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REVIEW

Epigenetics in Periodontics

Epigenética en Periodoncia

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ABSTRACT

Introduction: periodontitis is a pathology characterized by the destruction of dental support tissue, in its worst scenario it can cause the loss of the dental organ; Its etiological factor is periodontopathogenic bacteria, however, this is a multifactorial disease, that is, not only environmental factors are involved but also genetic factors that are responsible for modulating the progression of periodontal disease. Not all patients will have the same susceptibility to developing Periodontitis since basically this will depend on the immunity of the host and its genetic code.
Objective: to present the epigenetic mechanisms that have been applied in the field of Periodontics in order that these studies lead to the discovery of new regulatory treatments that offer to be an alternative to control inflammation in Periodontitis, that is, based on the findings already exposed in the future it is estimated that they can be translated into clinical practice.
Method: this article has prepared a compilation and analysis of the literature using the database of Scopus, Pubmed, EBSCO and Cochrane. We included experimental trials, case-control studies, review studies and meta-analyses.
Results: several studies have been presented that facilitate the understanding of the epigenetic mechanisms involved in pathological processes, such as specific biomarkers for certain diseases and genes that regulate inflammatory processes; In addition, it was mentioned that there are inhibitory molecules that allow the modulation of the inflammatory process of the host.

KEYWORDS

Epigenetics in Periodontitis, Periodontitis, Epigenetics.

RESUMEN

Introducción: la periodontitis es una patología que se caracteriza por la destrucción del tejido de soporte dentario, en su peor escenario puede ocasionar la pérdida del órgano dental; su factor etiológico son las bacterias periodontopatógenas, sin embargo, esta es una enfermedad multifactorial, es decir que no solamente se involucran factores ambientales sino también factores genéticos que son los encargados de modular la progresión de la enfermedad periodontal. No todos los pacientes presentarán la misma susceptibilidad a desarrollar Periodontitis ya que básicamente esto dependerá de la inmunidad del huésped y su código genético.
Objetivo: presentar los mecanismos epigenéticos que se han aplicado en el campo de la Periodoncia con la finalidad de que estos estudios encaminen el descubrimiento de nuevos tratamientos reguladores que ofrezcan ser una alternativa para controlar la inflamación en la Periodontitis, es decir, que en base a los hallazgos ya expuestos a futuro se estima que puedan traducirse a la práctica clínica.
Método: el presente artículo fue elaborado a través de una recopilación y análisis de la literatura usando bases de datos de alto impacto como Scopus, Pubmed, EBSCO y Cochrane. Se incluyeron estudios clínicos experimentales, estudios de casos y controles, estudios de revisión y metaanálisis.
Resultados: se han expuesto varios estudios que facilitan la comprensión de los mecanismos epigenéticos

involucrados en los procesos patológicos, tales como los biomarcadores específicos para ciertas enfermedades y los genes que regulan procesos inflamatorios; además, se mencionó que existen moléculas inhibidoras que permiten la modulación del proceso inflamatorio del huésped.

PALABRAS CLAVE

Epigenética en Periodontitis, Periodontitis, Epigénetica.

INTRODUCTION

The periodontal pathologies that most prevalently afflict the population worldwide are Periodontitis and gingivitis, infectious diseases that destroy the structures that surround the tooth, these being the protective periodontium and the supporting periodontium; periodontal disease is mainly characterized by inflammation of multifactorial origin. [1,2]

Periodontitis is a serious pathology that acts silently; the inflammation of the periodontal tissues progresses gradually until it becomes chronic; in fact, this is the main cause of tooth loss in adults, and the main etiological factor is the accumulation of biofilm. Within the entire population suffering from Periodontitis, there is a group of patients who do not respond positively to periodontal treatment, so the destruction of the affected periodontium cannot be controlled. When this occurs, the cause is attributed to the presence of a resistant periodontopathogenic microorganism or a genetic risk factor.[3]

The non-surgical periodontal treatment of scaling and root planing (mechanical action) in conjunction with chemical therapy (antibiotics and mouthwashes) constitutes a reliable therapy for the treatment of Periodontitis since it is a procedure through which the main etiological factor of the pathology is eliminated, i.e., dental biofilm;[4] however, basic periodontal therapy does not work equally in all patients, due to the genetic variability in the population. [3] Chronic inflammation in the body exacerbates the destructive activity of periodontal tissues and, if not effectively controlled, can trigger more serious diseases such as cancer. [5]

"The new classification of periodontal and peri-implant diseases and conditions" considers that Periodontitis is classified into four stages, each of which is assigned a degree of progression of the disease: either slow 'A,' moderate 'B' or fast 'C' [6]; that is to say that it does not evolve in the same way and with the same speed in all patients.

Genetic polymorphisms are specific variations in certain areas of the DNA, which can occur in a small group of the population (less than 1%). Some of these genetic compositions favor the development of diseases, including Periodontitis. [1,7] The "genetic polymorphism of IL-1 (interleukin-1) is the most studied genetic variation" and is directly related to patients with active periodontal destruction. Among other alterations in the human genome, the genes encoding "tumor necrosis factor (TNF), IL-6, IL-4, and IL-10" can be found. [1,7,8]

Cavani et al. [9] carried out an analysis of the different genes directly related to periodontal disease and identified "five leading genes: 1)NFKB1, 2)CBL, 3)GRB2, 4)PIK3R1 and 5)RELA", which play a fundamental role in regulating the development of the pathology; this set of genes is of great importance in the present study since they represent a genetic risk factor for the manifestation of periodontitis. That is why the objective of the research was to analyze the literature with reference to certain genes and to show a futuristic approach to periodontal treatment from the point of view of Epigenetics.

According to the NIH/National Center for Biotechnology Information [10], the "GRB2 gene or growth factor receptor binding protein two is located on chromosome 17 (17q25.1)" and "encodes a protein that binds to the epidermal growth factor receptor and is involved in the signal transduction pathway." It is expressed in some tissues in Homo sapiens, such as lymph nodes, salivary glands, appendix, ovaries, heart, pancreas, and lung, among others.

"NF-κB is a group of 5 homologous proteins belonging to mammals; these are 1) RelA, also called p65, 2) RelB, 3) c-Rel, 4) NF-κB1, also called p50 and its precursor protein p105, and 5) NF-κB2 also called p52 and its precursor p100 (between them they form homo- and heterodimers)". [11–13]

The location of the NFKB1 gene in the DNA is 4q24; that is, it is in exon 24 of the long arm of chromosome 4. [14,15] This gene, also known as "nuclear factor kappa B, subunit 1", actively participates in the immune system response and is expressed in various cell types of tissues such as bone marrow, skin, salivary glands, and prostate, among others. [16] That is to say that its main function is to regulate the immune response when there is infection in the organism. [5,17] Companioni et al. [18] point out that the NFKB1 gene favors the "expression of proinflammatory cytokines, chemokines, and cell adhesion molecules to provoke an immune response against bacterial infection". Marconcini et al. [19] point out that there is a strong relationship between the NFKB1 gene and inflammatory

activity and the bone resorption phase. Likewise, Paredes [20], in his study, concludes that "the NFKB1 gene is expressed in inflammatory processes"; therefore, it is directly related to Periodontitis due to the fact that it is an inflammatory pathology. In addition, it is important to add that there are mutations of certain genes, which constitute an important factor in the progression of periodontal disease. [7,8]

However, some mutations of the NFKB1 gene have caused two main problems; the first is that the correct activation of the gene can be affected, and therefore, the regulatory function of the immune system will be diminished, and the organism will be prone to infections. [21] [22] The second disadvantage is that the mutations in the gene are altered, and physiopathological changes occur at the molecular level, increasing the inflammatory response and causing an overproduction of inflammatory mediators that prolong the state of inflammation in the organism. [23]

Epigenetics involves mechanisms capable of regulating both individual immunity and inflammatory processes in the organism, which is why it constitutes a key tool for the development of new therapeutic methods for Periodontitis. [24]

Thanks to genetic and genomic research, knowledge about certain pathologies and their mechanisms has been expanded since certain genetic variations can be related to a certain disease or the susceptibility to develop it. This would eventually contribute to implementing new diagnostic and treatment techniques. [25,26]

Currently, to define the degree of Periodontitis, there are factors such as direct and indirect evidence and modifiers; in addition, Tonetti et al. [6] propose that in the future, the use of more specific tests such as "salivary biomarkers of gingival crevicular fluid and blood serum" should be integrated to provide concrete evidence on the biology of Periodontitis in each patient, especially in cases of aggressive or recurrent periodontal disease.

Based on this, the present research suggests the implementation of genetic tests that identify the presence of certain genes that present a direct relationship with the disease and that become a valid diagnostic method that complements the patient's diagnosis. It also seeks to present epigenetics as a novel component to design new techniques for the treatment of periodontal disease.

METHOD

The present research is a literature review with a literature search in relevant databases (Scopus et al.) using the keywords: "Genes in Periodontitis," "Pathogenesis of Periodontitis," and "Epigenetics in Periodontitis."

Inclusion criteria were articles written in English/Spanish, clinical experimental studies, case-control studies, review studies, and meta-analyses, available in full text. At the same time, the exclusion criteria were ecological studies, theses, books, or book chapters, and did not contain information on the main topic of interest.

A thorough analysis of the full articles was performed to determine whether they met the inclusion and exclusion criteria. Finally, the selected articles were analyzed for further data collection, which were expressed in a table to provide a better understanding of the data. The quality assessment of the articles was carried out using the PRISMA format. A quality study was considered to be of high quality if the results were related to the research topic and were useful to society.

The methodology used for the writing was analytical and descriptive of the existing literature sample on the relationship between epigenetics and periodontitis. The selection of the information was made by means of a qualitative data analysis to extract the main conclusions of this bibliographic analysis.

RESULTS

The results of this literature review are organized in the table below, which shows the most relevant information about the study (table 1).

DISCUSSION

Periodontitis is an oral pathology characterized by an inflammatory process that is directly related to dysbiosis; its main etiological factor is the presence of periodontopathogenic microorganisms that invade periodontal tissues and initiate their destruction; the periodontium reacts to bacterial infection with tissue inflammation, a mechanism in which not only local factors but also genetic factors participate [1][2]. A part of the population presents genetic modifications that directly affect the production of inflammatory cytokines, which makes them susceptible to periodontal disease.[6]

To understand the mechanisms at the cellular level and the cellular processes that precede the genetic polymorphisms observed in patients with Periodontitis, as well as to understand the pathophysiological consequences and the specific environmental factors, it is necessary to perform an analysis of epigenetics in addition to a study of the functioning of enzymes and proteins involved in the development and progression of Periodontitis. [24]

Table 1. Comparative table of the selected articles according to their objective, intervention, and results.

Author, year	Type of study	Objective	Intervention	Results
Fengzhen Lei et al.[27]/ 2022	Experimental in vitro study	"Analyzing the potential of exosomes secreted by periodontal ligament stem cells (PDLSC)" as a treatment for bone defects in periodontitis. [27]	In vitro experiment with rats. They isolated "exosomes secreted by PDLSC derived from healthy periodontal ligaments (h-PDLSC) and evaluated their action on PDLSC isolated from the inflammatory periodontal ligament of rats with periodontitis (i-PDLSC)" [27]	"Treatment of h-PDLSC exosomes led to increased mineralized bone nodule formation and osteogenic gene and protein expression in i-PDLSCs". [27]
Jurdziński et al.[24]/ 2020	Literature review study	To analyze "epigenetic regulation as an important factor in the pathogenesis of periodontitis".[24]	A review of the literature on the epigenetic regulation of inflammation in periodontitis, with an in-depth description of the cellular mechanisms and the therapeutic potential of epigenetic mechanisms, is provided.	Periodontal pathogens induce epigenetic changes that favor the inflammatory process. These cytokines can be suppressed by inhibitory molecules and modify "inflammation, osteoclastogenesis and alveolar bone resorption in animal models of periodontitis, suggesting their clinical potential as host-modulating therapeutic agents." [24]
Suzuki et al.[28]/ 2022	Literature review study	To analyze the epigenetic components related to periodontitis.	A review of the existing literature on epigenetics in the susceptibility, progression and diagnosis of periodontitis is performed.	There are "genetic factors, systemic diseases and local environmental factors, such as smoking, that alter gene expression, and epigenetics influences susceptibility to periodontitis". [28]
Asad et al.[29]/ 2020	Systematic review and meta-analysis	"To evaluate miRNA expression patterns in periodontal and peri-implant diseases, while identifying potential miRNAs with greater diagnostic capacity as a biomarker in oral fluids.".[29]	"Human and animal studies were included when evaluating miRNAs expression between health and different forms/stages of diseases, in which microarray and/or real-time polymerase chain reaction (RT-PCR) was performed to detect fold changes in gene expression. After full-text analysis, 43 articles were considered for qualitative assessment and 16 miRNAs were selected for meta-analysis". [29]	MicroRNA regulation provides positive results in periodontitis, exactly "more conclusive results were shown with miRNA-142-3p and miRNA-146a". However, there is still a lack of scientific evidence available about "specific miRNAs and their potential as therapeutic targets in periodontal and peri-implant diseases" to develop new techniques for treatment and control of inflammation.
Yoneda et al.[30]/ 2019	Case-control study	Identify the "association between periodontitis and the expression rates of certain microRNAs (miRNAs) in periodontal tissue". [30]	A "case-control study in patients with chronic periodontitis to investigate serum miRNA levels" is performed. [30]	"Hsa-miR-664a-3p, hsa-miR-501-5p and hsa-miR-21-3p are candidate serum biomarkers for chronic periodontitis, however, the association between periodontitis and miRNA levels in human serum is unknown". [30]

Fawzy et al.[31]/ 2018	Experimental in vitro study	To evaluate the "effect of total sonicated bacterial fragments of A.actinomycetemcomitans-bacterial on gingival mesenchymal mesenchymal stem/progenitor cells (G-MSCs) and their gene expression in vitro". [31] (G-MSCs) and their gene expression in vitro". [31]	G-MSCs "were isolated and exposed to 'total sonicated fragments of A.actinomycetemcomitans-bacterial" with a trol group and 4 experimental groups with different concentrations of the pathogenic mircroorganism "(0 µg/ml for negative control; 15, 60, 120 and 240µg/ml for experimental groups)". In addition, "cell proliferation and mRNA expression of NF-κβ (NFKB1), alkaline phosphatase (ALPL), collagen-I (COL1A1), collagen-III (COL3A1), osteonectin (SPARC) and osteopontin (SPP1) were analyzed; were evaluated by reverse transcriptase polymerase chain reaction (RT-PCR) at 24, 48 and 72 hours and CFU capacity was assessed at 12 days" [31]	G-MSCs demonstrated that when exposed to "A. actinomycetemcomitans bacterial fragments (up to 72 hours)" increased cell proliferation and the presence of biomarkers such as "elevated NFKB1 (p=0.017), COL1A1 (p=0.025), SPARC (p=0.025), decreased ALPL (p=0.017), with no significant differences for COL3A1 and SPP1 expression or stimulation times". [31]
Afonina et al.[12]/ 2017	Literature review study	To analyze the molecular mechanisms of the inflammatory process and the relationship of the inflammasome with NF-κB. [12]	A review of the existing literature on "negative regulation of NF-κB and the NLRP3 inflammasome" is performed. [12]	"Post-transcriptional and post-translational mechanisms regulating NF-κB and inflammatory signaling play a key role in the maintenance of immune specificity and homeostasis. [12]
Bhindi et al.[32]/ 2007	Literature review study	Tracking antigen therapies with a primary focus on DNA enzymes and short interfering RNA, which could play an integral role in the future.	A review of the existing literature on "DNA enzymes, short interfering RNA and the emerging wave of small molecule nucleic acid-based gene silencing strategies" is conducted. [32]	"With the ongoing identification of new genes and an appreciation of their regulatory pathways and pathological roles, small molecule antigen strategies have not only emerged as an important molecular approach to delineating the functions of these genes, but are now also a clinical therapeutic reality.". In the future, it is possible that "small molecule nucleic acids may be used to silence disease-causing genes in humans in a targeted manner and with minimal toxicity." [32]

Tomita et al.[33]/ 2000	Experimental in vitro study	To examine the "inhibition of the production of proinflammatory cytokines, adhesion molecules and matrix metalloproteinases (MMPs) from synovial tissue of patients with rheumatoid arthritis by introducing synthetic double-stranded DNA with high affinity for the NFκB binding site." [33]	"NFκB decoy oligonucleotides (ODNs) were introduced into synovial cells derived from rheumatoid arthritis patients. Levels of interleukin-1β (IL-1β), IL-6, TNF-α, intercellular adhesion molecule-1 (ICAM-1) and MMP-1 were determined by enzyme-linked immunosorbent assay (ELISA) and Northern blotting. A cell counting kit was used to study the effect of NFκB decoy ODN on synovial cell proliferation" [33]	"The production of these mediators was significantly inhibited by the introduction of the NFκB decoy ODN compared with the effect of the scrambled decoy ODN. Transfection of the NFκB decoy ODN resulted in significant inhibition of synovial cell proliferation compared with that of the scrambled decoy ODN." [33]
Paredes[20]/ 2022	Literature review study	To establish "the relationship of the NFKB1 gene with Periodontitis and its inflammatory process". [20]	A review of the existing literature on how the presence of the NFKB1 gene is associated with periodontitis is performed.	"The NFKB1 gene is expressed in inflammatory processes, therefore, since periodontitis is an inflammatory pathology, it is directly related to this gene. This data would allow implementing the use of a genetic test when treating patients with destructive or recurrent periodontal disease who do not react adequately to conventional periodontal treatments. Thus proposing a new approach in the diagnosis and treatment of periodontal disease".[20]

Asad et al. conclude that there is a difference in the expression of specific microRNA (miRNA) in cells from patients with periodontal disease vs. healthy samples; the presence of certain systemic conditions such as cardiovascular disease, obesity, and diabetes would also cause their change in gene regulation. Therefore, these microRNAs (miRNA-142-3p and miRNA-146) symbolize promising biomarkers for the diagnostic purposes of Periodontitis. [29] Similarly, Yoneda et al. indicates that "miRNAs, miR-664a-3p, miR-501-5p and miR-21-3p, may serve as serum biomarkers for chronic periodontitis". [30]
Jurdziński et al. [24] point out the importance of using a new approach through basic and clinical studies working in an integrated manner to "create a complete map of epigenetic changes in periodontitis and identify the cell types where these changes occur." Such is the case of the NFKB1 gene, whose polymorphism can cause overactivity of inflammatory cytokines and even cancer [13]; this is why innovative therapies are being developed to replace the use of drugs, i.e., the use of signaling molecules is promoted as an anti-inflammatory regulation technique that acts directly on the mechanism of genes involved in inflammatory diseases. [12]
Jurdziński et al. [24] also mention that in vitro studies about periodontal tissue cells should be directed more toward discovering the factors causing "dysregulation of epigenetic mechanisms in immune cells infiltrating the inflamed gingiva.".
There are extrinsic factors such as infections by "oral pathogens Porphyromonas gingivalis or Treponema dentícola that induce modifications in the expression of the inflammatory process" when these epigenetic changes occur, an "excessive production of inflammatory cytokines, chemokines and enzymes that degrade the matrix" is generated, protein inhibitor molecules can suppress this pathological process with the objective of improving the scenario of "inflammation, osteoclastogenesis and alveolar bone resorption in animal models of periodontitis," therefore the use of such molecules represents a potential therapeutic agent for the modulation of the inflammatory response of the host. [24]
Munegowda [25] used ruxolitinib and CAPE with the aim of inhibiting small molecules involved in the activation of the NKFB1 gene. As a result, the overproduction of cytokines secreted by macrophages was reduced, a fact that demonstrates the protective effect exerted by these inhibitory molecules in the treatment of respiratory diseases.
Tomita et al. [33] suggest the use of NFκB decoy-like Oligonucleotides (ODN) as a potential gene therapeutic for inflammatory synovitis in rheumatoid arthritis since it demonstrated in their in vitro experiment that it inhibits the "production of proinflammatory cytokines." It has also been demonstrated that the regulation of the molecular mechanisms of the inflammatory process offers positive effects [12]; in addition, the "silencing or deregulation of gene expression" promises to be an excellent future treatment for "inflammatory diseases and cancer, seeking to inhibit both oncogenes and genes involved in inflammation". [32]
Several studies have shown that there are "molecular mechanisms responsible for the anti-inflammatory and bone-protective effects of epigenetic drugs observed in cellular and animal models of periodontitis." This would mean that in the future, these studies of epigenetics and their relationship with Periodontitis could be incorporated as hypotheses that could lead to the possibility of using these gene inhibitor molecules as a novel treatment for periodontal disease. [24]
Paredes [20], in his study, concludes that the "discovery of the genes that lead the mechanism of Periodontal Disease would facilitate the creation of a genetic card for each patient and identify the patient's susceptibility to developing periodontitis, among other pathologies."
Marconcini [19] already proposes the use of epigenetics through a previous identification of the genetic risk factors for Periodontitis and that preventive methods can be implemented in patients with greater susceptibility to present periodontal disease. Suzuki[28] on the other hand, has pointed out that "the evaluation and modulation of the epigenetic status of periodontal ligament cells allows to evaluate and accelerate their regenerative tropism to predict more accurate prognoses of periodontal regeneration therapy and to develop precision medicine in periodontal regeneration therapy".

CONCLUSIONS

There are several factors involved in the development of periodontal disease, so its prevalence will depend on several factors, whether they are individual, environmental, or genetic. Therefore, it is concluded that the susceptibility will be varied and specific for each individual. Therefore, periodontal pathology represents a rather complicated process to understand and analyze in a general way, and it is recommended to examine each patient individually to provide a more effective treatment.
Several studies have been presented that facilitate the understanding of epigenetic mechanisms involved in pathological processes, such as specific biomarkers for certain diseases and genes that regulate inflammatory

processes; also, the application of inhibitory molecules that allow the modulation of the inflammatory process of the host has been pointed out.

This bibliographic review allowed the identification of causal relationships between certain altered genes and pathological mechanisms of several diseases, including Periodontitis, thanks to advanced studies in genetics and epigenetics. However, the great challenge at present is the regulation of the immune response by means of epigenetics with the aim of manipulating the expression of those genes that activate a specific process.

The study of epigenetics in periodontics is an adjuvant technique that could be implemented in the future as a new therapeutic aimed at improving diagnostic procedures in patients with fairly recurrent Periodontitis or in unusual cases where there is no positive response to periodontal treatment.

Epigenetics constitutes an important factor in the regulation of the pathophysiological processes of Periodontitis. Based on the present research, it is estimated that new studies will continue to be carried out focused on the discovery of new regulatory treatments that offer an alternative to control inflammation in Periodontitis; that is to say, based on the findings already presented, these can be translated into clinical practice in the future.

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