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Endodontic Herpesviruses: Prevalence, Pathogenicity and Systemic Risk

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Introduction

Viruses are the simplest and smallest microorganisms that can infect humans. They consist of either DNA or RNA surrounded by a protein coat termed a capsid. The most commonly known viruses within the oral cavity are Herpesviruses, being the most important DNA viruses that cause oral disease in humans. The hallmark of herpesvirus infections is immune impairment. Accordingly, this paper will mainly address herpesviruses in endodontic pathosis, for which the most amount of information is available.

Herpesviruses cause disease in humans, upon initial entry, in two ways. Infection may result at the site of entry through disruption of skin (Figure 1) or may enter the circulation and infect distant organs. The mode of release of the virions can determine the pattern of infection in the infected cell (Figure 2). If the virionis released from the apical part of the cell, the infection will become localized; however, if the virions are released from the basolateral side of the cell, the infection becomes a disseminating infection [1-3]. It has also been shown that the outcome of the viral infection is dependent on the cellular immune responses to block the viral DNA replication, interfering with herpesvirus infection by host defenses [3-5]. Herpesviral replication takes place in the nucleus of the host cell. Viral replication and the production of infectious virions involve activations of three sets of genes; immediate-early, early, and late classes of genes. Late (structural) genes are expressed during the productive (lytic) phase of herpesviral infections. Figure 3 describes the infection process of herpesviruses.

In past two decades, new viruses have been identified that have expanded our knowledge and understanding of viral infections and their pathogenicity. Human cytomegalovirus (HCMV) and Epstein-Barr virus (EBV) seem to be important putative pathogens of human periodontitis and symptomatic periapical lesions, causing pathosis either by inducing immunosuppression with a subsequent risk of aggressive bacterial infections, or by infecting of periodontal cells directly. Apical periodontitis and its etic-pathogenesis, especially the molecular events preceding and causing disease onset, is associated with a wide range of bacteria and viruses that interfere with innate and adaptive cellular and humoral immune responses, and affect cytokine networks. Pulpal and periapical infections exhibit complex microbial ecologies involving synergistic, antagonistic, and commensal interrelationships among resident microorganisms. Sundqvist [6] found strong positive associations between *Fusobacteriumnucleatum, Parvimonasmicra, Porphyromonasendodontalis, Selenomonassputigena*, and *Campylobacter rectus*, and negative or neutral associations with streptococcal species (*Propionibacteriumpropionica, Capnocytophagaochracea*, and *Veillonellaparvula*) in root canals of teeth with periapical lesions. Significant relationships may also exist between endodontic *Porphyromonasgingivalis* and *Tannerella forsythiaor Treponema* species [7]. *P. endodontalismay* cooperate with *Prevotella intermedia* or *Prevotellanigrescens* in the formation of abscesses [8]. A marked shift toward a more anaerobic microbiota has been demonstrated during the development of experimental endodontic infections in monkeys [9]. Varying nutritional demands and anaerobic requirements of the infecting organisms are important determinants of microbial interrelationships and population changes in the endodontic microbiota [10]. Differing levels of host resistance may also significantly influence the composition of the periapical microbiota.

Current hypotheses on the pathogenesis of periapical pathosis implicate both bacterial and host factors, but the pathogenic events that trigger the conversion of a stable, asymptomatic endodontic lesion to a progressive or a symptomatic lesion remain obscure. The commonly-held

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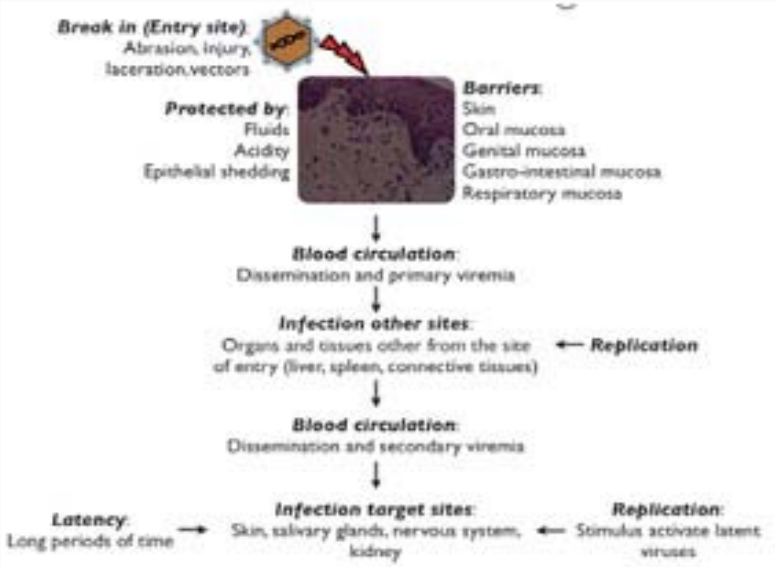

Figure 1: Viral infection steps: entry, replication, dissemination, and infection of target cells/organs. Virions enter the host organism and spread to target tissues/organs where they can replicate and/or cause a persistent (latency). Latent viruses can become reactivated by several immune compromising events, such as smoking, inflammation, stress trauma, and immunosuppressive disease.

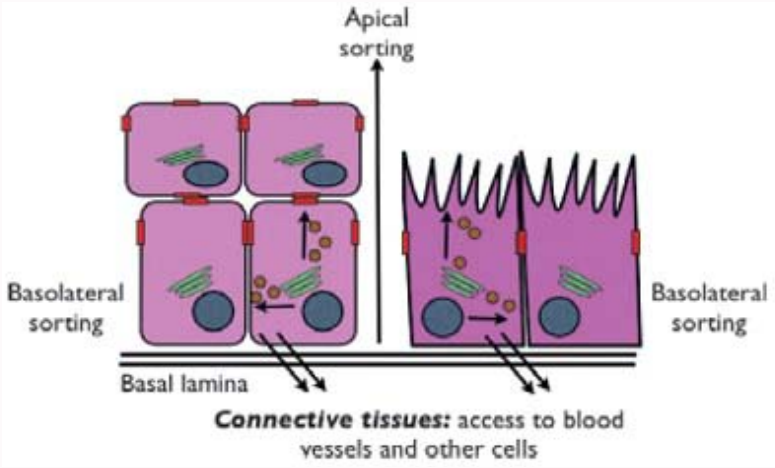

Figure 2: Different pathways of intracellular sorting of viruses. Virions released from Stratified epithelium (left) or intestinal epithelium (right), by either apical sorting or basolateral sorting, can infect adjacent cells, enter connective tissue and gain access to blood vessels, or dispersed to body lumens.

notion that apical pathosis is a bacterial disease cannot fully explain the pathogenesis of the disease, site –specificity, and tissue tropism. However, a combined bacterial-viral infection can, hypothetically, explain the major features associated with the disease [11]. Viral association with bacteria and apical disease is consistent with the pathological role of both infectious agents.Acute exacerbation of periapical disease may be caused by a combination of herpesviral and bacterial etiologies. This explanation is consistent with the findings of many studies, which have noted the presence of active herpesvirus infections in symptomatic periapical lesions, and the pro-inflammatory potential of herpesviruses [12].

Methodological Issues

Current clinical studies involving endodontic-related herpesvirus detection largely use RNA and/or DNA polymerase chain reaction (PCR) based methodologies. The high sensitivity and specificity, low cost, and speed in which PCR can identify the genetic material prove advantageous over serological, culture-based, or immunological-based techniques. Since its development in 1983, and particularly after the foundational patents expired in 2005, PCR based detection of genomic material has become ubiquitous. While there are many variations of experimental PCR techniques, the detection of herpesviruses in periapical lesions of endodontic origin has mostly involved reverse transcription PCR (RT-PCR). In these studies, complementary DNA (cDNA) is amplified from the RNA expression of the virus by using primers designed to target genes transcribed late in the infectious cycle [11-24]. Endpoint PCR could ultimately be useful for determining the presence or absence of the virus but is mostly non-quantitative. The fluorescence-based assays of real time PCR (quantitative or qPCR) are very useful in detecting and determining the number of nucleic acid copies of infectious agents in a sample. This technique has become commonly used for the diagnosis of infectious diseases in general, as well as for genetic abnormalities and various cancers [13-24].

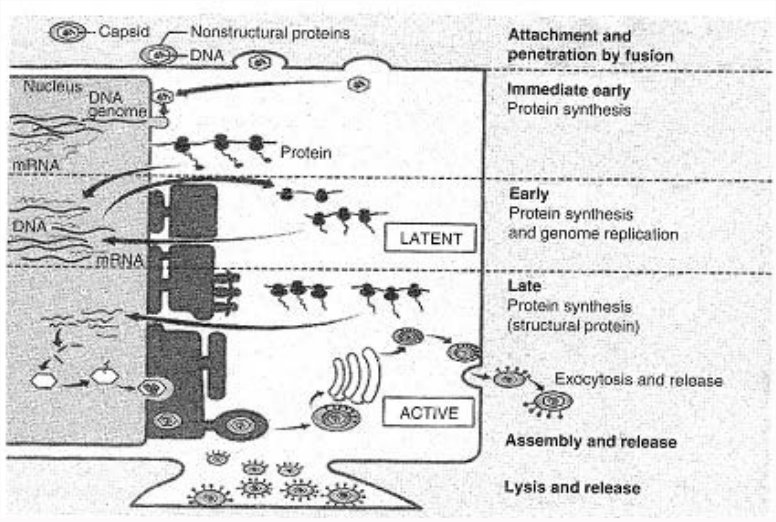

Figure 3: Schematic representation of the replication of herpesviruses. A virion initiates infection by fusion of the viral envelope with the plasma membrane after attachment to the cell surface. The capsid is transported to the nuclear pore, where viral DNA is released into the nucleus. Viral transcription and translation occur in three phases: immediate early, early, and late. Immediate early proteins shut off cell protein synthesis. Early proteins facilitate viral DNA replication. Late proteins are structural proteins of the virus that form empty capsids. Viral DNA is packaged into preformed capsids in the nucleus. Viral glycoproteins and tegument protein patches in cellular membranes and capsids are enveloped. Virions are transported via endoplasmic reticulum and released by exocytosis or cell lysis. Obtained from Slots et al. with the permission of the author.

Due to the high sensitivity and specificity of PCR care must be taken when incorporating the technique into the clinical detection protocol of herpesvirus in periapical lesions. The high seroprevalence of both CMV and EBV dictates that steps must be taken to test for the active virus, and not a latent infection [25,26]. This can be done by targeting specific genes that are expressed during the active infection, selection of non-cellular samples, or by using qPCR. Proper controls and clean technique must be used to prevent false-negative and false-positive PCR results. The use of exogenous and/or endogenous internal controls will monitor for PCR inhibition and proper sample purification. Cross-contamination of samples is easily avoided by using good laboratory techniques including the disposal of sample tubes after each use, and the use of clean reagents. To date, endodontic-related Herpesviruses have been detected using a variety of PCR primers and immunological studies making it unlikely those false- positive events have occurred.

Various Oral Pathosis

In addition to periapical lesions of endodontic origin, various herpesviruses have been shown to be associated with other oral conditions. There is a well-documented association of herpesviruses with aggressive periodontitis that is similar in fashion to endodontic lesions. Several studies have combined to show that herpesviruses intensify the pathogenicity of periodontal bacteria in the etiology of the disease [27-30]. As well, in cases of aggressive periodontitis up to 89% have been found to harbor EBV, while CMV was found in up to 78% [31]. CMV and EBV were found in 65% and 45% respectively of peri-implantitis sites versus 6% and 11% respectively in healthy periodontal sites [32]. In another study, peri-implantitis sites were found above 14 times more likely to contain EBV than healthy implant sites [33].

Association between Herpesviruses and Apical Disease

Several studies have investigated the occurrence of herpesviruses in periapical lesions ([13-24], Table 1). Herpes simplex virus infection demonstrated no relationship to periapical disease. In some older studies, *P. gingivalis/ P. endodontalis* were recovered only from symptomatic periapical lesions, supporting the notion that this group of organisms can induce acute endodontic infection [34]. However, most of the symptomatic periapical lesions studied failed to yield black-pigmented anaerobic rods. Acute exacerbation of periapical disease may be caused by unique constellations of pathogenic bacteria or, alternatively, may result from a combination of herpesviral and bacterial co-infection [35].

Herpesviruses possess several virulence factors of potential importance inperiapical pathogenesis, including the ability to induce immune impairment [36,37], with subsequent overgrowth of pathogenic microorganisms [38]. In periodontitis, presence of subgingival HCMV or EBV is related to elevated bacterial load and occurrence of the periodontal pathogens *P. gingivalis, T. forsythensis, D. pneumosintes, P. intermedia, P. nigrescens, T. denticola,* and *A. actinomycetemcomitans* [39]. Herpesviruses also seem to cooperate with pathogenic bacteria in producing a variety of non-oral diseases, including inflammatory bowel disease, enterocolitis, esophagitis, pulmonary infections, sinusitis, acute otitis media, dermal abscesses, and pelvic inflammatory disease [28]. Additionally, herpesviruses may give rise to periapical pathosis by inducing cytokine and chemokine release from inflammatory and non-inflammatory host cells [40]. Periapical sites having inadequate antiviral immune response may be particularly prone to tissue breakdown. Viruses other than HCMV and EBV that infect mammals, either alone or in combination with herpesviruses, may also play a role in the pathogenesis of pulpal and periapical disease [41,42].

The presence of cytomegalovirus in symptomatic periapical pathosis is consistent with the notion that inflammatory cells are the source of the virus. Indeed, latent cytomegalovirus resides in various myeloid progenitor cell types and in more differentiated hematopoietic cell lineages, and cytomegalovirus translocation in the body occurs in monocytes/macrophages and dendritic cells [43].

Table 1: Cytomegalovirus (CMV) and Epstein-Barr virus (EBV) active infection in periapical pathosis.

Study	Total No. of periapical lesions (sites) studied	Symptomatic lesions; No. (%) infected*	Asymptomatic lesions (sites); No. (%) infected	Large size lesions (5x7 mm or larger); No. (%) infected	Small size lesions (sites); No. (%) infected
Sabeti et al. (1) 2003	14 lesions, 2 healthy periapical sites	N=13* CMV+/EBV-: 5 (38%) EBV+/CMV-:0 CMV+/EBV+:8(62%) CMV-/EBV:0	N=1 CMV+/EBV-: 1(33%) EBV+/CMV-: 0 CMV+/EBV+: 0 CMV-/EBV-: 2 (66%)	CMV+/EBV-: 1 (14%) EBV+/CMV-: 0 CMV+/EBV+: 6 (86%) CMV-/ EBV: 0	CMV+/EBV-: 4 (44%) EBV+/CMV-: 0 CMV+/EBV+: 2 (22%) CMV-/EBV-: 3 (33%)
Sabeti et al. (2)	5 lesions with calcified necrotic pulp	CMV+/EBV+: 5 (100%)	Not done	CMV+/EBV+: 5 (100%)	Not done
Sabeti et al. (3)	14 lesions	N=7 * CMV+/EBV-: 1 (14%) EBV+/CMV-: 0 CMV+/EBV+: 6 (86%) CMV-/EBV-: 0	N=7 CMV+/EBV-: 0 EBV+/CMV-: 0 CMV+/EBV+: 1 (14%) CMV-/EBV-: 6 (86%)	CMV+/EBV-: 0 EBV+/CMV-: 0 CMV+/EBV+: 7 (58%) CMV-/EBV-: 5 (42%)	CMV+/EBV-: 1 (50%) EBV+/CMV-: 0 CMV+/EBV+: 0 CMV-/EBV-: 1 (50%)
Slots et al. 2004	44 lesions	n=25* EBV+755 CMV+100% EBV+/CMV+ 76%	N=19 EBV+ 37% CMV+ 26% EBV+/CMV+ 25%		
Sabeti & Slots (4) 2004	34 lesions	N=23* CMV+/EBV-: 6 (26%) EBV+/CMV-: 1 (4%) CMV+/EBV+: 16 (70%) CMV-/EBV-: 0	N=23 CMV+/EBV-: 1 (9%) EBV+/CMV-: 0 CMV+/EBV+: 4 (36%) CMV-/EBV-: 6 (55%)	CMV+/EBV-: 3 (13%) EBV+/CMV-: 0 CMV+/EBV+: 19(79%) CMV-/EBV-: 2 (8%)	CMV+/EBV-: 4 (40%) EBV+/CMV-: 1 (10%) CMV+/EBV+: 1 (10%) CMV-/EBV-: 4 (40%)
Yildrim et al 2006	12 lesions	N=12 CMV+/EBV-: 58%/0 EBV+/CMV-: 67%/0 CMV+/EBV+: 33% CMV-/EBV-: 0			
Andric et al. 2007	33 periapical cysts	N=16 CMV+/EBV-: 16/0	CMV+/EBV-: 17 (61.1%)/0		
Saboa-Dantas et al. 2007	26 HIV seronegative granulomatous (n=22) cysts(n=4)		granuloma CMV+/EBV-: 18.75% EBV+/CMV- 43.75% EBV+/CMV+ 0		
Yazdi et al 2008	50 lesions	N=28 CMV+/EBV-: 53.6% EBV+/CMV-: 3.6% CMV+/EBV+: 0 CMV-/EBV-: 0	N=22 CMV+/EBV-: 22.7% EBV+/CMV-: 0 CMV+/EBV+: 4.5% CMV-/EBV-:		
Sunda et al 2008	40 lesions	N=18 CMV+/EBV-: 0 EBV+/CMV-: 72% CMV+/EBV+: 0 CMV-/EBV-: 0	N=22 CMV+/EBV-: 0 EBV+/CMV-: 28% CMV+/EBV+: 0 CMV-/EBV-: 0		
Sabeti et al 2009	15 lesions	N=15 CMV+/EBV-: 67& EBV+/CMV-: 0 CMV+/EBV+: 0 CMV-/EBV-:			
Li et al 2009	53 lesions	% N=32 CMV DNA/mRNA+: 15.7/27.5%) EBV DNA/mRNA+: 43.1%/21.6%	N=21 CMV DNA/mRNA+: 16.1%/32.3% EBV DNA/mRNA+: 45.2%/32.3%	CMV DNA/mRNA+EBV+ 13.9%/33.3% EBV DNA/ mRNA+:50%/36.1%	% CMV DNA/mRNA+:0%/29.4% EBV DNA/mRNA+:47.1%/35.3%
Hernadi et al. 2010	40 lesions	N=17 CMV DNA/mRNA+: 6/0%) EBV DNA/mRNA+: 82%/71	N=13 CMV DNA/mRNA+: 13%/0%) EBV DNA/mRNA+: 65%/35%	CMV DNA/ mRNA+14%/0%) EBV DNA/ mRNA+91%/76%	CMV DNA/mRNA+: 0%/0%) EBV DNA/mRNA+: 53.3%/21%
Sabeti et al 2012	15 lesions	0 N=9 CMV+/EBV-: 55.3% EBV+/CMV-: 88.9% CMV+/EBV+: 0 CMV-/EBV-: 0	0 N=6 CMV+/EBV-: 0% EBV+/CMV-: 0% CMV+/EBV+: 0 CMV-/EBV-: 0		
Hernadi et al. 2013	58 lesions	N=28 CMV+/EBV-: 14.3% EBV+/CMV-: 89.3% CMV+/EBV+: 0 CMV-/EBV-:	N=30 CMV+/EBV-: 10% EBV+/CMV-: 63.3% CMV+/EBV+: 0 CMV-/EBV-:	N=31 CMV+/EBV- 16.1% EBV+/CMV- 93.5% CMV+/EBV 0 CMV-/EBV-: 0	N=27 CMV+/EBV-: 15% EBV+/CMV-: 7.4% CMV+/EBV+: 55.6% CMV-/EBV-: 0
Verdugo et al 2013	33 lesions	N=20 CMV+/EBV-: 15% EBV+/CMV-: 70% CMV+/EBV+: 15% CMV-/EBV-: 0	N=13 CMV+/EBV-: 0 EBV+/CMV-: 38.5% CMV+/EBV+: 0 CMV-/EBV		

Ozbeck et al 2013	28 lesions	n-16 CMV+/EBV-: 37.5% EBV+/CMV-: 18.7% CMV+/EBV+: 25% CMV-/EBV-: 0	n-12 CMV+/EBV-: 25% EBV+/CMV-: 8.3% CMV+/EBV+: 16.7% CMV-/EBV-: 0		SymptomaticCMV+/EBV-: 37.5% EBV+/CMV-: 18.7% Asymptomatic CMV+/EBV+: 0 CMV-/EBV-: 0

*symptomatic denotes swelling and pain

Table 2: Features of Cellular and Humoral Immunity.

Item	T-Cells	Lymphocytes	Major Histocompatibility complex	cytokines
Cellular Immunity	Th1	$CD4^+$ & $CD8^+$	MHC1	TNF-α, IL-1β, IL-17, prostaglandin E_2
Humoral Immunity	Th2	$CD4^+$ & B cells	MHC2	IL-4&10,

Also, cytomegalovirus exists within macrophages and T-lymphocytes in marginal periodontitis lesions [44]. CD178, or the Fas ligand, is a member of the tumor necrosis factor (ligand) superfamily. The Fas/Fas ligand system, which is an important cellular pathway mediating apoptosis [45] can potentially eliminate cytomegalovirus- infected cells [46]. CD178 was expressed in both cytomegalovirus-infected and non-infected cells; however, the magnitude of expression of CD178 and cytomegalovirus tended to be inversely related. Sabeti et al. found that forty-seven per cent of the lesions studied had a high CD178 expression level and low or barely detectable cytomegalovirus expression, while 33% of the lesions that demonstrated a low level of CD178 expression had a high level of cytomegalovirus expression [47]. They also clearly demonstrated the significance of active HCMV and EBV infection (high RNA expression) in the production of key cytokines. In this context, the comparative analysis exhibited a parallel, marked increased in the cytokines and HCMV& EBV expression in symptomatic periapical lesions when compared with asymptomatic ones. In fact, these findings agreewith other current studies that demonstrate the presence of heterogeneous and non-specific bacterial types, which indiscriminately and actively were present in normal, asymptomatic, as well as symptomatic periapical lesions. On this basis, bacterial infection may serve as a co-factor in lymphoid transvascular migration and cytokine expression involved in the pathogenesis of periapical lesions. IL-12 promotes Th1 population and suppresses Th2 cell type. Therefore, continuous production of IL-12 may play a role in chronic inflammatory processes. In parallel, HCMV and EBV have been shown to exert an anti-apoptotic activity.

It may be that a periapical cytomegalovirus infection can inhibit CD178 expression, which is involved in the regulation of apoptosis. Inhibition of apoptosis may then result in continuous inflammation and cytokines production, and the establishment of a chronic inflammatory state. The host may then fail to successfully control or eliminate the viral infection and subsequently, the bacterial infection.

Pathogenesis of Herpesvirus-Associated Apical Disease

Herpesviruses may cause disease as a direct result of viral infection and replication, or because of virally-induced impairment of the host defense. Herpesvirus-mediated pathogenicity may take place through several mechanisms, operating alone or in combination, and may involve both cellular and humoral (Table 2) host responses [48]. (I) Herpesviruses may cause direct cytopathic effects on periapical fibroblasts, endothelial cells, and bone cells, the result of which may be impaired tissue turnover and repair and ultimately, loss of the tissue. (II) HCMV and EBV may infect and alter functions of monocytes, macrophages, lymphocytes, and polymorpho nuclear leukocytes. Impairment of these host defense cells may then bring about overgrowth of endodontic pathogenic bacteria. Herpesvirus activation may induce significant immunosuppressive and immunomodulatory effects in periapical sites. Herpesviruses can trigger an array of host responses that include dysregulation of macrophages and lymphocytes, which serve to down-regulate the anti-viral host immune response [49]. Host impairment includes silencing of natural killer cells, inhibition of apoptosis, and destruction of components of MHC class I and class II pathways within macrophages, markedly impairing their principal role in antigen presentation [37]. In addition, HCMV encodes a unique homolog of interleukin (IL)-10, Th2 cytokine that antagonizes Th1 responses, and its immunosuppressive properties may help HCMV circumvent detection and destruction by the host immune system [50]. HCMV also can inhibit the expression of macrophage surface receptors for lipopolysaccharide, which impairs responsiveness to gram-negative bacterial infections [51]. (III) Herpesvirus infections elicit pro-inflammatory cytokine and chemokine release from inflammatory cells. Interleukin-1β and tumor necrosis factor α are present in significant levels in periapical lesions [52-55] and prostaglandin E2 (PGE_2) concentration is higher in acute than in chronic periapical lesions [56]. These inflammatory mediators, which are most likely produced locally by periapical macrophages [57,58], are potent bone resorption-stimulating agents [55,59]. Previous studies have focused on lipopolysaccharide as an inducer of macrophage cytokine production (59), but HCMV infection may possess higher potential to up-regulate interleukin-1β and tumor necrosis factor-α gene expression in monocytes and macrophages. It might be that the relationship of macrophages and their products to periapical pathosis is in part due to HCMV-mediated cytokine release from periapical macrophages. EBV is a potent polyclonal B-lymphocyte activator, capable of inducing proliferation and differentiation of immunoglobulin secreting cells. Periapical EBV infection may in part be responsible for the frequent occurrence of B-cells in periapical lesions. As mentioned Herpesvirus infections also affect cytokine networks [40]. Cytokines and chemokines play important roles in the first-line defense against human herpesvirus infections, and contribute significantly to the regulation of acquired immune responses. However, by diverse array of strategies, herpesviruses can interfere with cytokine production or divert potent antiviral cytokine responses, which allow the viruses to survive throughout the lifetime of the host [60,61]. HCMV infection typically induces a pro-inflammatory cytokine profile with production of IL-1β, IL-6, and IL-12, tumor necrosis factor (TNF)-α, interferon (IFN)-α/β, and IFN-γ [40], and prostaglandin E_2 (PGE_2)37, [62] EBV infection stimulates the production of IL-1β, IL-1receptor antagonist (IL-1Ra), IL-6, IL-8, IL-18, TNF-α, IFN-α/β, IFN-γ, monokine induced by IFN-γ (MIG), IFN-γ-inducible protein10 (IP-10), and granulocyte-macrophage colony-stimulating factor (GM-CSF) [40]. Pro-inflammatory activities normally serve a positive biological role by controlling infection or invasion by infectious agents;

however, they can also exert detrimental effects when a challenge becomes overwhelming or with a chronic patho-physiological stimulus. To counteract ongoing inflammation, the initial pro-inflammatory response triggers the release of anti-inflammatory mediators such as transforming growth factor-β and IL-1 [63]. Also, viruses display great uniqueness when it comes to diverting the potent antiviral cytokine responses to their benefit [40]. PGE_2, whichisa key mediator of the periapical inflammatory response [55], increases rapidly in response to exposure of cells to HCMV, bacterial lipopolysaccharide, and the cytokines IL-1β and TNF-α and PGE_2 may, under certain circumstances, support HCMV replication [64]. Undoubtedly, a periapical HCMV infection can induce a multiplicity of interconnected immunomodulatory reactions, and various stages of the infection may display different levels of specific inflammatory cells and mediators, underscoring the complexity of HCMV-host interactions in periapical disease. (IV) Herpesviruses may produce periapical tissue injury as a result of immunopathologic responses. Th1 cells, which predominate periapical lesions [28], are mediators of delayed-type hypersensitivity (68). HCMV has the potential to induce cell-mediated immunosuppression by down-regulating cell surface expression of major histo compatibility complex class I molecules, thereby interfering with cytotoxic T-lymphocyte recognition. EBV may induce proliferation of cytotoxic T-lymphocytes, the main purpose of which is to recognize and destroy virally infected cells, but may secondarily also inhibit various aspects of the immune response.

Control of herpes-viral replication and prevention of pathosis depend on both innate and adaptive immune mechanisms. Anti-viral antibodies help control infectious virions while cytotoxic T-lymphocytes play an important role in limiting the proliferation of herpesvirus-infected cells. The frequent presence of natural killer cells and CD8 (cytotoxic) T-lymphocytes in chronic periapical lesions [55,66] is consistent with an anti-herpes-viral host response. However, while anti-herpes-viral immune responses may be able to protect from disease, they are insufficient to eliminate reservoirs of persistent viral gene expression.

HCMV & EBV Biology and Pathogenicity

Membership in the herpesviridae family is based on the structure of the virion [67]. Herpesviruses contain a double-stranded DNA genome encased within an isosahedral capsid and an amorphous proteinaceoustegument. Surrounding the capsid and tegument is a lipid bilayer envelope derived from host cell membranes. The complete HCMV particle has a diameter of about 200nm and has one of the largest genomes (230kb) of any virus known to infect man. During their life cycle, herpesviruses execute an intricatechain of events geared towards optimizing their replication. HCMV & EBV transmission occurs by intimate contact with infected secretions including saliva [68]. Acquisition of herpesviruses takes place from an early age and sometimes in uterus. A notable exception is herpesvirus-8 that is contracted in adulthood. Clinical manifestations of herpesvirus infections are highly diverse and range from mild or subclinical disease in most systemically healthy individuals to encephalitis, pneumonia and other potentially lethal infections and various types of cancer including lymphoma, sarcoma and carcinoma in immunocompromised hosts. Cytomegalovirus infection is of great clinical significance in pregnant women, newborn infants with congenital or perinatal infection, immunosuppressed transplant patients and individuals with AIDS. Cytomegalovirus is the most common life-threatening infection in transplant and AIDS patients. Epstein-Barr virus is a known cause of infectious mononucleosis and almost certainly plays a role in the etiology of nasopharyngeal carcinoma, Burkitt's lymphoma and lympho proliferative disorders in the presence of immunosuppression. Less certain is the role of Epstein-Barr virus in rheumatoid arthritis, Hodgkin's disease and chronic fatigue syndrome.

The hallmark of HCMV & EBV infections is immune impairment. Herpesvirus infections trigger an array of host responses that include dysregulation of macrophages and lymphocytes [68]. Histopathologic features of periapical pathosis are consistent with a role of herpesviruses in symptomatic periapical disease. Periapical granulomas contain numerous macrophages [69] and T-lymphocytes [70], which are host cells of cytomegalovirus [58] and which seem to be important in periapical tissue destruction [71]. B-lymphocytes are present in periapical pathosis [70,72] and constitute the host cells of Epstein-Barr virus [68]. Cytotoxic CD8+ T-lymphocytes, which constitute the key element of the anti-herpes-viral host defense [73], can occur in high numbers in periapical pathosis [74-76]. Periapical granulomas also contain natural killer (NK)-cells [77], which are populations of large lymphocytes that accumulate at sites of viral replication and contribute to protective responses against herpesvirus infections through mechanisms of cytotoxicity and cytokine production without prior sensitization [78]. Herpesviruses interfere with innate and adaptive cellular and humoral immune effector mechanisms by affecting cytokine networks, activation and silencing of NK-cells, down-modulating antigen presentation in the major histocompat ability complex (MHC) class I and II pathways, and regulating apoptosis [79]. Cytomegalovirus infection gives rise to a typically pro-inflammatory cytokine profile, with production of interleukin (IL)-1β, IL-6, IL-12, tumor necrosis factor (TNF)-α, interferon (IFN)-α/β, and IFN-γ [80]. Cytokines and chemokines produced in Epstein-Barr virus infection includes IL-1β, IL-1receptor antagonist (IL-1Ra), IL-6, IL-8, IL-18, TNF- , IFN-α/β,IFN-γ, monokine induced by IFN-γ (MIG), IFN-γ-inducible protein10 (IP-10) and granulocyte-macrophage colony-stimulating factor (GM-CSF) [79]. GM-CSF tends to occur at elevated levels in symptomatic and large size periapical lesions [81]. Several of the herpesvirus-associated cytokines have been identified in periapical lesions [55,80-82] where they may exert bone resorption potential [83,84].

Herpesviruses may cause periapical pathosis as a direct result of virus infection and replication, or because of virally induced damage to the host defense. Some types of aggressive periapical pathosis may develop due to a series of interactions among herpesviruses, bacteria and host immune reactions. Specifically, we suggest that acute periapical disease is due to an escalation of patho-physiologic events, in which herpesvirus activation plays an important role. Initially, bacterial infection or mechanical trauma of the pulp cause herpesvirus-infected inflammatory cells to enter pulpal tissue through the periapical region. Subsequent herpesvirus reactivation gives rise to enhanced inflammatory mediator and cytokine responses in macrophages and other host cells. Lipopolysaccharide from resident gram-negative bacteria can also stimulate cytokine responses in inflammatory cells [85]. Triggering of pro-inflammatory cytokines may induce periapical bone resorption or, in a vicious cycle, reactivate latent herpes-viral infections. Diminished resistance of pulpal and periapical tissue may also lead to overgrowth of pathogenic bacteria or possibly cytotoxicity and tissue necrosis.

Clinical Implications

Endodontic treatments decrease the endodontic herpesvirus load and the destructive immune reactions of herpesvirus infections due to the close relationship between endodontic disease and herpesviruses. Cleaning and shaping and irrigation with sodium hypochlorite effectively suppress the endodontic infections since it is effective both against viruses and bacteria [86]. Also, at low concentrations, NaOCl can interfere with the ability of nuclear factor-kappaB cellular signalling to activate pro-inflammatory gene programs [87]. The root canal irrigants sodium hypochlorite and iodine are powerful anti-viral agents. If the etio-pathogenesis of AP indeed includes herpesvirus-mediated tissue destruction, a new direction to prevent and treat apical periodontitis may focus on controlling the causative viruses. If so, systemic antiviral therapy may be indicated for acute AP, which can harbor high herpesvirus counts within the tissue. Antiviral therapy has been suggested for treatment of periodontal disease. One study detected low EBV counts to undetectable level for one year after using Valacyclovir (5oomg). This treatment improved the clinical situation of refractory periodontal lesions [88].

In addition, the severity of periapical pathosis may be dampened with the development and administration of vaccinations against herpesviruses. Vaccines against herpesviruses, based on attenuated viral agents or subunits of viral antigens, are not just a Utopian dream, but the vaccines tested so far have not been able to match the robust cellular and/or humoral immune responses seen in herpes virus-infected individuals [89-91]. Also, immunomodulatory drugs that target AP cytokines or other inflammatory mediators involved in periradicular bone resorption may help to prevent or arrest AP as it did in periodontitis [92,93], and recent reviews have assessed immunomodulators for their potential usefulness in periodontal treatment [94,95]. MicroRNAs are short (20–24 nucleotides), non coding, functional RNA molecules that exist in many tissues including the gingiva [96,97], where they regulate cellular gene expression in a sequence-specific manner through RNA degradation or translational inhibition. MicroRNAs may influence T-cell activation and subtype differentiation, interfere with the macrophage nuclear factor-kappaB-regulated signaling pathway, and up-regulate the anti-inflammatory cytokine interleukin-10, and they can potentially serve a therapeutic purpose in the management of inflammation [98,99]. Long, non-coding RNA (lncRNA) molecules may also modulate translational outcome. However, it must be determined if AP immunemodulatory treatment can give rise to opportunistic infections with cytomegalovirus and Epstein–Barr virus. The linkage between AP and systemic diseases has attracted considerable research interest, and associations between APand cardiovascular disease, diabetes, these infectious agents, as can be the case with solid organ transplantation and other medical diseases, as described above, can have a herpesvirus component. Since herpesvirus virions from AP lesions are likely to enter the general circulation intermittently, they may infect and cause disease in a variety of extra-oral sites, especially in immunosuppressed individuals. If so, the ability of endodontic treatment to decrease endodontic herpesvirus counts may reduce the load of systemic herpesviruses and subsequently, the risk of non-oral disease. It is possible that a herpesvirus-induced overgrowth of AP bacteria may even explain, at least in part, the association between AP bacterial pathogens and systemic diseases.

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