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RESEARCH ARTICLE

VIRUSES: BYSTANDERS FOR THE PERIODONTAL DISEASE

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Abstract

Research during past 15 years has implied that herpes viruses are involved in the etiopathogeny of 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. The purpose of this review is to evaluate evidence supporting the hypothesis that viral infection plays a role in development of periodontitis.

INTRODUCTION

Periodontitis is a disease attributable to multiple infectious agents and interconnected 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. It is not understood why, in hosts with comparable levels of risk factors, some periodontal infections result in loss of periodontal attachment and alveolar bone while other infections are limited to inflammation of the gingiva with little or no discernible clinical consequences. Even though specific infectious agents are of key importance in the development of periodontitis, it is unlikely that a single agent or even a small group of pathogens are the sole cause or modulator of this heterogeneous disease.

Since the mid 1990s, herpes- viruses have emerged as putative pathogens in various types of periodontal disease. In particular, human cytomegalovirus (HCMV) and Epstein-Barr virus (EBV) seem to play important roles in the etiopathogenesis of severe types of periodontitis. Genomes of the two herpes viruses occur at high frequency in progressive periodontitis in adults, localized and generalized aggressive (juvenile) periodontitis, HIV-associated periodontitis, acute necrotizing ulcerative gingivitis, periodontal abscesses, and some rare types of advanced periodontitis associated with medical disorders. HCMV is the largest of the human herpes viruses. Herpes viruses are typically highly selective in regard to the specific tissues or organs they infect, reflecting their strong tendency to tissue tropism. Several herpes viruses reside in and may functionally alter cells of central importance for regulating the immune system. The herpes viral–bacterial hypothesis of periodontitis proposes that an active herpes virus infection initiates periodontal tissue breakdown and that host immune responses against the herpes virus infection are an important component of the etiopathogeny of the disease. Even though bacteria are recognized to be indispensable for the development of periodontitis, and although current hypotheses on the etiopathogenesis of periodontitis correctly emphasize the importance of assessing bacterial and host factors collectively, bacterial–host interaction alone seems insufficient in explaining important clinical characteristics of the disease. It seems clear that periodontal tissue breakdown occurs more frequently and progresses more rapidly in herpes virus infected than in herpes virus free periodontal sites. Herpes viruses may cause periodontal pathosis as a direct result of virus infection and replication, or as a consequence of virally induced impairment of the periodontal immune defense, resulting in heightened virulence of resident bacterial pathogens. It is assumed that the ability of herpes viruses to express cytopathogenic effects, immune evasion, immunopathogenicity, latency, reactivation from latency, and tissue tropism is of relevance for the development of periodontitis. Non specific hypothesis states that periodontal disease

were believed to result from accumulation of plaque over time, eventually in congestion with diminished host response and increased host suspectibilty with age. Specific hypothesis states that plaque is a pathogenic and its pathogenicity depends on presence of or increase in specific microorganism. Ecological plaque hypothesis states that carious disease can be attributed to changes to the environment which distrubes homeostatsis between plaque microflora and host.

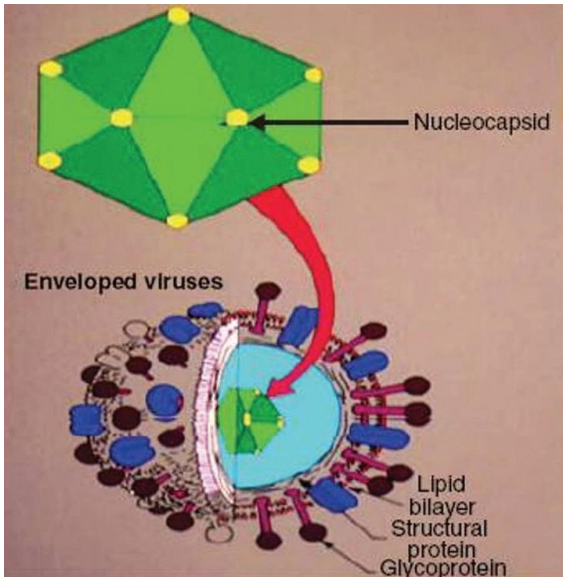

Fig. 1: Structure of a herpes virus virion

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, 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.

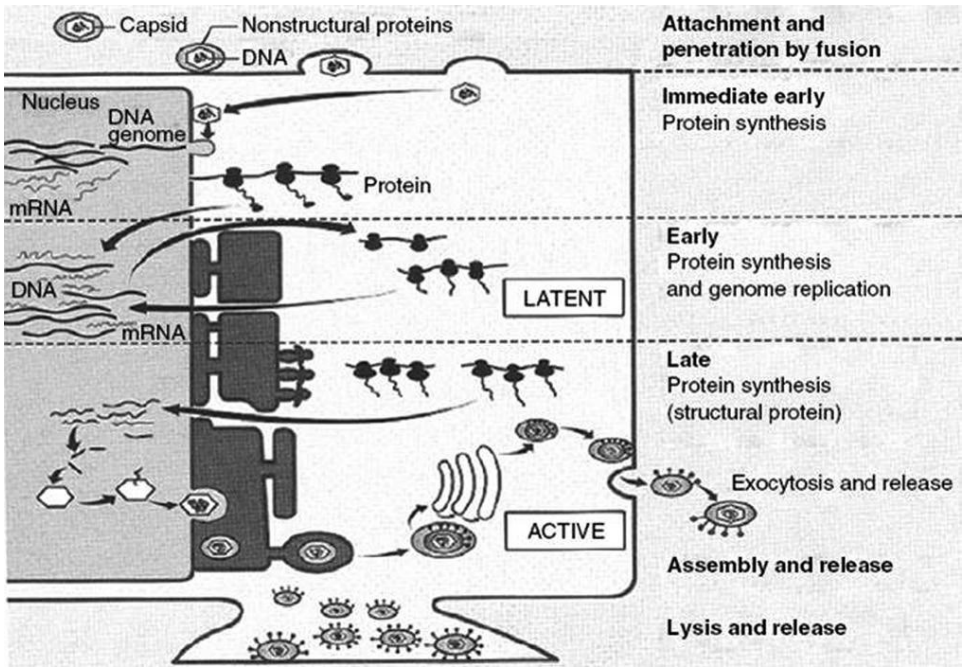

Fig. 2: Schematic representation of herpes virus replication

Various Studies Showing Effects of Viruses in Periodontal Diseases:

Conteras and Slots in 1996 reported that herpes viruses may cause direct cytopathic effects on fibroblasts, keratinocytes, and endothelial cells and on leukocytes. Klein reported that herpes infection may promote subgingival attachment and colonization of periodontopathic bacteria, similar to the enhanced bacterial adherence to virus-infected cells ob- served in medical infections.14 HCMV can cause metabolic abnormalities in lymphocytes and monocytes.

Hochman et al in 1998 detected antibodies against Epstein–Barr virus in 32%, and against cytomegalovirus in 71%, of gingival crevice fluid samples from 34 study sites. Antibodies against the herpesviruses were predominantly of the immunoglobulin A (IgA) isotype in the gingival crevice fluid and of the immunoglobulin G (IgG) isotype in serum samples. These antibody findings suggest a local synthesis by plasma cells rather than passive transudation from the blood, and thus provide further evidence of a close relationship between herpesviruses and periodontal disease.

Para and Slots in 1999 investigated 30 patients with advanced periodontitis and 26 gingivitis for presence of human cytomegalovirus (HCMC), cytomegalovirus (HCMV), Herpes Simplex Virus (HSV), Human Papilloma virus (HPV), and human immunodeficiency virus (HIV) in gingival crevicular fluid samples using PCR studies and found that HCMC was detected in 60% of periodontitis patients while only 31% gingivitis group. EBV in 30%, HSV in 20%, HPV in 17% and HIV in 2 % of periodontitis patients were detected positive, however they were not detected in gingivitis group.

Ting et al. in 2000 hypothesized that a primary cytomegalovirus infection at the time of root formation of permanent incisors and first molars can give rise to a defective periodontium. Viruses infecting odonto- genic cells of developing hamster teeth can disrupt normal cell differentiation, and an active cyto- megalovirus infection can change the morphology of developing teeth. Perhaps because of a cytomegalovirus infection early in life, teeth affected by localized aggressive periodontitis often show cemental hypoplasia.

Contreras et al. in 2000 studied necrotizing ulcerative gingivitis in non HIV-infected malnourished Nigerian children, 3–14 years of age. Cytomegalovirus has demonstrated a necrotizing potential in acute retinal necrosis of severely immunocompromised individuals, acute necrotizing esophagitis, necrotizing enterocolitis of preterm infants, necrotizing glomerulonephritis of renal transplant recipients, necrotizing myelitis and necrotizing encephalitis.

Saygun et al in 2001 investigated that 21 healthy controls and 30 chronic periodontitis patients anfd found that plaque samples showed HCMV (44.3%), EBV (17.7%), HSV (6.7%) compared to healthy sites with HCMV (14.3%), EBV (14.3%) and HSV (0%).

Kamma et al. in 2001 investigated the occurrence of DNA of HCMV, EBV-1 and selected periodontal pathogenic bacteria in 16 patients with aggressive periodontitis. Patients with an HCMV-EBV-1 periodontal coinfection

exhibited, on average, a more rapid progression of periodontitis than patients with a herpesvirus monoinfection. Other studies have also demonstrated a strong association between subgingival P. gingivalis, D. pneumosintes and P. gingivalis-D. Pneumosintes co-occurrence and disease-active periodontitis. He also studied 16 subjects from Greece with early onset periodontitis. Periodontal cytomegalovirus exhibited a particularly close association with the presence of P. gingivalis.

Yapar et al. in 2003 described a close relationship between herpesviruses and aggressive periodontitis, and the same research group from Ankara, Turkey, detected a lower qualitative and quantitative occurrence of herpesviruses in chronic periodontitis lesions. The predilection of herpesviruses for aggressive periodontitis emphasizes the need for a careful assessment of the periodontal disease status in clinical studies of periodontal herpesviruses.

Kuber et al in 2004 investigated plaque samples and found that patients with aggressive periodontits had HCMV (68.8%), compared to HCMV (0%) in healthy controls. According to **Taughels et al in 2007** cytomegalovirus can enhance the adherence of A.A to primarily epithelial cells of periodontal pockets. These viruses can alter the function of immune cells resulting in abnormalities in adherence, chemotaxis and phagoctyosis.

Michalowicz et al. in 2006 studied the presence of subgingival HCMV, EBV-1, P. gingivalis and A. actinomycetemcomitans Apparently, HCMV and P. gingivalis are independently and strongly associated with localized aggressive periodontitis in Jamaican adolescents, and the two infectious agents seem to act synergistically to influence the risk for both the occurrence and the severity of the disease.

Imbrouito et al in 2008 found increased HCMV detection (57%) compared to healthy controls (40%).

Billichodmath et al in 2009 investigated for herpes virus in chronic and aggressive patients and found association of herpes virus of 100% in chronic periodontitis compared to 57% in aggressive periodontitis patients.

Pawar et al 2012 studied that 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.

Zeyad T. Al-Rassam et al in 2014 studied high percentage of chronic periodontitis detected between 20-39 years old. Nested PCR showed detection of EBV, CMV and HSV in chronic periodontitis patient's pockets. EBV and HSV showed significance association with chronic periodontitis patient's pocket, but there was no association with CMV. ELISA assay was unsuitable technique to detect chronic periodontitis viruses. Also no statistical association was detected between pocket depth and type of viruses detected. He stated that the presence of viruses in periodontal pockets does not act as simple bystanders, but they play a critical role as putative pathogens in periodontitis. Usually human viral infection is followed by bacterial superinfections, this association between viruses and bacteria usually produces a greater pathogenic effect, and the viral–bacterial synergism could be applied in the oral cavity.

Table lists syndromes that have been associated with both periodontal herpesviruses and severe periodontitis.

Disease	**Periodontal viruses**	**Periodontal disease**	**References**
Guillain–Barre syndrome	Cytomegalovirus	A 37-year-old patient with localized periodontitis	Tabanella & Nowzari
Kostmann syndrome	Epstein–Barr virus	Two siblings (3 and 6 years of age) with severe gingivitis and periodontitis	Yildirim et al.
Fanconi's anemia	Herpes simplex virus, cytomegalovirus	An 11-year-old boy with severe gingivitis and moderate or advanced periodontitis sites	Nowzari et al.
Papillon–Lefe `vre syndrome	Epstein–Barr virus, cytomegalovirus	An 11-year-old girl with severe periodontitis around several teeth	Velazco et al.
Down syndrome	Herpes simplex virus (26%), Epstein–Barr virus type 1 (37%), cytomegalovirus (37%)	19 Down syndrome patients with moderate or advanced periodontitis	Hanookai et al.

The etiopathogenesis of periodontitis includes virulence factors of herpesviruses and bacteria, host immune responses against viral and bacterial infections, and manipulation of host-cell processes by the infectious agents. Herpesviruses may induce periodontitis by activating specific tissue-destroying pathways of the immune system and

by predisposing an individual to bacterial carriage or increased bacterial load. However, the molecular contribution of herpesviruses versus bacteria to periodontal pathosis remains little understood. The inflamed periodontium appears to be a major site for Epstein–Barr virus and cytomegalovirus accumulation and re-activation, especially in the progressive phase of periodontal disease. The detection of viruses within periodontal pockets by various studies proves that virus do have a role to play in periodontitis. However, there is 'what came first, hen or egg?' situation when it comes to considering viruses for periodontitis. The virus infection may be primary infection causing bacterial periodontitis as a superinfection or it may be the bacterial host response resulting in reactivation of latent virus affecting the severity and progression of periodontitis. A causal relationship may be inferred if the removal of herpesviruses by specific antiviral medication arrests, reverses or prevents periodontitis.

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
(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.

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