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VIRUSES IN THE ETIO-PATHOGENESIS OF PERIODONTITIS. ROLE OF HUMAN HERPES VIRUS (HHV)

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ABSTRACT

Periodontitis is a multifactorial disease. It is a result of complex interplay of pathogens, host and environment. Among the pathogenic organisms, the role of bacteria is fully explained. However the recent researches have focussed on other pathogens in the etiopathogenesis of periodontal diseases. Several studies have proved the association between viruses and periodontal diseases especially human herpes virus (HHV).The main aim of this review is to summarizes the evidence that link various herpes viruses to periodontitis, and to explain the possible mechanisms behind this process.

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INTRODUCTION

Periodontitis being a multifactorial disease is a complex interplay of infectious agents and cellular and humoral host immune responses (Slots *et al*., 1999). The precise role of various periodontal pathogens and host responses in the pathogenesis of periodontitis has not yet been clarified. Although specific bacteria like Porphyromonas gingivalis, Treponema denticola, Tannerella forsythia, Prevotella nigrescens, Prevotella intermedia, Campylobacter rectus and Actinobacillus actinomycetemcomitans (Slots, 2002) have been identified as main pathogens in the development of periodontitis, it is unlikely that a single agent or even a small group of pathogens are entirely responsible for this complex disease. The role of viruses in the etiopathogenesis of periodontal diseases has been proved in various studies. Herpes viruses have emerged as putative pathogens in various types of periodontal disease since the mid 1990s (Contreras, 2000). Eight herpes virus species have been identified. Oral disease has been attributed to herpes simplex virus (HSV) type 1,2 , varicella-zoster virus (VZV), Epstein-Barr virus (EBV), human cytomegalovirus (HCMV) and human herpes virus 8 (HHV-8).Active herpes virus infection in the oral cavity manifests in the form of ulcerations of gingival (Scully, 1996). Herpes simplex viruses Infections HSV-1 and HSV-2 mostly affect skin and mucosa and are transmitted by close person-to-person contact.HSV-1, principally shed in the saliva, is transmitted by intimate contact or indirectly through infected utensils or hands and is mainly involved in oral-facial infections. HSV-2 is usually transmitted sexually and causes genital infection. Primary infection occurs in childhood. At the site of epithelial infection, a cell-mediated immune response is induced. Following replication some viral nucleocapsid ascend the local sensory neurons by retrograde axonal transport to establish lifelong latency in the corresponding ganglion. Destruction of the neurons occur but most of them survive (Rozenberg, 2002). Immuno suppression, stress, trauma, ultraviolet irradiation, or fever are known to induce of reactivation the virus. Recurrences are known to be less severe than the primary infection and tend to diminish with time (Whitley, 2001). The clinical manifestations in oral cavity include gingivitis, vesicles that leave ulcerations, cervical lymphadenopathy and fever.

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Variceiia-zoster virus (VZV)

Varicella a highly infectious disease transmitted by inhalation of infective droplets or by direct contact with lesions is known to cause varicella (chickenpox) as primary infection, affecting mainly children. In adults its reactivation causes herpes zoster i.e shingles. Both primary and secondary infection produce gingival lesions (Laskaris, 1996) which are unilaterally distributed along the infected nerves. Vesicles quickly break to form ulcerated lesions with prominent red borders, resembling aphthous ulcers. Necrosis of the periodontium and mandibular bone, dental hypoplasia and retarded tooth eruption (Melbye, 1987) has also been reported.

Epstein–Barr virus (EBV)

A subclinical infection in children is noted and in adults it results in infectious mononucleosis characterised by fever, lymphadenopathy and pharyngitis. Oral ulcers, palatal petechia and less commonly gingival ulcerations can be diagnosed (Rivera-Hidalgo, 1999). The virus is known to cause proliferation and activation of T cells. Oral hairy leukoplakia, a non-malignant hyperplasic lesion of epithelial cells presenting as a bilateral raised, white, corrugated lesion on the ventral-lateral aspect of the tongue is the main lesion associated to EBV.

Human cytomegalovirus (HCV)

HCMV is emerging as an important opportunistic pathogen in immune compromised individuals, especially those with AIDS and transplant patients. Usually acquired in early childhood is known to infect gingival monocytes/ macrophages and T-lymphocytes (Contreras *et al*., 1999). The virus is known to cause oral ulcerations in immune suppressed patients and involve gingiva and periodontium with underlying bone destruction or osteomyelitis. HCMV-infection is also reported to give rise to gingival hyperplasia (Epstein *et al*., 1992).

Human herpesvirus 6

HHV-6 is also known as human B-lymphotropic virus.It is known to induce proliferation of CD4 and CD8 lymphocytes and natural killer cells, thereby increasing the severity of HIV infection (Lusso *et al*., 1991). HHV-6 may cause short-lived febrile illnesses and hepatitis in previously healthy individuals, as well as prolonged febrile illness in immunosuppressed patients. It is also involved in involved in oral squamous carcinoma (Yadav *et al*., 1997).

Human herpes virus 7

HHV-7 infection is usually acquired in childhood and most adults are HHV-7 seropositive. It appears to be associated with at least 2 pathological conditions: roseola and pityriasis rosea. Pityriasis rosea a self limiting exanthema is characterized by crops of maculo papular pale-red oval cutaneous lesions which may last for up to 2 wk. Lesions of the tongue and cheek are also present. The presence of HHV-7 has also been detected in inflamed gingival (Contreras *et al*., 2000).

Human herpes virus 8

Is known to be an etiological agent for AIDS-related oral Kaposi's sarcoma lesions.

HHV-8 is also known to be involved in non- Hodgkin's lymphomas, Castleman's disease and anti-immunoblastic lymphadenopathy. HHV-8 has been identified in periodontitis lesions of HIV-positive patients (Contreras *et al*., 2000).The most frequent site involved is palate, followed by attached gingiva. The lesions are known to progress from gingiva to the underlying alveolar bone.

Mechanism of Pathogenesis

HHV exhibits a lytic cycle, virus remains in latent form throughout the life of host and is periodically activated by stress or change in host immune status. An exaggerated periodontal tissue breakdown occurs more frequently and progress more rapidly in presence of HHV infection. Pathogenesis involves five mechanisms, operating alone or in combination. The virus is known to exert a direct cytopathic effect on inflammatory cells such as polymorphonuclear, leukocytes, lymphocytes, macrophages, and other cells such as fibroblasts, endothelial cells which in turn hampers tissue turnover (Contreras, 2000). An altered inflammatory mediator and cytokine response is induced by HHV infections (Passariello *et al*., 2009). Up regulation of interleukin 1-beta (IL-1β) and tumor necrosis factor-alpha (TNF-α) gene expression of monocytes and macrophages occurs in case of HCMV leading to enhanced susceptibility to destructive periodontal disease. HCMV interferes with cytotoxic T‑lymphocyte recognition through down‑regulation of cell surface expression of major histocompatibility complex class I molecules resulting in induction of cell‑mediated immunosuppression

In gingival herpes virus infection, increased sub gingival attachment and colonization of periodontopathic bacteria occurs, as a result of creation of new bacterial binding sites resulting in more severe periodontitis. Virus damages the epithelial cells and results in exposing of basement membrane and surface of regenerating cells which provide new sites for bacterial binding (Beader, 2011). The down regulation of periodontal B‑lymphocytes induced by EBV infection , and monocytes/macrophages and T‑lymphocytes by CMV infection results in diminution of host defence mechanism which in turn leads to bacterial superinfection and increased virulence of resident bacteria including Porphyromonas gingivalis, Prevotella intermedia, Prevotella nigrescens, Campylobacter rectus, Treponema denticola and Aggregatibacter actinomycetemcomitans.

Methods of diagnosis

Viral Cultures both *in vitro* and *in vivo* are considered as gold standard with increasing time consumption being the main disadvantage of these methods. Molecular techniques like PCR, Real time (RT)-PCR and sequencing have overcome the disadvantage of time consumption. Real-time PCR, not only offer a test for the viral presence, but also yield quantitative data**.** DNA microarrays that are able to detect simultaneously HHV, EBV, and CMV they use multiplex real-time PCR techniques to quantify simultaneously the number of genome-copies. Main limitation of PCR-based methods is that they only detect the viruses they are designed to detect. To overcome this drawback, two recent strategies have been developed: microarrays and pyro sequencing. Microarrays, detect all known viruses.

Probes detecting different viruses are applied to a slide and the sample DNA or RNA is hybridized onto the slide, thus sequencing, the complete nucleic acids present in the sample. Both methods share the drawbacks of being less sensitive than PCR and are considerably more expensive.

Conclusion

The etiology of various bacterial agents in the pathogenesis of periodontitis has been well known. However recent studies have suggested the role of viruses especially the association of herpes viruses with periodontal disease. Viral DNA has been detected in gingival tissue, GCF and sub gingival plaque from periodontal diseased sites. Gingival infection with certain herpes viruses decreases the resistance of the periodontal tissue, thereby permitting sub gingival overgrowth of periodontal pathogenic bacteria. Thus a transient immune suppression occurs which explains the episodic progressive nature of human periodontitis. Hence to conclude apart from various bacterial agents, viruses have also been found responsible in the etiopathogenesis of periodontitis thus demanding the increasing need for various treatment strategies to overcome it.

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