ISSN: 2455 – 9938
PubMed- National Library of Medicine - ID: 101731611

EIJO: Journal of Science, Technology and Innovative Research (EIJO–JSTIR)
Einstein International Journal Organization (EIJO)
Available Online at: www.eijo.in
Volume – 6, Issue – 3, May – June - 2021, Page No. : 10 - 16

Epigenetics and Its Role in Periodontitis - A Mini Review

[1]Dr Shilpa Jaryal, (Pg Student), Department of Periodontology and Oral Implantology, National Dental College and Hospital Derabassi, Mohali (Punjab) India

[2]Dr Jageer Chhina, BDS, Office Administrator, Aviation Dental Calgary, Alberta, Canada

[3]Dr Gurpreet Kaur, (Hod), Department of Periodontology and Oral Implantology, National Dental College and Hospital Derabassi, Mohali (Punjab) India.

Corresponding Author: Dr Shilpa Jaryal, (Pg Student), Department of Periodontology and Oral Implantology, National Dental College and Hospital Derabassi, Mohali (Punjab) India

Type of Publication: Review Article

Conflicts of Interest: Nil

Abstract

The focus of this review is to provide an overview of the recent findings on the role of epigenetic mechanisms in periodontal disease, including disease susceptibility, progression, and as potential treatment options. The findings on the influence of oral pathogens on epigenetic regulation of pathogen recognition receptors, such as Toll-like receptors, as well as pro-inflammatory cytokines suggest an important role for epigenetics in the regulation of the host immune response. Recent studies also show that the epigenetic pattern in periodontitis lesions differ from that of healthy and gingivitis tissue. In addition, these patterns differ between tissues in the same individual. Research is also indicating a role for both DNA methylation and histone acetylation on cells osteogenic differentiation and bone regeneration. Knowledge of epigenetic pattern in periodontal diseases may add not only to the knowledge of susceptibility of the disease but may also be a diagnostic tool to identify patients at risk to develop the severe form of periodontitis. In addition, recent research within gene therapy and tissue engineering indicate a role for epigenetics also to improve regeneration of periodontal tissues.

Keywords: Epigenetics, Genetics, Periodontitis.

Introduction

Epigenetics is the study of changes in organisms caused by modification of gene expression rather than alteration of the genetic code itself. [1] Epigenome refers to "epi" meaning outside the "genome." In epigenetics, we study mitotically and meiotically heritable changes in gene function that are not dependent on DNA sequence. Epigenetic modifications include chemical alterations of DNA and associated proteins, leading to the remodeling of the chromatin and activation or inactivation of a gene. There are three types of epigenetic modifications [2,3]

1. **DNA methylation,**
2. **Histone modification,and**
3. **RNA-associated silencing (micro-RNA).**

Out of these three mechanisms, enzymatic DNA methylation of the C-5 position of cytosine residues in the CpG islands of the promoter region of a gene is considered as the most important epigenetic mechanisms in mammals. Let us discuss these mechanisms in detail. [4,5]

DNA Methylation

In eukaryotes, it refers to the process by which a methyl group is covalently added to the carbon (at position 5) of cytosine in the DNA strand.Only those cytidine residues that are adjacent to guanidine i.e.the CpG sites (cytidine bound through a phosphate molecule to guanidine) in the DNA strand are targets for the methylation inducing enzymes. The DNA methylation is catalyzed by DNA methyl transferases (DNMT)[6] There are 4 DNA methyl transferases:

1. DNA methyl transferasel (DNMT 1),
2. DNA methyl transferase2 (DNMT 2),
3. DNA methyl transferase3a (DNMT 3a), and
4. DNA methyl transferase3b (DNl\ ll T 3b).

Methylation is an important step in gene transcription. Actively transcribed genes are characterized by the presence of CpG sites in their promoter regions that are hypomethylated.As the CpG sites in the promoter region are hypomethylated, it is possible for appropriate transcription factors to bind to their recognition sequence in the promoter region [7]

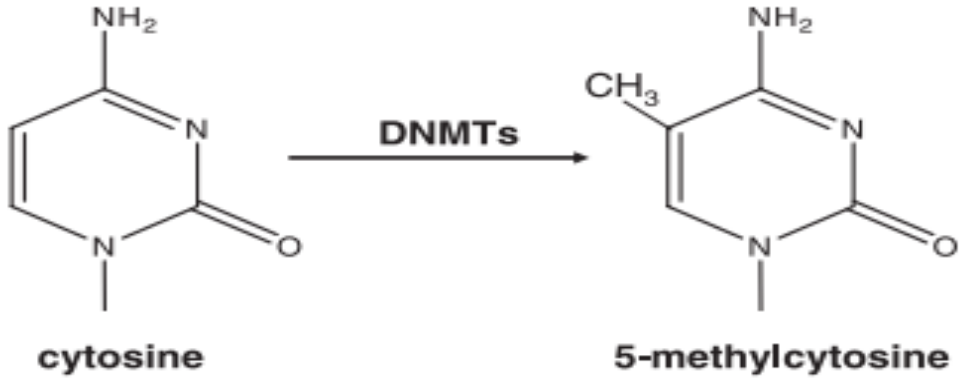

Figure 1: Mechanism of DNA methylation. DNA methylation involves the addition of a methyl group onto the 5 position of a cytosine residue, mediated by the enzymes DNMTs. DNA methylation happens almost exclusively on cytosines in front of a guanine in a CpG dinucleotide.

Hypermethylation of promoter region of genes is associated with transcriptional silencing of gene, thereby loss of gene expression. On the other hand, hypomethylation of promoter region of genes is associated with transcriptional activation of genes, there by leading to gene expression.

Histone modification

In the eukaryotic cells, the DNA is organized in a highly conserved structural polymer termed chromatin.The basic building block of chromatin is the nucleosome which consists of 146 bp of DNA wrapped around an octamer constituted of dimers of core histone proteins H2A, H2B, H3, and H4 held together by an H 1 linker 88. The core histones are evolutionarily highly conserved proteins. They consist of globular domains with a covalently modifiable N-terminal tail at level of lysine and/or arginine residues. There are at least 9 different types of posttranslational modifications (such as acetylation, phosphorylation, methylation, biotinylation, sumoylation, ADP ribosylation and ubiquitination) influence. [8]

Table

The proposed nomenclature for histone modifications

	Lysine (K)	Tri-	me3	H3K9me3
Acetylation	Lysine (K)	Mono-	ac	H4K5ac
Phosphorylation	Serine (S)	Mono-	ph	H3S10ph
	Threonine (T)	Mono-	ph	H3T11ph
	Tyrosine (Y)	Mono-	ph	H3Y41ph
Ubiquitination	Lysine (K)	Mono-	ub1	H2AK119ub1
	Lysine (K)	Di-	ub2	H2AK119ub2
	Lysine (K)	Poly-	ubn	H2AK119ubn
Sumoylation	Lysine (K)	Mono-	su	H4K14su
Biotynylation	Lysine (K)	Mono-	bio	H2AK9bio
Citrullination	Arginine (R)	Mono-	cit	H3R17cit
ADP-ribosylation	Glutamate (E)	Mono-	ar1	H1E15ar1
	Arginine (R)	Mono-	ar1	H1.3R33ar1
	Glutamate (E)	Poly-	arn	H2BE2arn
β-N-glycosylation	Serine (S)	Mono-	glc	H3T32glc
	Threonine (T)	Mono-	glc	H3S10glc
Isomerization	Proline (P)	*cis/trans*	iso	H3P38iso
	Aspartic acid (D)		iso	H2BD25iso?
Crotonylation	Lysine (K)	Mono-	cr	H2BK5cr
Formylation	Lysine (K)	Mono-	fo	H1K17fo
Propionylation	Lysine (K)	Mono-	prop	H3K23prop
Butyrylation	Lysine (K)	Mono-	buty	H4K5buty

RNA-Associated Silencing (MICRO-RNA)

MicroRNAs (miRNAs) are short, non-coding RNA molecules that mediate RNA silencing and regulate gene expression. miRNAs were discovered in 1993 and have been extensively studied ever since. miRNAs are responsible for changes in the cell epigenome because of their ability to modulate gene expression post-transcriptionally. [9]

These can directly target epigenetic factors, such as DNA methyltransferases or histone deacetylases, thus regulating chromatin structure. miRNAs predominantly regulate gene expression via translational inhibition, either by interfering

with the ribosome assembly or by inducing its early dissociation.[10] These miRNAs participate in the epigenetic mechanism by primarily three mechanisms,

1.The expression of miRNAs is regulated by multiple epigenetic mechanisms,

2. miRNAs can repress the expression of epigenetic factors; and

3. miRNAs and epigenetic factors can cooperate to modulate common targets.

Hence, from the above discussion,we can conclude that the following epigenetic modifications are observed, [11]

- DNA methylation- gene silencing.
- DNA demethylation- gene unsilencing.
- Histone acetylation- open chromatin,activetranscription.
- Histone methylation- dosed chromatin, silencing of transcription (generally).
- DNA methylation and miRNAs cooperate in the suppression of gene expression and protein translation of common targets.
- mi RNAs control the chromatin structure by affecting the "histone code" and targeting key enzymes, known as histone modifiers.

Role of epigenetic changes in periodontal disease

As already stated, the epigenetic changes affect gene expression by remodeling of chromatin and selective activation or inactivation of genes. These changes result in the changes in cytokine profile and immune mechanisms. There is a strong evidence in support of the role of genetic factors in the etiopathogenesis of periodontal diseases. [12] However, the role of epigenetics in periodontics is a new area of research.The rate of disease progression, as well as response to periodontal treatment, may vary from patient to patients and this variability is influenced by genetic, as well as epigenetic factors [13]

It has been found that in periodontitis, epigenetic modifications during inflammation occur locally at the biofilm-gingival interface around the teeth. Barros and Offenbacher (2014) stated that The IL17C and CCL25 cytokines play an important part in the immune response to bacteria and in the TH17 cell immune response. It was suggested that changes in their methylation pattern and subsequent increase in gene expression might add to the loss of periodontal attachment in periodontitis.

Toll-like receptors (TLRs) play an important role in pathogen recognition.Hypermethylation and a decreased transcription of Toll-Like Receptor 2 (TLR 2) in periodontitis tissues have been reported % De Oliveira et al. (20 11)

Studied DNA methylation pattern in the TLR2 and TLR4 genes in gingival samples from healthy subjects, smokers, and non-smokers affected by chronic periodontitis. The TLR4 gene promoter was unrnethylated in most samples in all groups, whereas the TLR2 promoter was both methylated and unrnethylated in most samples. [14]

Hypermethylation and subsequent low transcription of TLR2 in periodontitis tissues were reported .In a study on aggressive periodontitis patients, Baptista et al. (2014) found an overall demethylation pattern of the suppressor of cytokine signaling 1 (SOCS) gene. In healthy individuals, this demethylated level was higher, and also total

demethylated samples were found higher for this group compared to periodontitis. [15] A significant difference was also reported regarding the methylation pattern for the long interspersed element-1 (LINE-1) gene.

Epigenetic modifications have also been studied in the production of inflammatory cytokines in periodontitis. Studies have investigated DNA methylation of inflammatory cytokines in various forms of periodontitis. In one study, it was found that the IL-8 promoter was hypomethylated in oral epithelial cells from individuals with generalized aggressive periodontitis compared with healthy controls •

These results were in agreement with another study where analysis of the IL-8 promoter indicated a tissue -specific pattern in DNA methylation •

However, IL-6 promoter was found to be partially methylated in both healthy individuals and patients with periodontitis in spite of the fact that the expression of IL-6 was higher in patients with periodontitis.

Can Periodontal Pathogens Influence The Epigenetic ?

This question was addressed by Yin and Chung in 2011 • The authors reported that Fusobacterium Nucleatum stimulated gingival epithelial cells and these cells showed hypermethylation of the Mucosa-associated lymphoid tissue lymphoma translocation gene 1 (MALTl), thereby resulting in lack of Nuclear factor-kappa B production.

On the other hand, stimulation of gingival epithelial cells with Po1phyromonas gingivalis resulted in hypomethylation of ZNF287, a DNA binding protein believed to be involved in transcriptional regulation.Furthermore, P. gingivalis significantly decreased the tri-methylation of histone H3 K4 protein expression, but F. nucleatum did not. These findings supported the "stealth-like" properties of P. gingivalis supporting the concept of "keystone pathogens".

Epigenetic therapy in the management of periodontitis

Pharmacological agents can be used to revert the effects of epigenetic variations. Histone deacetylase inhibitors and DNA methyltransferase inhibitors have been investigated and are under research. Histone deacetylase inhibitors help in suppressing bone resorption by osteoclasts [16]. Also, the deacetylase inhibitors help in promoting the osteoblast maturation • However, these treatment strategies still need a lot of research before they can be introduced into clinical practice. [17]

Future of genetics in periodontics

A lot of research has been done to identify the genetic basis of periodontal diseases. The understanding of the genetics and periodontal disease progression has provided us valuable information for the identification of disease markers.

Identification of candidate genes and their use as periodontal disease biomarkers is the potential clinical application of the research done so far in this field. These biomarkers may be helpful in identifying patients with enhanced disease susceptibility and associated systemic conditions, identifying sites with active disease and predicting sites that may have active disease in the future. [18.19]

Epigenetics is a complex field with DNA methylation, histone acetylation and methylation linked together regulating gene expression, and just as we think we have come to understand the concept new epigenetic markers are identified. Up to now, it has been widely accepted that the 5mC/5hmC concept is the only form of DNA methylation. However, recently a new form was identified in mouse embryonic stem cells—the N6-methyladenin (6mA or m6A) [20]. This modification was associated with epigentic silencing that influence embryonic stem cell differentiation. In contrast, 6mA was

previously identified in Chlamydomonas green algae but was associated with transcriptional activation since it was mostly being situated near transcription start sites. An additional function suggested for 6mA was to regulate the positioning of nucleosomes, since it was only formed on the linker DNA between nucleosomes [21].

In addition, recently a new field within epigenetics has emerged, called epitranscriptome [22]. In addition to methylation of cytosine bases, and recently adenine bases, in the DNA it has now been discovered that adenine bases in the RNA can also become methylated [23,24]. This epigenetic modification affects RNA stability and translation as well as RNA splicing, i.e., a mechanism that makes it possible for a cell to produce different versions of a protein from one single gene [22]. Two variants of methylation of adenine within RNA have been identified, i.e., N6-methyladenosine (m6A) and the further methylated form N6,2-O-dimethyladenosine [25]. As for the epigenom, the epitranscriptome is dynamic and reversible and may further add to the regulation of mRNA transcription and gene expression.

Conclusion

Periodontal diseases are multi-factorial diseases. Genetics is an important part of these factors. Present knowledge suggests that genetic polymorphism is associated with the pathogenesis of periodontal diseases. Genetic factors, along with environmental factors are strongly associated with the development and progression of periodontal diseases. Identification of specific genes and genetic variants, aids in diagnosis and treatment of aggressive periodontal disease. In future, a lot of research is required in this direction to investigate different aspects of the genetic basis of periodontal disease.

References

1. Epigenetic Inheritance: Concepts, Mechanisms And Perspectives Irene Lacal1,* And Rossella Ventura.
2. Epigenetic Modifications: Basic Mechanisms And Role In Cardiovascular Diseasediane E. Handy, Phd, Rita Castro, Phd,1,2 And Joseph Loscalzo, Md, Phd..
3. Fedorova E, Zink D. Nuclear Architecture And Gene Regulation. Biochim Biophys Acta. 2008;1783:2174–2184.
4. Jirtle Rl, Skinner Mk (2007). Environmental Epigenomics And Disease Susceptibility. Nat Rev Genet 8: 253–262.
5. Dna Methylation And Its Basic Function Lisa D Moore,1 Thuc Le,1 And Guoping Fan1
6. Bhutani N, Burns Dm, Blau Hm. Dna Demethylation Dynamics. Cell. 2011;146:866–872.
7. Bostick M, Kim Jk, Esteve Po, Clark A, Pradhan S, Jacobsen Se. Uhrf1 Plays A Role In Maintaining Dna Methylation In Mammalian Cells. Science. 2007;317:1760–1764.
8. Histone Structure And Nucleosome Stability Leonardo Mariño-Ramírez, Maricel G Kann, Benjamin A Shoemaker, And David Landsman
9. Microrna: Biogenesis, Function And Role In Cancer Leigh-Ann Macfarlane And Paul R. Murphy
10. Berezikov E, Guryev V, Van De Belt J, Wienholds E, Plasterk Rh, Cuppen E. Phylogenetic Shadowing And Computational Identification Of Human Microrna Genes. Cell. 2005;120:21–24.
11. Griffiths-Jones S. Mirbase: The Microrna Sequence Database. Methods Mol. Biol. 2006;342:129–138.
12. The Epigenetic Paradigm In Periodontitis Pathogenesis Vamsi Lavu, Vettriselvi Venkatesan,1 And Suresh Ranga Rao.

13. Kim Ti, Han Je, Jung Hm, Oh Jh, Woo Km. Analysis Of Histone Deacetylase Inhibitor-Induced Responses In Human Periodontal Ligament Fibroblasts. Biotechnol Lett. 2013;35:129–33.
14. Hypermethylation And Low Transcription Of Tlr2 Gene In Chronic Periodontitis Simone Angélica De Faria Amormino 1, Telma Cristina Arão, Adriana Machado Saraiva, Ricardo Santiago Gomez, Walderez Ornelas Dutra, José Eustáquio Da Costa, Jeane De Fátima Correia Silva, Paula Rocha Moreira.
15. Role Of Toll-Like Receptors In Pathogen Recognition S. Janssens And R. Beyaert.
16. Role Of Genetic In Periodontal Diseaseanand Narayanrao Wankhede, Sayli Anand Wankhede1, Shilpa Prashantwasu.
17. Ha S-W, Jang Hl, Nam Kt, Beck Jrgr. Nano-Hydroxyapatite Modulates Osteoblast Lineage Commitment By Stimulation Of Dna Methylation And Regulation Of Gene Expression. Biomaterials. 2015;65:32–42. Doi: 10.1016/J.Biomaterials.2015.06.039
18. Du M, Duan X, Yang P. Induced Pluripotent Stem Cells And Periodontal Regeneration. Curr Oral Health Rep. 2015;2:257–265. Doi: 10.1007/S40496-015-0065-8.
19. Lorden Er, Levinson Hm, Leong Kw. Integration Of Drug, Protein, And Gene Delivery Systems With Regenerative Medicine. Drug Deliv Transl Res. 2001;5:168–186. Doi: 10.1007/S13346-013-0165-8
20. Wu Tp, Wang T, Seetin Mg, Lai Y, Zhu S, Lin K, Et Al. Dna Methylation On N6-Adenine In Mammalian Embryonic Stem Cells. Nature. 2016;532:329–333. Doi: 10.1038/Nature17640.
21. Fu Y, Luo G-Z, Chen K, Deng X, Yu M, Han D, Et Al. N6-Methyldeoxyadenosine Marks Active Transcription Start Sites In Chlamydomonas. Cell. 2015;161:879–892. Doi: 10.1016/J.Cell.2015.04.010.
22. Willyard C. A New Twist On Epigenetics. Nature. 2017;542:406–408. Doi: 10.1038/542406a.
23. Meyer Kd, Saletore Y, Zubo P, Elemento O, Mason Ce, Jaffrey Sr. Comprehensive Analysis Of Mrna-Methylation Reveals Enrichments In 2′ Utrs And Near Stop Codons. Cell. 2012;149:1635–1646. Doi: 10.1016/J.Cell.2012.05.003.
24. Dominissini D, Moshitch-Moshkovitz S, Schwartz S, Salmon-Divon M, Ungar L, Osenberg S, Et Al. Topology Of The Human And Mouse M6a Rna Methylomes Revealed By M6a-Seq. Nature. 2012;485:201–206. Doi: 10.1038/Nature11112.
25. Mauer J, Luo X, Blanjoie A, Jiao X, Grozhik Av, Patil Dp, Et Al. Reversible Methylation Of M6am In The 5′ Cap Controls Mrna Stability. Nature. 2017;541:371–375. Doi: 10.1038/Nature21022