro.* Int J Mol Sci., 2021;22(7):3641

Isola GP, Santonocito A, Dalessandri S, Migliorati D, Indelicato M (2021) New Frontiers on Adjuvants Drug Strategies and Treatments in Periodontitis. Sci Pharm 89:46. https://doi.org/10.3390/scipharm89040046

Karbalaei M et al (2021) Alleviation of halitosis by use of probiotics and their protective mechanisms in the oral cavity. New Microbes New Infect 42:100887

Kay-Arne Walther 1, J.R.G., Sabine Gröger 1, Benjamin Ehmke 2, Dogan Kaner 3 4, Katrin Lorenz 5, Peter Eickholz 6, Thomas Kocher 7, Ti-Sun Kim 8, Ulrich Schlagenhauf 9, Raphael Koch 10, Jörg Meyle 1, *The Role of Polymorphisms at the Interleukin-1, Interleukin-4, GATA-3 and Cyclooxygenase-2 Genes in Non-Surgical Periodontal Therapy.* (2022)

Kim H, Chen M-HF, Hoffmann S, Kebschull P, Papapanou M (2021) Differential DNA methylation and mRNA transcription in gingival tissues in periodontal health and disease. J Clin Periodontol 48(9):1152–1164

Kozak M, Mazurek-Mochol D-ZE, Pawlik M (2020) Cytokines and Their Genetic Polymorphisms Related to Periodontal Disease. J Clin Med 9(12):4045

Lagosz KB, Macina BA, Bereta JM, Kantorowicz GP, Lipska M (2020) HDAC3 Regulates Gingival Fibroblast Inflammatory Responses in Periodontitis. J Dent Res 99(1):98–106

Lafuente-Ibáñez-de-Mendoza I, Setién-Olarra M-MX, García-de-la-Fuente A, Martínez-Conde-Llamosas AM, Aguirre-Urizar R (2024) JM., *Genetic polymorphisms of inflammatory and bone metabolism related proteins in a population with dental implants of the Basque Country. A case-control study.* BMC Oral Health., 2024;24(1):659

Li W et al (2022) Inferring Latent MicroRNA-Disease Associations on a Gene-Mediated Tripartite Heterogeneous Multiplexing Network. IEEE/ACM Trans Comput Biol Bioinform 19(6):3190–3201

Li L et al (2024) Circulating immune cells and risk of osteosarcoma: a Mendelian randomization analysis. Front Immunol 15:1381212

Liaw A et al (2022) The relevance of DNA methylation and histone modification in periodontitis: a scoping review. Cells. https://doi.org/10.3390/cells11203211

Loos BG et al (2015) What is the Contribution of Genetics to Periodontal Risk? Dent Clin North Am 59(4):761–780

Loos BG (2020) The role of inflammation and genetics in periodontal disease. Periodontol 2000 83(1):26–39

Ma S, He H, Ren X (2024) Single-Cell and Transcriptome Analysis of Periodontitis: Molecular Subtypes and Biomarkers Linked to Mitochondrial Dysfunction and Immunity. J Inflamm Res 17:11659–11678

Mahmood AA, Hussein AR (2023) Oct-Dec;60(4):627–634 HM., *Novel association between single-nucleotide polymorphisms of IKKβ at rs17875746 and rs12676482 and periodontitis.* Dent Med Probl. https://doi.org/10.17219/dmp/170879. PMID: 37930783

Mongan NP, Emes RD, Archer N (2019) Detection and analysis of RNA methylation. F1000Res. https://doi.org/10.12688/f1000research.17956.1

Moreno C, Tellez Freitas BE, Pickett CM, Weber BE (2022) Meta-Analysis of Two Human RNA-seq Datasets to Determine Periodontitis Diagnostic Biomarkers and Drug Target Candidates. Int J Mol Sci 23(10):5580

Nabil K, Omar Kujan, Dorte Haubek, Leticia Algarves Miranda (2024) Occurrence of Aggregatibacter actinomycetemcomitans and Its JP2 genotype in a cohort of 220 Western Australians with unstable periodontitis

Naqvi AR (2021) Human and herpesvirus microRNAs in periodontal disease. Periodontol 2000 87(1):325–339. https://doi.org/10.1111/prd.12404. PMID: 34463985; PMCID: PMC8520140

Nibali L et al (2019) What Is the Heritability of Periodontitis? A Systematic Review. J Dent Res 98(6):632–641

Nibali L et al (2020) Heritability of periodontitis: a systematic review of evidence from animal studies. Arch Oral Biol 109:104592

Nolde M, Reckelkamm AZ, Kocher SL, Ehmke T, Holtfreter B, Baurecht B, Georgakis H, Baumeister MK (2023) SE., *Downregulation of interleukin 6 signaling might reduce the risk of periodontitis: a drug target Mendelian randomization study.* Front Immunol., 2023;14:1160148

Nuñez-Belmar J, Vicencio M-OM, Vernal E, Cárdenas R, Cortez JP (2022) Contribution of –Omics Technologies in the Study of Porphyromonas gingivalis during Periodontitis Pathogenesis: A Minireview. Int J Mol Sci 24(1):620. https://doi.org/10.3390/ijms24010620. PMID: 36614064; PMCID: PMC9820714

Olsson B, d.S.M., Lago C, Calixto RD, Ramazzotto LA, Barbosa Rebellato NL, Kirschneck C, Garcia Paula-Silva FW, Küchler EC, Scariot R (2021) Single Nucleotide Polymorphisms in Runt-related Transcription Factor 2 and Bone Morphogenetic Protein 2 Impact on Their Maxillary and Mandibular Gene Expression in Different Craniofacial Patterns - A Comparative Study. Ann Maxillofac Surg 2021 Jul–Dec(112):222–228

Omidiran O et al (2024) GWAS advancements to investigate disease associations and biological mechanisms. Clin Transl Discov. https://doi.org/10.1002/ctd2.296

Patel D et al (2019) *Epigenetics- Epidisease- Epidrug: A Key Context Folded inside of Periodontal Diseases.*

PM (2018) Lifestyle and periodontitis: The emergence of personalized periodontics. Periodontol 2000 78(1):7–11

Qin H, Xu LG, Zhang X, Zhong C, Xu W, Yin S, Song Y (2022) J., *The role of oral microbiome in periodontitis under diabetes mellitus.* J Oral Microbiol., 2022;14(1):2078031

Raut N et al (2019) Epigenetic regulation of bone remodeling by natural compounds. Pharmacol Res 147:104350

Razzouk S (2024) Single-cell sequencing, spatial transcriptome ad periodontitis: Rethink pathogenesis and classification. Oral Dis 30(5):2771–2783

Ruden DM, Rappolee SA (2023) Pathological epigenetic events and reversibility review: the intersection between hallmarks of aging and developmental origin of health and disease. Epigenomics 15(14):741–754

Santaló J (2022) Ethical implications of epigenetics in the era of personalized medicine. Clin Epigenetics 14(1):44

Santonocito S, Polizzi FS, Ronsivalle A, Sclafani V, Valletta R, Lo Giudice A, Cavalcanti A, Spagnuolo R, Isola G (2022) Therapeutic and Metagenomic Potential of the Biomolecular Therapies against Periodontitis and the Oral Microbiome: Current Evidence and Future Perspectives. Int J Mol Sci 23(22):13708

Shaddox LM, Morford LA, Nibali L (2021) Periodontal health and disease: The contribution of genetics. Periodontol 2000 85(1):161–181

shan. ZZ (2018) Association between COX2 -765G/C polymorphism and periodontitis in Chinese population: a meta-analysis. BMC Oral Health 18(1):32

Shah MS et al (2025) Unveiling the dental cellular landscape: A comprehensive review of single-cell RNA sequencing in human dental tissues. Jpn Dent Sci Rev 61:301–316

Shi Y, Da ZR, Wang N, Yang Y, Li J, He B (2023) X., *Aspirin loaded extracellular vesicles inhibit inflammation of macrophages via switching metabolic phenotype in periodontitis.* Biochem Biophys Res Commun., 2023;667:25–33

Shinji Matsuda TS 1, Miyagawa T 3, Yumoto H (2023) 4, Yasutaka Komatsu 5, Nanae Dewake 6, Takanori Iwata 7, Takatoshi Nagano 8, Toshiya Morozumi 9, Ryoma Goto 10, Satsuki Kato 11, Masahiro Kitamura 12, Kitetsu Shin 13, Satoshi Sekino 14, Akiko Yamashita 15, Keiko Yamashita 16, Atsutoshi Yoshimura 17, Tsutomu Sugaya 18, Shogo Takashiba 19, Yoichiro Taguchi 20, Eiji Nemoto 21, Hiromi Nishi 22, Noriyoshi Mizuno 23, Yukihiro Numabe 14, Hiroyuki Kawaguchi 22, *Effect of Periodontal Treatment on Reducing Chronic Inflammation in Systemically Healthy Patients With Periodontal Disease.* Am J Med., 2024;137(3):273–279.e2

Suleimenova D, Li HS, Ivanovski M, Mattheos S (2017) N., *Gene expression profiles in guided bone regeneration using combinations of different biomaterials: a pilot animal study.* Clin Oral Implants Res, 2017;28(6):713–720

Suzuki S, Yamada S (2022) Epigenetics in susceptibility, progression, and diagnosis of periodontitis. Jpn Dent Sci Rev 58:183–192

Tanaka U, Finoti KS, Palioto LS, Kinane DB, Benakanakere DF (2021) Decitabine Inhibits Bone Resorption in Periodontitis by Upregulating Anti-Inflammatory Cytokines and Suppressing Osteoclastogenesis. Biomedicines 9(2):199

Tatman PD, Fringuello WT, Scherer AR, Foreman SR, Damek WB, Lillehei DM, Jensen KO, Youssef RL, Ormond AS, Graner DR (2022) Targeting DNA Methyl Transferases with Decitabine in Cultured Meningiomas. World Neurosurg 162:e99–e119

The impact of CYP2C19 genotype on phenoconversion by concomitant medication. (2023)

Toy VE (2019) Do genetic polymorphisms affect susceptibility to periodontal disease? A literature review. Niger J Clin Pract 22(4):445–453

Ustianowska K et al (2024) The genetic aspects of periodontitis pathogenesis and the regenerative properties of stem cells. Cells. https://doi.org/10.3390/cells13020117

Uttamani JR, Estepa NA, Kulkarni AMV, Brambila V, Martínez MF, Chapa G, Wu G, Li CD, Rivas-Tumanyan W, Nares S (2023) Downregulation of miRNA-26 in chronic periodontitis interferes with innate immune responses and cell migration by targeting phospholipase C beta 1. J Clin Periodontol 50(1):102–113. https://doi.org/10.1111/jcpe.13715. Epub 2022 Aug 25. PMID: 36054706; PMCID: PMC10087579

Valverde A, Naqvi NS (2020) Impaired cell migration and structural defects in myeloid cells overexpressing miR-30b and miR-142-3p. Biochim Biophys Acta Gene Regul Mech 1863(11):194628

Valverde A, Nares GA, Naqvi S (2024) AR., *Emerging therapeutic strategies targeting bone signaling pathways in periodontitis.* J Periodontal Res. Jul 23. https://doi.org/10.1111/jre.13326. Epub ahead of print. PMID: 39044454

Wang T, ML, White, Bradshaw AJ, Xu X, Cho YH, Terry MB, Teitelbaum SL, Neugut AI, Santella RM, Chen J, Gammon MD (2019) Prediagnosis aspirin use, DNA methylation, and mortality after breast cancer: A population-based study. Cancer 2019(12521):3836–3844

Wielento A et al (2023) The Role of Gingival Fibroblasts in the Pathogenesis of Periodontitis. J Dent Res 102(5):489–496

Yang YF et al (2024) Evaluating the role of DNA methyltransferases in trophoblast fusion and preeclampsia development: insights from methylation-regulated genes. FASEB J 38(13):e23706

Yin L, Li X, Hou J (2022) Macrophages in periodontitis: A dynamic shift between tissue destruction and repair. Jpn Dent Sci Rev 58:336–347

Yoo D, Pyo MK, Kim JS (2023) NY., *Diagnostic and Prognostic Roles of GATA3 Immunohistochemistry in Urothelial Carcinoma.* Medicina (Kaunas). 2023;59(8):1452

Yousefi B et al (2019) Probiotics importance and their immunomodulatory properties. J Cell Physiol 234(6):8008–8018

Zalewska EA, Grygorczuk ŁR, Nowosielska P, Kicman M, Ławicki A (2024) Importance of Metalloproteinase 8 (MMP-8) in the Diagnosis of Periodontitis. Int J Mol Sci 25(5):2721. https://doi.org/10.3390/ijms25052721. PMID: 38473967; PMCID: PMC10931783

Zhang X et al (2021) m6A regulator-mediated RNA methylation modification patterns are involved in immune microenvironment regulation of periodontitis. J Cell Mol Med 25(7):3634–3645

Zhang L, You ZL, Sun H, Liao S, Zhao Z, Chen G (2021) Inhibition of osteoclastogenesis by histone deacetylase inhibitor Quisinostat protects mice against titanium particle-induced bone loss. Eur J Pharmacol 904:174176

Zhao JH et al (2023) Genetics of circulating inflammatory proteins identifies drivers of immune-mediated disease risk and therapeutic targets. Nat Immunol 24(9):1540–1551

Zhu S et al (2026) Cell signaling and transcriptional regulation of osteoclast lineage commitment, differentiation, bone resorption and diseases. Cell Discov 12(1):6

Authors and Affiliations

Maryam Jalili Sadrabad[1] · Parham Mohammadian Semnani[2] · Farid Ghadyani[3] · Nika Moghadamnia[2] · Sahar Maleki[2] · Mohammad Amin Hemmati[4] · Majid Eslami[5,6]

✉ Majid Eslami
M.eslami@semums.ac.ir

[1] Maxillofacial Medicine Department, Dental Faculty of Semnan, University of Medical Sciences, Semnan, Iran

[2] Student Research Committee, School of Dentistry, Semnan University of Medical Sciences, Semnan, Iran

[3] Universal Scientific Research and Education Network (USERN), Tehran, Iran

[4] Clinical Research Development Unit, Kowsar Educational, Research and Therapeutic Hospital, Semnan University of Medical Sciences, Semnan, Iran

[5] Research Center of Physiology, Neuroscience Research Institute, Semnan University of Medical Sciences, Semnan, Iran

[6] Department of Bacteriology and Virology, Semnan University of Medical Sciences, Semnan, Iran