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RESEARCH ARTICLE

EPIGENETICS – AN AVANT GARDE BEACON IN PERIODONTICS

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ABSTRACT

Epigenetics is the study of the mitotically and meiotically heritable changes in the gene function that cannot be explained by changes in the DNA sequence. Epigenetics means "above" or "on top of" genetics. It means the external change or tempering of the DNA that turn genes "on" or "off." These modifications are brought on by several external or environmental factors like diet, stress, smoking, infections etc. They do not change the DNA sequence, but instead, they affect how cells "read" genes. As the quote by Dr Oz goes "Your genetics load the gun. Your lifestyle pulls the trigger." Studies have demonstrated that epigenetic alterations contribute to a number of diseases like cancer, metabolic and autoimmune disorders. An understanding of the epigenetic mechanisms helps to develop novel therapeutic aids which target the specific epigenetic sites. This article aims to review the effects of Epigenetics in Periodontology.

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INTRODUCTION

Epigenetics is defined as heritable changes in gene activity and expression that occur without alteration in DNA sequence. (Bird, 2007) The term "Epigenetics" was coined by Conrad Waddington, who defined it as "the branch of biology that studies the causal interaction between genes and their product, which bring the phenotype into being." (Goldberg *et al*., 2007) The Greek prefix 'epi' in epigenetics means 'on top of' or 'in addition to' genetics. (Berger *et al*., 2009) Epigenetic change can have more damaging effectsthat can result in diseases like malignancies. DNA methylation, Histone modification (methylation, acetylation, ubiquitylation, and phosphorylation) that affect chromatin structure and Non-coding RNA-associated genesilencing are three systems currently considered to initiate andsustain epigenetic change. (Bilian *et al*., 2011) DNA Methylation. (Fig.1) Within the nucleus, chromosomal DNA is tightly associated with proteins, and these interactions form the ordered structure known as chromatin. The methylation takes place in Cytosine-phosphate-Guanine (CpG) dinucleotides of the DNA chain with the covalent transfer of a methyl group from S-Adenosyl Methionine (SAM) to cytosine. (Ji-Yun Seo *et al*., 2015) The enzymatic DNA methylation of the C-5 position of cytosine residues in the CpG islands of the promoter region of a gene is considered to be the most important epigenetic mechanism in mammalscell. Different methylation patterns associated with pathways regulating differentiation, apoptosis, Lipopolysaccharide (LPS) mediated signalling, oncogenesisand cell adhesion were found in inflamed tissue of periodontitis patients compared with tissue from healthy individuals.

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Methylation in Periodontitis

1. Hypermethylation of E-Cadherin and COX-2 in similar proportions in breast cancer and chronic periodontitis subjects. (Loo *et al*., 2010)
2. A positive correlation was found between TLR2 methylation and periodontal probing depth. (De Oliviera *et al*., 2011)
3. A study on Aggressive periodontitis showed an overall demethylation pattern of the SOCSI gene. (Baptista *et al*., 2014)
4. The IL-8 promoter was hypomethylated in oral epithelial cells of generalized Aggressive periodontitis. (Andia *et al*., 2010)
5. CpG sites reported hypomethylation and increased expression of INF-γ in periodontitis biopsies compared with healthy tissue biopsies. (Zhang *et al*., 2010)

6. Tumor Necrosis Factor (TNF-α) It was found to be hypermethylated in Chronic periodontitis. (Zhang *et al*., 2013)

Histone modification

The basic unit of chromatin is the nucleosome. It consists of a DNA segment and eight core histones. The regulation of gene transcription through the post-translational modification of core histones either condenses or relaxes the chromatin. (Ji-Yun Seo *et al*., 2015) The modification of histones takes place mostly at the N-terminal tails of the protein. (Fuchs *et al*., 2006) Acetylation of the core histones results in an 'open' chromatin conformation that facilitatestranscription. Deacetylation of histones removes the acetyl groups, causing the chromatin to become more condensed and inhibit gene transcription. A strong electrostatic interaction occurs between the positively charged acetylated histone residues and the negatively charged DNA causing the deacetylation of histone proteins. Then the gene expression is repressed creating a condensed nucleosomemaintaining histone acetylation of genes related to osteoclastogenesis for preventing bone loss.

Epigenetic Influence of biofilm on periodontitis pathogenesis

Recent evidence has shown that bacteria belonging to the orange and red complex can cause epigenetic changes in the periodontal tissues. Epigenetic modifications may influence periodontal pathogens, because it was shown that an aberrant methylation mechanism can alter the virulence. (Iacopino, 2010) A.actinomycetemcomitans: Methylatyion decreases the ability of the bacteria to invade oral epithelial cells (Wu *et al*., 2006) Campylobacter rectus: Promotes DNA hypermethylation of the IGF2 gene. (Bobetsi *et al*., 2006) Treponemadenticola on periodontal ligament cells showed a decrease in methylation of the MMP-2 promoter. (Miao *et al*., 2014) Porphyromonasgingivalis: produces butyric acid which inhibits HDACs and increases histone acetylation. This in turn was shown to reactivate Epstein-Barr Virus (EBV) as well as human immunodeficiency virus 1, suggesting that periodontal disease may contribute to EBV-related diseases (Imai *et al*., 2009; Imai *et al*., 2012) Herpes viruses may impair the local host defences and thus increase the pathogenic potential of the bacteria. The bacteria in turn may increase the virulence of the herpes viruses. The microbe-induced epigenetic modification of the viral genome may explain the link between viruses and bacteria in the pathogenesis pathway. (Slots, 2010)

Environmental stressors as epigenetic modifiers (Fig.2)

Smoking: The severity of attachment loss was associated with age. (Ohi *et al*., 2006) The increase in attachment loss may be a result of epigenetic changes due to an increase in methylation in the collagen type 1 alpha 1 (COL1A1), a protein in the periodontal ligament seen in elderly individuals compared to younger individuals. (Hillemacher *et al*., 2008) Influence of smoking on global DNA methylation showed that smoking induces generalized alterations in DNA methylation across multiple tissues Intrauterine nutrition**:** Folate deficiency during pregnancy leads to a lack of S-Adenosylmethionine a substrate required for the enzyme DNMT to methylate CpG residues during embryonic development (Okano *et al*., 1999).

Age: There was marked difference in both DNA methylation and histone acetylation in the lymphocytes in older twins. (Fraga *et al*., 2005)

Epigenetic basis for immune regulation in periodontitis pathogenesis

SLE: Increase in gene expression in T cells in these patients. (Mi and Zeng, 2008) The authors suggested that the increase in cytokine expression and pathological T cells might be a result of spontaneous demethylation in certain cytokines. Inflammatory signals that activate nuclear factor kappa B has been shown to alter the histone methylation pattern and activate gene expression. (Yung and Julius, 2008)

Non-coding RNA-associated gene silencing: The non-coding RNA's do not encode for a protein, but they are functionally relevant RNA molecules. These include transfer RNAs (tRNA's), ribosomal RNAs (rRNA's), micro- RNA's (mi-RNA's), and short-interfering RNA's (siRNA's). MicroRNAs (miRNAs) are non coding RNAs that inhibit gene expression by binding to mRNA, by a sequence pairing homology to regulate and fine tune gene expression. miRNA expression is said to be altered in response to bacterial products but also inflammatory cytokines can influence the regulation of miRNA production. Another class of non coding RNAs, the long non-coding RNAs (IncRNAs) bind to chromatin regulatory proteins there by controlling access or inhibition of proteins binding to enhancer regions in the DNA. One function of these RNAs in the immune response has been suggested to involve the regulation of host response, including innate immunity.

Dental implants

Based on the several studies, advance epigenetics will be able to turn on or off the genes responsible for body's negative response. Epigenetic treatment may be able to turn off body's response to periodontal disease to give time for treatments and antibiotics to work. This could protect dental implants. (Williams *et al*., 2014)

Periodontitis as a risk for systemic diseases – an epigenetic link: Histone deacetylase inhibitors have been used for the treatment of chronic inflammatory diseases involving bone.Perrietal studied the expression profile of micro-RNA in obese individuals with and without periodontitis.[27]In obese individuals with periodontal disease, different mi-RNAs were upregulated. These micro-RNAs are said to be involved in the regulation of genes coding for cytokines, collagen, chemokines and some important lipid mediators. According to studies by Meng and Aiko periodontal infection could lead to placental-fetal exposure and when coupled with a fetal inflammatory response leading to preterm delivery (Bobetsis *et al*, 2006).

Methods for analysing epigenetic mechanisms: Technological advances have enabled the analysis of epigenetic analysis on a large scale. DNA methylation can be detected and quantified by the following techniques: Bisulphite conversion.-In this technique sodium bisulphite modification of DNA enables the conversion of unmethylatedcytosinesto uracil, while the methylated cytosines remain unchanged. (Clark *et al*., 1994) Global DNA Methylation Analysis-High Performance Liquid Chromatography (HPLC) is a classical method to quantify global DNA methylation. (Ehrlich *et al*., 1982) Gene-specific methylation analysis-can be characterized as either "candidate gene" or "genome-wide" approach.

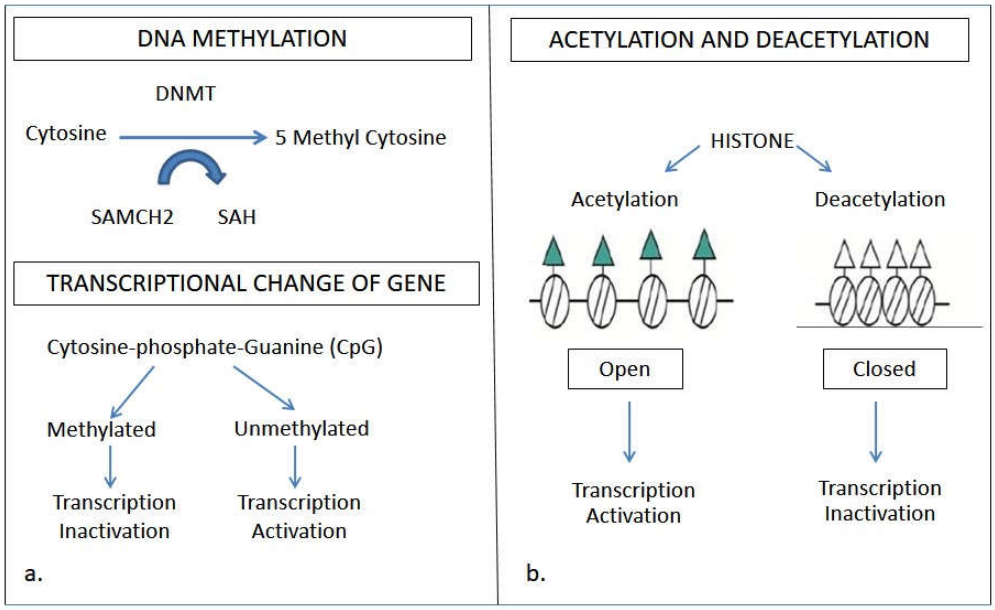

Fig.1. a.DNA Methylation and transcriptional inactivation of gene. b.Acetlation and deacetylation of histones

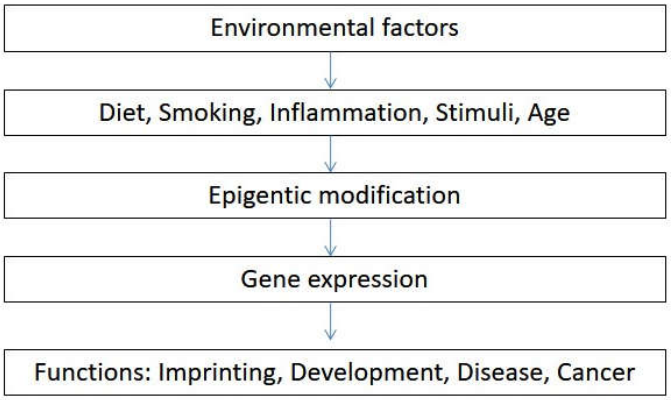

Fig 2. Environmental factors as epigenetic modifiers

Methods for genome-wide analysis: Microarray-based genome-wide analysis. Three main classes of microarray methods have been developed to map the 5-methylcytosine patterns in genomes

1. Methods which enrich the highly methylated regions using an antibody specific for 5-methylcytosine or methyl-binding proteins.
2. Methods based on bisulphite modification.
3. Methods using methylation-sensitive restriction enzymes.

Analysis of histone modifications: The histone modification signals can be captured by chromatin immuno-precipitation (ChIP), in which an antibody is used to enrich DNA fragments from modification sites. ChIP-chip, ChIP-PET, ChIP-SAGE are some of the several ChIP based techniques (Impey *et al*., 2004; Kim and Ren, 2006).

Clinical Applications of epigenetic therapy: Epidrugs are defined as ‘‘drugs that inhibit or activate disease-associated epigenetic proteins for ameliorating, curing, or preventing the disease. (Ivanov *et al*., 2014) Histone deacetylase inhibitors and DNA methyltransferaseinhibitors have been in the vanguard of these approaches.

Histone deacetylase inhibitors: It helps in supressing bone resorption by osteoclasts. The deacetylase inhibitors help in promoting osteoblast maturation using a HDAC inhibitor, 1179.4b showed reduced alveolar bone loss and less osteoclasts/mm2 in mice with P.gingivalis induced periodontitis. (Cantley *et al*., 2011)

Bromodomain and Extraterminal Domain (BET inhibitor)

JQ1 proteins are the epigenetic regulatory proteins. They scan the acetylated histone tails and convert transcription complexes to regulate gene transcription. In inhibiting inflammatory response and alveolar bone loss in experimental periodontitisin. A study conducted by Meng *et al*, the findings suggested that JQ1 may be a potential treatment model for periodontitis. (Meng *et al*., 2014) The results of the above studies represent preliminary work on epigenetics as part of host modulation therapy for the management of periodontitis. Histone deacetylase inhibitor and sodium butyrate act by inducing the differentiation of periodontal ligament fibroblasts into osteoblasts. Kim *et al* concluded that this histone deacetylase inhibitor was a potential therapeutic agent for periodontal regeneration. (Kim *et al*., 2013)

Conclusion

These epigenetic changes can cause "silencing/ shut down" of genes involved in local defences and so the chances of survival of the microbes in the local microenvironment is significantly enhanced. it needs to be ascertained whether these epigenetic alterations lead to increased susceptibility to the disease or whether they are a consequence of the long-standing chronic inflammatory response. It is a "chicken or egg" scenario which is most perplexing. Geneticists have made terrific progress and have developed drugs that target the "epigenetic sites." These drugs can be used as valuable adjuncts to conventional periodontal therapy. This type of therapeutic approach is showing great promise in the treatment of other diseases affected by aberrant epigenetic marks like cancer, lupus, The challenge with this approach is to specifically target the epigenetic marks which have negatively influenced the gene, leaving alone the beneficial ones that help maintain health. It has always been thought that "our genes are set in stone" and are beyond our influence. The concept that the epigenome can be altered by pharmacologic intervention is very profound and empowering.

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