Review Article

Herpes virus: A key missing piece of the periodontopathogenic jigsaw puzzle

Abstract

A solid understanding of the etiology of periodontitis is critical for developing therapies that can ensure long-lasting disease control. Research during the past 15 years has implied that herpes viruses are involved in the etiopathogeny of destructive periodontal disease. Because of the high copy counts of Epstein–Barr virus and cytomegalovirus in aggressive and chronic periodontitis, it is unlikely that these pathogenic viruses are acting merely as innocuous bystanders present in proportion to the severity of the underlying periodontal pathosis. However, herpes viruses are probably not stand-alone periodontopathic agents but cooperate with specific bacteria in periodontal tissue breakdown. A coinfection of active herpes viruses and periodontopathic bacteria may constitute a major cause of periodontitis and explain a number of the clinical characteristics of the disease. The purpose of this review is to evaluate the evidence supporting the hypothesis that viral infection plays a role in the development of periodontitis.

Key words:
Herpes virus, pathogenesis, periodontal disease, periodontitis, periodontopathogenic bacteria

Introduction

Periodontitis is a disease attributable to multiple infectious agents and interconnected cellular and humoral host immune responses.[1] It has been difficult to unravel the precise role of various putative pathogens and host responses in the pathogenesis of periodontitis. It remains an enigma why periodontitis of many subjects affects relatively few teeth despite the omnipresence of periodontopathic bacteria in saliva. Also, a pure bacterial cause of periodontitis seems unable to explain why the disease tends to develop in a bilaterally symmetrical pattern around the midline of the mouth. These uncertainties have galvanized efforts to find additional etiologic factors for periodontitis.

This review summarizes evidence that links herpes viruses, to the development of severe types of periodontitis, and outlines potential mechanisms by which it contributes to periodontal tissue breakdown.

Access this article online	
Website: http://www.cysonline.org	Quick Response Code
DOI: 10.4103/2229-5186.103090	

Herpesvirus: Emergence of a New Periodontal Pathogen

Since the mid-1990s, herpes viruses have emerged as putative pathogens in various types of periodontal disease.[2] In particular, human cytomegalovirus (HCMV) and Epstein–Barr virus (EBV) seem to play important roles in the etiopathogenesis of severe types of periodontitis. Herpes virus may cause periodontal disease as a direct result of virus infection and replication, or as a consequence of virally induced impairment of periodontal host defences with heightened aggressiveness of resident bacterial pathogens.

The hallmark of herpes infection is immune impairment.

Herpes Virus Structure

Membership in the family Herpesviridae is based on a four-layered structure of the virion [Figure 1].[3]

Babita R. Pawar, Avneesh H. Tejnani, Pramod P. Marawar, Ameet M. Mani

Department of Periodontology, Pravara Institute of Medical Sciences, Rural Dental College, Rahata, Ahmednagar, Loni, Maharashtra, India

Address for correspondence:
Dr. Avneesh H. Tejnani,
Department of Periodontology, Pravara Institute of Medical Sciences, Rural Dental College, Rahata, Ahmednagar, Loni, Maharashtra – 413 736, India.
E-mail: avneesh316@yahoo.co.in

Envelope

Herpes viruses are enveloped viruses. Envelope has a structure similar to cellular membrane; it consists of lipids, proteins, and glycoproteins. The viral membrane is quite fragile and a virus with a damaged envelope is not infectious.

Tegument

The space between the envelope and the capsid is the tegument. This contains virally encoded proteins and enzymes involved in the initiation of replication.

Capsid

Herpes viruses have a doughnut-shaped capsomere of about 100–200 nm in diameter with an icosahedral nucleocapsid.

Genome

Herpes viruses have double-stranded DNA. The size of the genomes differs ranging from 120 to 250 kbp with cytomegalovirus having the largest genome.

Herpes viruses are the leading cause of human viral diseases. The name herpes comes from the Greek word "Herpein," which means to creep. This reflects the creeping or spreading nature of the lesions caused by many herpes virus types. Herpes viruses seem to be the most important DNA viruses in oral pathology. The hallmark of herpes virus infections is immune impairment.

There are 25 families in the Herpetoviridae, but till date eight of them are known to infect humans, which are divided into three subgroups, namely, α, β, and γ based on details of tissue tropism, pathogenicity, and behavior under conditions of culture in the laboratory [Table 1]. Alpha herpes viruses are neurotropic, have a rapid replication cycle, and display a broad host and cell range. The β- and γ–herpes viruses differ in genomic size and structure but replicate relatively slowly and in a restricted range of cells, mainly of lymphatic or glandular origin.

To survive, herpes viruses need to exploit macrophages, lymphocytes, or other host cells for replication, while minimizing antiviral inflammatory responses of the host. Herpes viruses can occur in a latent or a productive (lytic) state of replication. During latency, the herpes virus DNA is integrated into and seems to behave like the host chromosomal DNA. Latency ensures survival of the herpes viral genome throughout the lifetime of the infected individual. From time to time, latent herpes viruses may undergo reactivation and re-enter the productive phase as a consequence of declining herpes virus-specific cellular immunity. The balance between herpes virus latency and activation involves the regulation of herpes virus gene expression, but the genetic and biochemical mechanisms governing a herpes virus latent infection and reactivation from latency are not fully understood. In general, the herpes virus latent phase shows little tendency to transcription, whereas reactivation from latency results in a general viral gene expression.[4]

The virus depends on the synthetic machinery of the host cell for replication. The viral multiplication cycle can be divided into six sequential phases, although the phases may sometimes be overlapping:

1. Adsorption or attachment
2. Penetration
3. Uncoating
4. Biosynthesis
5. Maturation
6. Release

In the viral productive cycle, the herpes virus genome is amplified 100- to 1000-fold by the viral replication machinery. [Figure 2] outlines the mode of the productive replication of herpes viruses. Herpes virus transcription, genome replication, and capsid assembly occur in the host cell nucleus. The herpes virus replication cycle includes binding of viral envelope glycoproteins to cell-membrane receptors, internalization and dismantling of the virus particle, migration of the viral DNA to the cell nucleus,

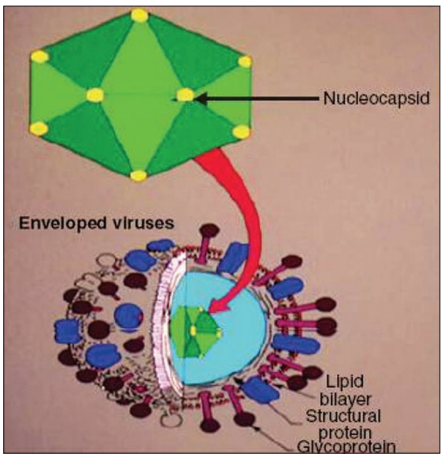

Figure 1: Structure of a herpes virus virion

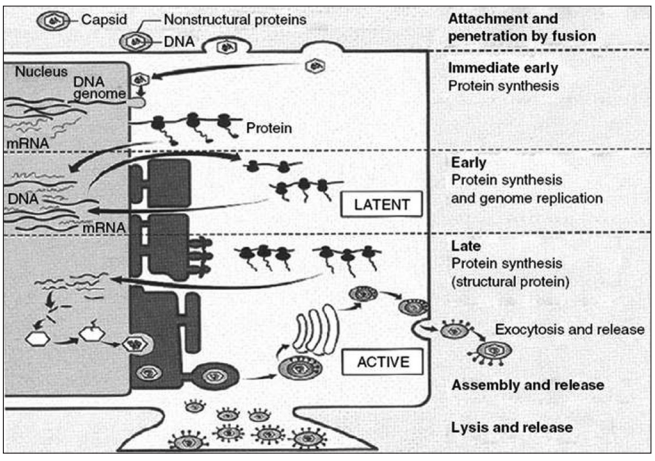

Figure 2: Schematic representation of herpes virus replication

Table 1: Human herpes viruses

Human herpesviruses	Abbrevation	Herpes group	Most commonly associated illness	Genome size kbp	Guanine + cytosine
Herpes simplex virus type 1	HSV-1	α	Cold sores	152	68.3
Herpes simplex virus type 2	HSV-2	α	Genital lesions	155	70.4
Varicella-zoster virus	VZV	α	Chicken pox/shingles	125	46
Epstein–Barr virus	EBV	γ	Glandular fever (Burkitt's lymphoma, nasopharengeal carcinoma)	172	60
Cytomegalovirus	HCMV	β	Congenital abnormalities	>229	557
Human herpes virus 6	HHV-6	β	Infant rash exanthema subitum	159	42
Human herpes virus 7	HHV-7	β	Febrile illness	145	45
Kaposi's sarcoma herpes virus	KSHV, HHV-8	γ	Kaposi's sarcoma	16-170	

transcription of viral genes, assembly of the virion, and viral egress from the infected cell Herpes viruses destroy infected cells by active lytic replication. After primary infection, herpes viruses remain latent with limited expression of viral genes, albeit retaining the transcriptional and replicational capacity. Latency / persistence is maintained for EBV in resting memory B lymphocytes, and for HCMV in dendritic cells and in monocytes and their progenitors. Psychosocial and physical stress, hormonal changes, infections, immunosuppressive medication, and other events impairing cellular immunity can trigger herpes viral reactivation. Transforming growth factor-β1 in saliva seems also to have the potential to reactivate herpesviruses.[5]

Herpesviruses in Periodontal Diseases

Taken collectively up to now, data in the literature suggest an increased frequency of detection of specific members of the Herpesviridae family, such as EBV-1, HCMV, and herpes simplex virus (HSV) in various forms of periodontal disease. Studies have reported that these viruses can infect and alter functions of polymorphonuclear leukocytes, lymphocytes, and macrophages and exert diminished ability to defend against bacterial challenge. This may potentiate the virulence of periodontopathogenic microbiota and dysfunction of polymorphonuclear leukocytes in periodontal sites can set the stage for overgrowth of periodontopathic bacteria and subsequent progression of destructive periodontal disease.[6]

Herpes virus-associated periodontal sites also tend to harbor elevated levels of periodontopathic bacteria, including *Porphyromonas gingivalis*, *Tannerella forsythia*, *Dialister pneumosintes*/*Dialister invisus*, *Prevotella intermedia*, *Prevotella nigrescens*, *Treponema denticola*, *Campylobacter rectus*, and *Aggregatibacter actinomycetemcomitans*.[7] It is suggested that the coexistence of periodontal HCMV, EBV, and possibly other viruses, periodontopathic bacteria, and local host immune responses should be viewed as a precarious balance that has the potential to lead to periodontal destruction.

Herpes virus pathogenicity is complex and is executed through direct virus infection and replication, or via a virally induced alteration of the host immune defence. The early phases of periodontitis in immunologically naive hosts may predominantly involve cytopathogenic events, whereas most clinical manifestations in immunocompetent individuals are secondary to cellular or humoral immune responses.

Herpes viruses may exert periodontopathic potential through the following mechanisms:

1. Herpes viruses can exert direct cytopathic effects on fibroblasts, keratinocytes, endothelial cells, and inflammatory cells, including polymorphonuclear leukocytes, lymphocytes, macrophages, and possibly bone cells. EBV and cytomegalovirus can also infect and alter the functions of monocytes, macrophages, and lymphocytes in periodontitis lesions. Perhaps as result of a herpes virus periodontal infection, aggressive periodontitis lesions contain fewer overall viable cells, more T-suppressor lymphocytes and more B lymphocytes (EBV effect) than chronic periodontitis lesions or healthy periodontal sites. Herpes virus-induced cytopathic effects may hamper tissue turnover and repair.[8]
2. A periodontal herpes virus infection may increase the pathogenicity of the periodontal microbiota. Herpes virus proteins expressed on eukaryotic cell membranes may act as new bacterial binding sites. Cytomegalovirus can enhance the adherence of *A. actinomycetemcomitans* to primary periodontal pocket epithelial cells and to HeLa cells.[8]
3. Herpes viruses may 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. EBV active infection can also generate anti-neutrophilic antibodies and neutropenia, and polyclonally stimulate the proliferation and differentiation of B lymphocytes. The pathogenic mechanisms of herpes viruses cooperate in exacerbating disease, and probably for that reason, a periodontal dual infection with cytomegalovirus and EBV, or with cytomegalovirus and HSV, tends to occur in severe types of periodontitis.[9]

4. Herpes viral infections can give rise to altered inflammatory mediator and cytokine responses. HCMV infection can upregulate interleukin 1-beta (IL-1β) and tumor necrosis factor-alpha (TNF-α) gene expression of monocytes and macrophages. EBV infection of B lymphocytes can induce a shift in lymphocyte subpopulation toward predominance of B lymphocytes/plasma cells. B lymphocytes/plasma cells are particularly prominent in progressive periodontitis lesions.[10]
5. Herpes viruses can produce tissue injury as result of immunopathological responses to virally infected cells. HCMV and HSV can induce cell-mediated immunosuppression by reducing the cell surface expression of MHC (major histocompatibility complex) class I molecules, thereby interfering with T-lymphocyte recognition. HCMV can cause metabolic abnormalities in lymphocytes and monocytes. HCMV can suppress antigen-specific cytotoxic T-lymphocyte functions, resulting in decreases in circulating CD4+ cells and increases in CD8+ suppressor cells, which in turn may lead to global impairment of cell-mediated immunity. Acute EBV infection and infectious mononucleosis can induce polyclonal B-lymphocyte activation with generation of anti-neutrophil antibodies and neutropenia. EBV-infected B lymphocytes may shed viral structural antigens that result in production of blocking antibodies, immune complex formation, and T-suppressor cell activation.[11]

Herpesviral: Bacterial Interactions in Periodontal Diseases

The interaction between herpesviruses and bacteria is probably bidirectional, with bacterial enzymes or other inflammation-inducing factors having the potential to activate periodontal herpesviruses.[8] Experimental mice infected with murine cytomegalovirus—*P. gingivalis* exhibited a significantly higher mortality rate than mice infected with murine cytomegalovirus—*Escherichia coli*.[12] The potential of *P. gingivalis* to suppress the interferon-gamma antiviral host response may partly explain the increase in cytomegalovirus pathogenicity.[12] Antigens of viruses and bacteria play a causal, or at least a contributory, role in destructive periodontal disease. Proinflammatory and anti-inflammatory balances controlled by different subsets of lymphocytes are thought to be crucial in the pathogenesis of periodontitis. Increased levels of proinflammatory cytokines in periodontal sites are associated with an enhanced risk of periodontal tissue destruction. The herpes virus-associated proinflammatory cytokines and chemokines can hamper the antibacterial host defence, stimulate bone-resorbing osteoclasts, upregulate matrix metalloproteinase, and downregulate tissue inhibitors of metalloproteinase, thereby impeding tissue turnover and repair and increasing the risk of periodontal tissue breakdown.[13]

[Figure 3] proposes an infectious disease model for the development of periodontitis based on herpes virus bacteria–host interactive responses. Herpes virus infection of periodontal sites may be important in a multistage pathogenesis by altering local host responses. Initially, bacterial infection of the gingival causes inflammatory cells to enter gingival tissue, with periodontal macrophages and T lymphocytes harboring latent HCMV and periodontal B lymphocytes harboring latent EBV.[14] IgA antibodies against HCMV, EBV, and HSV in gingival crevice fluid seem to originate mainly from local plasma cell synthesis rather than from passive transudation from serum, which is a further indication of a gingival herpes virus presence.[15] Reactivation of herpes viruses from latency may occur spontaneously or during periods of impaired host defence, resulting from immunosuppression, infection, physical trauma, hormonal changes, etc. Herpes virus-activating factors are also known risk factors/indicators for periodontal disease.[16]

Herpes viral activation leads to increased inflammatory mediator responses in macrophages and probably also in connective tissue cells within the periodontal lesion. After reaching a critical virus load, activated macrophages and lymphocytes may trigger a cytokine/chemokine "storm" of IL-1β, TNF-α, IL-6, prostaglandins, interferons, and other multifunctional mediators, some of which have the potential to propagate bone resorption.[17] Several of the herpes virus-associated cytokines and chemokines are prominent in periodontal lesions.[18] Herpes virus-

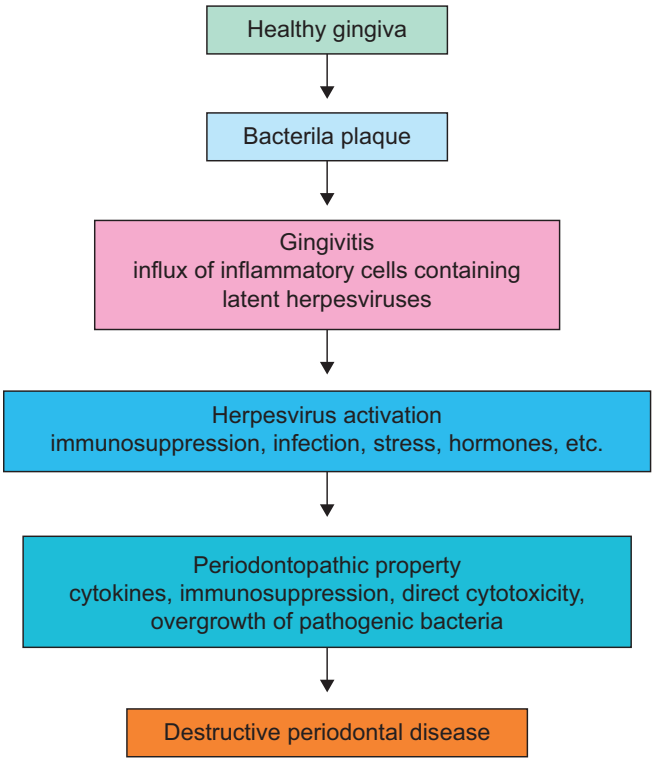

Figure 3: Herpes viral-bacterial model of periodontitis

induced immune impairment may also cause an upgrowth of resident gram-negative anaerobic bacteria,[19] whose lipopolysaccharide together with HCMV, as discussed above, can induce cytokine and chemokine release from various mammalian cells and may act synergistically in stimulating IL-1β gene transcription.[20] In a vicious circle, the triggering of cytokine responses may activate latent herpes viruses, and in so doing may further aggravate periodontal disease. It is conceivable that herpesviruses rely on coinfection with periodontal bacteria to produce periodontitis and, conversely, periodontopathic bacteria may depend on viral presence for the initiation and progression of some types of periodontitis.

Current State of Diagnostics: Viral Diagnostic Methods

Viral diagnostics is a rapidly changing field in terms of assay principles and available diagnostic kits. Identification of viruses has traditionally been based on cell culture to detect characteristic cytopathic effects, morphologic determination of intracytoplasmic and intranuclear inclusion bodies, immunohistochemical techniques, immunoassays to identify viral antigens in clinical specimens, or the measurement of total or class-specific antibodies against specific viral antigens. The era of relying upon *in vitro* cell culture for routine laboratory diagnosis of viral infections has truly passed. Viral isolation indicates an active and possibly disease-producing infection, but isolation of viruses is difficult, costly, and time-consuming.

High-fidelity PCR-based techniques have become the standard for identification and quantification of periodontal herpes viruses, and the transcription of late herpes virus genes for structural proteins is understood to signify productive viral replication and is commonly used to indicate an active herpes virus infection. PCR identification of oral HSV may yield two- to fourfold more positive samples than viral culture.[21]

Therapeutic Implications

The herpes viral–bacterial model of periodontitis provides a rationale for considering new approaches to disease prevention and treatment. Saygun *et al*. and Pacheco *et al*. reported that antimicrobial periodontal therapy can greatly reduce the herpes viral load in the periodontium, probably because the persistence of periodontal herpesviruses depends on the presence of gingival inflammatory cells. HCMV infects periodontal monocytes/macrophages and T cells, and EBV infects B cells,[14] and since inflammatory cells have a lifespan of up to a few months, an extended periodontal presence of herpesviruses may require repeated influx of infected cells or, possibly, a herpes virus-mediated inhibition of apoptosis.[22] The ability of thorough antimicrobial therapy to markedly reduce or eliminate periodontal herpes viruses may in part be responsible for a positive therapeutic outcome. Conventional periodontal therapy can reduce the periodontal load of herpesviruses. Mechanical debridement has suppressed subgingival EBV to undetectable levels in 12 of 21 patients,[23] and has decreased subgingival EBV genome copies by sixfold and subgingival cytomegalovirus genome copies by 38-fold.[24] After repeated debridement, 24 patients with periodontitis yielded no cytomegalovirus but were found to have EBV and herpesvirus-7,[25] suggesting that cytomegalovirus is particularly susceptible to the effects of periodontal therapy. The decrease in post-treatment herpes virus counts is probably caused by a reduction in gingivitis and thus in the numbers of virally infected inflammatory cells. Similarly, the low herpes virus counts in healthy periodontal sites are probably the result of a virtual absence of infected inflammatory cells.

Anti-herpes virus chemotherapy can also decrease the salivary viral load. A short course of valacyclovir, 2 g twice on the day of treatment and 1 g twice the following day resulted in a significant decrease in the salivary occurrence of EBV compared with controls.[26] Valacyclovir 500 mg orally twice daily for 1 month, given to elite male distance runners, reduced the salivary load of EBV by 82% compared with placebo.[27] Valacyclovir therapy, 3 g per day for 14 days, resulted in a reduction, of more than 100-fold, of EBV genome copies in oral wash fluid of patients with acute infectious mononucleosis.[28] Chemotherapeutics are effective against viruses in the lytic phase, but not against viruses in the latent phase, limiting their potential use to disease-active infections. Acyclovir types of drugs are acyclic nucleoside analogues that inhibit herpes viral DNA polymerase and replication of the viral genome. The orally administered acyclovir prodrug, valacyclovir, can reach serum concentrations similar to those of intravenously administered acyclovir and is prescribed for a variety of herpes viral diseases.[29] Prolonged treatment with valacyclovir at dosages of 500–1000 mg/day is well tolerated, perhaps except in immunosuppressed individuals, and the adverse events are infrequent and generally mild, with headache being reported most often.[30] To date, resistance to valacyclovir has not been clinically significant.

Future Directions

Research on the importance of herpes viruses in periodontal disease is in its infancy. The notion of a herpes viral–bacterial coinfection in periodontitis may turn out to be the pathogenetic Rosetta stone that unlocks many of the intricacies of the disease. Herpes virus-induced periodontitis implies that anti-herpes virus immunity constitutes an important aspect of achieving a long-lasting state of stable periodontal conditions. The development of herpes virus vaccines in the not too distant future makes the topic of periodontopathic herpes viruses particularly

intriguing. Control of herpesviruses by vaccination may foreshadow a future with a diminishing role for the traditional periodontal therapies of surgery and antibiotics and offers hope for low-cost prevention of periodontitis in large groups of individuals.

Summary and Conclusion

The current paradigm of the pathogenesis of periodontitis needs to be revisited based on the concept of a herpes viral–bacterial coinfection. Periodontitis may develop stepwise in a series of simultaneous or sequential infectious disease events, including (i) a high herpes virus load (gingivitis level) in periodontal sites, (ii) activation of periodontal herpesviruses, (iii) an insufficient antiviral cytotoxic T-lymphocyte response, (iv) the presence of specific periodontal pathogenic bacteria, and (v) an inadequate antibacterial antibody response. In most individuals, these five suggested pathogenic determinants of periodontitis may collaborate in a detrimental constellation relatively infrequently and mainly during periods of suppressed cellular immunity.

Herpes viruses play a major role as activators of the disease process in this model of periodontitis. Indeed, herpesviruses may be a key missing piece of the periodontopathogenetic jigsaw puzzle that would explain the transition from gingivitis to periodontitis or from stable to progressive periodontitis. It is hoped that the issues raised in this review will help to steer periodontal research into new fertile fields of investigation.

References

1. Ezzo PJ, Cutler CW. Microorganisms as risk indicators for periodontal disease. Periodontol 2000. 2003;32:24-35.
2. Contreras A, Slots J. Herpesviruses in human periodontal disease. J Periodontal Res 2000;35:3-16.
3. Slots J, Contreras A. Herpesviruses: A unifying causative factor in periodontitis? Oral Microbiol Immunol 2000:15:276-9.
4. Jarvis MA, Nelson JA. Mechanisms of human cytomegalovirus persistence and latency. Front Biosci 2002:7:1575-82.
5. Nagata Y, Inoue H, Yamada K, Higashiyama H, Mishima K, Kizu Y, *et al*. Activa tion of Epstein-Barr virus by saliva from Sjogren's syndrome patients. Immunology 2004:111:223-9.
6. Saygun I, Sahin S, O¨ zdemir A, Kurtis B, Yapar M, Kubar A, *et al*. Detection of human viruses in patients with chronic periodontitis and the relationship between viruses and clinical parameters. J Periodontol 2002:73:1437-43.
7. Saygun I, Kubar A, O¨ zdemir A, Yapar M, Slots J. Herpesviral- bacterial interrelationships in aggressive periodontitis. J Periodontal Res 2004:39:207-12.
8. Slots J. Herpesviral–bacterial interactions in periodontal diseases. Periodontol 2000 2010:52:117-40.
9. Slots J, Saygun I, Sabeti M, Kubar A. Epstein–Barr virus in oral diseases. J Periodont Res 2006;41:235-44.
10. Slots J. Herpesviruses in periodontal diseases. Periodontol 2000 2005;38:33-62.
11. Slots J. Human viruses in periodontitis. Periodontol 2000 2010;53:89-110.
12. Stern J, Shai E, Zaks B, Halabi A, Houri-Haddad Y, Shapira L, *et al*. Reduced expression of gamma interferon in serum and marked lymphoid depletion induced by Porphyromonas gingivalis increase murine morbidity and mortality due to cytomegalovirus infection. Infect Immun 2004:72:5791-8.
13. Page RC, Offenbacher S, Schroeder HE, Seymour GJ, Kornman KS. Advances in the pathogenesis of periodontitis: Summary of developments, clinical implications and future directions. Periodontol 2000 1997:14:216-48.
14. Contreras A, Zadeh HH, Nowzari H, Slots J. Herpesvirus infection of inflammatory cells in human periodontitis. Oral Microbiol Immunol 1999:14:206-12.
15. Hochman N, Mizrachi E, Ehrlich J, Morag A, Schlesinger M, Ever-Hadani P, *et al*. Prevalence of viral antibodies in gingival crevicular fluid. New Microbiol 1994:17:75-84.
16. Nunn ME. Understanding the etiology of periodontitis: an overview of periodontal risk factors. Periodontol 2000 2003:32:11-23.
17. Kawashima N, Stashenko P. Expression of bone-resorptive and regulatory cytokines in murine periapical inflammation. Arch Oral Biol 1999:44:55-66.
18. Graves DT, Cochran D. The contribution of interleukin-1 and tumor necrosis factor to periodontal tissue destruction. J Periodontol 2003:74:391-401.
19. Sabeti M, Slots J. Herpesviral-bacterial coinfection in periapical pathosis. J Endod 2004:30:69-72.
20. Wara-aswapati N, Boch JA, Auron PE. Activation of interleukin 1b gene transcription by human cytomegalovirus– Molecular mechanisms and relevance to periodontitis. Oral Microbiol Immunol 2003:18:67-71.
21. Kubar A, Saygun I, Yapar M, O¨ zdemir A, Slots J. Real-time PCR quantification of cytomegalovirus in aggressive periodontitis lesions using TaqMan technology. J Periodont Res 2004:39:81-6.
22. Zhu H, Shen Y, Shenk T. Human cytomegalovirus IE1 and IE2 proteins block apoptosis. J Virol 1995:69:7960-70.
23. Slots J. Herpesviral–bacterial interactions in periodontal diseases. Periodontol 2000 2009:51:1-24.
24. Saygun I, Kubar A, O¨ zdemir A, Slots J. Periodontitis lesions are a source of salivary cytomegalovirus and Epstein–Barr virus. J Periodontal Res 2005:40:187-91.
25. Rotola A, Cassai E, Farina R, Caselli E, Gentili V, Lazzarotto T, *et al*. Human herpesvirus 7, Epstein–Barr virus and human cytomegalovirus in periodontal tissues of periodontally diseased and healthy subjects. J Clin Periodontol 2008:35:831-7.
26. Miller CS, Avdiushko SA, Kryscio RJ, Danaher RJ, Jacob RJ. Effect of prophylactic valacyclovir on the presence of human herpesvirus DNA in saliva of healthy individuals after dental treatment. J Clin Microbiol 2005:43:2173-80.
27. Cox AJ, Gleeson M, Pyne DB, Saunders PU, Clancy RL, Fricker PA. Valtrex therapy for Epstein–Barr virus reactivation and upper respiratory symptoms in elite runners. Med Sci Sports Exerc 2004:36:1104-10.
28. Balfour HH Jr, Hokanson KM, Schacherer RM, Fietzer CM, Schmeling DO, Holman CJ, *et al*. A virologic pilot study of valacyclovir in infectious mononucleosis. J Clin Virol 2007:39:16-21.
29. Patel R. Valaciclovir: Development, clinical utility and potential. Expert Opin Investig Drugs 1997:6:173-89.
30. Bakaletz LO. Viral potentiation of bacterial superinfection of the respiratory tract. Trends Microbiol 1995:3:110-4.

How to cite this article: Pawar BR, Tejnani AH, Marawar PP, Mani AM. Herpes virus: A key missing piece of the periodontopathogenic jigsaw puzzle. Chron Young Sci 2012;3:245-50.

Source of Support: Nil, **Conflict of Interest:** None declared