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Exploring the role of epigenetics in periodontal disease progression: A narrative review

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Abstract

Periodontal disease remains a significant global health concern, characterized by chronic inflammation and destruction of the tooth-supporting structures. While microbial dysbiosis is a well-established factor in its pathogenesis, emerging evidence suggests that epigenetic modifications play a crucial role in the initiation and progression of periodontal disease. This narrative review aims to synthesize current knowledge on the intricate interplay between epigenetics and periodontal disease progression.

Epigenetic mechanisms, including DNA methylation, histone modifications, and non-coding RNAs, regulate gene expression patterns without altering the underlying DNA sequence. Dysregulation of these mechanisms can disrupt inflammatory and immune responses, exacerbating periodontal tissue damage. Various studies have highlighted specific epigenetic alterations associated with periodontal disease, such as aberrant DNA methylation patterns in promoter regions of key inflammatory genes and dysregulated microRNA expression profiles implicated in tissue remodeling processes.

Moreover, environmental factors, such as smoking, diet, and stress, can modulate epigenetic signatures, further influencing periodontal disease susceptibility and severity. Understanding the epigenetic landscape of periodontal disease offers new avenues for therapeutic interventions and personalized treatment strategies. Targeting epigenetic regulators may provide innovative approaches to mitigate inflammation, promote tissue regeneration, and ultimately improve clinical outcomes in patients with periodontal disease.

In conclusion, epigenetics plays a significant role in periodontal disease progression by regulating inflammatory and tissue remodeling pathways. Future research should continue to elucidate the complex epigenetic mechanisms underlying periodontal disease pathogenesis, paving the way for novel therapeutic interventions and personalized management strategies.

Keywords: Epigenetics; Periodontal Disease Progression; Tissue Remodeling Pathways; Global Health Concern

1. Introduction

Epigenetics, the study of heritable changes in gene expression without alterations in the DNA sequence, has emerged as a promising avenue for elucidating the complex interplay between genetic predisposition and environmental factors in periodontal disease [1]. Epigenetic modifications, including DNA methylation, histone modifications, and non-coding

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RNA-mediated gene regulation, exert fine-tuned control over inflammatory and immune responses, as well as tissue remodeling processes, which are integral to periodontal health and disease.

Recent studies have underscored the significance of epigenetic alterations in periodontal disease pathogenesis. For instance, aberrant DNA methylation patterns in promoter regions of pro-inflammatory cytokines and matrix metalloproteinases have been implicated in dysregulated host responses and tissue destruction characteristic of periodontitis [2, 3]. Furthermore, dysregulated expression of microRNAs, small non-coding RNAs that post-transcriptionally regulate gene expression, has been linked to altered immune cell functions and impaired tissue repair in periodontal disease [4, 5].

Importantly, environmental factors such as smoking, diet, and stress can influence epigenetic modifications associated with periodontal disease susceptibility and severity [6]. Understanding the dynamic interplay between genetic predisposition, environmental exposures, and epigenetic regulation holds promise for identifying novel therapeutic targets and personalized treatment approaches in periodontal medicine."

1.1. Epigenetic Mechanisms in Periodontal Disease

Periodontal disease, encompassing gingivitis and periodontitis, is characterized by chronic inflammation and destruction of the periodontium. While microbial dysbiosis is a well-established factor in its pathogenesis, emerging evidence implicates epigenetic mechanisms in modulating disease progression. Epigenetics refers to heritable changes in gene expression that occur without alterations in the DNA sequence, and it plays a pivotal role in regulating inflammatory responses, immune cell functions, and tissue remodeling processes in periodontal tissues. Here, we delve into the key epigenetic mechanisms involved in periodontal disease and their implications for disease pathogenesis and clinical management.[5,6]

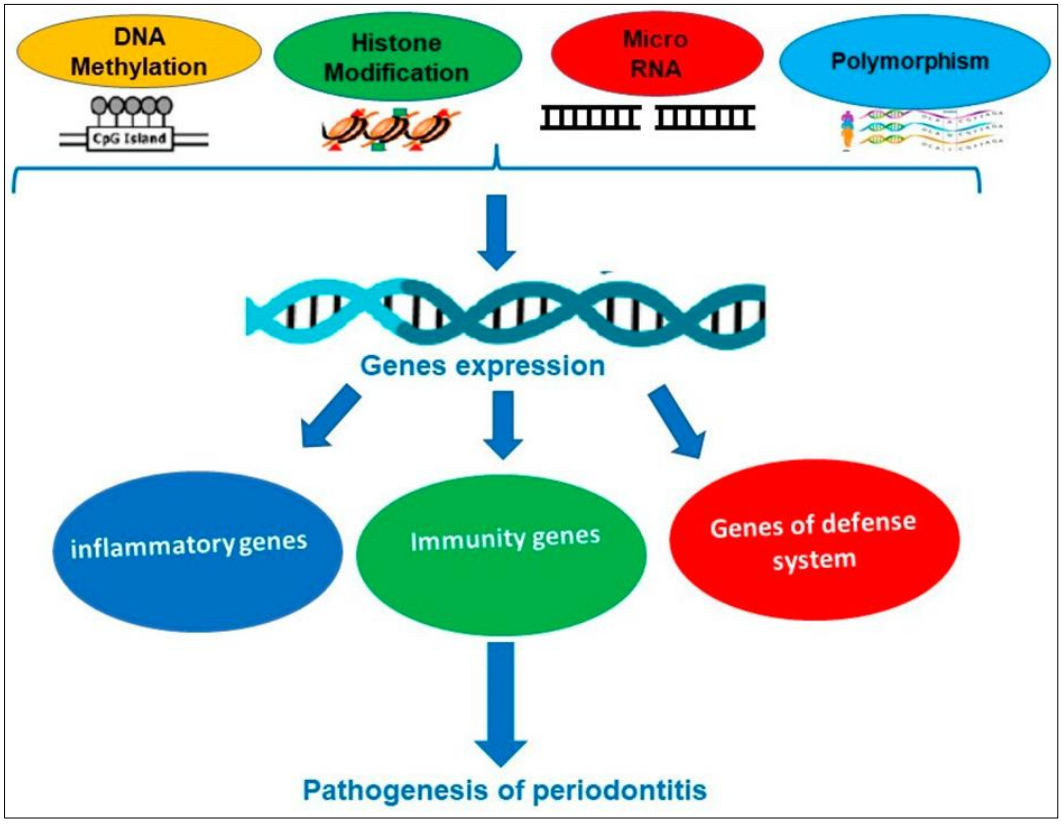

Figure 1 Epigenetic mechanisms involved in periodontal diseases[5]

With advancements in genetic analysis and epidemiology, the significance of epigenetic modifications in the development and progression of periodontal disease (PD) has gained prominence. These modifications, including polymorphisms, gene expression, and microRNA regulation, play crucial roles in both diagnostic tests and responses to

treatment proposals . An inquiry by Chatzopoulos et al.,[7] as highlighted in recent publications, delved into the impact of gene polymorphisms on the effectiveness of PD treatment, whether surgical or nonsurgical.

Their 2017 study concluded that specific gene variants, namely IL-6 −572 G/C and IL-10 −592 C/A, either individually or in combination, did not influence the outcomes of nonsurgical therapy among chronically ill Caucasian individuals. Subsequent validation was provided by a 3-year study[8]. Notably, data regarding the influence of gene polymorphisms on surgical treatment remain scarce. Traditional treatment methods targeting bacteria or pathogens have limitations in predicting disease recurrence or antibiotic resistance. Consequently, there's a growing need for novel treatment approaches, particularly those addressing chronic inflammation of the periodontium, rooted in the host's innate immune response mechanisms. Lavu et al. underscored that unraveling how histones are modified, DNA is methylated, and microRNAs are regulated could enhance understanding of the molecular basis of chronic inflammatory conditions. To confirm the influence of the epigenome, comprehensive analyses have been published on this topic.[9,10,11]

DNA Methylation: DNA methylation, the addition of methyl groups to cytosine residues predominantly in CpG dinucleotides, is a crucial epigenetic modification involved in regulating gene expression. Aberrant DNA methylation patterns have been observed in periodontal disease, particularly in the promoter regions of genes encoding pro-inflammatory cytokines, chemokines, and matrix metalloproteinases (MMPs). Hypermethylation of these gene promoters leads to transcriptional silencing, impairing host defense mechanisms and exacerbating tissue destruction in periodontitis.[12,13] Conversely, hypomethylation of certain genes may enhance their expression, contributing to dysregulated immune responses and tissue damage. Studies have identified differential DNA methylation profiles in periodontal tissues from patients with periodontitis compared to healthy controls, highlighting the potential diagnostic and prognostic utility of DNA methylation biomarkers in periodontal disease.[14] Figure 2

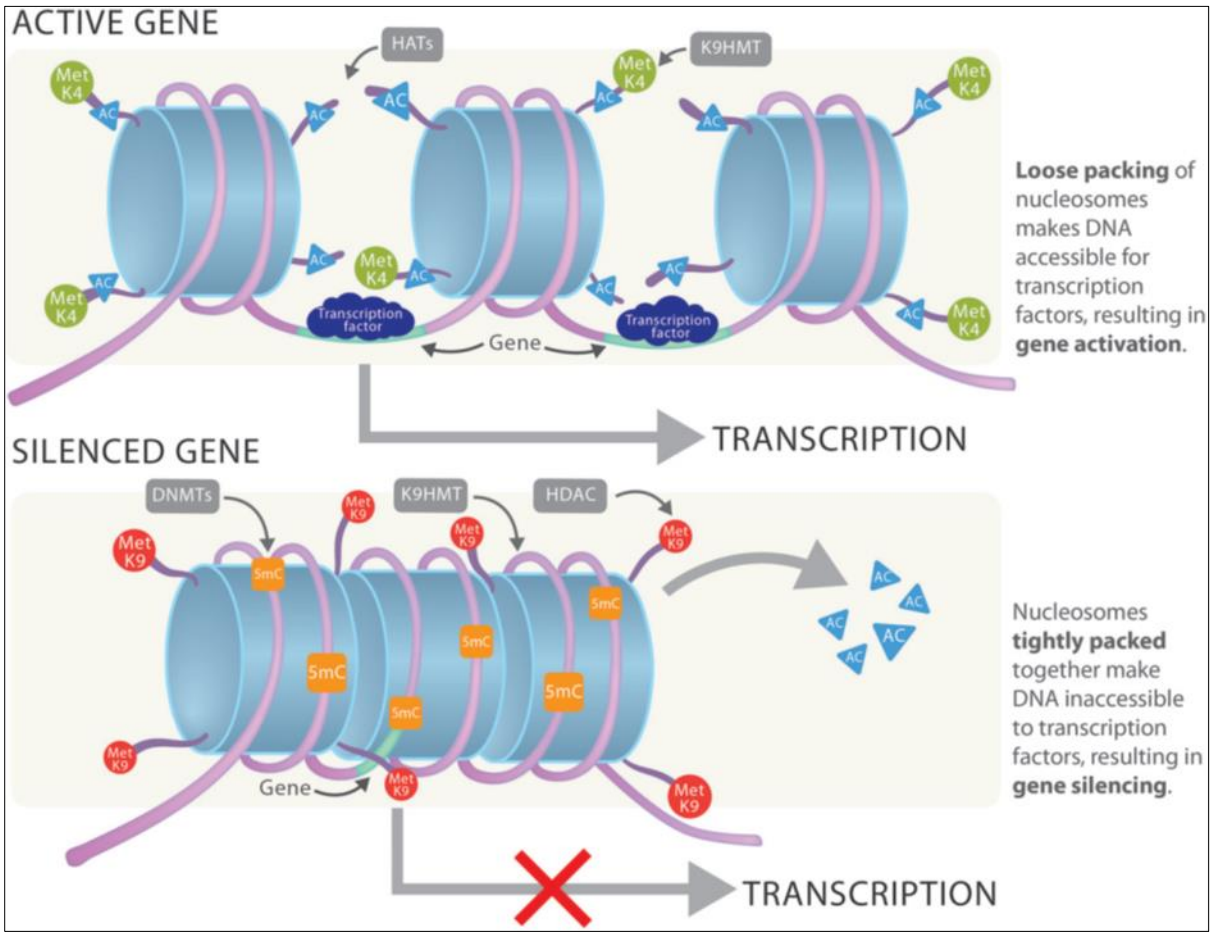

Figure 2 Schematic illustration of the influence of histone acetylation on gene transcription. Met = methylated; DNMTs = DNA methyltransferases; 5mC = 5-methylcytosine, K9HMT = Lysine 9 histone methyltransferase; AC = acetylation.[14]

Several studies have investigated the DNA methylation of inflammatory cytokines in chronic periodontitis (CP) and aggressive periodontitis (AgP).[8-14]Analysis of the interleukin (IL)-8 promoter indicates a tissue-specific pattern in DNA methylation. In epithelial cells, the methylation frequency of IL-8 was higher in controls than in patients with periodontitis. No difference was seen in gingival cells or blood leukocytes.[14]These findings are in line with data that found that the IL-8 promoter was hypomethylated in oral epithelial cells from individuals with generalized AgP compared with healthy controls. The IL-6 promoter was found to be partially methylated in both healthy individuals and patients with periodontitis,even though the level of expression of IL-6 was higher in patients with periodontitis.

Histone Modifications: Histone proteins undergo various post-translational modifications, including acetylation, methylation, phosphorylation, and ubiquitination, which influence chromatin structure and gene expression. Dysregulated histone modifications have been implicated in periodontal disease pathogenesis, affecting inflammatory gene expression, osteoclastogenesis, and extracellular matrix remodeling. For instance, histone acetylation mediated by histone acetyltransferases (HATs) and histone deacetylases (HDACs) regulates the transcriptional activity of pro-inflammatory genes in response to microbial challenge in periodontal tissues. Moreover, histone methylation marks, such as H3K4me3 and H3K27me3, modulate the accessibility of gene promoters, thereby influencing the expression of genes involved in immune responses and tissue repair processes. Understanding the dynamic interplay between histone modifications and gene expression in periodontal disease may reveal novel therapeutic targets for inflammation resolution and tissue regeneration.

Non-coding RNAs: Non-coding RNAs, including microRNAs (miRNAs) and long non-coding RNAs (lncRNAs), play critical roles in post-transcriptional gene regulation and epigenetic modulation in periodontal tissues. Dysregulated expression of miRNAs has been associated with altered immune cell functions, impaired wound healing, and alveolar bone loss in periodontitis.[10,12] For example, miR-146a-5p has been shown to attenuate IL-1β-induced inflammatory cascades in periodontal ligament cells by targeting IRAK1 expression, suggesting therapeutic potential for miRNA-based interventions in periodontal disease management. Additionally, lncRNAs have been implicated in regulating osteogenic differentiation, inflammatory responses, and extracellular matrix remodeling in periodontal tissues, thereby influencing disease progression and tissue repair mechanisms.[,13,14]

1.2. Influence of Periodontal Pathogens on Chromatin Modifications

Periodontal pathogens have been implicated in inducing chromatin modifications, thereby contributing to the pathogenesis of periodontal disease (PD). These microorganisms, such as Porphyromonas gingivalis, Treponema denticola, and Tannerella forsythia, can directly interact with host cells and alter chromatin structure through various mechanisms. For instance, studies have shown that these pathogens can induce histone modifications and DNA methylation patterns in host cells, leading to altered gene expression profiles associated with inflammatory responses and tissue destruction in the periodontium [15]. Additionally, the dysregulation of microRNAs mediated by periodontal pathogens has also been linked to chromatin modifications and the progression of PD [16].

Furthermore, the interplay between periodontal pathogens and chromatin modifications highlights the intricate relationship between microbial virulence factors and host epigenetic responses. For example, bacterial virulence factors such as lipopolysaccharides (LPS) and outer membrane vesicles (OMVs) can activate host signaling pathways that ultimately lead to chromatin remodeling and altered gene expression profiles favoring the persistence of inflammation and tissue destruction in the periodontium [17]. Understanding these mechanisms is essential for developing targeted therapeutic interventions aimed at disrupting the crosstalk between periodontal pathogens and host chromatin modifications to mitigate the progression of PD.These microbial interactions with host chromatin contribute to the dysregulation of inflammatory and immune responses, ultimately leading to periodontal tissue destruction. Further research into the molecular mechanisms underlying these interactions is crucial for identifying novel therapeutic targets for the management of PD.

1.3. Environmental Influences on Epigenetics in Periodontal Disease:

Environmental factors play a significant role in shaping epigenetic modifications associated with periodontal disease susceptibility and progression. Among these factors, tobacco smoke exposure stands out as a well-established risk factor for periodontitis. Cigarette smoke contains a myriad of toxic compounds that can induce epigenetic alterations in periodontal tissues, including DNA methylation changes and histone modifications. Studies have demonstrated differential DNA methylation patterns in periodontal tissues of smokers compared to non-smokers, particularly in genes associated with inflammation and immune responses.[15] For instance, hypermethylation of the IL-6 promoter region has been observed in smokers with periodontitis, leading to reduced IL-6 expression and impaired host defense mechanisms. Additionally, cigarette smoke exposure can modulate histone acetylation and methylation patterns,

thereby influencing the expression of genes involved in oxidative stress, inflammation, and tissue remodeling in the periodontium.[16]

In addition to smoking, dietary habits have emerged as important environmental determinants of epigenetic regulation in periodontal disease. High-sugar diets, for example, have been linked to epigenetic modifications associated with inflammatory gene expression and tissue destruction in periodontitis. Excessive sugar consumption can induce DNA hypermethylation and histone modifications in periodontal tissues, exacerbating inflammatory responses and compromising periodontal health. Conversely, dietary components with anti-inflammatory and antioxidant properties, such as omega-3 fatty acids and polyphenols, may exert protective effects by modulating epigenetic regulators involved in periodontal inflammation and tissue repair.[17]

Psychosocial stress represents another environmental factor that can impact epigenetic mechanisms in periodontal disease. Chronic stressors, such as socioeconomic adversity, work-related stress, and psychosocial trauma, have been associated with altered DNA methylation patterns and dysregulated immune responses in periodontal tissues. Stress-induced epigenetic modifications may contribute to heightened inflammatory signaling, impaired wound healing, and increased susceptibility to periodontal disease progression. Moreover, stress-related behaviors, such as poor oral hygiene and maladaptive coping strategies, can further exacerbate periodontal inflammation and tissue damage, highlighting the complex interplay between environmental stressors and epigenetic regulation in periodontal health.[18]

Understanding the influence of environmental factors on epigenetic mechanisms in periodontal disease is essential for developing targeted interventions and personalized treatment approaches. By elucidating the epigenetic consequences of tobacco smoke exposure, dietary habits, and psychosocial stress, researchers can identify novel therapeutic targets and preventive strategies aimed at mitigating periodontal disease burden and improving oral health outcomes. Moreover, integrating environmental epigenetics into clinical practice may facilitate risk assessment, disease management, and patient education in periodontology.[19]

1.4. Clinical Strategy Targeting Epigenetic Modifications

A focused investigation has explored the potential of HDAC or DNA methylation inhibitors as a clinical strategy for treating periodontitis or oral inflammation. [20]While research in this area remains confined, there are promising reports on the efficacy of epigenetic inhibitors, particularly in cancer research.[21] In a specific experiment targeting periodontitis, treatment with the HDAC inhibitor (1179.4b), which acts on Class I and II HDACs, demonstrated reduced alveolar bone loss in mice with P. gingivalis-induced periodontitis compared to untreated mice [22,23]. Additionally, Imai et al. reported that P. gingivalis produces butyric acid, which inhibits HDACs and increases histone acetylation. This mechanism was observed to reactivate Epstein-Barr Virus (EBV) and human immunodeficiency virus 1, suggesting a potential link between periodontal disease and EBV-related conditions [24].

Another avenue of interest lies in the Bromodomain and Extraterminal Domain (BET) proteins, which serve as epigenetic regulatory factors. These proteins scan acetylated histone tails and modulate transcription complexes to regulate gene expression. A recent study by Meng et al. (2014) demonstrated that the BET inhibitor JQ1 effectively suppressed both inflammatory responses and alveolar bone loss in experimental periodontitis [25].

1.5. Future Concepts Within the Field of Epigenetics

The future of epigenetics in the field of periodontics holds significant promise, with emerging evidence pointing towards a deeper understanding of the role of epigenetic modifications in periodontal disease (PD) pathogenesis and progression. Advanced technologies such as high-throughput sequencing, chromatin immunoprecipitation sequencing (ChIP-seq), and single-cell epigenomics have enabled researchers to explore the intricate epigenetic landscape of periodontal tissues with unprecedented resolution.

One key area of interest is the investigation of how specific epigenetic modifications, such as DNA methylation and histone modifications, regulate gene expression in periodontal cells and tissues. For instance, studies have demonstrated aberrant DNA methylation patterns in genes associated with immune responses, inflammation, and tissue remodeling in patients with periodontitis compared to healthy controls [26]. Similarly, dysregulated histone modifications, such as histone acetylation and methylation, have been implicated in the pathogenesis of periodontal disease, influencing the expression of genes involved in periodontal tissue homeostasis and inflammation[27].

Furthermore, the emerging concept of epigenetic reprogramming suggests that environmental factors, such as microbial dysbiosis and host immune responses, can induce persistent epigenetic changes that contribute to the chronicity of periodontal disease. For example, periodontal pathogens like Porphyromonas gingivalis have been shown to produce butyric acid, which inhibits histone deacetylases (HDACs) and promotes histone acetylation, leading to dysregulated gene expression and exacerbation of periodontal inflammation [28]. This interaction between microbial virulence factors and host epigenetic machinery highlights the dynamic nature of the host-microbe interface in shaping the epigenetic landscape of periodontal tissues.

In terms of therapeutic implications, targeting epigenetic modifications has emerged as a promising strategy for the management of periodontal disease. Preclinical studies have demonstrated the efficacy of epigenetic inhibitors, such as histone deacetylase inhibitors (HDACis) and bromodomain and extraterminal domain (BET) protein inhibitors, in mitigating periodontal inflammation and alveolar bone loss in experimental models of periodontitis [29]. These findings underscore the potential of epigenetic-targeted therapies as adjunctive treatments for periodontal disease, particularly in cases refractory to conventional periodontal therapies.[30]

2. Conclusion

The future of periodontics lies at the intersection of epigenetics and personalized medicine, where a deeper understanding of epigenetic mechanisms informs the development of innovative therapeutic strategies tailored to individual patient needs. As research in this field continues to advance, we anticipate transformative discoveries that will revolutionize the prevention, diagnosis, and treatment of periodontal disease, ultimately leading to better oral health outcomes for populations worldwide.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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