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REVIEW

Jovanova et al: Genome-wide insights into periodontitis

The role of genome-wide DNA methylation and polymorphisms in periodontitis etiology: A narrative review

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ABSTRACT

Periodontitis is a multifactorial inflammatory disease influenced by genetic, epigenetic, and environmental factors. Recent advancements in genomic and epigenomic research have highlighted the role of genetic polymorphisms and genome-wide DNA methylation in its pathogenesis. DNA methylation regulates gene expression, affecting immune responses and inflammatory pathways, while genetic polymorphisms may predispose individuals to altered host-microbial interactions and increased susceptibility to periodontal destruction. Recent studies have identified promising periodontal biomarkers, including specific genetic and epigenetic markers, that may aid in early diagnosis, risk assessment, and monitoring of disease progression. This narrative review synthesizes current evidence on the genetic and epigenetic mechanisms involved in the etiology of periodontitis, with a focus on genome-wide DNA methylation and genetic polymorphisms. It also explores their potential implications for disease pathogenesis, diagnostics, and therapeutic strategies. Future research directions include integrative multi-omics approaches to better understand the complex interplay between genetic, epigenetic, and environmental factors. Such efforts aim to support the development of personalized therapeutic strategies. Overall, this review underscores the critical role of genetic and epigenetic mechanisms in the pathogenesis of periodontitis and emphasizes the need to translate these findings into clinical practice through molecular diagnostics and personalized treatment approaches.

Keywords: DNA methylation; periodontitis; GWAS; genetic polymorphisms; epigenetic mechanisms.

INTRODUCTION

Periodontitis is a chronic, multifactorial inflammatory condition caused by a dysbiotic biofilm that can cause, if not properly and preventively treated, a progressive disruption of the supporting periodontal tissues and finally tooth loss [1]. Periodontal pathogens, present in the plaque biofilm, trigger continuous attacks on the host, which then activates an immune response that may gradually result in tissue damage due to inflammation. However, the presence of pathogenic subgingival bacteria alone does not typically cause periodontal destruction in most cases. Therefore, although bacteria play a crucial role in the onset of periodontitis, the amount of plaque and specific bacterial species do not necessarily correlate with the severity of the disease [2].

Each individual may exhibit a dose-dependent response to bacterial exposure that influences their susceptibility to periodontitis. The majority of individuals are resistant to the disease and will not develop periodontitis. The pathophysiology of periodontitis, like other complex diseases, is driven by several biological pathways that ultimately lead to the same clinical manifestations [3]. Complex diseases are typically polygenic, involving variations in multiple genes, each contributing a small effect and relative risk to the disease process, with these genes considered disease-modifying, especially when periodontitis is combined with systemic diseases [4]. Several aspects of the inflammatory and immune response implicated in the development of periodontitis have a well-defined genetic foundation. Genetic predisposition is thought to influence the progression of periodontitis, particularly in its aggressive and rapidly advancing forms [5]. There has been a significant surge in scientific publications suggesting associations between genetic polymorphisms and various medical conditions, particularly chronic immune and inflammatory disorders and consequently, this growing body of knowledge indicates that most diseases, including periodontitis, have a genetic basis [6]. The disease often maintains a bidirectional relationship with genetic factors alongside environmental and behavioral influences, which play a role in the initiation of the disease in susceptible individuals and the rate at which it progresses [7]. Considering the known impact of these factors, and systemic health on the epigenome, along with the established role of external exposures in shaping disease predisposition, epigenetic factors, and genetic polymorphism are significant in the pathobiology of periodontitis [8,9]

In contrast to the genome, which remains consistent across all cells and throughout life, the epigenome is dynamic and varies between different cells and tissues. Epigenetics is a

developing field of science that is not directly related to gene mutations but focuses on changes in gene expression that occur without modifications to the underlying DNA sequence. It evolves in response to alterations in the cellular microenvironment and external influences that are associated with inflammation and the risk of disease, and it can induce the silencing or overexpression of specific genes that generate different molecules (9, 10, 11). The primary mechanisms of epigenetic regulation encompass DNA methylation, small non-coding RNAs, and histone modification [12,13]. Research on gene methylation in the pathology of periodontitis may offer valuable genetic insights for a more comprehensive understanding of the disease, potentially aiding in the development of effective therapies [14]. Several studies have examined global DNA methylation patterns in periodontitis, suggesting that various methylation changes play a crucial role in the disease's pathogenesis [15].

A wide range of scientific literature has examined the impact of gene variants, including polymorphisms, on host immune responses and the pathogenesis of periodontitis [16]. Specific alterations in the genetic code can lead to changes in function or secretion of the encoded proteins, potentially contributing to heightened disease severity or a greater susceptibility to the disease [17].

In this context, this review provides an overview of current research on the role of genome-wide DNA methylation and genetic polymorphisms in the pathogenesis of periodontitis, highlighting their role in disease mechanisms, advanced precision diagnostics, developing targeted therapies, and ultimately improving long-term outcomes in periodontal care.

To provide a comprehensive and focused synthesis, we performed a targeted literature search in PubMed and Scopus using keywords including "periodontitis", "DNA methylation", "genetic polymorphisms", "GWAS", "EWAS", and "epigenetics". Studies were selected based on methodological rigor, sample size, relevance to human periodontitis, and their contribution to elucidating genetic and epigenetic mechanisms. Preference was given to peer-reviewed research providing clinically or biologically meaningful insights into the etiology, pathogenesis, and potential diagnostic or therapeutic applications related to periodontal disease.

GENETIC POLYMORPHISMS IN PERIODONTITS

Key susceptibility genes and polymorphisms associated with periodontitis

Genetic polymorphisms are variations at specific loci within the genome that affect more than 1% of the population. These polymorphisms can alter the structure or expression of encoded proteins, potentially leading to modifications in both innate and adaptive immune responses [18]. Furthermore, some gene polymorphisms may also be preventive against specific diseases including periodontitis, by influencing the immune system's response to pathogens [19]. Genetic variations that modulate the effectiveness of the cellular and humoral immune responses, influence an individual's risk of developing the disease [17]. The immune system is widely recognized as playing a significant role in the pathogenesis of periodontitis. In periodontal tissues, numerous genes are believed to contribute to the development of periodontitis. These include genes that modulate the expression of interleukin (IL)-1, IL-6, tumor necrosis factor (TNF)- α and its receptors, IL-10, selenoprotein S, Fc- γ receptor, CD14 molecule, toll-like receptors (TLRs), caspase recruitment domain 15 and vitamin D receptor [20].

Genome-wide association studies GWAS and their contributions

Genome-wide association studies (GWAS) have proven to be a powerful tool for uncovering genetic variants associated with complex human diseases and traits. Multiple GWAS have been carried out to elucidate the genetic underpinnings of periodontitis [21]. In recent years, GWAS has emerged as the primary approach for analyzing genetic polymorphisms, with numerous studies focusing on periodontal disease. In an early investigation, Schaefer et al. identified a significant association between aggressive periodontitis (AP) and the single nucleotide polymorphism (SNP) rs1537415 in the glycosyltransferase gene GLT6D1 [22]. More recently, several studies have reported associations between periodontal disease and polymorphisms in the SIGLEC5 gene, which encodes sialic acid-binding immunoglobulin-like lectin 5 [23,24]. The application of bioinformatics and GWAS has enabled the extensive detection of SNPs associated with periodontitis in multiple population groups. According to one study, SNPs in NPY, IL37, and NCR2 genes were found to be

associated with increased susceptibility to moderate or severe periodontitis, while a variant in TLR9 was linked to a reduced risk of developing severe disease. These SNPs exhibited sex- and smoking-dependent effects on periodontitis, further supporting the role of genetic predisposition in the disease's pathogenesis [25].

Functional implications of genetic polymorphisms in periodontal disease pathogenesis

The primary antibody subclass produced in response to infection of the periodontium by pathogenic microorganisms is IgG2. Elevated levels of these antibodies were detected in the serum of patients with localized aggressive periodontitis compared to those with generalized periodontitis, indicating higher antibody levels may play a role in restricting the severity of the disease [26,27]. Notable differences in IgG2 antibody production were observed across racial and individual groups, with enhanced production linked to the presence of the n+allele in the gene encoding the antibody heavy chain (γ2 locus), commonly referred to as the Gm allele [27], [28]. Genetic differences in the production of IL-1 family cytokines may account for the varying levels of severity observed in periodontal disease. Some identified polymorphisms are thought to contribute to the detection of individual variations in cytokine production, which are proportional to the extent of the disease [29]. Furthermore, cytokines trigger multiple signaling pathways that regulate osteoclastic activity and the resorption of alveolar bone. Prior research has indicated that polymorphisms in cytokine genes may be linked not only to the susceptibility to periodontal disease but also to its progression, intensity, and clinical outcomes [30]. Studies indicate that TNF-α plays a critical role in the pathogenesis and progression of periodontal disease, potentially contributing to its development [31,32]. Dysregulated cytokine gene expression may contribute to the persistent cycles of tissue inflammation observed in these disorders [32]. Kornman et al. were among the earliest researchers to identify genetic markers associated with periodontal disease [33]. The authors investigated several polymorphisms in the interleukin 1 (IL-1) gene and found a correlation between IL-1 gene variants and the severity of periodontal disease in non-smokers, distinguishing between mild and severe cases. These findings laid the groundwork for subsequent genetic studies on periodontal disease, which employed various methodological approaches. Identifying genetic risk factors associated with periodontal disease is crucial for the development of effective prevention and treatment strategies for the disease [30].

EPIGENETIC MECHANISMS IN PERIODONTITS

Epigenetic factors are inheritable alterations to the genome that can influence gene expression, potentially contributing to the development of diseases. These epigenetic modifications are crucial in chronic inflammatory conditions, such as periodontal diseases, where they facilitate microbial persistence or enable microbial damage, thus supporting the 'hit-and-run' infectious mechanism, which results in prolonged pathogen disruption of the host genome [34]. Epigenetic modifications are driven by mechanisms such as chemical changes to DNA and chromatin remodeling (e.g., via DNA methylation and histone modifications), as well as by the actions of small noncoding RNAs [35]. These changes enable the genome to modify its transcriptional activity to adapt to dynamic environmental conditions [36] (Figure 1).

Overview of epigenetic regulation

DNA methylation

Within the cell nucleus, DNA is organized into a chromatin structure, in which it is tightly wrapped around histone proteins. These histones can undergo post-translational modifications such as acetylation and methylation. The specific pattern of these histone modifications influences chromatin accessibility and modulated transcription factor binding, thereby regulating the initiation of gene expression and contributing to distinct cellular responses [37,38]. The most prominent examples of epigenetic modification are DNA methylation, which generally represses gene expression, and involves the addition of a methyl group to cytosine residues that are followed by guanine or adenine in the DNA sequence [34]. It is an extensively explored epigenetic process, recognized for its contribution to disease development, including cancer, and its essential role in maintaining normal cellular functions [12]. DNA methylation represents an epigenetic mechanism that is both heritable and potentially reversible and is subject to modulation by external environmental agents, such as tobacco use, as well as internal factors like infection and inflammation. These influences can induce dynamic changes in epigenetic regulation throughout an individual's lifespan, enabling phenotypic plasticity in response to varying stimuli. This epigenetic adaptability underscores the potential for implementing precision medicine strategies that incorporate both genomic and epigenomic profiles [39]. Additionally, these changes may also act as potential biomarkers for the early stages of cellular transformation [40]. DNA can be chemically altered by the addition of methyl groups to cytosine bases within CpG sites- regions where cytosine and guanine are

linked by a phosphate group, commonly referred to as CpG islands [41]. This methylation process is mediated by a group of DNA methyltransferases (DNMTS), which transfer a methyl group from S-adenosylmethionine (SAM) to the fifth carbon of a cytosine base, resulting in the formation of 5-methylcytosine (5mC) [42]. Hypomethylation of CpG sites within gene promoters is generally associated with enhanced transcriptional activity, whereas hypermethylation in the same regions is commonly correlated with gene silencing and reduced transcriptional output [43]. In vitro evidence indicates that distinct epithelial cell types such as oral keratinocytes, immortalized human keratinocytes (HaCaT), and gingival epithelial cells experience a significant downregulation of DNA methyltransferase-1 (DNMT1) expression when exposed to *Fusobacterium nucleatum*, *Porphyromonas gingivalis*, or isolated lipopolysaccharide [39].

Previous studies investigating DNA methylation at pre-selected gene loci have shown that methylation levels in inflammatory gene promoters such as interferon-gamma (IFNγ), TLR2, and TNFα are altered in periodontitis tissues, often correlating inversely with gene expression [44–46]. Barros and Offenbacher, applying laser capture microdissection, detected widespread methylation alterations in chemokine and cytokine genes in gingival epithelial cells from periodontitis sites [47]. Hypomethylation of promoter regions in genes encoding pro-inflammatory cytokines- including IL-6, IL-8, INF-γ, and IL-17- has been observed in human gingival biopsy samples and is potentially linked to host immune responses to periodontal pathogens [8,10,48]. Moreover, upon stimulation with the periodontal pathogen *P. gingivalis*, gingival epithelial cells exhibited promoter-specific hypermethylation of IL12A, TLR2, and GATA3, alongside hypomethylation of ZNF287 and STAT5A genes [49], [50]. TLR2 promoter hypermethylation was found to be associated with increased periodontal pocket depth [45]. Differential CpG methylation of the thioredoxin gene, involved in IL-1 β driven innate immune responses, has been identified in periodontitis patients [34].

Given the multifactorial etiology of periodontal disease, which is heavily influenced by environmental exposures and modifiable systemic conditions, integrative approaches may enhance the understanding and management of the disease. In this regard, the role of DNA methylation in the progression of periodontitis has been examined (Table 1).

Histone modifications

Posttranslational histone modifications influence chromatin structure and gene transcription through the addition of methyl groups to lysine or arginine residues on histones H3 and H4, facilitated by histone methyltransferases or histone demethylases. The most prevalent of these modifications are lysine modifications on histones, with H3 being the most extensively modified histone [51], [52]. Lysine methylation occurs in the form of mono-, di-, or trimethylation, and the specific methylation state is linked to changes in gene transcription activity. In recent years, the number of lysine methylation sites identified as being linked to transcriptional activation (e.g., H3K4, H3K36, and H3K79) and repression (e.g., H3K9, H3K27, and H4K20) has expanded [53]. Among these, H3K4, H3K9, and H3K27 methylation sites are the most extensively studied and are recognized for their impact on dental tissues [54,55]. Few studies have explored histone modifications, particularly in response to bacterial lipopolysaccharides. Larsson et al. reported that LPS promotes H3 methylation and acetylation of H3 and H4 in B cells, while other research has shown that HDAC inhibitors, which enhance histone acetylation, protect against LPS-induced bone resorption [56,57]. Alterations in the histone methylation status regulate periodontal gene expression and have significant impacts on periodontal development, health, and treatment [52].

Non-coding RNAs

Non-coding RNAs (ncRNAs) are RNA molecules that do not encode proteins but regulate gene expression and cell differentiation at the genomic and chromosomal levels. They are mainly classified into microRNAs (miRNAs) and long non-coding RNAs (lncRNAs) based on length. MicroRNAs are short, evolutionarily conserved RNA molecules ranging from 17 to 25 nucleotides in length, derived from longer precursor transcripts. In contrast, long non-coding RNAs are linear RNA transcripts exceeding 200 nucleotides in length. Microarray analysis revealed differential expression of 159 miRNAs and 8925 lncRNAs, suggesting their potential involvement in the pathogenesis and progression of periodontitis [58]. In the context of inflammatory diseases such as periodontitis, lncRNAs are increasingly being implicated in modulating immune responses, cytokine expression, and the activity of signaling pathways involved in tissue destruction and repair [59,60]. These lncRNAs have been demonstrated to modulate a range of cellular processes in periodontal cells, including osteogenic differentiation, inflammatory responses, cell proliferation, autophagy, and apoptosis [61]. Several microRNAs were identified as differentially expressed in these studies, with the majority being functionally associated with processes such as inflammatory responses and cellular homeostasis. Moreover,

circulating microRNA in serum may have potential utility as biomarkers for various diseases [62]. The increased expression levels of miR-664a-3p, miR-501-5p, and miR-21-3p were confirmed by real-time PCR, and these microRNAs were identified as potential serum-based biomarkers for the diagnosis of periodontitis [63]. A comprehensive meta-analysis examining miRNA expression in periodontitis and peri-implantitis identified miRNA-146a and miRNA 142-3p as significantly associated with periodontitis, indicating their potential role in the disease's pathogenesis [64]. Notably, miRNA-146a is one of the most extensively investigated microRNAs in periodontitis, further supporting its relevance in periodontal inflammation and immune regulation [65]. It has been reported to negatively regulate the innate immune response, with significantly higher levels found in chronic periodontitis patients. Additionally, miRNA-146a expression is inversely correlated with the expression of pro-inflammatory cytokines TNF- α and IL-6 [66] (Table 2).

Genome-wide DNA methylation studies in periodontitis

Given the substantial heterogeneity and limited replication of SNPs identified through GWAS in periodontitis, integrating epigenome-wide DNA methylation analyses may enhance the interpretation of genetic findings by elucidating regulatory mechanisms that mediate genetic susceptibility to periodontal disease [67]. A recent meta-analysis of GWAS identified two novel risk loci: one located within the MTND1P5 pseudogene on chromosome 8 and another near the SHISA9 gene on chromosome 16. These loci reached genome-wide significance, providing new genetic insights into disease susceptibility [68]. Methylation at several CpG sites, is partially under genetic control is consistent with previous GWAS of periodontitis, which have identified SNPs in or near genes such as WHAMM. These results suggest that inherited genetic variants are environmentally responsive epigenetic modifications that may interact to influence disease susceptibility [69]. However, replication of these findings across independent cohorts remains limited, reflecting challenges related to heterogeneity in sample size, phenotype definitions, and study populations [68]. To advance understanding and clinical utility, future research should emphasize large, multi-ethnic cohort with integrative multi-omics approaches to validate and expand these genetic and epigenetic associations [70] (Table 3).

Impact of epigenetic modifications on immune response and inflammation

Epigenetic modifications, including DNA methylation and histone modifications, are critical in modulating immune responses and inflammatory pathways by regulating gene expression in immune cells [71]. Epigenetic changes in innate immune genes may disrupt normal inflammatory responses [47].

Lipopolysaccharide (LPS), a major constituent of outer membrane vesicles derived from Gram-negative bacteria, is recognized as the most potent immune-activating component. Exposure to purified LPS is known to provoke a strong pro-inflammatory response and, at elevated levels, can lead to septic shock [72]. Specific periodontal pathogens and their components, such as lipopolysaccharides, have been implicated in inducing epigenetic alterations within periodontal tissue. In vitro studies show that oral bacteria induce cell type-specific epigenetic changes, with methylation alterations and their effects on gene regulation depending on the cell's function and its interaction with specific pathogens.

Elevated levels of DNA methylation within the promoter region of a gene are typically correlated with decreased gene expression, whereas promoter hypomethylation is generally linked to enhanced transcriptional activity [73]. Alterations in DNA methyltransferase activity have been observed in cells exposed to either whole bacterial lysates or isolated lipopolysaccharides [39]. Research indicates that *P. gingivalis* LPS induces hypermethylation of RUNX in periodontal cells, suggesting that targeting epigenetic changes could aid in periodontal disease treatment. Runt-related transcription factor 2 (RUNX2) is a crucial transcription factor linked to osteoblast differentiation, and the inhibition of osteoblastic differentiation is associated with a reduction in RUNX2 expression [74].

Significant suppression of nuclear DNA methyltransferase-3a (DNMT3A) mRNA expression was also observed in HaCaT cells following stimulation with *Porphyromonas gingivalis* lipopolysaccharide, indicating a similar regulatory response [75]. Kim et al. noted that selective modulation of the immune response alters the activity of DNA (cytosine-5)-methyltransferase 1 and histone deacetylases (HDACs), which are two critical regulators of DNA methylation and histone modification processes [76].

INTERPLAY BETWEEN GENETIC AND EPIGENETIC FACTORS

Gene-environment interactions and their role in periodontal susceptibility

Gene-environment interactions describe the combined influence of genetic predisposition and environmental exposures on the susceptibility to human diseases [77]. Numerous exogenous and endogenous risk factors engage in prolonged interaction with the host organism, often over several years, prior to the manifestation of chronic degenerative diseases. Tobacco use and chronic inflammation driven by particular bacterial pathogens are key contributors to the onset of periodontitis. A central pathogenic mechanism involves oxidative damage, supported by the identification of mitochondrial DNA lesions within the gingival tissue of individuals diagnosed with the disease [78]. Although microbial and environmental factors are recognized as key initiators and modulators of periodontal disease progression, individual susceptibility to these conditions varies significantly and is largely determined by the host's immune response to periodontal pathogens [79]. The biofilms implicated in gingivitis and periodontitis are localized, complex communities of multiple microbial species that exhibit strong resistance to both antimicrobial therapies and the host's immune system. More recently, it has been established that systemic risk factors within the host significantly influence individual variability in disease onset, progression rate, and severity insight made possible through advancements in epidemiological study of periodontal disease and risk factor analysis [80].

Influence of lifestyle factors on epigenomic modifications

According to Fraga et al., variations in epigenetic modifications observed between monozygotic twins were likely induced by environmental factors, such as tobacco exposure and nutritional differences [81]. Seddon et al. proposed that behavioral and nutritional factors, including vitamin D, betaine, and methionine, can induce epigenetic modifications, thereby impacting the progression of disease [82] Various nutritional factors, including folate, vitamin B12, and vitamin A, have been shown to influence epigenetic modifications. Folate, a water-soluble vitamin found in dark green leafy vegetables, strawberries, and asparagus, has been widely studied in the context of cancer due to its role as a methyl group donor in DNA methylation processes. Consequently, reduced folate intake is associated with decreased levels of DNA methylation [83]. The progression of attachment loss may be influenced by epigenetic mechanisms, as evidenced by Ohi et al., who reported elevated methylation levels in the

collagen type 1 α1 (COL1A1) gene - a key structural protein in the periodontal ligament- in older individuals compared to younger counterparts [84].

Multiple studies have indicated a link between oral microbiota and host genetic factors. Specific polymorphisms in the IL-6 gene observed in individuals with severe periodontitis have been consistently associated with the presence of *Aggregatibacter actinomycetemcomitans* and *Porphyromonas gingivalis* [85]. The data imply that a particular genotype could be linked to a unique subgingival bacterial profile, thereby affecting the host's vulnerability to periodontal disease. Additionally, epigenetic alterations may play a role in modulating periodontal pathogens, as disrupted DNA methylation has been observed to diminish the invasive potential of *Aggregatibacter actinomycetemcomitans* in oral epithelial cells, thereby attenuating its virulence [86].

A prominent environmental determinant tobacco exposure has been shown to significantly alter DNA methylation patterns [87]. Initially, cigarette smoke may alter this mechanism by causing DNA damage, subsequently triggering the recruitment of DNA methyltransferases (DNMTs) [88]. Differential hypermethylation and hypomethylation of genes in response to smoking have been associated with smoking-related disorders, particularly inflammatory diseases. A significant association was identified between the HIVEP3 (Schnurri-3) gene and smoking, likely mediated through DNA methylation, It is a recently characterized zinc finger protein that links osteoblast and osteoclast functions. It inhibits osteogenic differentiation, leading to bone destruction [89]. Smokers were shown to experience more advanced periodontitis, marked by increased loss of attachment and deeper periodontal pockets when compared to individuals who had never smoked or had quit smoking [90]. Olivera et al. identified distinct methylation patterns in the IL-8 gene promoter region in smokers with chronic periodontitis, in contrast to healthy non-smokers [91]. In another study, DNA methylation was examined in the promoter regions of TLR2 and TLR4 in gingival tissues from healthy individuals, smokers, and non-smokers with chronic periodontitis TLR4 promoters were largely unmethylated across all groups. In contrast, TLR2 showed a mixed methylation pattern, with a tendency toward methylation at CpG sites targeted by the Hhal enzyme [92]. Integrated transcriptomic and methylomic analysis of human gingival tissues from smokers and non-smokers demonstrated that genes involved in extracellular matrix (ECM) and extracellular structure organization exhibited reduced expression levels in smokers, which was associated with increased DNA methylation relative to non-smokers [93]. A

comprehensive assessment of miRNA expression in periodontal ligament (PDL) cells exposed to nicotine demonstrated selective modulation of the Toll-like receptor signaling pathway, nicotine addiction pathway, transforming growth factor-β (TGF-β) signaling, and the hypoxia-inducible factor-1 (HIF-1) pathway, in contrast to untreated PDL cells [94] (Figure 2).

Integrative multi-omics approaches to understanding periodontitis etiology

In recent years, extensive research has been conducted to identify molecular signatures of periodontitis originating from diverse periodontal tissues, aiming to elucidate disease initiation and progression and to elucidate disease initiation and progression and to enhance understanding of its complex pathophysiology. Various omics approaches have been employed to systematically analyze the pathological processes and development of periodontitis [95]. One analysis revealed that combining multiple omics approaches improves the differentiation of disease states and the evaluation of treatment responses, especially when metabolomic data is incorporated. Furthermore, multi-omics analysis of biofilm instability offers valuable insights into the ecological dynamics that drive the progression of periodontal disease [96]. Shotgun metagenomics approaches have been employed to investigate the microbial communities associated with periodontitis. These techniques offer a less biased characterization of microbial diversity, although they may be limited by lower sequencing depth. Importantly, metagenomics enables the functional profiling of microbial diversity by assessing their gene content in relation to disease status. Evidence from these studies suggests that deeper periodontal pockets, indicative of more severe disease, exhibit a higher prevalence of metabolic pathways and virulence factors, alongside a reduced representation of biosynthetic functions, when compared to shallower, clinically healthy patients [97–99]. Richter et al. conducted an epigenome-wide association study (EWAS) to identify biologically active methylation marks of the oral masticatory mucosa [100]. These investigations aim to elucidate the epigenetic mechanism underlying the pathogenesis of periodontitis.

Moreover, the expanding understanding of genetic and epigenetic mechanisms underlying periodontal disease has potential clinical relevance, particularly in regenerative therapies. Recent research suggests that tissue engineering approaches-such as the use of stem cells and biologically active matrices, may benefit from targeting these molecular pathways to enhance periodontal healing and implant integration [101].

CLINICAL AND THERAPEUTIC IMPLICATIONS

Potential biomarkers for early diagnosis and risk assessment

Traditional biomarkers, including proteins, metabolites, and matrix metalloproteinases (MMPs), have been employed in the diagnosis of periodontal disease. Furthermore, epigenetic biomarkers, which modulate gene expression and its regulatory mechanisms, play significant roles in the onset and progression of periodontal disease. For instance, chronic inflammation within the periodontium can disrupt DNA methylation patterns in genes encoding both proinflammatory (e.g., TNF-, IL-6) and anti-inflammatory (e.g., IL-4, IL-10) cytokines. The identification of these molecular and epigenetic biomarkers in oral biofluids holds promise for the early detection of periodontal disease during its initial stages of progression [102]. Cytokines and host-derived enzymes represent the most well-characterized emerging biomarkers, particularly in relation to immune system activity [103]. The composition of genetic variants underlying a specific trait, known as the genetic architecture, along with external factors such as lifestyle, influences the host's capacity to preserve the structural and immunological integrity of the gingival tissues. As a result, understanding the genetic predisposition to periodontitis offers the potential for the development of biomarkers to estimate individual genetic risk [104].

A recent review indicated that certain salivary microRNAs possess significant potential for diagnostic prognostic, and therapeutic applications [105]. MicroRNAs are emerging as promising biomarkers for periodontitis due to their regulatory role in inflammation. Studies have shown that specific salivary miRNAs, such as hsa-miR-381-3p and miR-143-3p, are altered in patients with periodontitis and correlate with disease severity [106,107]. Recent developments in microfluidic and biosensor technologies enable detection of these miRNAs in saliva, suggesting the feasibility of non-invasive diagnostic platforms that could be applied directly in clinical environments. Nonetheless, broader clinical application depends on further validation across diverse populations and the development of standardized protocols to ensure consistent and accurate detection [108]. Alongside salivary biomarkers, periodontitis significantly alters specific microRNAs in gingival crevicular fluid, highlighting their role as local biomarkers involved in key regulatory pathways. Due to their stability in oral fluids, these microRNAs hold promise as non-invasive tools for early diagnosis and monitoring of disease [109,110].

MMP-8 is an enzyme predominantly secreted by neutrophils, extensively studied as a biomarker [111,112]. MMP-8 and MPO demonstrated the highest discriminatory potential between gingival disease and healthy tissue. The diagnostic utility and role of active MMP-8 (aMMP-8) in the classification of periodontal disease and its application in point-of-care (POC) settings have been rigorously studied, significantly influencing the classification frameworks for periodontitis and peri-implantitis [113]. Studies have shown an association between protease and collagenase concentrations in gingival cervical fluid (GCF) and alterations in periodontal pocket depth characteristic of periodontal disease. Barros et al. emphasized that GCF functions as a reservoir for numerous biomarkers capable of indicating disease presence, with the potential to differentiate between active and inactive periodontal sites [47]. CD163 exhibited diagnostic potential for periodontal disease, with its expression levels significantly elevated in diseased tissue compared to healthy tissue, identifying CD163 as a promising biomarker for periodontitis [114]. Another multi-omics integrative analysis identified a gene-metabolite-pathway network implicating PDGFD, NRTN, and IL2RG as potential periodontitis biomarkers that may modulate disease progression through deoxyinosine and the ABC transporter pathway [115] (Figure 3).

Epigenetic therapy and personalized medicine approaches

Emerging paradigms such as precision medicine and personalized medicine offer enhanced predictive capabilities by enabling detailed patient stratification and individualized therapeutic strategies. Implementation of these approaches necessitated the development of advanced diagnostic frameworks that integrate conventional clinical assessments with comprehensive data on patient-specific factors, including biomarkers, genetic profiles, environmental influences, and lifestyle characteristics [116]. By integrating environmental and lifestyle factors, and utilizing artificial intelligence (AI), precision medicine enables the identification of individual risk profiles and characteristics, facilitating the development of targeted prevention and treatment strategies [117]. Recently studies have increasingly underscored the necessity for active involvement of researchers and oral health professionals in the integration of salivary diagnostic approaches. These methodologies demonstrate significant potential for early detection of oral pathologies, enable more precise patient risk stratification, and support efforts to mitigate the global burden of oral diseases, particularly within the paradigm of personalized medicine for conditions such as malocclusion, dental transposition, and periodontitis [118]. Bartold et al. introduced a clinical model for

periodontitis management known as P4 Periodontics, which applies the principles of P4 medicine-prediction, prevention, personalization, and participation the foundational elements of patient-centered care [119]. The purpose of the revised classification system is to introduce a multidimensional diagnostic approach that accounts for individual risk factors, in contrast to the traditional method focused solely on periodontal tissue destruction [120]. This framework is designed to optimize patient care and facilitate the advancement of precision and personalized medicine [116]. Individuals exhibiting epigenetic modifications are related pathologies and often show limited responsiveness to standard therapeutic approaches. Consequently, personalized medicine strategies, including the use of targeted pharmacological agents tailored to the patient's unique genomic profile, may offer more effective management of these conditions [121].

Challenges and future perspectives in translating research into clinical practice

Examining alterations in DNA methylation offers valuable insights into the pathogenic mechanisms of periodontitis, potentially explaining why individuals with the same clinical subtype exhibit differing rates of disease progression and variable responses to standardized treatments. Future research should incorporate the analysis and reporting of lifestyle and environmental factors that may influence the emergence of epigenetic modifications at both cellular and tissue levels. Such studies may also facilitate the identification of consistent epigenetic markers indicative of individual susceptibility to disease progression, thereby advancing the development of precise and personalized therapeutic strategies for periodontitis.

Although current evidence suggests a role for epigenetic modifications in regulating gene expression, further research is essential to elucidate their specific impact on periodontal tissue degradation and their potential influence on the progression and severity of systemic conditions. A deeper understanding of these mechanisms will help clarify the broader implications of epigenetic regulation in oral and systemic health.

CONCLUSION

The insights from genome-wide studies on DNA methylation and genetic polymorphisms have deepened our understanding of how host genetic and epigenetic landscapes modulate immune and inflammatory responses, contributing to periodontal tissue breakdown. These molecular alterations not only influence disease susceptibility and progression but also hold promise as

biomarkers for improved diagnosis and as targets for personalized therapeutic interventions. Advancing research through integrative multi-omics approaches will be crucial for unraveling the multifaced mechanisms underlying periodontitis and for translating these insights into precision diagnostic tools and targeted treatment strategies to individual risk profiles. The combined analysis of genetic and epigenetic factors reveals the multifactorial nature of periodontitis, emphasizing the importance of comprehensive approaches to disease characterization and management. Future research should focus on translating these molecular insights into practical clinical applications, enabling improved diagnostics to enhance patient outcomes.

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TABLES AND FIGURES

Table 1. DNA methylation changes and their implications in periodontitis

Study	Mechanism	Finding
Barros S et al. 2014 [47]	DNA methylation	methylation alterations in chemokine and cytokine genes in epithelial cells from periodontitis sites
Amormino et al. 2013 [45]	DNA methylation	TLR2 promoter hypermethylation associated with increased periodontal pocket depth
Yin L et al. 2011 [49]	DNA methylation	gingival epithelial cells showed hypermethylation of IL12A, TLR2, GATA3, and hypomethylation of ZNF287 and STAT5A
Almiñana-Pastor et al. 2019 [10]		

Stefani et al. 2013 [8] Schulz et al. 2016 [48]	DNA methylation	IL-6, IL-8, IL-10, INF-γ, and IL-17 potentially linked to host immune responses to periodontal pathogens

Table 2. Histone methylation and non-coding RNA changes and their implications in periodontitis

Modification Type	Gene/Region	Modification	Associated Finding
Histone Methylation	H3 (H3K4, H3K36 H3K79	Mono-, Di-, Trimethylation	Transcriptional activation in periodontal tissues
Histone Methylation	H3 (H3K9, H3K27), H4 (H4K20)	Mono-, Di-, Trimethylation	Transcriptional repression in periodontal tissues
Histone Acetylation	H3, H4	Acetylation	LPS-induced acetylation in B cells; HDAC inhibitors protect against bone resorption
Non-coding RNA (miRNA)	miR-664a-3p, miR-501-5p, miR-21-3p	Differential Expression	Potential serum biomarkers for periodontitis
Non-coding RNA	miRNA-146a	Increased expression	Regulates immune response in periodontitis;

(miRNA)			inversely correlated with TNF- α, IL-6
Non-coding RNA (lncRNA)	Various lncRNAs	Differential expression	Involved in immune response and tissue repair in periodontitis

Table 3. Genome-wide DNA methylation studies related to periodontitis

Locus/Gene.	Type	Finding
MTND1P5	GWAS Locus (chr8)	Identified as a novel risk locus for aggressive and chronic periodontitis.
SHISA9	GWAS Locus (chr16)	Newly linked to periodontitis at genome-wide significance.
WHAMM	GWAS-associated gene	SNPs near this gene associated with periodontitis.
ZNF804A	GWAS-Linked CpG site	Methylation at this site is partially genetically controlled.

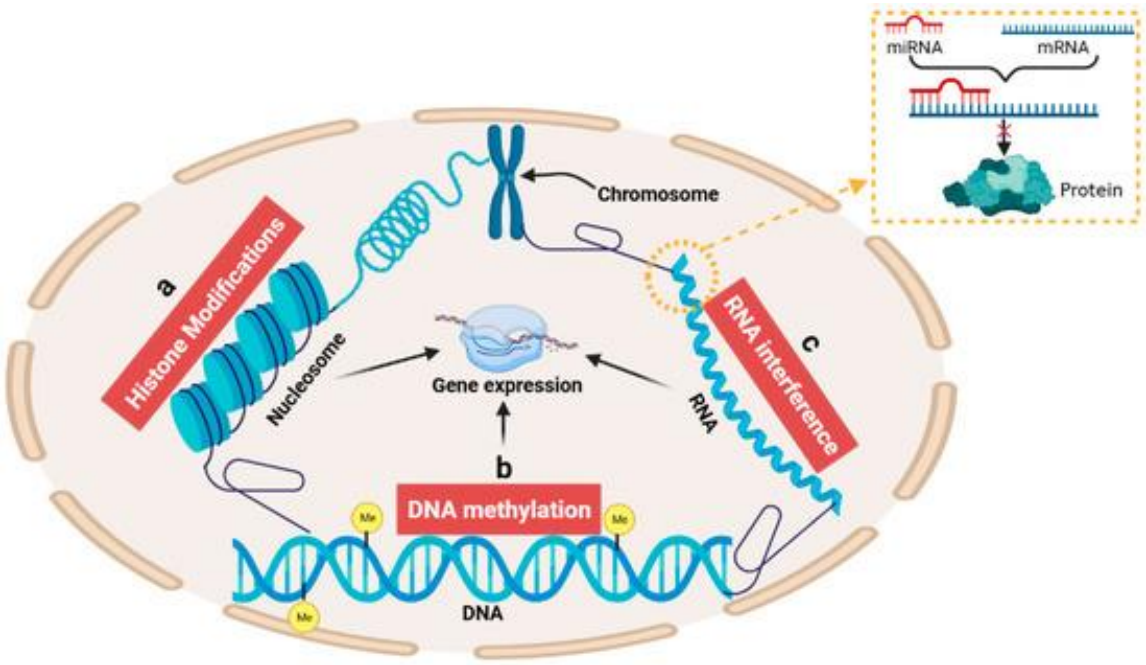

Figure 1. Schematic representation of the epigenetic mechanisms. (a) Histone modifications; (b) DNA methylation; and (c) Non-coding RNAs. Adapted from [122], with permission under the terms of the Creative Commons Attribution (CC BY) license©.

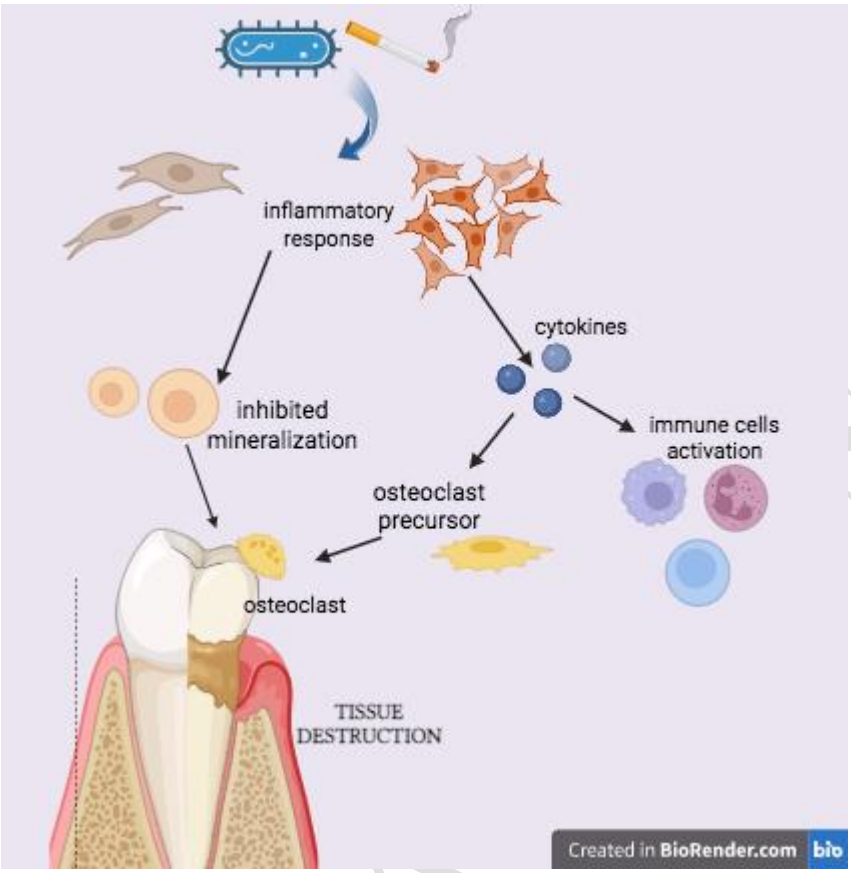

Figure 2. Impact of lifestyle factors on epigenetic modifications. Created with biorender.com

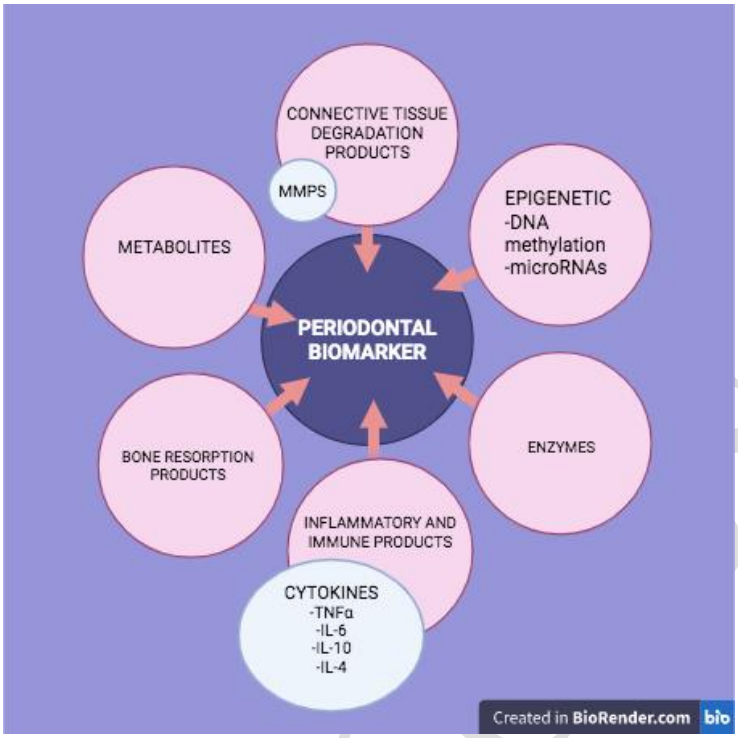

Figure 3. Biomarkers in periodontal disease. Created with BioRender.com