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Opinion

Personalised Periodontal Medicine (ppm) Based on-Omics for Eradication of the Pathogenesis of Periodontal Disease and Its Associated Disorders

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Gingivitis (gum-inflammation) is a type of gum disease which is the mildest form of periodontal disease where there is multifactorial polymicrobial infection induced by the accumulation of bacteria in the gingival crevice region when untreated can advance to chronic and aggressive periodontitis. The oral biofilm which consists of complex population of billions of bacteria in the oral-cavity is under control when there is homeostasis protecting each individual's health. However, when this homeostatic balance is disturbed, then the oral biofilm produces pathogenic bad bacteria which cause gum disease. Furthermore, these pathogenic bacteria and their toxins enter into the circulatory system causing various medical conditions. Subsequently, there is an activation of the immunity system, initiating an inflammation process which induces production of C-reactive proteins (CRPs) whose enhanced levels exert inflammatory effects on the arteries of the circulatory system permitting attachment of the pathogenic bacteria on their linings forming atheromatic plaques which may block these vessels causing heart attacks, strokes etc. Other inflammatory responses include enhancement of IL-6,NO,TNF-a,MPO and WBC. The continuous process of gum disease causes chronic low grade inflammation which reduces the immune response of the body causing irreversible immune suppression which enhances the risk of oncogenesis. However, gum disease before it exerts its pathogenic implications may be treated and reversed completely. The first symptom is the formation of dental plaque which indicates disturbed homeostasis in the oral biofilm that will implicate inflammatory and immune responses with pathogenic consequences if it is left untreated leading to an immune suppression which may lead to pancreatic cancer, RCC, blood (liquid) cancers such as leukemia, lung cancer etc.

The resulted persistent bacterial gum infections with its inflammatory signals may induce alterations in the immune responses allowing oncogenesis which acts synergistically with the interactions of the oral microbiome, host genome and epigenome called infecto-epigenomics which can be managed under a personalized periodontal approach with pharmacogenomics and nutrigenomics. More analytically, methylation variable positions (MVPs) are associated with genes which influence growth, transcription, differentiation, metabolism and oncogenesis. Changes in MVP methylation cause epigenetic alterations that influence expression of genes linked to cell-growth, development, differentiation and cancer. Environmental stressors such as toxins and viral or bacterial infections and inflammatory immune responses may contribute to pathogenesis of periodontal diseases such as gingivitis and periodontitis.

The inflammation linked to biofilm which is caused by periodontal pathogens may cause epigenetic alterations such as DNA methylation which regulates transcription of genes in the adaptive and innate immune responses in periodontal diseases. The

immunoinflammatory responses to subgingival microbiota depend upon genetic susceptibility which may be used for individualized treatment. The infectious stimuli which are derived by viruses and bacteria in periodontal diseases may alter the cross-talk between genomics including SNPs, SNVs and copy number variants [1], and epigenomics with heritable reversible changes that do not alter DNA sequence leading to reduced or silenced gene expressions which regulate the molecular and cellular responses of the host [2].

Thus, the epigenetic alterations which can be caused by smoking, infections, immunoinflammatory conditions, age, stimuli etc may interfere with the transcription system influencing the conversion of the genetic code into functional proteins affecting not only the local periodontal tissues but the whole system with many associated disorders such as cardiovascular diseases, pneumonia, diabetes, rheumatoid-arthritis, cancer, obesity etc. All these start with a disturbed host-microbial homeostasis which causes epigenetic alterations due to specific stages of the maturational process of the oral biofilm consisting of the intermediate colonizers such as orange complex bacteria, and late colonizers such as red complex bacteria which include Campylobacter rectus, Porphyromonas gingivalis and C. rectus which may cause epigenetic alterations in periodontal cells silencing expression of genes involved in local immune defenses and healing, mechanism of the host supplying carbohydrates to bacteria for enhancing their growth and proliferation, and angiogenic factor enhancing tissue damage by inflammatory components and reducing tissue perfusion where all of them are related with the traditional clinical indices including gingival index, pocket depth, plaque index, probing bleeding and risk factors such as sys temic diseases, genetics etc which can lead to personalized dental medicine [3].

The mainest epigenetic alterations in periodontal disease which regulate inflammatory responses consist of histone and DNA methylation and histone acetylation. Periodontopathogenic (gingival) bacterial infections in oral epithelial cells cause gene promoter methylation leading to silencing of apoptotic tumour suppressor genes leading to oncogenesis. Other factors besides to inflammation and innate immune responses involved in periodontal disease involve an imbalance between proteases and protease inhibitors. Thus, periodontitis in gingival involves intrinsic systemic mechanisms including genetics, transcriptomics, metabolomics, proteomics, metagenomics, microbiomics, and immunogenomics which interact with epigenetics in environmental stimuli such as infections by pathogenic bacteria, smoking, nutrition, oral hygiene etc regulating intracellular downstream signaling cascades, inflammatory cytokines and immune response to infection after interaction with pathogenic oral microbiome [4].

Fortunately, only 10-15% of all populations have destroyed periodontal ligament and adjacent supporting bone leading to tissue destruction, dental mobility, loss of teeth and associated periodontal diseases due to gingival inflammation caused by periodontopathogenic bacteria [5] such as Aggregatibacter actinomycete-comenrans, Tannarella-forsythia, Prevotella-intermedia and Porphyromonas-gingivalis. This bacteria-mediated plaque induced inflammatory periodontal disease depends upon acquired and genetic factors. Periodontitis can be prevented by stopping occurrence of gingivitis through regular oral hygiene that may be facilitated by daily flossing and brushing. Otherwise, the inflammatory process associated with periodontitis occurs with accumulation of neutrophils and macrophages releasing cytokines and chemical mediators such as prostaglandins, TNF-a, and IL-1 which stimulates fibroblasts. Also, polymorphonuclear neutrophils may release matric metalloproteinases (MMPs) such as collagenase which dissolves collagen. Other enzymes produced are phospholipases and extracellular amino peptidases, lipopolysaccharides, epithelium-toxin, acid-phosphatase and alkaline-phosphatase which may cause bone-resorption.

Nuclear factor kappa-B ligand (RANKL) released by T-lymphocytes in synergy with TNF-a enhance osteoclast activity leading to bone resorption. Vascular endothelial cells, fibroblasts, osteoblasts and monocytes release the proinflammatory cytokine IL-6 which induces production of CRP. Inflammation induced periodontitis has been reported to be associated with over expression of IL-23p19, IL-1b, IL-17 and IL-21 [6]. On the other hand, we can inhibit or reverse inflammation induced periodontitis by activating STAT6 via over expression of type 2 receptors of IL-4 which inhibits release of IL-11 and leukemia inhibitory factor (LIF) by human gingival fibroblasts. Also, release of anti-inflammatory cytokine IL-10 may control bone-resorption and inflammation in periodontal diseases [7]. The main

cause in the pathogenesis of periodontal disease is oxidative stress where free radicals may cause damage to periodontal tissues by lipid-peroxidation, protein and DNA damage, release or stimulation of pro-inflammatory cytokines, and oxidation of antiprotease enzymes. The generation of reactive oxygen species (ROS) damages molecules of the cell-structure such as nucleic-acids, proteins, lipids and carbohydrates.

Oxidative stress in synergy with lipid-peroxidation (malonilaldehyde) generated by pro-oxidants in the cigarette-smoke which contain 4,000 chemicals, where forty are carcinogenic combined with depletion of diet- antioxidants may cause oral cancer such as OSCC. Thus, diet high in anti- oxidants combined with living a healthy life without smoking may function as chemopreventive measures against oral cancer. This way, we can stop the tissue destruction caused by a few of the 300-400 species of oral bacteria which can generate products of marginal periodontitis inhibiting influence-radioplate in periodontitis that damages tissues in a radius of 1.5-2.5 mm around the plaque. With antioxidants, we may block the reactive oxygen species and the elastase/lysosomic enzymes inhibiting the hydrolysis of the connective tissue which is linked with the inflammation. Subsequently, we block release of gelatinase, collagenase, IL-1/J, lipopolysaccharide and prostaglandin E which inactivates osteoclasts inhibiting resoprtion of alveolar bone. By boosting the humoral and cellular components which are involved in the periodontal immune response (PIR) including the complement system, immunoglobulins, leukocytes, lysozyme, neutrophils, antibodies, in addition to the secretory with the immune regulatory system, we may protect the periodontium by the infectious destructive and hazardous effects generated by the toxic substances which are released by the pathogenic microbes which can cause gingivitis (type I), mild periodontitis (type-II), moderate periodontitis (type-III), advanced periodontitis (type-IV) and other inflammatory conditions such as acute gingivitis, chronic gingivitis, ulceronecrotic acute gingivitis, superficial marginal periodontitis, marginal periodontitis, and deep marginal periodontitis.

Now the medical conditions which are associated with all types of periodontal disease include inflammatory diseases such as cardiovascular diseases (CVD) and diabetes, rheumatoid arthritis, upper respiratory diseases such as acute bronchitis, pneumonia and chronic obstructive pulmonary disease (COPD), oral and other cancers such as pancreatic cancer, stroke, dementia, prostatitis, pregnancy problems with premature and small babies, vasculogenic erectile dysfunction, metabolic syndrome etc.

Concluding, the differential gene expression of coding and non-coding RNA may be used for individualized treatment of periodontal disease based on genomics, epigenomics, immunogenomics, nutrigenomics, microbiomics, metabolomics, pharmacogenomics and pharmacoepigenomics tailoring nutrition and therapeutic molecular targeting approaches for the eradication of infection, inflammation, and subsequent gingivitis and periodontal disease and systemic associated disorders.

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