INTRODUCTION

Periodontitis is a disease attributable to multiple infectious agents and interconnects cellular and humoral host immune responses. However, it has been difficult to unravel the precise role of various putative pathogens and host responses in the pathogenesis of periodontitis. Some uncertainties about the differences in loss of periodontal attachment and alveolar bone or limited gingival inflammation with comparable levels of risk factors have galvanized efforts to find additional etiologic factors for periodontitis (SLOTS, 2005). Recently, it was suggested that certain viruses might also influence the development and severity of periodontal diseases, though the cause of gingivitis and periodontitis is credited to bacteria colonizing tooth surfaces and initiating the major mechanisms of periodontal destruction (CAPPUYNS et al, 2005). It’s obvious that others factors beyond biofilm are important in the pathogenesis of periodontitis, like tobacco smoking and genetically determined variations in inflammatory response patterns. But viruses can also interfere on immune responses though immune modulators encoded within viral genomes, which include proteins that regulate antigen presentation, function as cytokines or cytokine antagonists, inhibit apoptosis,
and interrupt the complement cascade (Spriggs, 1996). Thus, a situation of viral-bacterial interaction could occur in the oral cavity without a denial of the argument for a major etiological role of bacteria in human periodontal disease.

The purpose of this review is giving an overview of the viruses and its mechanisms of immune evasion and pathogenesis, highlighting specifically those viruses that may be potentially involved in periodontal diseases, in the absence of HIV viruses and AIDS.

**MATERIAL AND METHODS**

A search was performed on Medline (http://ncbi.nlm.nih.gov/PubMed/medline.html) using the search terms “viruses periodontal” and Limits: Publication Date from 2006/07. Humans. This search resulted in 35 articles and all related to AIDS were excluded. Another search was performed on these articles references, including all that bring relevant information about the theme.

**Mammalian viruses**

Viruses occupy a unique position in biology. They are restricted intracellular agents, which are metabolically and pathogenically inert outside the host cell (SLOTS, 2005), depending on living cells for replication.

Individual virus families have targeted many common immunological principles. Viruses that belong to different families are subject to different constraints. The genome size of RNA viruses is limited and they have the advantage of being able to use mutation to escape immune control while the genome size of DNA viruses allows a larger number of genes to be devoted to host control (Alcamí & Koszinowski, 2000).

Viruses can exist in two forms: extracellular virion particles and intracellular genomes. Virions are more resistant to physical stress than genomes but are susceptible to humoral immune control. Virus genomes can be maintained in host cells by limited gene expression and can evade the host immune response. Nevertheless, viruses’ replication and transfer to a new host are essential for them, so they have evolved strategies to evade immune control mechanisms like with the immunoregulatory proteins with homolog sequencing cellular genes. These “stolen” genes from the host modify the viruses for their benefit and the viral homology of host genes involved in the immune system are mainly found in large viruses, like the herpesviridae (Alcamí & Koszinowski, 2000), a virus family of DNA, double-stranded, enveloped viruses. DNA viruses replicate in the nucleus and are more likely to persist in the host. Enveloped viruses typically initiate cell-mediated inflammatory responses and delayed type hypersensitivity, which affect viral replication by killing mammalian cells that express viral proteins. Disease is often due to inappropriate immune responses and this explains why herpesvirus reactivation is triggered by a number of immunosuppressing factors. Naked viruses are controlled mainly by antibody, and vaccines are generally effective (SLOTS, 2005). Because of the lack of effective therapeutics and vaccines, herpesvirus diseases continue to constitute a significant problem for public health (SLOTS, 2005). Recent studies have revealed an association between some of the members of herpesvirus family and destructive human periodontal disease.

**Herpesviruses and mechanisms of immune evasion**

Of the approximately 120 identified different herpesviruses, eight major types are known to infect humans (table 1), namely, herpes simplex virus (HSV) type 1 and 2, varicella-zoster virus (VZV), Epstein-Barr virus (EBV), human cytomegalovirus (HCMV), human herpesvirus HHV-6, HHV-7, and HHV-8 (Kaposi’s sarcoma virus). Humans are the only source of infection for these eight herpesviruses. Human herpesviruses are classified into three groups (α, β, γ) based upon details of tissue tropism, pathogenicity, and behavior under conditions of culture in the laboratory (SLOTS, 2005).

Herpesviruses can occur in a latent or in a productive (lytic) state of replication. During the latent phase the viral genome integrates within the host cell’s genome. They may undergo reactivation and re-enter the productive phase as consequence of declining herpesvirus-specific cellular immunity. The genomic transcription may induce changes in host cell expression of genes that encode proteins involved in immunity and host defense (SLOTS, 2005).

The innate host response consists of a complex system of mechanical and secreted defenses, immediate chemokine and interferon responses, and rapidly recruited cellular defenses. Cellular lymphocyte response attempts to eliminate virus-infected cells. It is essential to limit initial viral replication and to facilitate appropriate adaptive immune response. Cytotoxic T-lymphocyte (CTL) and NK cells are the most important effectors in the maintenance of latency. T-cell response to herpesvirus changes from a predominantly CD4+ response early in infection to a CD8+ response during latent infection (SLOTS, 2005).

The mechanisms that viruses use to perpetuate themselves within the host is reflected in the varied immune modulators encoded in viral genomes which include selective regulation of host antigen presentation, production of growth factors that function on host cells, and antagonism of
immune function through the use of soluble versions of cytokine receptors. In many cases, these viral proteins function to assist the virus in avoiding host immune surveillance, while in other instances they clearly function to protect the host from the sometimes deleterious effects of the virus-induced inflammatory response. Not surprisingly, herpesviruses are considered masters of host immune evasion, employing a variety of strategies that ultimately allow the establishment of latent infections and occasional reactivations that ensure efficient perpetuation of the virus within a population (SPRIGGS, 1996).

Cytokines are potent, soluble proteins that play key roles in the induction and maintenance of inflammation, immune response, differentiation, and embryonal development (SPRIGGS, 1996). Th1 proinflammatory immune responses aim to clear the host of intracellular pathogens. Th1 cytokines favor the development of a strong cellular immune response whereas Th2 cytokines favor a strong humoral immune response. IL-10, a Th2 cytokine, antagonizes Th1 proinflammatory responses (SLOTS, 2005). Herpesviruses modulate the activity of chemoattractant cytokines that regulate leukocyte trafficking to sites of infection, preventing Th1 anti-viral responses. HCMV and EBV express IL-10 homologs downregulating the production of IL-12 and also inhibiting the production of TNF, IL-1 and other cytokines in macrophages. IL-12 is required for the production of IFN which induces an anti-viral state in the cell limiting virus replication (SLOTS, 2005; SPRIGGS, 1996; ALCAMI & KOSZINOWSKI, 2000). Viruses also display great inventiveness when it comes to diverting potent antiviral cytokine and chemokine responses to their benefit. Prostaglandin E2 (PGE2), which is a major mediator of periodontal inflammatory response, increases rapidly in response to exposure of cells to herpesviruses and to bacterial lipopolysaccharide; however, PGE2 may under certain circumstances serve to support HCMV replication (SLOTS, 2005). Some cytokine homologs might also increase proliferation of cells that are targets for viral replication (ALCAMI & KOSZINOWSKI, 2000). One interesting mechanism is the mimicry of cytokines (virokines) and cytokine receptors (viroceptors) by large DNA viruses like herpesviruses.

The complement system is a major non-specific host defense mechanism. Viruses protect the membranes of infected cells and the lipid envelopes of virus particles from complement lysis by encoding homologs inhibitors of the membrane-attack complex. HCMV “borrows” host cellular factors (CD59), which normally protects cells from complement lysis, and incorporating them into the viral envelope (ALCAMI & KOSZINOWSKI, 2000).

Apoptosis can be triggered by a variety of inducers, including infectious agents such as viruses. Apoptosis can be considered an innate cellular response to limit viral propagation, and viruses express proteins that block death response; however, apoptosis might also facilitate virus dissemination, and viral pro-apoptotic mechanisms have also been described (ALCAMI & KOSZINOWSKI, 2000). Expression of the EBV latent proteins protects latently infected B cells from apoptosis but cannot inhibit apoptosis of naive B lymphocytes as a result of primary EBV infection (SPRIGGS, 1996).

The major histocompatibility complex (MHC) class I molecules are expressed on the surface of virtually all somatic cells. CTL recognition of the viral antigen in the context of the “self” MHC molecules leads to cellular activation, resulting in both lysis of the infected cell and production of cytokines and other factors that allow the expansion of the virus-specific CTL population. HSV provides an example of interference with virus-specific CTL recognition through regulation of MHC class I/peptide complex expression. HSV-1 and HSV-2, like all herpesviruses, shut off MHC class I expression late in infection as a result of overall diminished host protein synthesis. HCMV can exhibit a structure with significant homology to MHC class I playing a role in interfering with normal MHC class I transport and function (SPRIGGS, 1996).

Increased attention has focused on the possible clinical significance of HCMV-induced immunosuppression in immunocompetent individuals. HCMV seropositivity is associated with higher degrees of CD8+ clonality in the immunocompetent elderly, which may be associated with aging (BOECKH & NICHOLS, 2003).

<table>
<thead>
<tr>
<th>Herpesviruses</th>
<th>Abbreviation</th>
<th>Herpes group</th>
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<tbody>
<tr>
<td>Herpes simplex virus type 1</td>
<td>HSV-1</td>
<td>α</td>
</tr>
<tr>
<td>Herpes simplex virus type 2</td>
<td>HSV-2</td>
<td>α</td>
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<tr>
<td>Varicella-zoster virus</td>
<td>VZV</td>
<td>α</td>
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<tr>
<td>Epstein-Barr virus</td>
<td>EBV</td>
<td>γ</td>
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<tr>
<td>Human cytomegalovirus</td>
<td>HCMV</td>
<td>β</td>
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<tr>
<td>Human herpesvirus 6</td>
<td>HHV-6</td>
<td>β</td>
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<tr>
<td>Human herpesvirus 7</td>
<td>HHV-7</td>
<td>β</td>
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<tr>
<td>Human herpesvirus 8</td>
<td>HHV-8</td>
<td>γ</td>
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Table 1 HERPESVIRUSES THAT INFECT HUMANS (ADAPTED FROM SLOTS, 2005)
Pathogenesis of herpesvirus in periodontal disease

The pathogenic process of periodontitis includes dynamic interactions among various infectious agents and interconnects cellular and humoral host responses. However, despite a long history of research into the pathobiology of periodontitis, a definitive statement about its probable causes on a molecular level remains elusive. Bacterial pathogens are necessary antecedents for the development of periodontitis but the mere amount of biofilm does not seem to provide sufficient basis for explaining important clinicopathologic features of the disease. Bacterial infection alone may not explain the conversion of gingivitis to periodontitis (SLOTS et al., 2002), rapid tissue destruction around teeth exhibiting little plaque, the propensity of periodontitis to proceed with periods of exacerbation and remission, and the tendency of periodontal tissue breakdown to advance in a localized and bilaterally symmetrical pattern (KUBAR et al., 2005). Recent studies (some examples in table 2) suggest that periodontal herpesviruses comprise an important source for triggering periodontal tissue destruction (SAYGUN et al., 2004) and the identification of a herpesvirus factor in the development of periodontitis may help clarify hitherto unexplained clinical and pathophysiologic characteristics of the disease (KUBAR et al., 2005).

The involvement of herpesviruses in the etiology of periodontal diseases is suggested by: 1) higher frequency of virus detection in gingival tissue and subgingival plaque of periodontitis sites than in healthy sites; 2) higher frequency of virus detection in gingival crevicular fluid (GCF) from periodontal disease sites than from gingivitis/healthy sites; 3) detection of activated herpesvirus in the GCF of periodontal lesions; 4) interaction of herpesviruses with periodontal pathogens (CAPPUYNS et al., 2005).

A “herpesvirus-bacterial pathogen” model has been proposed in which viral infection may exert periodontopathic potential. Herpesviruses can infect or alter structural cells and host defense cells of the periodontium and thereby reduce host resistance against subgingival colonization and multiplication of periodontal pathogens (CONTRERAS et al., 2000; CASSAI et al., 2003) or exert direct cytopathic effects on fibroblasts, keratinocytes, endothelial cells, inflammatory cells, such as PMN leukocytes, lymphocytes and macrophages, and possibly on bone cells (SLOTS & CONTRERAS, 2000). Several studies examined a possible association between potential periodontopathic bacteria and herpesviruses in subgingival plaque (KAMMA et al., 2001; SLOTS et al., 2002; KAMMA & SLOTS, 2003; SLOTS et al., 2003; SAYGUN et al., 2004).

HCMV genomic sequences, detected by PCR, occur with elevated frequency in severe adult periodontitis, localized and

### Table 2

<table>
<thead>
<tr>
<th>Author</th>
<th>Sites</th>
<th>Herpesvirus (rates %)</th>
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<tbody>
<tr>
<td>CONTRERAS et al, 2000</td>
<td>Periodontal pocket (paper points)</td>
<td>HSV (21<em>e 0**); HCMV (64</em>e 9**); EBV-1 (43<em>e 18**); EBV-2 (21</em>e 0**); HHV-6 (not found); HHV-7 (7*e 0**); HHV-8 (not found)</td>
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<tr>
<td></td>
<td>Gingival tissue</td>
<td>HSV (57<em>e 9**); HCMV (86</em>e 18**); EBV-1 (79<em>e 27**); EBV-2 (50</em>e 0**); HHV-6 (21<em>e 0**); HHV-7 (43</em>e 0**); HHV-8 (29*e 0**);</td>
</tr>
<tr>
<td>CONTRERAS &amp; SLOTS, 2001</td>
<td>Periodontal pocket**.B.,** (paper points)</td>
<td>HSV-1(100); HCMV (not found)</td>
</tr>
<tr>
<td>CASSAI et al, 2003</td>
<td>Gingival tissue</td>
<td>HHV-6 (88.0<strong>e 10</strong>); HHV-7 (77.0<strong>e 70</strong>); HHV-8 (7.7<strong>e 7.7</strong>e 0***);</td>
</tr>
<tr>
<td>KUBAR et al, 2004</td>
<td>Periodontal pocket (curette)</td>
<td>HCMV (68.8*e 0**);</td>
</tr>
<tr>
<td>KUBAR et al, 2005</td>
<td>Periodontal pocket, gingival tissue**.B.</td>
<td>HCMV (78 <strong>e 33</strong>) ; HCMV (86 <strong>e 9</strong>); EBV (89 <strong>e 78</strong>); EBV (46 <strong>e 46</strong>);</td>
</tr>
<tr>
<td>SAYGUN et al, 2005</td>
<td>Periodontal pocket (curette), gingival tissue and saliva</td>
<td>EBV (88**); HCMV (86**);</td>
</tr>
<tr>
<td>KONSTANTINIDIS et al, 2005</td>
<td>Periodontal pocket (paper points)</td>
<td>EBV (50 <strong>e 23</strong>);</td>
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</table>

(Periodontal status at sample sites: periodontitis*, healthy sites**, periodontally healthy subjects***, chronic periodontitis*, aggressive periodontitis*, HIV-associated periodontitis†.)
generalized aggressive periodontitis, Papillon–Lefèvre syndrome periodontitis, acute necrotizing ulcerative gingivitis, periodontal abscesses, and it is also closely associated with symptomatic periapical diseases (SLOTS et al, 2004). Herpesviruses establish lifelong persistent infections. HCMV infection involves an asymptomatic latent phase interrupted by periods of recrudescence where viral replication and possibly clinical disease become manifest. HCMV reactivation is triggered by a number of immunosuppressive factors, some of which have been shown also to be risk factors/indicators of periodontitis. Stressful events induce the release of corticosteroids, which have the potential to activate HCMV. Tobacco products may interact with and reactivate periodontal herpesviruses and may decrease herpesvirus infectivity titers, which may partly explain the increased risk for periodontitis from tobacco usage. The ability of HCMV and other herpesviruses to cause latent infections that periodically reactivate has some similarity with the relapsing-remitting course of periodontitis (SLOTS, 2004). Active herpesvirus infections are potentially more deleterious than latent herpesviruses, thus both differences in periodontal distribution and rate of activation among herpesvirus-positive sites may contribute to the site-specific nature of periodontal disease progression (SLOTS & CONTRERAS, 2000).

In nonoral diseases, it is known that HCMV infection can increase the incidence of bacterial and fungal infections, aggravate the severity of concurrent microbial infections, and accelerate the tempo of infectious disease progression. Although less studied, EBV and bacterial pathogens may also act synergistically in nonoral infectious diseases. A similar theory for periodontitis focuses on the potential of periodontal HCMV/EBV to subvert local host defenses, thereby enhancing the aggressiveness of subgingival bacteria (KUBAR et al, 2005).

The effectiveness of host immune response in dealing with periodontal pathogens is a major determinant of clinical periodontal disease. Impaired immune responses in periodontal sites may take place due to local hypoxia decreasing host cell activity, diabetes mellitus, genetic immune deficiencies, and various viral and bacterial infections. Actually, increased attention has focused on the possible significance of HCMV-induced immunosuppression in immunocompetent individuals (BOECKH & NICHOLS, 2003).

Herpesvirus infections can cause both cytopathogenic and immunopathogenetic events, and although the relative contribution of the two pathogenic mechanisms to destructive periodontal disease is not known, it is likely that the early stages of periodontitis in immunologically naive hosts mainly comprise cytopathogenic events, whereas most clinical manifestations in immunocompetent individuals are secondary to cellular or humoral immune responses (KUBAR et al, 2005).

Bacterial components such as lipopolysaccharide can potently activate production of interleukin-1α and other bone resorative mediators at inflamed sites, causing connective tissue destruction and alveolar bone loss. Periodontal infection may also induce host cells to elaborate increased levels of IL-1α, TNFα, PGE2, and other tissue-destructive products. However, it has proved difficult to elucidate host responses that are associated with periodontal disease stability or progression (SLOTS et al, 2002). Even if proinflammatory activities basically serve a positive biological goal by aiming to overcome infection or tissue invasion by infectious agents, they can also give rise to detrimental effects when a challenge becomes overwhelming or with a chronic pathophysiological stimulus (SLOTS et al, 2004).

Bacterial infection and other conditions that promote diapedesis of inflammatory cells into tissue would increase the possibility of initiating a local HCMV infection (CONTRERAS et al, 1999). Reactivation of HCMV commonly occurs in patients with bacterial sepsis (BOECKH & NICHOLS, 2003). Recent studies have shown that reactivation of HCMV in periodontitis lesions may be related to progressing periodontal disease due to the upregulation gene IL-1α and TNFα expression in monocytes and macrophages by active HCMV infection at the periodontitis site (CONTRERAS et al, 2000; WARA-ASWAPATI & AURON, 2003. These cytokines are positively associated with the severity of destructive periodontal disease and may subsequently upregulate matrix metalloproteinases activity, which may mediate destruction of the extracellular matrix of gingiva, periodontal ligament and alveolar bone and also down-regulate tissue inhibitors of metalloproteinases (CONTRERAS et al, 1999).

In tissues with periodontitis a high proportion of inflammatory cells are infected by herpesvirus. Neutrophils, monocytes/macrophages, T and B-lymphocytes were isolated from gingival biopsies of periodontitis lesions. HCMV and HSV mainly infect periodontal monocytes/macrophages and T-lymphocytes while EBV-1 infects periodontal B lymphocytes (CONTRERAS et al, 1999). PMN leukocytes have consistently been found to carry greatest viral burden compared with monocytes but they do not carry latent HCMV, whereas monocytes are a true site of virus latency (GERNA et al, 2004).

HCMV infection may induce abnormalities in adherence, chemotactic, phagocytic, oxidative, secretory, and bactericidal activities of neutrophils. Phagocytic and bactericidal capacities of periodontal neutrophils seem to be significantly impaired...
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REFERENCES