Review Article

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Periodontal Diseases and Viruses - Changing Concepts

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Abstract

The oral cavity has a rich flora of bacteria; more than 500 distinct microbial species are found in dental plaque. Mycoplasma, yeast, protozoa and viruses are found in the plaque as the non-bacterial microorganism. Viruses are known to be immunosuppressive and facilitate establishment of subgingival pathogens and have been detected in the gingival crevicular fluid. Viruses infect the inflammatory cells of the periodontium and they are present more frequently in diseased sites than in healthy sites. The aim of this literature review was to report the role of viruses in periodontal diseases. Clearer understanding of roles of viruses in periodontal diseases will facilitate the provision of effective periodontal disease prevention and treatment.

Keywords: Periodontal Diseases; Dental Plaque; Periodontitis; Viruses; Herpes; HIV.

Introduction

Periodontitis affects the majority of adults' worldwide [1], but relatively few patients receive adequate treatment for the disease [2].Different classifications of periodontal diseases have been used over the years and have been replaced as the understanding of the aetiology and pathology of the diseases of the periodontium improved with increased scientific knowledge. The most recent classification is based on the 1999 International Workshop for the Classification of the Periodontal Diseases organized by the American Academy of Periodontology [3,4]. Here viral diseases of the periodontium were placed under non-plaque induced gingival lesions, and they include herpetic gingivastomatitis, varicella zoster and others.

Viruses are one of the smallest forms of microorganism (10-100 nm) which can only multiply inside living cells [5]. It consist of the nucleocapsid, which may be "naked," or "enveloped" within a lipoprotein sheath derived from the host cell membrane.

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It is generally believed that both gingivitis and periodontitis are caused by bacteria colonizing the tooth surfaces, and that the major mechanisms of periodontal destruction are initiated by bacteria. This view is based on a large number of studies essentially demonstrating an association between bacterial plaque and clinical signs of gingivitis and periodontitis. Cross-sectional studies of human populations have shown a positive correlation between the amount of plaque and the severity of gingivitis as well as bone loss [6,7].

The inflammatory alterations are resolved or reversed when the bacterial deposits removed from the tooth surfaces. Studies indicated that antiseptic agents such as chlorhexidine are able to suppress the bacterial colonization and the development of gingivitis [8,9,10], and that antibiotics could reduce plaque scores and improve gingival conditions in subjects with periodontal disease.[11,12] The benefit of adjunctive antibiotic therapy to mechanical debridement procedures in controlling several forms of periodontitis further strengthens the argument for a major etiological role of bacteria in human periodontal disease [13].

While the role of bacterial plaque in general seems to be evident, for the etiology of periodontal disease, certain other factors which may contribute to the development of periodontal diseases. Although all subjects with poor oral hygiene develop gingivitis, not every gingivitis lesion invariably leads to attachment loss. Global epidemiological data allow the inference that the progression of destructive

periodontitis is subject related and comparatively few individuals in the population show advanced periodontal breakdown.

The above observations lead to the hypothesis that factors beyond dental plaque are important in the pathogenesis of periodontitis. This includes, exogenous factors, such as tobacco smoking as well as endogenous factors, such as genetically determined variations in inflammatory response patterns [14]. Thus, it is unlikely that a single agent or even a small group of pathogens are the sole cause or modulator of this heterogeneous disease. Since the middle of 1990s viruses like herpes viruses have emerged as putative pathogens in various types of periodontal disease. In particular, human cytomegalovirus (HCMV) and Epstein-Barr virus (EBV) seem to play important roles in the etiopathogenesis of severe types of periodontitis [15].

The purpose of this review was to evaluate the evidence supporting the hypothesis that viruses play a role in the development of periodontal disease.

The Role of Viruses in Periodontal Diseases

Viruses can cause severe acute oral and oro-facial disease, produce oral signs of systemic infection and be transmitted to patients and dental staff. Therefore, the role of viruses in the etiology of periodontal diseases can be divided into direct and indirect roles depending on whether they cause periodontal disease locally or as a result of the presence of a systemic infection.

Direct role in periodontal disease etiology

Herpes simplex virus infection

Herpes simplex virus, are of two types: HSV-1 and HSV-2 are known to commonly cause skin and mucous membranes infections. Herpes simplex virus-1 infections occur in the oral cavity while HSV-2 infections occur in the genital area. However, they can occur in either area and at other sites in the body. These viruses can be carried in body fluids or in fluid from herpes lesions. For an infection to occur, the viruses must gain entry into the body of the uninfected persons through their skin or mucous membrane in the intraoral or genital area. Once the virus has contact with the cells of the mucous membranes or skin tissue, it tries to replicate in the cell nuclei. This can result in symptoms following multiplication and destruction of the vulnerable cells of the skin and mucus membrane in previously uninfected individuals with inflammation and appearance of vesicles. After this initial infection, the virus is transported through the nerve cell to their sensory dorsal root ganglion where it becomes latent for a period of time [16].

Herpes simplex viruses are transmitted by close person-to-person contact by mucosal secretion or lesions. HSV-1, principally shed in the saliva, is transmitted directly (kissing) or indirectly (infected utensils or hands) and is mainly involved in oral-facial infections and encephalitis. HSV-2 is usually transmitted sexually and causes genital infection. However, HSV-1 and HSV-2 can both be found in oral-facial and genital infection [17,18]. Other ways of transmission include autoinoculation by fingers to the eyes or genital tract and transmission from infected mothers to neonates.

The primary oral infection causes symptoms, which can be very painful, particularly in young children. This primary lesion is called primary herpetic gingivostomatitis, which is characterized by the formation of vesicles on the gingival, lips, tongue and buccal mucosa. The rupture of the vesicles results in painful erosion and ulceration with yellowish membrane development before healing, but disappears within 3-14 days. There is also associated increased salivation and bad breath. Rarely, chills, myalgia, dysphagia, or hearing loss may occur [19].

Recurrences known commonly as herpes labialis, usually affects the lips or the adjacent skin, are usually milder than the primary infections. It is usually caused by the reactivation of the latent virus. Following the primary HSV infection, virions travel from the initial site of infection on the skin or mucosa to the sensory dorsal root ganglion, where latency is established. When the dormant virus in the ganglion is activated, it begins to multiply again and moves down the trigeminal nerve usually to the site of initial inoculation and infects the epithelial cells causing a recurrent infection [20]. Reactivation of latent virus can be triggered by physical injury, trauma, surgery, sunlight, wind, cold, fever, immune suppression, upper respiratory tract infection, emotional stress and physiological event like menstruation. Trigger of latent virus within about 3 days of intense dental work like root canal treatment or tooth extraction have been reported [16].

Varicella zoster virus

The vesicular stomatitis virus or human herpes virus-3 (HHV-3) cause Chicken pox, which is the primary infection of varicella zoster virus and this is followed by latency. Recurrence can occur as herpes zoster often after many decades. The virus is

presumed to spread through air droplets or direct contact with an active lesion. The periodontal lesion is indistinguishable from HSV except that the lesion of chicken pox tends to be relatively painless. Herpes zoster is characterized by pain and rash in one dermatome [21].

Kaposi's sarcoma herpes virus

This is also known as HHV8 and has been identified in all forms of Kaposi's sarcoma lesions. This virus is believed to have a significant role in the induction and / or maintenance of Kaposi's sarcoma. Different clinical patterns of Kaposi's sarcoma have been described: The classic, endemic, iatrogenic immunodeficiency-associated as well as Acquired Immune Deficiency Syndrome (AIDS)-related Kaposi sarcoma. Oral lesions are frequently seen in the immunodeficiency state than in other forms of Kaposi sarcoma. Kaposi's sarcoma has been described in most oral regions, although the palate, gingiva and tongue seem to be the most common affected sites [22].

Cytomegalovirus infection

Cytomegalovirus or Human Herpes Virus (HHV)-5 is a herpes virus that infects most persons at some time during their lives. It is similar to other HHV that is, after infection, latency is established and reactivation is possible after conditions favorable to the virus. This infection is often subclinical and usually occurs in young children but may also be seen in adolescents and adult. It is common among the low socioeconomic group. In infants, the virus is contracted through the placenta, during delivery or during breast feeding. Transmission occurs during adolescence and during sexual activity. Transmission has also been documented during blood transfusion and organ transplantation. Patients with immune defects are liable to severe and / or protracted infections, or the virus reactivation [16].

Indirect role in periodontal disease etiology

Human immunodeficiency virus

The most frequent routes of transmission of HIV are sexual contact, parenteral exposure to blood or mother to child transmission. The primary target of HIV is CD4 [4] helper T cells. The HIV become incorporated into the DNA of the lymphocyte and present for the life of the cell. It may remain latent for a period of time but soon becomes active and cause cell death. A subsequent decrease in the number of T helper cell number occurs with a resultant loss in immune function. It is this reduction in immune function that predisposes the individual to a number of opportunistic infection including periodontal diseases and some of the viral infection discussed above [16].

Periodontal diseases are common among HIV-infected patients, and they are characterized by gingival bleeding, bad breath, pain / discomfort, mobile teeth, and sometimes sores. Four forms of HIV-associated periodontal disease have been described: Linear gingival erythema, necrotizing ulcerative gingivitis (NUG), necrotizing ulcerative periodontitis (NUP), and necrotizing stomatitis.

Linear gingival erythema is characterized by the presence of a 2-3 mm red band along the marginal gingiva, associated with diffuse erythema on the attached gingiva and oral mucosa. The degree of erythema is disproportionately intense compared with the amount of plaque present on the teeth.

NUG is more common in adults than in children. It is characterized by the presence of ulceration, sloughing, and necrosis of one or more interdental papillae, accompanied by pain, bleeding and mouth odor.

NUP is characterized by the extensive and rapid loss of soft tissue and teeth

Necrotizing stomatitis is thought to be a consequence of severe, untreated NUP. It is characterized by acute and painful ulcer on necrotic lesions on the oral mucosa that expose underlying alveolar bone.

Role in pathogenesis of periodontal diseases

Viral infection contributes to the development of various forms of periodontal diseases including severe chronic periodontitis, localized and generalized aggressive periodontitis, HIV-associated periodontitis and acute NUG [23]. The possible role of viruses in periodontal diseases is suggested by the recovery of a patient from a chronic and highly treatment refractory periodontal condition upon antiviral treatment [24]. Moreover, these viruses are found significantly more frequently in samples taken from disease active pockets, and gingival-crevicular fluid compared to healthy pockets [25,26]. Whereas several viruses are known to be involved in oral diseases, Herpes virus, as well as the HIV play a more relevant role in periodontal diseases [14]. These viruses play a fundamental role in the pathogenesis of periodontal diseases by a number of mechanisms operating alone or in combinations namely:

- Direct cytopathic effect on inflammatory cells such as polymorphonuclear, leukocytes, lymphocytes, macrophages, and other cells such as fibroblasts, endothelial cells and even bone cells.
- Cytokines and chemokines release: The releases from inflammatory and non inflammatory host cells are mediated by viruses, resulting in destruction of the connective tissue alveolar bone.
- Interference with the immune system of the host: EBV infects periodontal B-lymphocytes, and CMV infects periodontal monocytes/ macrophages and T-lymphocytes in periodontitis lesions. The down regulations of these cells involved in the periodontal defense may lead to bacterial super infection resulting in increased virulence of resident bacteria including*Porphyromonas gingivalis, Prevotella intermedia, Prevotella nigrescens, Campylobacter rectus, Treponema denticola* and *Aggregatibacter actinomycetemcomitans* Human CMV (HCMV) and EBV have been reported frequently in aggressive periodontitis sites, in chronic periodontal disease as well as periodontal disease associated with systemic diseases [27].
- Promotion of bacterial colonization: The promotion of subgingival attachment and colonization of periodontopathic bacteria by enhanced bacterial adherence to virus-infected cells that exists in some other viral infections.
- Herpes virus - Bacteria Synergy: Herpes viruses interaction with specific bacterial species are considered as an important pathogenetic feature of periodontitis. Initially, dental plaque bacteria cause gingival inflammation, which facilitates the entry of herpes virus-infected inflammatory cells into the periodontium. The subsequent reactivation of the herpes virus in the gingival tissue spontaneous or as a result of various types of the host immune defense impairment may then aggravate the periodontal disease [28].
- Immunopathologic responses: HCMV can induce cell-mediated immunosuppression by interfering with cytotoxic T-lymphocyte recognition through the down-regulating cell surface expression of major histocompatibility complex class I molecules. HCMV may lead to global impairment of cell-mediated immunity by suppressing antigen-specific cytotoxic T-lymphocyte functions, which now results in an increase in $CD8^+$ suppressor cells and a decrease in circulating $CD4^+$ cells
- EBV may induce proliferation of cytotoxic T lymphocytes whose main purpose is recognition and destruction of virally infected cells. Various aspects of the periodontal immune response may be hampered secondarily by EBV. Together, these mechanisms contribute to the pathogenesis of periodontitis [16].

Role in disease progression

Viruses, as evident by most of the herpes viruses, go into latency after the primary infection and reactivation is possible in the condition favorable to the virus. Immunocompromised patients tend to experience more severe symptoms than the immunocompetent individuals. HIV also goes into latency after the initial infection to recur later. They predispose the individual to a number of opportunistic infections that progress faster and present more severe symptoms than those occurring in immunocompetent individuals [16].

Role in response to treatment

Although most periodontal diseases of viral origin resolve spontaneously, antiviral agents such as acyclovir, ganciclovir, valacyclovir and famciclovir accelerate the healing of the lesion and reduce the duration of pain. However, these drugs must be begun early enough for treatment to be effective [16].

Conclusion

Human viruses are involved in the development of various types of oral ulcers, oral tumors, classical oral infectious diseases and periodontitis. Herpes simplex virus-1 and Cytomegalovirus are linked to oral ulcers; Ebstein-Bar virus, Herpesvirus-8 and Papillomaviruses to oral tumors; and Ebstein-Bar viruses and Cytomegalovirus to aggressive periodontitis. Rapid advances in medical virology may also help to uncover the pathogenesis and treatments of viral diseases of mouth. Research is encouraged on the topics on antiviral chemotherapeutic agents and augmentation of host defences by means of vaccination. Prevention and therapy based upon antiviral approaches may avert the debut of periodontitis or result in long lasting arrest and ultimate cure of existing periodontitis, as well as of other virally related diseases of the human mouth.

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