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Epigenetics -A Step Forward In Understanding Periodontitis

[1]Dr. Anjalie Prakash, Dept of periodontics, Amrita Vishwa Vidhyapeetham, Kochi.

[2]Dr Amala K, Dept of periodontics, Amrita Vishwa Vidhyapeetham, Kochi.

[3]Dr. Angel Fenol, Dept of Periodontics, Amrita Vishwa Vidhyapeetham, Kochi.

[4]Dr. Rajesh Vyloppillil, Dept of Periodontics, Amrita Vishwa Vidhyapeetham, Kochi.

[5]Dr. Biju Balakrishnan, Dept of Periodontics, Amrita Vishwa Vidhyapeetham, Kochi.

[6]Dr. Ashmy Stephen, Dept of Periodontics, Amrita Vishwa Vidhyapeetham, Kochi.

Correspondence Author: Dr Amala K, Dept of periodontics, Amrita Vishwa Vidhyapeetham, Kochi.

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Abstract

Periodontitis is one of the most common oral diseases characterized by infection and inflammation of supporting tissues of the teeth which is caused by extrinsic and intrinsic factors. The prevalence of periodontitis is closely correlated with the outgrowth of the pathogenic micro biota, few signs of susceptibility and recurrence are seen even after therapy. An increased risk for periodontitis has been shown with the variations in genes related to the inflammatory response. Interestingly, some of the genes regulated by epigenetic modifications are modified in response to environmental stimuli. Conditions such as cancer, autoimmune or inflammatory diseases have been dispensed by epigenetic mechanisms. Despite decades of study, our understanding of several aspects of periodontal pathogenesis remains inadequate. Epigenetics allows complex evaluation of different variations of gene expression to be carried out, giving a great advantage to the static measurement of genetic markers. Recent research in genetic variants and genome-wide study indicates that differences in genes related to inflammatory response are associated with increased risk of periodontitis. Understanding these molecular mechanisms and early detection of susceptibility can lead to potential diagnosis, treatment and prevention of periodontal disease.

Keywords: Epigenetics, Periodontitis, Epigenetic Modification, Gene Expression, Genetics.

Introduction

Periodontitis is a multi-factorial inflammatory disease which includes both extrinsic (modifiable) and intrinsic (non-modifiable) factors. Even though the definitive mechanisms remains unclear, many opportunistic microorganisms such as P.gingivalis, T.forsythia and A.actinomycetemcomitans, through their outgrowth

causes inflammation and infection in the oral environment. The epithelial cells within the oral cavity are continuously exposed to high levels of bacterial stimuli, mainly gram negative anaerobic bacteria, activating molecular signaling, which in effect initiates an immune inflammatory response in the host to inhibit or eliminate these microbial cells. This immune response if excessive results in the destruction of tissue and loss of alveolar bone in certain individuals.

It has been indicated that genetic polymorphisms, environmental risk factors, lifestyle factors and epigenetic factors relate to the severity of a disease and susceptibility in developing periodontitis by the individual. The interaction between genetics and environmental or lifestyle factors is considered by epigenetics. Altered epigenetic patterns can lead to inflammation and disease susceptibility as there is individual difference in local gene expression.

Epigenetics was defined as a “stably heritable phenotype resulting from changes in a chromosome without alterations in the DNA sequence”. The meaning of the prefix ‘epi’ in Greek means 'on top of' or 'in addition to' genetics[1]. The concept epigenetics refers to modifications in gene expression which are not encoded in the DNA sequence. Chemical alterations in DNA and the related proteins, leading to chromatin remodelling and the activation or inactivation of a gene, are epigenetic modifications. Such modifications may result in the development and maintenance of cancer and autoimmune and inflammatory disorders, including periodontitis. It is interesting to note that some epigenetic modifications are reversible, and environmental factors can cause or alter them and therefore linking the genome inherited and the environment. DNA methylation, histone acetylation and methylation are the two primary epigenetic modifications. DNA methylation is a mechanism that adds methyl groups to the DNA molecule.

Methylation may modify the behaviour of the DNA fragment without modifying the sequence. When present in a gene promoter, DNA methylation usually acts to suppress gene transcription. Histone methylation is the transition by histone methyltransferase (HMT) of one, two or three methyl groups from S-adenosyl-L-methionine to lysine or histone protein residue arginine. The enzymatic addition of acetyl group (COCH3) from acetyl coenzyme A, results in histone acetylation. The mechanism of histone acetylation is closely involved in the regulation of several cellular processes, like chromatin dynamics and transcription, differentiation, DNA replication, DNA repair, gene silencing, cell cycle progression, apoptosis, neuronal repression and nuclear import[2]

Role of epigenetics

In an effort to develop improved diagnostic tools and patient care, researchers are now actively studying epigenetic changes seen during initiations, development and metastatic stages of cancer. Epigenetic changes have been observed during fetal development, cancer progression, or chronic diseases such as autoimmune diseases, diabetes mellitus, cardiovascular diseases, and mental illness in adult. The epigenetic mechanisms related to gene regulation are:

Imprinting

Diploid organisms attain two copies of each gene, one from each parent. Mostly, both copies are either repressed or transcribed identically. Researchers have proposed that genes inherited from each parent have been permanently marked or imprinted. Therefore, patterns of expression, depending on the maternal and paternal inheritance, will exhibit a mosaic pattern from the parents[3]. The main mechanism behind imprinting is DNA methylation. During this process a copy of gene is labelled with the

DNA methylation according to the parental origin and this methylation is retained during the cell division by 5-cytosin DNA methyltransferase-1 (DNMT1). DNMT1 performs methylation within CpG hemimethylating regions and these methylated patterns are repeated with the newly synthesized DNA strands. During fetal development IGF2 imprinting is regulated. IGF2 is an important somatic growth factor for the fetus and any disruption or misregulation may have adverse effects. Therefore, an important component for proper development is the epigenetic program that regulates IGF2 gene expression.

Development

The somatic epigenetic inheritance such as DNA methylation and chromatin remodelling patterns, is very important in multicellular eukaryotic organisms development. Although the sequence of genes is constant, differentiation of cells are into many different types. They perform dissimilar functions and respond to the environment and intercellular signaling differently. The underlying epigenetic mechanisms are therefore the key to the various kind of cellular differentiation and functions. In tooth development epigenetic processes also play a key role. The developmental processes can be affected by epigenetic factors present in each developmental stage. For example, histone demethylase can control the differentiation of the stem cells. Some studies suggest, that dental differences in monozygotic twins of the same genotype is a result of epigenetic implications during tooth development.

Environmental factor

Due to environmental factors, modulation of DNA methylation has been shown to start as early as the prenatal stage. According to Baker et al, intrauterine exposures could result in fetal programming that even persists at adulthood, and could increase the risk of adult diseases like cardiovascular disease and type 2 diabetes[4]. Intrauterine nutrition may therefore have an important effect on the fetal's epigenetic programming. Maternal folate deficiency may lead to the development of DNA hypomethylation, which may lead to excessive gene expression and genetic instability in fetal stage. Moreover epigenetic changes may be influenced by multiple dietary or other environmental factors throughout life.

Inflammation

Several studies suggest inflammation as a result of epigenetic changes, including methylation of DNA, histone modification, and microRNA targeting. Several experiments have shown that triggering immune responses can lead to potential epigenetic changes. Ito reported that inflammatory signals promote the activity of nuclear factor kappa- light chain -enhancer of activated B cells (NF-kB), thereby potentially modifying histone methylation patterns and promoting gene expression[5]. Such findings can impact diseases such as periodontitis. Several studies have documented that infected pulp and periodontal tissue can modify inflammatory cytokine patterns of gene expression. It is therefore necessary to determine the roles of these modifications as epigenetic biomarkers for the prevention and treatment of dental diseases.

Cancer

In cancer DNA methylation is a well charecterized epigenetic modification. As key factors of carcinogenesis, these epigenetic changes are verified hypomethylation occurs in most tumors, which increases the activity of transcription. This often happens in an unstable sequence and is associated with increased incidence of tumors. It has been considered as the earliest epigenetic modification indicating changes from normal to pre-malignant cells. In contrast, several studies have indicated that

hypermethylation of tumor suppressor gene is also associated with carcinogenesis.

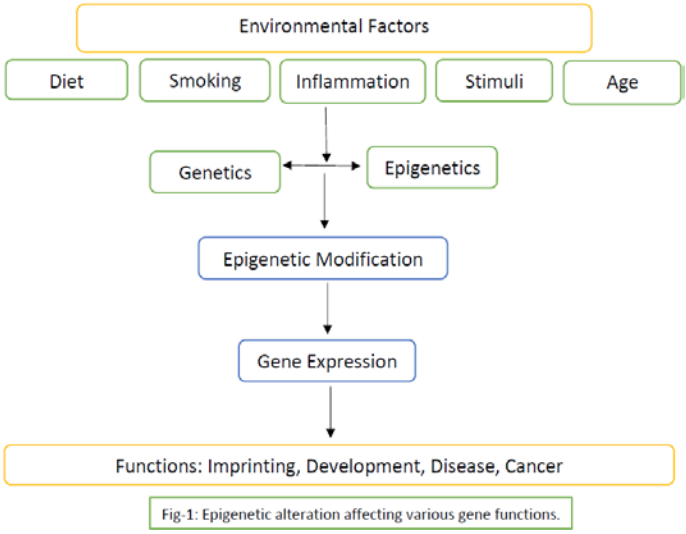

Fig-1: Epigenetic alteration affecting various gene functions.

Epigenetics in Periodontitis

Inflammation-specific gene expression and epigenetic regulation.

Typical inflammatory response leads to the upregulation of genes associated with the formation of lectins, which then coat the surfaces of epithelial cells with the purpose of recruiting neutrophils at the infection site. It initiates an immune response involving processes linked to both innate and adaptive related process. At this point, the most important role seems to be played by epigenetic regulation of patterns of gene expression and is crucial in the upregulation of proinflammatory cytokines and other signalling molecules to trigger a full response from immune cells while at the same time reducing anti-inflammatory cytokines. The cytokine genes are indicated as targets for several epigenetic activities, including transcriptional activation by loss of DNA methylation and active histone modification in regulatory elements.

Epigenetic mechanisms can regulate the genes IL-1, IL-2, IL-6, IL-8, IL-10, and IL-12. Proinflammatory cytokines are strongly expressed in chronic obstructive pulmonary disease by increased H3K9 acetylation in CBP / p300 promoters and reduced histone deacetylase activity following the addition of NF-kB to gene promoters. TNFA, encoding TNF-α, is also regulated in response to acute stimulus in myeloid cells by epigenetic modifications. DNA methylation also requires cytokine expression like interferon gamma andIL-10 through transcriptional inactivation and skewed segregation of IL-10 regulatory T cells, respectively. In contrast to cytokines, DNA methylation in bronchial and intestinal epithelial cells regulates TLR-2 and TLR-4, associated with increased proinflammatory response. The TLRs, expressed on the cell surface, are involved in the recognition of bacterial components such as lipoproteins, lipo-polysaccharide, flagellin, and DNA, so that DNA methylation-mediated regulation of their expression is crucial to determining the magnitude of the bacteria-induced response[7]. Signalling inflammation itself influences cells during epigenetic changes. IL-6 and IL-1b both facilitate DNMT transcription and protein activity Increases in cytokine-induced methylation lead to multiple target genes being repressed in transcription. Taken together, cytokine profiles are determined by the selection of cytokine profiles to satisfy environmental stimuli and by regulating downstream target genes to respond to cytokines as a major role in the initiation and progression of inflammation.

Epigenetic alterations in periodontitis

Epigenetic experiments on the epithelial lining of the oral cavity are in their beginnings, but several studies have shown that these cells have a remarkable ability to respond to environmental factors. The inflammatory response in the periodontal cavity includes upregulation of transcription factors and related alterations in epigenetic chromatin to other inflammatory diseases. Patients with chronic periodontitis showed overexpression in their inflamed tissues of cytokines such asIL-6and IFN- γ[8]. Genetic evidence further confirms the relationships

between IL-6 and periodontitis. The expression modifications of some loci occur as a result of the lack of methylation in their promoters. On the other hand, the overexpression of IL-6 is not associated with DNA methylation at its promoter. Upregulation of IL-6 can activate the DNMTs, resulting in methylation changes in the target genes induced by IL-6 and development of chronic inflammation [7].

Zhang et al. [8] showed that the TNF-α promoter was hypermethylated at two CpG sites, resulting in decreased expression. In reversing methylation by treatment with an in vitro demethylating agent, TNF-α increased expression was shown to be regulated by methylation. Lower expression in patients compared to healthy controls was, however, in conflict with a previous report [9]. The authors speculated that the discrepancy might be due to the difference in the state of inflammation of the patients, considering the fact that only severely afflicted patients showed elevated TNF-α [10]. It could also be attributed to the not always direct relationship between the level of mRNA and the level of protein. In either way, further experiments are needed to determine the role of TNF-α in periodontitis.

More confirmation of epigenetic changes associated with periodontitis is given by COX-2 data an enzyme regulating the production of prostaglandins that facilitate inflammation and pain. It has been reported that COX-2 inhibitors have been able to reduce the symptoms in patients with periodontitis. Similarly to TNF-α, methylation modifications occur more frequently in periodontitis than in healthy individuals, but it remains unclear whether it is consistent with periodontitis aetiology, or rather suggests the influence of DNMT activation on persistent chronic inflammation.

In addition to DNA methylation, periodontitis encompasses other epigenetic changes such as histone modifications. Maintaining histone acetylation of osteoclastogenesis-related genes was found to be critical for the prevention of bone loss in periodontitis. Treatment with the histone deacetylase inhibitor (HDACi) resulted in increased bone levels. In some experiments, it has been shown that various epigenetic changes in DNA and histone affect IL-10 gene expression.

Clinical Applications Targeting Epigenetic Modifications

There are numerous reports about the use of such epigenetic inhibitors in cancer research. Different areas for use of the epigenetic factors have been identified to enhance individualized drug therapy during which pharmacoepigenetic biomarkers can be used to anticipate drug reaction. It would be possible to observe epigenetic changes in specific tissues by using more easily accessible bodily fluids. Epidrugs are defined as" drugs that inhibit or activate disease-associated epigenetic proteins for ameliorating, curing or preventing the disease”[11]. However, current researchers have discovered that the use of epidrugs (HDACi) can prevent the accumulation of head and neck cancer cells and increase in the sensitivity to chemotherapy by tumor cells. HDACi was found not only to regulate histone acetylation, as well as to influence DNA methylation.

Future Epigenetics Scope: Numerous genomic studies have been conducted in the field of medicine. Whereas in dentistry there is little focus on the role of genetics in preventing the disorder or in providing treatment on the basis of genetic variations. Most periodontology research focuses on molecular analysis which focuses on aetiology, pathogenesis and disease prognosis. The application of genetic research is complicated, but the common use of genome-wide analysis in the future will lead to a preventional regimen.

Conclusion

Periodontitis is a chronic inflammatory disease and its recurring nature could also have a substantial systemic impact on health by serving a risk factor for atherosclerosis, chronic obstructive pulmonary disease, diabetes mellitus, pregnancy complications, and rheumatoid arthritis. The traditional method of periodontal disease management includes procedures targeted at bacteria or pathogens. These have drawbacks, such as disease recurrence and resistance to bacteria. It is therefore highly desirable to develop new therapeutic approaches for chronic inflammation based on the regulation of the innate immune response of the host. Knowledge of the role of epigenetics in the production of periodontal diseases is still limited, although the prevalence of the disease is higher. The detection of genetic factors and epigenetic changes in periodontitis will therefore be helpful in developing effective therapeutic interventions. Progress in studies of epigenetic modifications during inflammatory response opens up opportunities for the development of effective therapy for specific targets and restoring normal cell function.

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