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Review Article

Exploring Epigenetic Mechanisms in Aggressive Periodontitis; Unraveling the Molecular Dynamics of Disease Progression: A Narrative Review

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Abstract

Aggressive periodontitis is an inflammation of the periodontal tissue that usually affects adolescents and young adults aged <30 years, caused by attachment loss and fast bone degradation. The correlation between the epigenetic status and the initiation and progression of numerous acquired diseases was documented. Consequently, targeting epigenetic factors within periodontal tissues stands as an appealing prospect for both the diagnosis and treatment of periodontitis. In addition to the role of pathogenic bacteria and their products, alterations in gene expression due to extrinsic and intrinsic factors can cause disturbances in the host's immune response. Epigenetic changes, whether DNA methylation or microRNA (miRNA) dysregulation, can cause changes in gene expression in aggressive periodontitis and lead to more severe and rapid loss of the periodontal tissues. This study aimed to elucidate the relationships between oral hygiene, pathogenic bacteria, and genetics in periodontitis development to promote targeted prevention and treatment for enhanced oral health in individuals at risk of aggressive periodontitis. The method employed in this study entailed a comprehensive review and analysis of scholarly literature on the relationship between epigenetic mechanisms and the development of aggressive periodontitis. In conclusion, epigenetic regulation plays an important role in the pathogenesis of periodontitis through DNA methylation mechanisms that begin with Toll-like receptors (TLRs), cytokine signaling pathways, promoter genes, and progress to pro-inflammatory cells. When periodontal tissue inflammation occurs, miRNA inhibits protein translation from messenger ribonucleic acid (mRNA), which contributes to its aggressiveness.

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What's Known

- Currently, periodontitis is caused by pathogenic bacteria, host-related elements, and acquired factors.

What's New

- Epigenetic elements within periodontal tissues represent potential targets for both diagnosis and treatment. The present review outlined the evidence on the influence of epigenetic alterations such as DNA methylation and microRNA dysregulation and their association with the progression rate of periodontitis.

Introduction

Periodontitis is considered the sixth most prevalent osteolytic disease in humans. In fact, systemic disorders are significantly associated with periodontitis, which affects approximately 11.2% of the global population and is regarded as a public health issue.[1] As outlined by the Global Burden of Disease Study (2016), severe periodontal disease ranked 11th in terms of global prevalence.[2] The

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incidence of periodontal disease was estimated to affect 20% and 50% of the world's population. This condition significantly contributes to tooth loss, potentially affecting masticatory function, aesthetic appearance, self-confidence, and overall quality of life.[3, 4]

The two most prevalent types of periodontitis are categorized into two pathophysiologically distinct groups: aggressive periodontitis, which is less frequent and characterized by early onset and rapid progression, and chronic periodontitis, which typically manifests with late onset and slow progression. On average, bone loss occurs 3-4 times faster in aggressive periodontitis than in chronic periodontitis.[5] Aggressive periodontitis is a type of gingiva disease that typically affects individuals under the age of 30; however, it can arise later in life. It varies from chronic periodontitis due to the patient's age, rapid progression, and minimal plaque involvement. This condition is associated with bacteria such as *Aggregatibacter actinomycetemcomitans* and *Porphyromonas gingivalis*, immune response changes, and family history. Aggressive periodontitis can manifest as localized aggressive periodontitis (LAP) or generalized aggressive periodontitis (GAP) forms. LAP frequently arises during puberty, affecting the first molars and incisors, resulting in increased pocket depth and significant bone loss. To resist periodontal pathogens, an excessive amount of cytokines, chemokines, and matrix-degrading enzymes are produced in periodontitis-affected gingival tissue by resident gingival cells and infiltrating immune cells, particularly gingival epithelial cells (GECs) and fibroblasts.[6]

While oral hygiene and the presence of pathogenic bacteria play crucial roles in aggressive periodontitis, genetic alterations caused by both external and internal factors can contribute to deficiencies in immune cells. Consequently, individuals may experience an exaggerated immune response, causing more severe and rapid damage to periodontal tissue. The development of periodontitis is significantly influenced by epigenetic regulation, providing a potential focus for host modulation therapy. Specific gene mutations or disruptions in gene expression that cause the production of pro-inflammatory proteins might result in a hypersecretory genotype of inflammatory chemicals, increasing susceptibility to aggressive periodontitis.[7] In summary, a comprehensive study is required to unravel the complicated relationships between oral hygiene, pathogenic bacteria, and genetic factors in the development of periodontitis. The present study aimed to clarify the genetic basis and epigenetic regulation of aggressive periodontitis to pave the way for more targeted and effective strategies for both the prevention and treatment of this disease, ultimately improving oral health outcomes for individuals at risk of aggressive periodontitis.

Epigenetic

Conrad H. Waddington introduced the term 'epigenetic' in 1940 to describe the 'causal process' by which genes produce phenotypes.[8] Epigenetic changes involve modifications in gene activity that are not part of the DNA sequence and are affected by environmental factors. Epigenetics is the study of gene expression changes that are not caused by alterations in DNA sequence.

The two levels of information that constitute DNA are as follows:[9]

The first layer consists of the coding DNA region, which serves as the foundation for our genetic code. This coding region accounts for only 2% of the total DNA. The body's essential proteins are synthesized from the various messenger ribonucleic acids (mRNAs) that the genetic code is translated into.

The second layer is the non-coding DNA layer, which accounts for 98% of the genome and regulates the timing, location, and selection of gene expression. Epigenetics refers to a variety of processes, including non-coding RNA, histone modification, and DNA methylation. Cellular differentiation is based on tightly regulated epigenetic mechanisms found at the cellular level of all organisms. Disruption of this mechanism by external environmental factors causes alterations in gene expression and function.

Epigenetic mechanisms play a vital role in controlling gene expression through a range of activities. One such mechanism is DNA methylation, which involves the addition of methyl groups to cytosine nucleotides, predominantly at cytosine-guanine (CpG) dinucleotides, and is facilitated by enzymes such as DNA methyltransferases (DNMTs) 1, 3a, and 3b. This modification induces chromatin condensation, which disrupts interactions with transcription factors and results in transcriptional repression.[6, 7, 10] Histone modification, which includes processes such as acetylation and methylation, plays a pivotal role in regulating chromatin condensation and gene expression. Histone acetyltransferases (HATs) add acetyl groups to histones, which promotes gene transcription, while histone deacetylases (HDACs) eliminate acetyl groups, resulting in chromatin condensation and transcriptional repression.[6, 10] Noncoding RNA,

particularly long non-coding RNA (lncRNA) and microRNA (miRNA), also play a role in gene regulation. miRNAs, small non-coding RNAs, can degrade target mRNA or suppress translation, thereby influencing gene transcription. LncRNAs, or longer non-coding transcripts, regulate miRNA function and can serve as diagnostic biomarkers. Dysregulation of these epigenetic mechanisms is associated with various diseases, including cancer, coronary heart disease, diabetes, and autoimmune disorders. Understanding these mechanisms provides insights into disease pathophysiology.[7, 11]

Aggressive Periodontitis

Aggressive periodontitis is a type of periodontal disease that impacts young individuals who are otherwise healthy. This disease can be distinguished from chronic periodontitis by the patient's age, and rapid disease activity, which is characterized by rapid bone destruction and attachment loss despite minimal plaque accumulation. The bacteria which is most typically found in the infected area are *Aggregatibacter actinomycetemcomitans* and *Porphyromonas gingivalis*. Changes in the host's immune response and family history are also associated with aggressive periodontitis.[12]

In 1923, Gottlieb initially characterized this disease as a noninflammatory, degenerative condition, while Weinmann and Orban coined the term "periodontosis" in 1942 to describe its prevalence among young individuals. However, subsequent investigations conducted twenty years later dispelled the notion of noninflammatory periodontal diseases. As the causes of aggressive periodontitis were better understood, Butler changed the term "periodontosis" to "juvenile periodontitis" in 1969. Aggressive periodontitis is recognized for its swift attachment loss and bone damage, which primarily affects healthy adolescents and young adults. This condition is associated with alterations in gene expression in the host.[13] However, in 2018, a new classification method for periodontal tissue diseases was implemented, leading to the discontinuation of the use of the term "aggressive periodontitis".[14, 15] Periodontal disease is classified according to its degree and severity. An example of a change in the diagnosis of LAP is its classification as grade C periodontitis with a molar-incisor pattern.[14]

Aggressive periodontitis manifests in two primary forms: GAP and LAP, which are distinguished by the number and specific teeth affected. LAP mainly affects the incisors and first molars and is marked by deeper pockets and significant bone loss. On average, aggressive periodontitis causes bone loss 3-4 times faster than chronic periodontitis. The familial clustering of this disease suggests a genetic predisposition that correlates with susceptibility to aggressive periodontitis.[12]

The prevalence of aggressive periodontitis varies significantly across different ethnic groups. A study of 11,007 American adolescents under 17 years old revealed that black teenagers had a 15.1 times higher risk of LAP and a 24.6 times higher risk of GAP than white teenagers. Additionally, females appear to have a higher incidence of aggressive periodontitis than males.[13, 16]

Aggressive periodontitis is associated with unique clinical features such as distolabial migration and increased mobility of the maxillary incisors and first molars. Additionally, there is increased sensitivity in exposed root surfaces. The diagnosis of aggressive periodontitis considers the absence of local factors such as calculus and plaque. The condition usually begins from late childhood through adolescence and can persist until the age of 30. Moreover, inflammation is found in deep periodontal pockets. Radiography serves as a conventional confirmation method for the disease, indicating vertical bone loss around incisors and first molars, coupled with wider bone defects than chronic periodontitis (ChP). Additionally, the typical arc-shaped structure of the alveolar bone, which extends from the distal side of the second premolar to the mesial side of the second molar, becomes interrupted.[17] In recent years, cone-beam computed tomography (CBCT) has emerged as an effective diagnostic tool for aggressive periodontitis. This advanced imaging technique enables meticulous examination of osseous defects surrounding all teeth. Measurements taken with a periodontal probe on surgically exposed osseous defects are nearly identical to those identified by CBCT, overcoming the limitations of traditional radiography.[18]

Due to its complex nature, the primary risk factors for aggressive periodontitis involve oral microbiota, genetics, and, to a lesser extent, lifestyle choices. Numerous studies have consistently demonstrated an association between aggressive periodontitis and the presence of specific bacteria, such as *A. actinomycetemcomitans*, *P. gingivalis*, *Tannerella forsythia*, *Selenomonas sputigena*, and *Treponema denticola*.[19, 20] These microbial species are significantly less prevalent in healthy individuals, particularly *A. actinomycetemcomitans*.[21]

Aggressive periodontitis is a complex disorder influenced by interactions among multiple gene loci, making it a polygenic condition. In cases

of autosomal recessive heredity, nonprotective inflammatory responses are predominantly implicated, leading to dysbiotic alterations in the microbial environment. Additionally, this condition exhibits genetic heterogeneity and susceptibility to environmental influences. Recent studies have emphasized certain genetic variations associated with aggressive periodontitis. Polymorphisms in genes such as IL-6 (-174) and IL-10 (-597) were found in aggressive periodontitis subjects using PCR-restriction fragment length polymorphism (RFLP) analysis. Importantly, the anti-inflammatory cytokine IL-10 inhibits the production of proinflammatory cytokines such as IL-6, which regulates osteoclast differentiation.[22]

Additional investigations revealed associations between the tumor necrosis factor-α (TNF-α) rs1800629 (-308G/A) polymorphism and aggressive periodontitis across Asian, Caucasian, and eastern Indian populations. This polymorphism increases the transcriptional activity of TNF-α, a proinflammatory cytokine associated with gingival tissue destruction. Bacterial pathogens trigger the secretion of TNF-α, which stimulates osteoclast differentiation and subsequent bone resorption. Additionally, TNF-α stimulates the release of matrix metalloproteinase enzymes (MMPs), contributing to the degradation of the gingival extracellular matrix.[23, 24]

Cigarette smoking emerges as the most influential risk factor in both the occurrence and advancement of GAP. Smokers with this condition experience more severe attachment loss and tooth loss than non-smokers. The reduction in protein levels potentially disrupts calcium homeostasis, a crucial aspect in the migration of neutrophils, thereby reducing their antimicrobial effectiveness against invading microorganisms.[25] Smoking alters the differentiation of B-cells and T-cell immune regulation, leading to reduced immunoglobulin synthesis. This reduction compromises the usual protection of the oral mucosa against periodontal bacteria. Tobacco metabolites inhibit neutrophil activity and impair the role of polymorphonuclear (PMN) cells in processes such as chemotaxis and phagocytosis. This interference occurs by disrupting immunoglobulin production.[26, 27]

A comparison of transcriptomic and methylomic data in human gingival tissue from smokers and non-smokers indicated a significant decrease in genes responsible for proteins linked to extracellular matrix (ECM) and extracellular structure organization in the smoking group. Simultaneously, there was an evident increase in DNA methylation levels among smokers compared to non-smokers.[28] In a separate combined analysis, nine hypomethylated CpG sites showed a significant correlation with current smokers compared to non-smokers. Remarkably, three of these nine CpG sites were located in the Cytochrome P450 Family 1 Subfamily B Member 1 (CYP1B1) gene locus, indicating that smokers had higher CYP1B1 expression than non-smokers.[29] Furthermore, bruxism, a condition characterized by teeth grinding or clenching, is significantly associated with higher rates of tooth loss due to periodontal disease (TLPD), particularly when combined with smoking and specific characteristics such as abfractions (wedge-shaped lesions at the gum line) and vertical bone defects.[30]

Aggressive periodontitis is characterized by proteolytic degradation of periodontal tissues, which involves the expression and secretion of MMPs. The degradation of fibronectin by high-temperature requirement A1 (HtrA1) results in the expression and release of these MMPs. High levels of plasma cell HtrA1 in patients with aggressive periodontitis may stimulate the overproduction of MMPs and increase the levels of inflammatory mediators IL-1β and TNF-α. This occurs through the inhibition of transforming growth factor beta (TGF-β), contributing to an exacerbated inflammatory response.[31] Moreover, the phenotypic profile of blood mononuclear cells in individuals with GAP reveals a distinct pattern, with a significant increase in activated cytotoxic T cells, particularly CD8+/CD28+ cells. These activated cell populations, which are found in both defect sites and systemic circulation blood samples, are associated with increased inflammation and may contribute to severe tissue damage.[32]

Combining moxifloxacin treatment with scaling and root planing resulted in significant improvements in clinical attachment level (CAL) and reduction in probing depth (PD) at the 6-month mark post-treatment in patients affected by GAP. Sites classified as healthy had a PD of less than 5 mm.[33]

A non-surgical treatment combining chlorhexidine, amoxicillin, and metronidazole demonstrated positive outcomes, including an increase in CAL (0.97 mm) and improved PD (2.54 mm), as well as a reduction in bleeding on probing (BOP), and the absence of detectable pathogenic bacteria in periodontal pockets.[34] Furthermore, the adjunctive use of metronidazole and amoxicillin was shown to be more effective in reducing MMP-8 concentrations in GCF than photodynamic therapy (PDT).[35] Non-surgical treatment, such as full-mouth scaling and root planing, was found to impact the composition of the subgingival bacterial community in patients with GAP.[36]

In LAP, open flap debridement significantly reduced PD and attachment loss in patients with bilateral intrabony abnormalities.

A hydroxyapatite graft combined with platelet-rich plasma led to enhanced defect fill. Another approach, which included papilla preservation, flap surgery, and bone grafts, effectively treated advanced bone defects in maxillary anterior teeth, resulting in less bleeding and improved attachment levels. Additionally, modified flap surgery and ridge augmentation showed potential clinical and microbiological enhancements in GAP, including increased bone levels and decreased pocket depth.[37-39]

Epigenetics on Aggressive Periodontitis

Epigenetic modifications involve chemical changes in both DNA and its associated proteins, resulting in the restructuring of chromatin and influencing the activation or deactivation of specific genes. These alterations play a significant role in the onset and persistence of conditions such as cancer, autoimmune diseases, and inflammatory disorders, such as periodontitis. Importantly, certain epigenetic modifications are reversible and can be influenced or changed by environmental factors, establishing a connection between genetic inheritance and the surrounding environment.[40, 41]

Genetic variation can alter gene expression, affecting an individual's response to microbial load. Individual immune response is influenced by gene characteristics and gene regulation. Cytokines play a significant role in the host inflammatory response.[42] Epigenetic mechanisms in patients with periodontitis could be observed through various mechanisms and samples obtained samples, including:

a. DNA Methylation on Aggressive Periodontitis

DNA methylation is a well-studied epigenetic process that involves the covalent attachment of methyl groups to the fifth carbon on the cytosine base (5 mC) within CpG islands located in the promoter region of a gene. This modification is catalyzed by enzymes known as DNMTs.[43] DNA methylation is influenced by various factors, including smoking, oxidative stress, infections, and deficiencies in vitamin B, methionine, choline, zinc, and folate.[44-48]

Several studies investigated the effect of epigenetic modifications on aggressive periodontitis using gingival biopsy samples from both aggressive periodontitis patients and control groups.[13, 49] Schulz and colleagues investigated the presence of promoter methylation in various genes, including those encoding chemokines, cytokines, components of the inflammatory cascade, and autoimmune-related genes associated with periodontal tissue inflammation. They compared areas of inflammation (CAL 6 mm) in gingival biopsies from individuals with aggressive periodontitis to areas without or with minor attachment loss (CAL 3 mm) in patients with no periodontitis or moderate chronic periodontitis.[49]

Toll-like receptors (TLRs) Pathway (TLR2 and TLR4)

Toll-like receptors (TLRs) play a vital role in recognizing pathogens and initiating the host inflammatory response.[50]

These critical single, membrane-spanning, non-enzymatic receptors can identify bacterial lipopolysaccharides, triggering a signaling cascade that ultimately leads to the activation of numerous genes associated with inflammatory responses.[51]

TLR2 and TLR4 play a role in periodontal diseases. A wide variety of bacterial compounds, such as peptidoglycans, bacterial lipoproteins, and lipoteichoic acid, can interact with TLR2.[52] Due to the crucial role of TLRs, dysregulation of these receptors can impair and disrupt the inflammatory process. Patients with aggressive periodontitis might experience systemic hyperresponsiveness to TLR stimulation, possibly due to changes in TLR signaling within host immune cells. This alteration can lead to increased cytokine production as a reaction to TLR4 and TLR2 ligands. Ghotloo and others discovered that patients with periodontitis had higher TLR2 levels due to DNA methylation mechanisms.[53] Systemic hyperresponsiveness to TLR stimulation results in increased TLR function as intracellular signalers. TLR activation and recruitment of various adaptor molecules, including TIR domain containing adaptor molecule 1 (TICAM-1), interleukin-1 receptor-associated kinase 1 (IRAK1), and FBJ Murine Osteosarcoma Viral Oncogene Homolog (FOS), can lead to the generation of significant cytokines that promote innate immunity and inflammation.[13]

The TLR pathway adaptor protein TICAM-1, also known as Toll-interleukin-1 receptor domain-containing adaptor molecule-1 (TRIF), modulates protein-protein interactions and facilitates TLR downstream signaling. TRIF activation can also attract the IRAK1/TRAF6 complex, which activates AP-1. The proto-oncogenes FOS and Jun Proto-Oncogene (JUN) generate the transcription factor heterodimer complex known as AP-1, which regulates various processes such as cell division, proliferation, and immunological and inflammatory responses.[13, 54] The increased release of cytokines, chemokines, and other

inflammatory mediators in LAP patients might be attributed to TLR activation and the involvement of adaptor molecules.

The signaling pathways linked to TLRs are pivotal in determining the outcomes of inflammatory diseases. Consequently, Shaddox and colleagues analyzed the methylation patterns affecting specific genes within the TLR signaling pathways, leading to either the upregulation or downregulation of TLR-mediated inflammatory responses.[51] Remarkably, individuals with a moderate level of LAP exhibited hypermethylation in both the upregulating and downregulating genes. This observation suggested a persistent regulatory effort by signaling molecules to delicately adjust the thresholds to restrain or prevent further tissue destruction.[51]

Suppressors of Cytokine Signaling (SOCS)

Given the complexity of the inflammatory response, a complex regulatory network is required to execute functions at both the signal and gene-specific levels. The Janus-kinase signal transducer and activator of transcription (JAK-STAT) pathway stands out as one of the most significant intracellular signaling pathways activated by cytokines. The JAK/STAT system is tightly regulated to prevent excessive cytokine signaling, with the primary regulators being a class of proteins known as suppressors of cytokine signaling (SOCS). The eight proteins that comprise SOCS include SOCS1–7 proteins and the inducible cytokine protein with an SH2 domain. Given its ability to specifically inhibit JAK, SOCS1 emerges as one of the most effective inhibitors of cytokine signaling.[42, 55]

The methylation patterns of SOCS1 and Long Interspersed Nuclear Element-1 (LINE-1) were assessed using oral gingival buccal epithelial cells. In samples from patients with aggressive periodontitis, SOCS1 methylation was found to be reduced. Additionally, Ghafouri-Fard and colleagues observed dysregulation of SOCS1, SOCS2, and SOCS3 genes in the circulatory system of individuals with periodontitis. These gene transcripts could serve as peripheral markers indicating the presence of periodontitis.[56] This suggests that the JAK-STAT pathway is not well regulated, resulting in excessive production of cytokines. This is also associated with an increased inflammatory response in patients with aggressive periodontitis. The temporal dynamics of SOCS1 and SOCS3 expression were found to be directly correlated with the intensity of inflammation, alveolar bone resorption, levels of pro-inflammatory cytokine expression, and the activation status of STAT1 and STAT3 transcription factors throughout the progression of experimental periodontal disease.[57]

Changes of Gene Promotor (Cytokines and Chemokines)

Cytokines are peptide mediators responsible for signaling and cell communication. Meanwhile, chemokines, a subfamily of cytokines, can control the recruitment and activation of leukocytes. Epigenetic changes in gene promoter methylation associated with inflammation of periodontal tissues upregulate CCL25, contributing to an increased host immunological response. IL-17C is a member of the IL-17 group and is predominantly produced in inflammatory conditions.[58] IL-17 plays a role in inducing proinflammatory cytokines. Increased IL-17 levels significantly enhance the expression of IL-1β and TNF-α. IL-17 also promotes osteoclast formation by regulating the expression of RANKL and osteoprotegerin.[59] *P. gingivalis* bacteria and its lipopolysaccharide (LPS) product increase IL-17 expression in the periphery of mononuclear cells. Lower CpG methylation levels were found in CCL25 and IL-17C, indicating increased promoter activity and higher gene expression. Patients with aggressive periodontitis exhibited distinct expression patterns of inflammatory cytokines as a result of these epigenetic traits.[49]

Changes in Gene Expression

Several cytokines, such as Interleukin-1, Interleukin-6, TNF-α, and Interferon-gamma, were found to be implicated in the pathogenesis of periodontal disease. Ghotloo and colleagues found that persons with periodontitis have altered gene expression in TNF-α, E-cadherin, TLR2, and lipopolysaccharide (COX-2) due to DNA methylation.[53, 60]

MiR-146a, serving as a pivotal regulator of post-transcriptional gene expression, plays essential roles in physiological processes. It acts as a major negative regulator of the innate immune response and is upregulated in monocytes when exposed to inflammatory cytokines and bacterial components such as LPS. This increase results in the reduction of IL-1 receptor-associated kinase-1 and TNF receptor-associated factor 6, which are crucial adaptor proteins following toll-like and cytokine receptors. Consequently, there is a suppression of nuclear factor-kappa B (NFκ-B1) activation, a crucial transcription factor involved in the expression of numerous inflammatory genes, including TNFα, IL-1β, IL-6, IL-8, chemokines, adhesion molecules, and prostaglandins.[53, 61]

In the context of aggressive periodontitis, bacterial components, particularly LPS within plaque, activate TLRs, which could lead to an

increase in miR-146a levels. This establishes a negative feedback loop that regulates the levels of pro-inflammatory cytokines. miR-146a, as a regulator of gene expression at the post-transcriptional level, plays a key role in this process. It inhibits periodontal tissue repair and regeneration, which are initiated by epidermal growth factor receptors and TGF-β. This disruption is evident through the downregulation of these growth factors by the altered expression of miR-146a, as observed in its regulatory effects on epidermal growth factor receptor and TGF-β.[53]

The development of active osteoclasts contributes to alveolar bone loss in periodontitis, with epigenetic mechanisms playing a role in osteoclastogenesis within periodontal tissue. Specifically, Lysine (K)-Specific Demethylase 3C (KDM3C), a histone Lys-specific demethylase expressed in macrophages, experiences reduced expression following treatment with LPS-Pg. The absence of KDM3C was associated with the enhancement of NF-κB signaling, osteoclastogenesis, and subsequent alveolar bone loss in a murine model of ligature-induced periodontitis.[58]

b. Noncoding RNA (Micro RNA/miRNA)

Numerous studies demonstrated the involvement of miRNAs and DNA methylation in the etiology of periodontal disease.[13] MiRNAs, which are small noncoding RNAs approximately 22 nucleotides in length, regulate gene expression by binding to specific mRNA target sites. This interaction inhibits protein translation or degradation of mRNA. MiRNAs regulate gene expression, and their dysregulation can cause inflammation or immune diseases.[62]

Studies on the regulatory function of miRNAs, either from gingival biopsy samples or in peripheral blood mononuclear cells without stimulation (PBMC), in patients with aggressive periodontitis compared with healthy controls, can periodically identify potential candidate genes and altered regulatory genes in this disease. Fernandes and colleagues found that miRNAs associated with immunological and inflammatory responses were up to two-fold overexpressed in PBMCs from aggressive periodontitis patients.[63] The miRNAs selected for validation included miR-9-5p, miR-147a, miR-182-5p, miR-183-5p, miR-155-5p, and miR-203a-3p. Notably, miR-223-3p was not selected due to its lack of difference from the control group.[13]

MiR-203a-3p plays a role in regulating cytokine signaling pathways in the immune response. Meanwhile, miR-155-5p serves as both an inflammatory and anti-inflammatory stimulus, with a significant and complex involvement in immune response modulation. Dysregulation of miR-155-5p can lead to increased production of TNFαMiR-9-5p, plays a role in down-regulating NFκ-B1, a transcription factor that regulates inflammation-related genes such as IL-1β, IL-6, IL-8, TNFα, adhesion molecules, chemokines, and prostaglandins. Similarly, miR-147a plays a role in controlling the inflammatory response by regulating TLR signaling. Therefore, dysregulation of these miRNAs might trigger an increased inflammatory response, ultimately exacerbating the rapid destruction of periodontal tissue.[13, 64]

In another study by Ghotloo and colleagues, overexpression of miR-146a was observed in gingival biopsy samples from patients with aggressive periodontitis. The presence of miR-146a overexpression in these patients interfered with the process of repair and regeneration of periodontal tissue. Therefore, in addition to rapid destruction, the process of repair and regeneration of periodontal tissue was also disrupted.[53]

Conclusion

The signs and progression of periodontitis are determined by subgingival bacterial infection, its byproducts, and the individual's immune system. Epigenetic modifications are critical in increasing the severity of periodontitis. These modifications occur through DNA methylation mechanisms, which affect various pathways including TLRs, cytokine signaling pathways, promoter genes, and pro-inflammatory cells. Furthermore, miRNA plays a crucial role in the severity of periodontal tissue inflammation by inhibiting protein translation from mRNA during inflammation. The epigenetic condition of periodontal tissue significantly influences the success of regeneration therapy. By assessing and modifying periodontal ligament (PDL) cell epigenetics, we can enhance predictive accuracy and advance regenerative tropism, paving the way for precision medicine in periodontal regeneration therapy.

Authors' Contribution

R.G: design of the study and drafting of the work; A.W.S: research conception, and drafting of the work; A.H.R.A: analysis, drafting, and revising the manuscript. E.I.A: design of the study, supervision, and Finalising the manuscript. All authors have reviewed and approved the final manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflict of Interest: None declared.

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