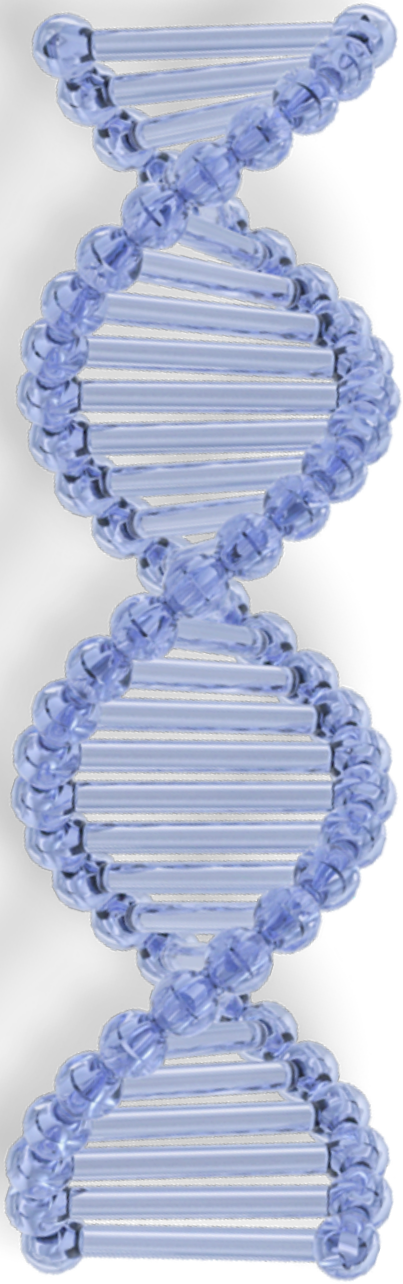

# PERSONALIZED PERIODONTAL DISEASE - OUTCOME OF EPIGENETIC ALTERATIONS IN PERIODONTIUM

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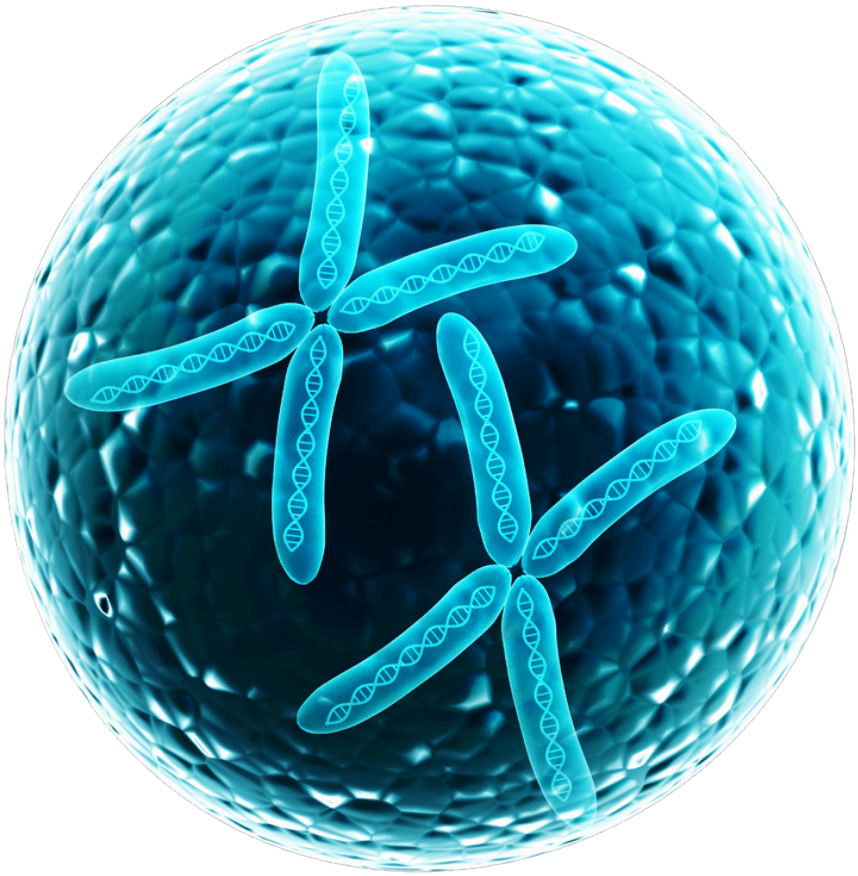
Periodontitis is the 6th most prevalent chronic inflammatory disease worldwide (1). The homeostatic imbalance in the epithelium and connective tissue and dysregulated host-immune-inflammatory reaction lead to periodontitis. Swollen bleeding gums, bone loss, and loose teeth characterize it. The loss of teeth, not limited to one but all is the most devastating outcome of periodontitis. The quality of life of patients deteriorates with the severity of the disease. Tartar (plaque) is considered the major culprit in causing periodontal disease. Periodontitis is a disease of a lifetime; it requires proper and timely maintenance. Finding the right etiology is the key to arresting periodontal disease progression. With the advent of technology and increased awareness, research has been widely expanded to explore other causes of periodontitis.

**Periodontitis – A Multifactorial Disease**

The periodontal treatment plan could be divided into three segments: 1- Removal of etiological factors, 2- Relieving symptoms, and 3- Reconstruction and regeneration of lost structures. Concerning periodontitis, the primary etiological factor is tartar, and its removal halts the disease progression but does not completely cure it. The etiology is not just limited to plaque and involves other factors such as smoking, chewing tobacco, stress, and comorbidities like diabetes mellitus, hypertension, thyroid disorders, etc. This makes periodontitis a multifactorial disease. The periodontal structures respond well to treatment, but complete regeneration of lost structures is yet to be achieved. The factors that determine plaque deposition are numerous. The severity of periodontal destruction is known to correspond with the amount of plaque and calculus deposited.



## Periodontal Epigenomic Alterations – The Path Less Explored

Surprisingly, several cases present with a severe form of the disease with minimal or no plaque. This has also led to the discovery of genetic and epigenetic modifications as one of the underlying causative agents for periodontitis. The inherited changes in genome activity without causing any change in the DNA sequence per se are termed epigenetic changes and the study of the same is called epigenetics. It was initially coined by Waddington (2).

**The epigenetic mechanisms include:**

**1- DNA methylation,**
**2- posttranslational modification of histone proteins,**
**3- noncoding RNA (ncRNA).**

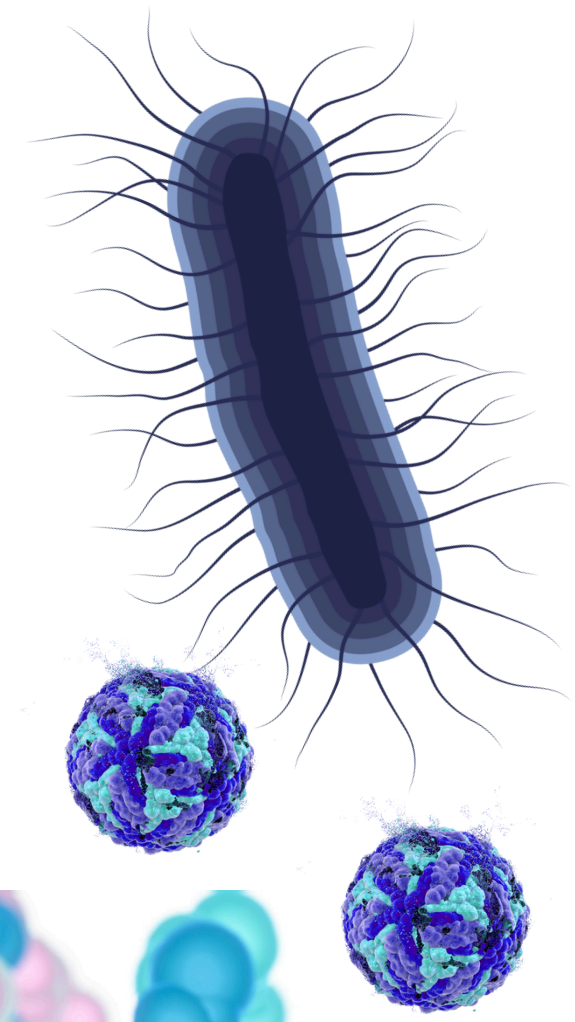
These alterations in the periodontal epigenome govern the magnitude of the host response to plaque biofilm, leading to 'Personalized Periodontal Disease' (2). The way every individual presents with periodontal disease is different. The same stimulus has the capacity to induce severe, moderate, mild, or even no disease in humans. This diversity in response to the same stimulus could be explained by epigenetics.

Encounters with pathogenic bacteria, allergens, or toxins trigger the host's immuno-inflammatory response in the periodontium. The activation of immune cells (both innate and adaptive) and inflammatory components (pro-inflammatory cytokines like IL-6, TNF-alpha, etc.) takes place simultaneously. It is both protective and destructive. The degree of activation determines the outcome of the disease. Epigenetic factors play a significant role in regulating this cycle of events. Evidence regarding periodontal epigenetic alterations is collected through in vitro and in vivo animal models as well as clinical studies. Some of the results include

1-DNA hypermethylation of IL-6, IL-1, TNF-α (Tumour Necrosis Factor-alpha), and TLR2 (Toll-Like Receptor2), which has shown an exaggerated host inflammatory response in gingival tissues obtained from periodontitis patients (2).

**Consequences of TLR2 hypermethylation**: TLRs play a role in recognizing pathogens and signaling innate immune activation. Dysregulation in TLRs negatively influences the host's response. It creates a hyper-pro-inflammatory environment and increases susceptibility to periodontitis. One of the overt consequences of altered TLR2 is hyperactivation of NF-kB (Nuclear Factor kappa B), resulting in bone resorption.

**The consequence of Interleukin hypermethylation:** Interleukins (e.g. - IL-6, IL-1) play a pivotal role in the initiation and progression of periodontal disease. They fall under the group of pro-inflammatory cytokines. Hypermethylation of the promoter region of DNA of IL-1 and IL-6 signals the host immune response to create a hyper-inflammatory state, resulting in significant damage to periodontal



2- P. gingivalis-induced upregulation of CCL25 gene expression. This shows pathogen-mediated epigenetic alterations. Gingival epithelial cells infected by P. gingivalis and F. nucleatum have shown methylation modifications in the promoter region of DNA of various cytokine-producing genes. Consequences of CCL25 methylation modification: Modified CCL25 enhances the chemotaxis of macrophages and dendritic cells. Overactivated macrophages mediate tissue damage as a result of CCL25 dysregulation (2).

**Consequences of MMP2 hypomethylation:** T. denticola-induced hypomethylation of the MMP2 promoter has been shown to hyperactivate the MMP2 enzyme in periodontal fibroblasts, ultimately enhancing tissue destruction. The consequences of epigenetic changes on the occurrence and progression of periodontal disease could be significant. These epigenetic alterations could occur locally at specific sites in the oral cavity (site-specific), explaining the reason for the localized form of periodontitis.

**To summarize:**

1. The way the body responds to any kind of insult/stimulus determines disease occurrence and progression. In the case of periodontitis, it is mainly the plaque biofilm (periodontopathic bacteria).
2. The host's immune inflammatory response is the driving force behind the fate of the disease.
3- Epigenetic alterations in key components of the host immune-inflammatory complex contribute to periodontal disease susceptibility and progression.
4- Microbial dysbiosis and negative environmental exposures significantly influence periodontal epigenetic modifications.
5- Periodontitis is an infectious inflammatory condition and shows a diverse response to external and internal stimuli among individuals. The way periodontitis presents is unique to every individual. Epigenetic modifications in two individuals with periodontitis are not similar. The outcome of epigenomic alteration is also different. This could explain 'Personalized Periodontal Disease'.
6- Epigenome-wide association studies are the need of the hour to better understand the underlying epigenetic mechanisms regulating complex diseases