

Epigenetic Landscape of Periodontal Diseases

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Abstract

Epigenetic changes are heritable changes that do not depend on changes in DNA sequence. Epigenetic mechanisms are essential for regulation of transcription and provide a dynamic, reversible, and mechanistic framework that could explain the way in which environmental and behavioural factors interact with the genome to alter disease risk. Epigenetic factors play an important role in chronic inflammatory conditions by allowing microbial persistence to play a role in the infectious mechanism, resulting in pathogen interference with the host genome. Thus, periodontal pathogens containing lipopoly-saccharides can be a cause of epigenetic modifications affecting expression of inflammatory mediators in periodontal tissue, and low-grade chronic inflammation present in periodontal disease has been shown to promote DNA methylation. Periodontal disease is closely linked with diabetes mellitus complications, which are related to epigenetic changes.

Key words: Epigenetic changes, DNA methylation, Histone modification, Non-coding RNA, Periodontal disease.

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. Epigenetic modifications, including DNA methylation, histone modifications, and non-coding NA-mediated gene regulation, exert fine-tuned control over inflammatory and immune responses, as well as tissue remodelling processes, which are integral to periodontal health and disease.

These changes are influenced by:

- Environmental factors
- Lifestyle choices
- Systemic conditions

SUSCEPTIBILITY AND SEVERITY

Periodontal disease susceptibility is influenced by a combination of genetic, environmental and lifestyle factors. Genetic predisposition and systemic conditions like diabetes significantly increase risk. Other factors such as smoking, age and stress also play a role in whether someone develop the disease and its severity.

Epigenetics play a significant role in the severity of periodontal diseases by influencing gene expression and cellular responses to inflammation and infection. Epigenetic modifications can alter the activity of genes involved in inflammatory pathways and tissue remodelling processes which affect the severity of periodontal disease.

EPIGENETIC MECHANISM IN PERIODONTAL DISEASES

Epigenetic mechanisms includes the following

1. DNA methylation
2. Histone modification
3. Non-coding RNA (ncRNAs)

These mechanisms can be influenced by both genetic and environmental factors and may contribute to inflammatory and immune responses that characterize periodontal disease.

DNA Methylation

This involves the addition of methyl group to a DNA base, typically cytosine, which can affect gene expression, by influencing whether a gene is turned 'on' or 'off'. DNA methylation is a process where a methyl group is chemically attached to the DNA strand. This action frequently results in silencing the gene's activity and

making the chromatin structure denser (condensing it). In diseases like periodontitis, unusual methylation patterns have been observed in genes that play a major role in inflammation.

Histone modification

Modification like acetylation and methylation of histones can alter chromatin structure, affecting gene accessibility and expression. Histone modifications are chemical changes made to the histone proteins. These changes can alter the packing density of the DNA (the chromatin structure). For instance, processes like acetylation (adding an acetyl group) and deacetylation (removing an acetyl group) can either boost or hinder the activity of certain genes, particularly those that play a role in inflammation.

Non-coding RNA(ncRNAs)

Dysregulation of ncRNAs (microRNAs and long ncRNAs) has been implicated in various aspects of periodontal disease, including tissue remodelling and immune responses. Non-coding RNAs (ncRNAs), such as microRNAs (miRNAs) and long non-coding RNAs (lncRNAs), are molecules that control how genes are expressed after the initial genetic blueprint (DNA) has been copied into an RNA message (at the post-transcriptional level). For example, abnormal levels of certain miRNAs, like miRNA-146a, are known to be involved in the inflammatory processes seen in periodontal disease.

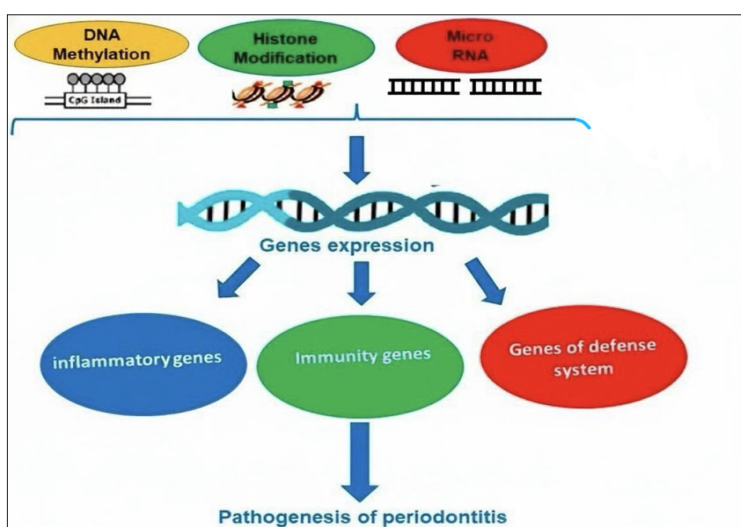


Figure 1. Epigenetic mechanism in periodontal diseases.

INFLUENCE OF EPIGENETICS ON PERIODONTAL PATHOGENS AND INFLAMMATION

Periodontal pathogens significantly impact inflammation, contributing to both local and systemic effects. These bacteria (*P.gingivalis*, *T.denticola*, *F.nucleatum*) trigger immune response that, if chronic can lead to tissue damage and bone loss.

LOCAL VS SYSTEMIC EFFECTS

Local effect

- Poor oral hygiene allows bacteria to accumulate on teeth, triggering initial inflammatory response

(INITIATION)



- This inflammation can lead to destruction of gum tissue, formation of pockets between teeth & gums and eventually bone loss

(PROGRESSION)



- The body releases inflammatory mediators like cytokines and prostaglandins

Systemic effect

Inflammatory mediators and bacteria can enter the blood stream, potentially affecting other organs and contributing to systemic diseases such as

1. Cardiovascular Diseases
2. Diabetes
3. Pneumonia
4. Rheumatoid Arthritis
5. Dementia

ENVIRONMENTAL INFLUENCES ON EPIGENETICS IN PERIODONTAL DISEASES

Environmental factors play a significant role in shaping the epigenetic outline and influencing the development

and progression of periodontal disease. They affect the epigenetic mechanisms of periodontal disease by inducing alterations in gene expression without changing the underlying DNA sequence. These environmental exposures can trigger epigenetic modifications, such as DNA methylation and histone modification, which alter the structure of chromatin. This leads to the activation or silencing of genes involved in inflammation and tissue destruction, ultimately influencing host susceptibility, disease progression, and the body's response to periodontal challenges. Three of the environmental factors include:

1. Smoking
2. Diet
3. Stress

Among these factors, smoking stands out as a well-established risk factor for periodontitis. Cigarette smoke contains large number of toxic compounds that can induce epigenetic alterations in periodontal tissues including DNA methylation and histone modification.

Excessive sugar consumption can induce DNA hypermethylation and histone modification in periodontal tissues which worsen inflammatory responses and compromise periodontal health.

Stresses such as socio-economic adversity, work related

stress and psycho-social trauma have been associated with altered DNA methylation patterns and dysregulated immune response in periodontal tissues.

CLINICAL STRATEGY TARGETING EPIGENETIC MODIFICATION

A clinical strategy targeting epigenetic modifications in periodontal disease focuses on modulating gene expression without altering the DNA sequence to manage and potentially treat the condition. The clinical strategies are:

1. DNMT (DNA methyl transferase)

They reverse methylation of DNA, potentially activating genes that promote tissue repair and reduce inflammation.

2. HDAC (Histone deacetylase)

They affect histone acetylation, influencing the accessibility of DNA to transcription factors and impacting gene expression related to inflammation and bone loss.

3. BET (Bromodomain and extra terminal domain)

They target BET proteins which are involved in converting transcription complexes and helps in reducing inflammation and bone loss.

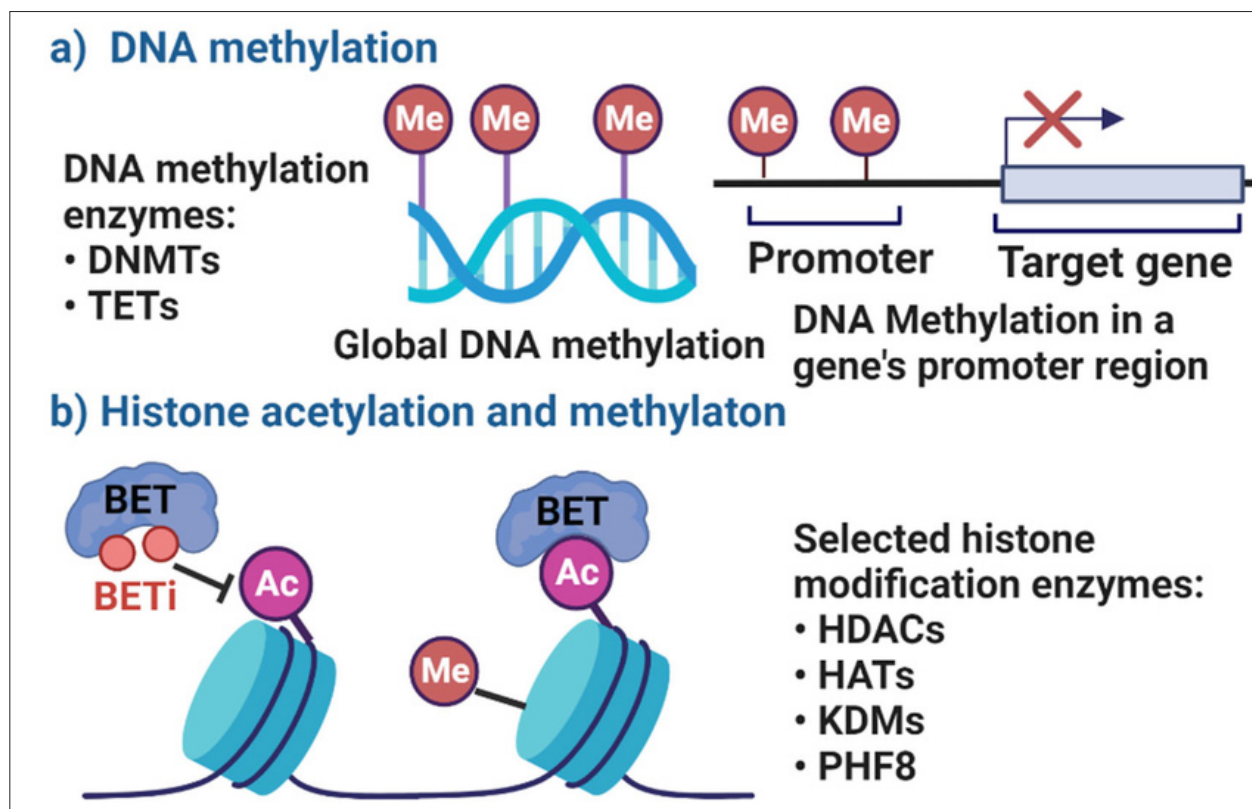


Figure 2. Clinical strategy targeting epigenetic modification

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 epigenetics modification in periodontal disease pathogenesis and progression. Advanced technologies such as high-throughput sequencing, chromatin immune precipitation sequencing and single cell epigenomics are some of the newer concepts.

Future concepts in epigenetics include advanced epigenome editing with CRISPR, enhanced single-cell epigenomics, and the use of multi-omics to integrate genetic and epigenetic data. Future applications are expected in personalized medicine for cancer and chronic disease, regenerative medicine, and agricultural biotechnology.

Epigenetics is also integrated with other technologies such as genomics and bioinformatics and Artificial Intelligence (AI) and machine learning. Understanding how microbial communities in the mouth influence epigenetic changes in periodontal tissues is crucial for developing targeted therapies.

Some of the methods are briefed below:

- Precision epigenome editing: Advanced technologies are improving the ability to precisely and efficiently modify specific epigenetic marks at targeted genomic

locations. This is expected to minimize off-target effects and increase treatment efficacy.

- Single-cell epigenomics: Researchers are developing sophisticated single-cell assays to analyze DNA methylation, histone modifications, and chromatin structure. These methods are crucial for understanding cell-to-cell differences within tissues and tumors, and for mapping epigenetic changes during development.
- Multi-omics integration: The future of epigenetic studies involves combining epigenetic, genomic, and transcriptomic data from the same single cell. This comprehensive approach, known as multi-omics, will provide a deeper understanding of how epigenetic modifications influence gene expression and phenotype.
- Artificial intelligence (AI) and bioinformatics: AI and machine learning will play a growing role in analyzing and interpreting the vast amounts of complex data generated by epigenomic studies. Computational tools will help identify regulatory networks and predict functional outcomes.
- Nanopore sequencing: New sequencing technologies, such as nanopore sequencing, are expected to enable direct and routine detection of modified bases like 5mC and 5hmC, potentially at the single-cell level.

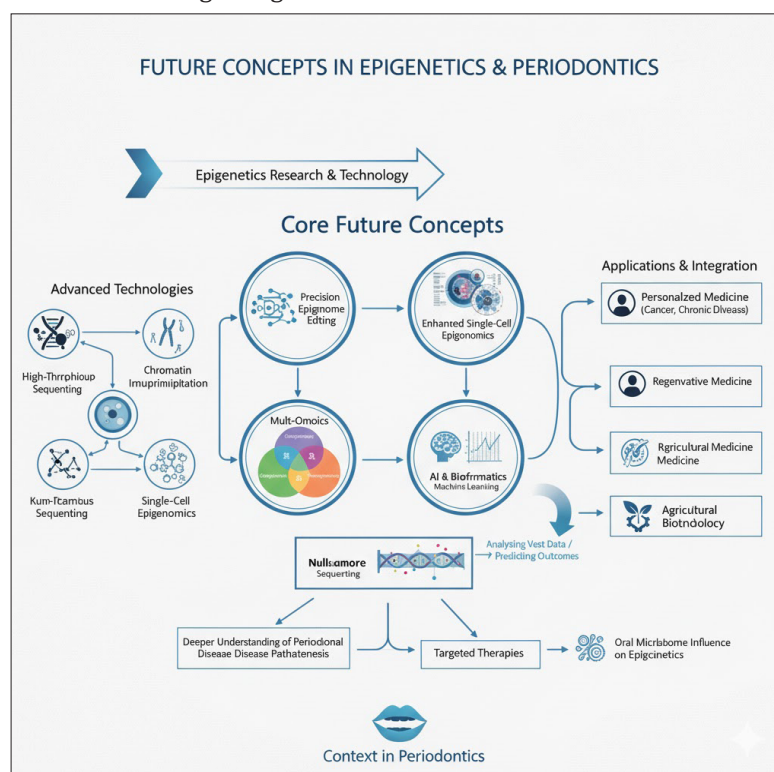


Figure 3. Future concepts within the field of epigenetics

CLINICAL IMPLICATIONS

Therapeutic targets: The reversibility of epigenetic modifications makes them promising targets for new therapies ("epidrugs") to treat periodontal disease.

Biomarkers: Epigenetic modifications may serve as biomarkers for early diagnosis, disease severity, and predicting treatment outcomes, potentially enabling personalized management strategies.

Disease progression: Epigenetic changes are crucial in local inflammatory and tissue remodelling pathways, contributing to the progression and severity of the disease.

CONCLUSION

The future of periodontics lies at the intersection of epigenetics and personalised medicine. The knowledge on the role of epigenetics in development of periodontal diseases is of great significance. It will be useful in developing innovative therapeutic methods and ideas.

Periodontal disease is understood as a dynamic condition influenced by the interaction of environmental factors and an individual's genetic makeup through epigenetic mechanisms. This epigenetic process, particularly involving DNA methylation driven by microbial pathogens and inflammation, plays a key role in susceptibility and disease progression, potentially linking periodontal disease to systemic conditions.

Periodontitis is a chronic inflammatory disease, and its persistent nature could also exert a significant systemic impact on health, by serving a risk factor for atherosclerosis, chronic obstructive pulmonary disease, diabetes, adverse pregnancy outcomes, and rheumatoid arthritis. The traditional method for periodontal disease management involves techniques targeting the bacteria/pathogens. These have limitations, such as recurrence of the disease and bacterial resistance. Thus, developing new therapeutic strategies for chronic inflammation based on regulation of the host innate immune response is highly desirable. Knowledge about alterations in histone modifications, DNA methylation, and microRNA regulation will provide a better understanding of the molecular basis for various chronic inflammatory diseases. Progress in studies of epigenetic alterations during the inflammatory response opens opportunities for the development of effective medications for specific targets. Among the drugs currently proposed for epigenetic therapy are histone deacetylase inhibitors and demethylating agents, which target chromatin in rapidly dividing tumour cells and restore normal cell functions. The integration of the latest

technological achievements in whole-genome microarray expression profiling and chromatin immunoprecipitation-based sequencing (ChIP-seq) methods will be instrumental in the development of epigenetic drugs with greater specificity.

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