

# Epigenetics- Epidisease- Epidrug: A Key Context Folded inside of Periodontal Diseases

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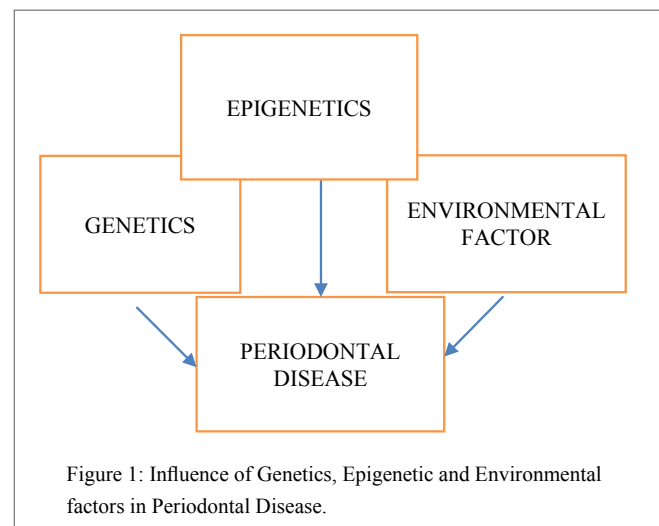
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## Abstract

Compelling evidence has covered potential risks that may trigger a wide spectrum of illnesses (e.g., cardiovascular, stroke, mental diseases, rheumatoid arthritis, and diabetes) in association with chronic inflammatory events. Of the inflammatory events, the focus of this review is on periodontitis. Periodontitis facilitates an oxidative stress-mediated, imbalanced immune system through aberrant epigenetic regulatory machinery. Connectivity default, as a chain of surveillance (or immune) system between genomics and epigenetic modules, lead to onset of disease pathogenesis. The method to link the sensitivity in epigenetic molecular networks and vulnerability against various environmental threats is still unclear. Adverts new era of omics include advanced traditional imaging skills and its tools, and oral health care by adapting new paradigm of epigenomes, which could reduce potential risk such as chronic periodontics disease, followed by other secondary disorders. A part of the epigenetic, post-translation approach could contribute to the prevention and prediction scale in personalized sampling and analyzed outcomes, which are being updated by empowering systematic assessments from bench to clinic after uploading them with molecular epigenetic tools. Current progress in drug development application unveils the connective value of epigenetic in terms of sequential molecular deficit, referring to infection pathogenesis focus on advanced periodontal disease- periodontitis. In addition, Health burden is increasing with the aging population and must be considered in order to reduce medical expenses and improve quality of disease monitoring and surveillance (QDMS). Therefore, another connective value is lessening health burden by understanding the impact of epigenome as countermeasures in the future asset.

## Introduction

The term epigenetic describes the machinery that acts over DNA and controls gene expression and cellular phenotype. With this mechanism, the epigenome controls gene expression by silencing or activating gene transcription [1]. Gene regulation mainly regulated by mechanism called DNA methylation, Histone modification and Non-Coding RNA. Epigenetic modification is responsible for wide variety of cellular process from cell differentiation and proliferation, to stress response mechanism and apoptosis [2]. Epigenetic mechanisms including DNA methylation and histone modifications are the link between environment and genome [3]. These mechanisms control DNA expression and determine the genetic outcomes. The epigenome is prone to changes after receiving direct and indirect environmental factors that can eventually cause perturbations in the epigenetic patterns [3]. It has been already reported that adverse social environment and stressing early life experiences can have impact on gene regulation, which leads to initiation and progression of periodontal disease (Figure 1). The implications of the relation between periodontal disease, environmental factors and epigenetics have been established through a number of studies [4] (Figure 1).



Epigenetic modifications, such as methylation and acetylation, are the most researched modifications, due to the fact that they are correlated with many diseases including periodontitis.

## DNA Methylation

It occurs by addition of methyl group to a cytosine, one of the nucleotides of DNA [5]. However, it only occurs where cytosine is next to guanine. This modification is often localized at CpG (Cytosine-phosphate-Guanine)-rich sites. The addition of a methyl group is controlled by enzymes called DNA methyltransferases (DNMTs) - DNMT1, DNMT3a and DNMT3b. Hypermethylation results in inhibition of gene transcription whereas hypomethylation results in activation of gene [5].

## Histone Modification

Histone is a core proteinaceous structure in which DNA is wrapped around. DNA condensation and expression of gene are highly determined by inner core nucleosome. Histone can be modified by the addition of acetyl, methyl, or phosphate group that can affect chromatin condensation and allow or prevent gene expression. The common form of histone modification is acetylation which is mediated by an enzyme called histone acetyl transferase (HAT) [6].

## Non-Coding RNA

Unlike coding RNA, Non-coding RNA (NcRNA) does not possess an open reading frame (ORF) and translated to protein. It inhibits gene expression by interaction with the nascent RNA molecule [7].

## Histone Code: A Writer, Reader and Eraser

The “writers” (e.g., methyltransferases, acetyltransferases) are modifying enzymes, capable of incorporating methyl, acetyl or other epigenetic group on histones [8]. The feedback is mainly provided by the “readers”, which recognize specific modifications or combination of modifications on the histones. The readers are effect or proteins containing interaction domains capable of recognizing epigenetic modifications [8]. In addition, the “erasers” (e.g., demethylases, deacetylases), through which enzymatic activity remove the histone modification, can also be recruited (both by readers and the modification itself) and regulate the distribution pattern of the marks [8].

## Periodontal Disease as an Epi-Disease

Periodontal disease is a chronic inflammatory disease in which persisting inflammation leads to tissue destruction. Like other chronic disease periodontal disease is no longer considered a disease caused by a single factor but is now considered a multi factorial disease [9]. Genetic and epigenetic factor contribute to periodontal diseases. It is found that epigenetic processes such as methylation, demethylation, acetylation, deacetylation and a combination of all activities are key factors in inflammatory diseases such as periodontal disease [10]. These processes triggered by environmental influences like smoking, stress, aging, race, gender, diabetes, BMI etc. [11]. Evidence suggest that oral pathogens, such as *Porphyomonas gingivalis* (*P. gingivalis*) and *Fusobacterium nucleatum* (*F. nucleatum*), play an important role in Histone acetylation [12]. Furthermore, activation of oral pathogen recognition receptors and pro-inflammatory cytokines further induce histone methylation in oral epithelium [12]. The study suggested that chronic inflammation in periodontal disease may be associated with DNA methylation [13]. It is also found that in chronic inflamed tissue, hypermethylation of the PTGS2 associated with a reduce level of PTGS2

transcription resulted in reduced COX-2 expression [13]. Similarly, decreased expression of INFA was reported when it was hypermethylated at CpG site. Oppositely, hypomethylation and increased expression of IFNG have been reported in literature [14]. Similarly, the results of another study have revealed that Histone acetylation caused an enhanced over expression of pro inflammatory cytokines (such as IL-1, IL-2, IL-8 and IL-12), initiation and development of periodontitis [15].

## Epi-Drug for Periodontal Disease

Because of the fact that epigenetic malfunctions are reversible, aberrant distribution of epi-markers can be corrected. In recent years several drugs have been exploited that can reverse DNA methylation and Histone deacetylation [16]. These so-called epi-drugs are the inhibitors of DNA methyltransferases (DNMTs), histone deacetylases (HDACs), and histone methyltransferase enhancer. There are two types of enzymes regulating the acetylation patterns across the genome – histone acetyltransferases (HATs) and deacetylases (HDACs).

## Histone Methyltransferase inhibitors HMTi

### Chaetocin

A natural secondary fungal metabolite produced by the mold species. It inhibits selectively HMTs, specific for H3K9 methylations, such as SUV39H1 (predominantly), G9a, SETDB1, in a SAM-competitive manner. It has been shown to have antimicrobial, anti-inflammatory and, more importantly, anticancer properties [17]. Chaetocin have been proven to be an effective drug candidate for prevention of bone resorption in periodontal diseases. Results from animal study suggest that chaetocin suppresses RANKL-induced osteoclastogenesis and cell growth through blimp1 down regulation, followed by induction of anti-osteoclastogenic genes and cell growth suppressors [18].

### BIX01294

It specifically targets GLP and G9a HMTs. Unlike Chaetocin, its inhibitory effect is by occupying the histone binding pocket of the HMTs, rather than competing with SAM. These HMTs are involved not only in the methylation of H3K9, but also in non-histone methylation of proteins such as p53 (a tumor suppressor protein) [19]. As hypermethylation of p53 has been linked to periodontal disease, the possibility of selectively inhibiting G9a and GLP provides promising direction for periodontal therapy. The effect of BIX01294 on osteoclast differentiation has been reported in many studies. BIX01294 dose-dependently reduced RANKL (receptor activator of nuclear factor- $\kappa$ B ligand) -induced osteoclast-like cell differentiation [20].

## Histone Acetyltransferase Inhibitors (HATi)

By far only few natural HAT inhibitors have been identified as potentially promising epi-drugs. These include Anacardic acid (isolated from cashew), Garcinol (derived from Kokum) and the popular Indian spice Curcumin. Anacardic acid has an antimicrobial and antioxidant property. Thus, it is capable of protecting oral cells from oxidative stress and providing an antimicrobial effect against periodontal pathogens [21]. Therapeutic effects, such as anti-oxidative, anti-inflammatory and anti-cancer property of garcinol have been reported in both in vivo and in vitro animal studies [22]. Similarly, naturally occurring anti-inflammatory agent like curcumin also found to be effective as an adjunct to traditional periodontal therapy [23]. Due to these functions, HAT inhibitor (HATi) has been proposed to be a useful therapeutic agent in periodontal therapy.

## Histone Deacetylase Inhibitors (HDACi)

Histone deacetylases, naturally, exert the opposite effect, by removing the acetyl groups from histone Lys residues which alters its charge and thus promotes compaction of DNA in the nucleosome [24]. By altering the transcriptional activity of bone-associated genes, HDACs control both osteogenesis and osteoclastogenesis. As a result Class I and class II HDACi were found effective in suppressing alveolar bone loss in mouse model [25]. Functional aspect of sodium butyrate ( $C_4H_7NaO_2$ ) as HDACi indicates that potential capability as a periodontal regenerative agent by inducing differentiation of periodontal ligament fibroblast into osteoblast. Therefore, HDACis have the potential to be used for the management of periodontitis [26].

## Conclusion

Currently, it appeared the connectivity matter between inter- or intra-molecular networks in chronic disease paradigm by which molecular rearrangement /re-shaping could affect intricate symptomatic change in disease progression covering infection diseases like pneumoniae and neurodegenerative disorders, including Alzheimer diseases (AD), etc. Aspect of stability and adaptation of survival signaling in genomics spur to visualize the potential value to explore consequences and provide new solution to lead new avenue of drug discovery. Oral disease is a challenging issue that is highlighted the need to evaluate the medical cost, and its prevention under a public health umbrella could possibly trigger other chronic disease. In that point, periodontal disease is good model for epigenome as a post-translational model to understand the interface between stimuli from environmental threats to internal flora of micro biome influences. In addition, accumulation of environmental threats such as diet, pollution, stressor and aging is enough to alter genetic backbone along with their small micro-regulators such as RNA, micro RNAs, long non-coding RNA (lncRNA), and transcription factors. To determine its cause and modify new molecular shape with regard to its functional endpoints reflecting genomics stability, epigenomics as a part of Omics similar to epigenetic and transcriptomics, this review illuminates the imbalance of each chromatin modification players such as histone methyl transferase (HMT) and histone acetyl transferase (HAT) which play a key role in the disease determination process. In addition, the impact of DNA modifier such as DNA methyl transferases (DNMTs) on inflammatory machinery could be influenced to onset of infection process such as periodontal disease due to skewed immune regulatory guidance. Furthermore, potential efforts like molecular targeting could lead to therapeutic countermeasures after unveiling multi-dimensional catalytic interaction site upon structural and molecular reassembling affect to phenotypic(or symptomatic) endpoint. Epigenetic as endogenous surveillance system and potential adaptation molecules should be evaluated on how the molecular network cope to environmental change along with ecology of micro flora within oral milieu shed light on the new avenue to target in the prevention and prediction to determine potential risks in genetic level by patterning molecular behavioral change as a byproduct following sequential interact me (molecular interaction +omics) or cellomics (cell tropism +Omics) in periodontal diseases.

## Future Perspectives

With an emerging foundation systemic approach with functional analysis stemming from an advancement of genomics tools and skills, genomics instability alteration of HDACs signature along with balance of HAT and/

or HMT in the category of epigenetic modification enzymes could affect the transcriptomics level and inflammation aspects along with DNMTs as a consequence in the disease pathogenesis. Fragmentation of epigenetic consequences could connect to secondary diseases during aging. On a similar note, there is a need to counteract rare oral diseases with unknown causes such as aberrant chromosomal in chronic and acute disorders, which could be associated with mucosal immune deficiency. In overcoming continuous challenges through innovative efforts, advancements in determining cell tropism and molecule determinants will bolster the Omics platform in the periodontal pathogenesis to reveal the impact of epigenetic imbalance, which is rooted in the exposure of environmental and genetic factors combined with exposure of various food toxins. These potential threats in micro milieu could lead to visualization of new avenues to develop new therapeutic options involving small molecules or functional biologics.

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