ROLE OF VIRUSES IN PERIODONTAL DISEASES

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Abstract
Periodontitis is one of the most complex infectious diseases of the human body. Individual periodontal lesions may harbour a multitude of viral phenotypes. A co-infection of active herpes viruses and periodontopathic bacteria may constitute a major etiological factor for periodontitis. Current research on herpes virus infections of the periodontium may produce significant progress in the prevention and treatment of periodontitis. This article reviews findings on human viruses in periodontal health and disease, and briefly summarizes pathogenic features of the herpes viral-bacterial mixed periodontal infection.
Key words: Periodontitis, Viruses, Herpes-virus.

Introduction

Viruses in periodontal diseases

Studies on virus as a causative factor for periodontitis mark a turning point in periodontal research, which until recently was centered almost exclusively on a bacterial etiology.[1] The presence of virus in the periodontium has been confirmed using high-performance polymerase chain reaction techniques, labelled DNA probes, flow cytometry, immunofluorescence staining and culture .[2-4] Epstein–Barr virus (EBV) and cytomegalovirus (CMV) are the most common viruses researched in the field of Periodontology. More than one million herpes virus genome-copies can be present in a single periodontitis site.[3] Periodontontally involved sites can also harbor papillomaviruses, HIV, human T-lymphotropicvirus type 1, hepatitis B virus, hepatitis C virus and torquetenovirus. [1] A wide variation in the occurrence of viruses in periodontitis sites have been reported; herpes simplex viruses (HSV) (13–100%), EBV (3–89%) and CMV (0.3–83%).[4]Association have been established between human T-lymphotropic virus type 1 and gingivitis as well as periodontitis, between hepatitis B and C viruses and periodontitis and between torquetenovirus obtained in gingival biopsies and periodontal lesions. [5-8] Most studies revealed greater levels of EBV and CMV in sites of aggressive periodontitis than in sites of chronic periodontitis.[9-12] Prevalence of genome-copies of various viruses present subgingivally in periodontal health and disease are summarised in Table 1.

Study (Country)	Virus	Aggressive periodontitis; % positive samples	Chronic periodontitis; % positive samples	Gingivitis; % positive samples	Healthy periodontium; % positive samples
Botero et al.(Columbia)[2]	CMV	No data	80%	No data	25%
Li et al. (China)[10]	EBV	58%	23%	19%	No data
Imbronito et al. (Brazil)[13]	HSV-1	No data	No data	53%	20%
	EBV-1	33%	47%	20%	0%
	CMV	48%	50%	40%	57%
Saygun et al (Turkey)[14]	HSV-1	No data	No data	No data	0%
	HSV-2	No data	No data	No data	0%
	EBV	60%	No data	13%	No data
	CMV	53%	No data	7%	No data
Grande et al. (Brazil)[15]	EBV	No data	48%	No data	No data
	CMV	No data	80%	No data	No data
Moghim et al. (Iran)[16]	EBV	No data	61%	No data	3%
Botero et al. (Columbia) [17]	CMV	40%	60%	No data	18%
Wu et al. (China)[18]	EBV-1 + 2	No data	66%	32%	17%
Chen et al. (China)[19]	CMV	No data	59%	No data	32%
Chalabi et al. (Iran)[20]	EBV-1 + 2	No data	79%	No data	7
	CMV	No data	59%	No data	0
Konstantinidis et al. (Greece)[21]	EBV	No data	55%	No data	9%
Kubar et al. (Turkey)[22]	EBV	89%	46%	No data	No data
	CMV	78%	27%	No data	No data

Table 1: Prevalence of genome-copies of various viruses subgingivally in periodontal health and disease.

The Herpes viral–Bacterial interaction

The synergistic interactions between herpes viruses and periodontopathic bacteria and the pathogenicity EBV and CMV in oral and non-oral diseases have been proven to exist.[4,22,23] The herpes viral–bacterial hypothesis of periodontitis proposes that an active herpes virus infection initiates periodontal tissue breakdown and the host immune responses against the herpe svirus infection are significant component of the etio-pathogenicity of periodontitis. [1]
The herpes virus infection triggers a release of pro-inflammatory cytokines that have the ability to activate osteoclasts and matrix metallo-proteinases and to impair

antibacterial immune mechanisms, causing an up-growth of periodontopathic bacteria. [2]Herpesviruses can exert direct cytopathic effects on fibroblasts, keratinocytes, endothelial cells and inflammatory cells, including polymorphonuclear leukocytes, lymphocytes, macrophages and possibly bone cells. Herpes virus proteins expressed on eukaryotic cell membranes may act as new bacterial binding site. Herpes viruses as well as EBV and CMV have been known to induce abnormalities in the adherence, chemotaxis, phagocytic and bactericidal activities of polymorphonuclear leukocytes, which are cells of key importance for the control of periodontopathic bacteria.[23] CMV can enhance the adherence of Aggregatibacter. Actinomycetemcomitans (A.a) to primary periodontal pocket epithelial cells.[24] EBV active infection can also generate anti-neutrophilic antibodies and neutropenia, and poly-clonally stimulate the proliferation and differentiation of B-lymphocytes.

Linkage between viruses and Aggressive periodontitis

The affluence of herpes viruses in aggressive periodontitis sites implies a role of the virus in the disease.[25, 26] The presence of subgingival herpes viruses was studied in Afro-Caribbean adolescents with classical localized aggressive periodontitis (LAP).[1] A strong association with CMV and P. gingivalis, and the markedly higher odds ratio of the CMV–P. gingivalis combined infection was observed that indicates a pathogenic synergy between the two.

Ting et al gave a hypothesis that a primary CMV infection at the time of root formation of permanent incisors and first molars can give rise to a defective periodontium. [25]Viruses infecting odontogenic cells of developing hamster teeth can disrupt normal cell differentiation, and an active CMV infection can change the morphology of developing teeth. [26]Perhaps because of a CMV infection early in life, teeth affected by LAP often show cemental hypoplasia.[27] Profound hormonal changes at the onset of puberty may re-activate a periodontal CMV infection, resulting in suppression of antibacterial immune defense and overgrowth, A.a being major pathogen in the early phases of LAP.[13]

LAP lesions harbouring an active CMV infection tend to be more deliberately infected with A.a.[28] The affinity of A.a for colonizing CMV-infected epithelial cells by means of a cytolethal distending toxin may partly explain the close association of the organism with the disease.[29] CMV-mediated damage to the periodontal tissue constituents, antiviral pro-inflammatory cytokine responses, and bacteria-induced injury of the epithelium, may allow gingival tissue invasion by A.a and breakdown of the periodontal attachment and alveolar bone.[30]

Viruses in periodontal abscess

EBV was detected in 72%, CMV in 67%, and co-infection with the two viruses in 56% of 18 abscesses studied, and the herpes viruses were not identified in healthy periodontium or after treatment of the periodontal abscess.[31]It is proposed that re-activation of a periodontal herpes virus latent infection impairs the periodontal host defense, which allows bacterial pathogens to enter the gingiva and cause formation of abscess.

Viruses in HIV-associated periodontitis.

The high prevalance of herpes viruses in periodontitis and in oral mucosal pathosis of HIV infected patients provides substantial evidence of a pathogenic role of herpes viruses in these diseases.[32]CMV was detected in 81% of HIV associated periodontitis lesions and in 50% of non-HIV-associated periodontitis lesions.[33] In HIV infected individuals, CMV has also been identified in acute periodontitis, in periodontal abscess formation, in mandibular osteomyelitis and in refractory chronic sinusitis. Herpes virus-like virions were observed electron microscopically in 56% of gingival tissue from HIV-seropositive patients with necrotizing ulcerative periodontitis.[34]EBV type 1 was identified more frequently in subgingival sites of HIV-positive patients than that of HIV-negative patients. EBV type 2, which is frequently observed in HIV-infected subjects, was detected in 57% of biopsies from HIV-associated periodontitis lesions, but was absent in non-HIV associated periodontitis biopsies. Human herpesvirus-8 was present in periodontitis lesions of 24% of HIV-infected individuals.[34]

Necrotizing ulcerative gingivitis/periodontitis (NUG/NUP)

NUG and NUP influences immunocompromised, malnourished and psychosocially stressed individuals. Contreras et al. studied NUG in non HIV-infected malnourished Nigerian children, where HSV (23% of study lesions), EBV (27%) and CMV (59%) was revealed, whereas periodontal lesions of malnourished, but periodontally normal children showed nearly no herpesviruses.[35]

Viruses and Syndromes associated with periodontal diseases

Table 2 lists syndromes associated with periodontal herpes viruses and severe periodontitis.

Diseases	Periodontal viruses
Guillain–Barre´ syndrome	CMV
Kostmann syndrome	EMV
Fanconi'sanemia	HSV, CMV
Papillon–Lefe`vre syndrome	EBV , CMV
Down syndrome	HSV, EBV type I, CMV

Table 2: Viruses and Syndromes associated with periodontal diseases[36-40]

Therapeutic implications

Future management of periodontal diseases may gain from anti-herpes viral immune therapeutics either prophylactic vaccines, which employs the immune system of healthy individuals to prevent infection from disease-causing viruses; or therapeutic vaccines, which triggers the immune system to combat existing viruses and disease. [1]The notion of herpes viral– bacterial synergism in periodontitis suggests that vaccination against herpes viruses can also play a significant role in the control of periodontopathic bacteria.

Conclusion

The existing information justifies adding human periodontitis to the list of diseases that has EBV, CMV and other human viruses as likely contributory etiological factors. The current paradigm of the pathogenesis of periodontitis needs to be revisited based upon the concept of a herpes viral–bacterial co-infection that explains a number of the clinical features of the disease. Viral studies may lead to elucidation of the clinical characteristics of periodontitis, and to new propositions for managing the disease. Detection or quantification, Assessment of the re-activation status of a periodontal herpes virus infection may help to guide the treatment of patients with severe periodontitis. Development of anti-herpes virus vaccines foreshadows a future for low-cost prevention of periodontitis in large groups of individuals with a diminishing role for the traditional periodontal therapies of surgery and antibiotics.

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