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Herpesviruses in Human Periodontal disease. Reality or Myth…?

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Abstract:

Viruses are known to be immunosuppressive and facilitate establishment of subgingival pathogens and have been detected in the gingival crevicular fluid. Virus-like inclusions have been identified in gingival inflammatory cells from localized juvenile periodontitis. Viruses are known to infect the inflammatory cells of the periodontium; they are present more frequently in diseased sites than in healthy sites. Progressing periodontal disease may be associated with reactivation of HCMV in periodontitis which harbor elevated levels of putative periodontal pathogens like tannerella forsythia, treponemadenticola to name a few. The following review is an attempt to explore the reality behind the above said inter-relationship.

Introduction:

Herpesviruses seem to be the most important DNA viruses in oral pathology. The hallmark of herpesvirus infections is immune impairment.

Eight human viruses of the family herpesviridae have been identified. Studies have demonstrated that Human Cytomegalovirus and Epstein Barr Virus type 1 occur with high frequency in actively progressing periodontitis lesions[1]. Active herpesvirus infection in the oral cavity often involves ulceration of gingiva[2-4]. They have also implicated EBV-1 and HCMV in the pathogenesis of human periodontal disease[5, 6]. The following is not only an attempt to elaborate the established

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association between herpes viruses and periodontal disease, but also an attempt to throw light on the fact that there are reports which refute the above association.

Association between herpesviruses and periodontal disease

The literature presents only few data on herpesviruses in periodontal disease. Sabiston suggested an association between HCMV and periodontal disease. In inflammatory cells of juvenile periodontitis gingival biopsy specimens; Burghelea& Serb described the presence of nuclear body-type structures and virus-like inclusions which, considering recent findings by Ting et al., might have been herpesviruses.[7] Recently, Contreras and coworkers have employed a sensitive and specific nested polymerase chain reaction (PCR) detection method to study herpesviruses in periodontal sites.[6]

In adult periodontitis lesions, HSV infects T-lymphocytes and monocytes/macrophages, EBV-1 infects B-lymphocytes and HCMV infects monocytes/macrophages and T-lymphocytes.Herpesvirus-infected inflammatory cells may exert diminished ability to defend against bacterial challenge.

Similar to medical infections, in which herpesvirus can reduce the host defense and give rise to overgrowth of pathogenic microorganisms, herpesvirus-infected periodontal sites seem to be associated with increased levels of periodontal pathogens.[7]

Herpesviruses may also interfere with periodontal healing. In guided tissue regeneration, Smith MacDonald et al. found that 4 periodontal sites showing either EBV-1 or HCMV had an average gain in clinical attachment of 2.3 mm compared with 16 virally negative sites that showed a mean clinical attachment gain of 5.0 mm ($p \sim 0.004$). By infecting and altering functions of fibroblasts.[6,7] Herpesviruses may reduce the regenerating potential of the periodontal ligament.

Pathogenesis of herpesvirus-associated periodontal disease

Herpesviruses may cause periodontal pathology as a direct result of virus infection and replication, or as a result of virally mediated damage to the host defense. Herpesviruses may exert periodontopathic potential through at least 5 mechanisms, operating alone or in combination.

1. Herpesviruses may cause direct cytopathic effects on fibroblasts, keratinocytes, endothelial cells,[8,7] on inflammatory cells such as polymorphonuclear leukocytes,[7] lymphocytes, macrophages, and possibly on bone cells. Since the above cells are key constituents of inflamed periodontal tissue, herpesvirus-induced cytopathic effects may hamper tissue turnover and repair.[7,9]

2. Herpesviral periodontal infections may impair cells involved in host defense, thereby predisposing to microbial superinfection. HCMV and EBV-1 can infect and/or alter functions of monocytes, macrophages and lymphocytes.[10]

3. Gingival herpesvirus infection may promote subgingival attachment and colonization of periodontopathic bacteria, similar to the enhanced bacterial adherence to virus-infected cells observed in medical infections,[11,12] Viral proteins can act as bacterial receptors and generate new bacterial binding sites. Loss of virus-damaged epithelial cells can expose the basement membrane and the surface of regenerating cells, providing new sites for bacterial binding.[7]

4. Herpesviral infections can give rise to altered inflammatory mediator and cytokine responses.[13] In periodontitis, HCMV-induced expression of cytokines is particularly intriguing. HCMV infection can upregulate interleukin 1-beta (IL-1b) and tumor necrosis factor-alpha (TNF-a) gene expression of monocytes and macrophages. Increased production of the proinflammatory cytokines IL-1b and TNF-a by macrophages and monocytes has been associated with enhanced

susceptibility to destructive periodontal disease. In turn, IL-1b and TNF-a may up-regulate matrix metalloproteinase, downregulate tissue inhibitors of metalloproteinase and mediate periodontal bone destruction.[7]

EBV and other members of the Herpesviridae family elaborate compounds that may exert important regulatory effects on host cell cytokine synthesis. EBV-encoded protein BCRF1 possesses a striking structural and functional similarity with IL-10, which can suppress TH1 cell-mediated IL-2, interferon-c and lymphotoxin production and polarize the immune system toward a TH2-type response,[12] TH1-type response has been associated with protection against perioodntitis whereas TH2-type seems to be related to progressive periodontal disease.[7]

In addition, EBV infection of B-lymphocytes can induce a shift in lymphocyte subpopulations toward predominance of B-lymphocytes/plasma cells. EBV-mediated transformation of B-lymphocytes to plasma cells may occur in periodontal disease as evidenced by a B-lymphocyte dominance and polyclonal B-lymphocyte activation in periodontitis lesions. B-lymphocytes/ plasma cells are particularly prominent in progressive periodontitis lesions.[7]

5. 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.[9] HCMV can cause metabolic abnormalities in lymphocytes and monocytes.[14] In addition, 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. EBV may trigger a proliferation of cytotoxic T-lymphocytes capable of recognizing and destroying virally infected cells.[13,8] Moreover, acute EBV infection and infectious mononucleosis can induce polyclonal B-lymphocyte activation with generation of anti-neutrophil antibodies and neutropenia.[7]

Initially, gingival inflammation permits herpes virus infected inflammatory cells to enter the periodontium herpes virus reactivation in the periodontium may then occur , which may then aggravate the inflammatory response and accelerate the existing disease. Thus, various immunosuppressive events may aggravate periodontal disease, suggestive of accompanying herpes virus activation.

Active herpes virus infection decreases the resistance of the periodontal tissues thereby permitting subgingival overgrowth of pathogenic bacteria.

The recognition that periodontitis is a multifactorial disease involving herpes viruses , bacteria and host reaction may explain why aggressive periodontitis is relatively uncommon in most populations despite a high prevalence of individuals harboring both herpes viruses and bacterial pathogens.[1]

Salient features of periodontal disease pathogenesis and herpes viruses

The probable pathogenesis is based on:

1) Presence of nucleic acid sequences of EBV-1 and HCMV and other herpesvirusesin juvenile and adult periodontitis lesions;

2) The association between herpesviruses and acute necrotizing gingivitis

3) The demonstration of mRNA gene HCMV expression in adult and localized juvenile periodontitis lesions and the apparent association with progressive disease.

4) The demonstration of increased frequency of periodontopathic bacteria in heresvirally positive periodontitis lesions

5) The detection of nucleic acid sequences of herpesviruses in inflammatory periodontal cells

6) The probable prominent effect of herpesvirus infection on periodontal defense cells.

7) The ability of herpesviruses to augment the expression of tissue-damaging cytokines in periodontal inflammatory cells.

The suggestion is that gingival infection with certain herpesviruses decrease the resistance of the periodontal tissue, thereby permitting subgingival overgrowth of periodontal pathogenic bacteria.

Herpesvirus reactivation in periodontal tissue resulting in transient immunosuppression might in part explain the episodic progressive nature of human periodontitis.

Tissue tropism in herpesvirus infection might help explain the localized pattern of destruction in many cases of periodontitis.

Absence of periodontal herpesvirus infection or reactivation could allow for some individuals carrying periodontopathic bacteria in their subgingival microbiota while maintaining periodontal health.

Other perspectives:
If some types of destructive periodontal disease are indeed the result of a herpesvirus-mediated opportunistic bacterial infection, a new approach to preventing and treating periodontitis may focus on controlling the virus(es) that enable overgrowth of periodontopathic bacteria.

Vaccination against herpesviruses as a consequence constitutes an attractive approach in periodontal prophylaxis and treatment. Despite circumstantial evidence of a role of herpesviruses in destructive periodontal disease, a cause-and-effect relationship remains to be established.

Questions remain as to whether active periodontal HCMV infection gives rise to destructive periodontal disease or whether destructive periodontal disease reactivates a latent HCMV infection. The possible involvement of human herpesviruses in the etiology and pathogenesis of destructive periodontal diseases merits further investigation.

In contrast to the growing evidence which suggests that certain viruses may play a role in the pathogenesis of periodontal disease, very low prevalence of such viruses has been detected in periodontally healthy individuals
Furthermore herpes viruses have been associated with severity and activity of Periodontitis and with presence of periodontopathogenicbacteria recent review suggested that viruses may directly induce immunosuppression and may have a direct cytopathic effect on fibroblast and keratinocytes and inflammatory cells. However large studies confirming the association between Periodontitis and presence of subgingival viruses are still lacking.

However, Luigi Nibali et al do challenge the high prevalence of herpes virus DNA and also they make it known that such a mammoth difference in the results may be due to study methods and difference in the populations analyzed (different ethnic groups.) The sample size of this study was relatively higher than the others. However, apart from surrogate methods of assessing the periodontal disease activity (probing pocket depth and bleeding on probing) the low prevalence itself can be attributed to the fact that the viruses might have been latent at that point in the disease process.[15] Furthermore in 2008 Rotola[16] et al found low prevalence of HCMV in gingival biopsies in Caucasian populations. They attributed the discrepancies of prevalence of infections in different ethnic populations. They also found low amounts of HHV-7 an EBV which were exclusively by sensitive nested PCR technique.

Conclusion:
The concept of herpes viruses playing a role in the pathogenesis of periodontal diseases is questioned in a few of these studies. So it can be concluded that high prevalence may not be a universal feature of periodontal disease but it may depend on the studied population and to some extent on the

methods used. Therefore further research is needed in the area with more uniformity incorporated in the methods.

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