REVIEW ARTICLE

Viruses in periodontics

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Abstract

The main purpose of this review was to assess the documentation supporting the preposition that viruses will cause periodontal disease. Human immunodeficiency virus and herpes viruses are found to be involved in periodontitis. Viral DNA has been disclosed in gingival tissue, gingival crevicular fluid (GCF) and subgingival plaque from periodontally diseased sites. The presence of these viruses in periodontal sites may suggest that these viral re-activation triggers periodontal disease activity. Periodontal disease shows the alternate periods of activity and inactivity, this suggests that the viruses along with bacteria's might be responsible for the above. Reverences regarding sampling, methods and elucidation will bring an uncertainty regarding the viruses as the causative factor for periodontal disease.

Keywords: Epstein-Barr virus, herpes virus 1, human cytomegalovirus, periodontal disease, polymerase chain reaction

Background

Most of the bacterial infections occur due to super infections by various viruses. The most common seen example is the bacterial complication which is seen in influenza epidemics, in elderly people, death is seen mainly due to secondary bacterial pneumonia which is caused by *Staphylococcus aureus*, *Streptococcus pneumonia*.[1,2] The same viral-bacterial interactions can be seen in the oral cavity.

Gingivitis and periodontitis are caused by bacteria present in plaque. Studies have shown a consistent positive link between the amount of plaque and severity of gingivitis as well as bone loss[3,4] when the plaque is eliminated, the signs of inflammation is resolved. Chlorhexidine is able to suppress the growth of bacteria's as well as gingivitis.[5,6] Adjuvant use of mechanical debridement and chlorhexidine have brought about control in severity of periodontal disease, which states that bacteria cause's periodontal disease in humans.[7] Gingivitis will occur in the patients with poor oral hygiene, but all the patients with gingivitis will not progress into periodontitis, progression of periodontitis depends on the subjects, and only few subjects show severe destruction.[8] Sporadic activity of disease is seen in specific sites, this aids that viruses might be involved in the pathogenesis of periodontal disease.[9]

Herpesviruses

Herpes viral infections are seen in children from secretions such as saliva, and they cause lesions in the oral cavity as well as on the mucosa during the primary infection, after primary infection the viruses remain latent, and the virus is reactivated under various conditions such as immune loss, and infections may cause severe diseases in acquired immunodeficiency patients.[10]

Herpesviruses are divided into three types:

- Alpha-herpes viruses,
- Beta herpes viruses and
- Gamma herpes viruses.

Most viruses potentially involved in periodontal disease are DNA viruses. The DNA viruses are conracted in childhood or early adulthood, through contact with blood, saliva or Genital secretions and they remain latent in the Dorsal root of the trigeminal ganglion. The viruses may get activated during emotional stress, fever, exposure to ultraviolet radiation, concurrent infections, drugs, tissue trauma, and when the body's immunity is reduced.[11]

Herpes simplex viruses (HSV)

The primary herpetic gingivostomatitis is caused by HSV-1[12,13] as part of the primary infection, the virus ascends through sensory and autonomic nerves, where it remains latent. The virus

remain symptomless in early childhood, as the age advances it gives rise to more severe exposition.[14] Rekindling of HSV can occur having no clinical signs of disease, but few individuals are prone to the recurrence of the lesions. The recurrences are usually found at the skin and the mucous membrane junction of lips, palate or the gingiva.

Varicella zoster virus (VZV)

VZV causes two diseases, chicken pox in children and herpes zoster in older individuals and immunocompromised persons.

Epstein-Barr virus (EBV)

EBV is usually transmitted by saliva or blood. EBV infection in children is most often symptomless. In adults EBV causes infectious mononucleosis. EBV causes proliferation and activation of T-cells. EBV has also been associated to a other disease such as cancers and autoimmune diseases. Oral hairy leukoplakia is the main lesion attributes to EBV.

Human cytomegalovirus (HCMV)

This virus is found in saliva, urine, semen, and breast milk.

Herpes Viruses May Exert Periodontopathic Potential through at least Five Mechanisms by Operating alone or in Combination

1. Herpes viruses may cause direct cytopathic effects on fibroblast, keratinocytes, epithelial cells,[15,16] on inflammatory cells such as neutrophils,[17,18] lymphocytes,[19] macrophages, and possibly on bone cells. Since the above cells are key constituents of inflamed periodontal tissue, herpes viruses will bring about cellular changes which may affect tissue turnover and repair
2. Herpes viral periodontal infections may hamper the cells involved in host defense, thereby prejudice to microbial super infection. HCMV and EBV-1 can infect and/or alter functions of monocytes, macrophages and lymphocyte[20,21]
3. Gingival herpes virus infection may bring about allocation and growth of periodontal bacteria[22]
4. Herpes viral infections will alter the inflammatory pathway and response of cytokines. In periodontitis, HCMV-induced expression of cytokines is particularly fascinating. HCMV infection can upregulate interleukin 1-beta (IL-1β) and tumor necrosis factor-alpha (TNF-α) gene expression of monocytes and macrophages. Increased production of the proinflammatory cytokines IL-1β and TNF-α by macrophages and monocytes has been related to the increased chance of development of periodontal disease

   EBV and other members of the Herpesviridae family elaborate compounds that may exert important regulatory effects on host cell cytokine synthesis. EBV-encoded protein BCRF-1 possesses a striking structural and functional similarity with IL-10, which can suppress THI cell mediated IL-2, interferon-c and lymhotoxin production and polarize the immune system toward a TH2-type response. TH1 type response has been associated with protection against periodontitis whereas TH2-type seems to be related to Progressive periodontal disease[23-25]
5. HCMV and HSV can bring about the inhibition of cell-mediated immunity by suppressing the release of MHC Class I molecules, thereby interfering with T-lymphocyte recognition. HCMV will induce metabolic bizarre patterns in lymphocytes and monocytes. In addition, HCMV will also down regulate antigen-specific cytotoxic T-lymphocyte functions, resulting in decrease in circulating CD4 cells and increase in CD8 suppressor cells, which leads to overall impairment of cell-mediated immunity.[26]

Polymerase chain reaction (PCR) is a cipher for PCR. PCR produced the large quantities of specific DNA from a complex DNA template in a simple enzymatic reaction.

PCR was thought to be perceived by Dr. Mullis in 1990,[27] while working at the Cetus Corporation in Emeryville, CA. However, some pioneering work was also done by Gobind Khorana in 1971 who described a basic principle of replicating a piece of DNA using two primers. Progress then was limited by primer synthesis and polymerase purification issues. Mullis's performed limited dideoxynucleotide sequencing of unique human genes using synthetic oligonucleotides for the purpose of diagnosing common human disease mutations.[28]

Nested PCR is a very sensitive virus detection method, and the presence of just a few numbers of the viruses can produce a positive result, and it is affected to contamination giving a false positive result (Burkardt, 2000). Real-time quantitative PCR is highly accurate and less labor-intensive than previous quantitative PCR methods. The TaqMan real-time PCR assay generates a signal by cleaving a target specific fluorogenic oligodeoxynucleotide probe during amplification. Since amplification products are measured during the exponential phase of DNA amplification regardless of the initial target concentration, the TaqMan method provides exquisite sensitivity and a broad dynamic range.

Multiplex PCR method is also used to detect HCMV, EBV, and HSV, and this PCR is precise and very quick and is very important for clinical diagnosis so that treatment can be started as early as possible. Large samples can be augmented by this PCR with very minimal time, and it is economical.[29]

Review Results

Herpes viruses as a causative factor for periodontal diseases?

The involvement of herpes viruses in the periodontal disease is implied by their presence in gingival crevicular fluid (GCF), plaque samples, salivary samples, and in gingival biopsy.

Virus detection in gingival tissue

- Study was performed by Cassai *et al.*, 2003 were in gingival tissue was collected from 23 subjects. It included 13 patients

affected by chronic periodontitis and ten healthy controls. This study was performed to check the presence of human herpes virus (HHV-6), HHV-7 and HHV-8 in gingival tissue. It was concluded that gingival tissue may act as basin for HHV-7. High percentage of HHV-7 was seen in both health as well as disease, whereas the presence of both HHV-6 and HHV-8 was similarly low[30]

- Study was conducted by Rotola *et al*., 2008 to evaluate the presence of HHV-7, EBV and HCMV and the transcription pattern of HHV-7 in gingival biopsies from patients suffering from periodontitis and periodontally healthy subjects. The results indicated that gingival tissue can be considered as a basin for HHV-7 and the presence of EBV seems to be correlated with the disease[31]
- Study was performed by Horewicz *et al*., in 2010 were in the presence of HPV-16 in the gingival tissue of periodontal health or disease was investigated. Virus was detected by real-time PCR. It was concluded that HPV-16 may not have participated in the pathogenesis of chronic periodontitis and the gingival tissue did not act as a reservoir for this virus[32]
- Study was conducted by Kolliyavar *et al*., in 2013 to assess the presence HSV-1, HCMV and EB Viruses in subjects with chronic periodontitis and periodontally healthy subjects. In a test group, gingival biopsy was taken from the lining of the pocket during the first incision given for flap surgery, and in the control group gingival biopsy was taken during orthodontic tooth extractions. Hot Staurt multiplex PCR method was used to detect the viruses (HSV-1, HCMV, and EBV) in the biopsy sample, and the presence of these viruses were more in the chronic periodontitis group, compared to control group and based on the above results it was concluded that gingival epithelium may serve as the reservoir for this viruses.[33]

Higher frequency of virus detection in GCF from periodontally diseased sites than from gingivitis/healthy sites

- Study was performed by Ting *et al*., and he found out that herpes viruses are frequently detected in localized juvenile periodontitis (LJP) lesions. Active HCMV infection appears associated with the onset of LJP, and latent HCMV infection with the established LJP. Herpes virus mediated host damage impairment of the host defense may give rise to subgingival overgrowth of periodontal pathogens and subsequent attachment loss.[34]

Higher frequency of virus detection in subgingival plaque from periodontally diseased sites than from gingivitis/ healthy sites

- Study was performed by Kamma *et al*., in which 16 individual subgingival plaque samples were collected from 2 active and 2 inactive periodontal sites. The presence of HCMV, EBV and HSViruses and bacterial co-infection was statistically associated with periodontitis[35]
- A study was performed by Yapar *et al*., 2003 wherein a PCR method was used to determine the presence of HCMV and EBV-1. A subgingival plaque samples from 17 aggressive periodontitis and 16 healthy controls were collected. Clinical parameters were assessed pretherapy and at 3 months following surgical therapy, it was suggested that EBV-1 and HCMV were strongly associated with aggressive periodontitis[36]
- A study conducted by Kubar *et al*., in 2005 to compare the levels of HCMV in aggressive periodontitis patients and in periodontally healthy subjects. HCMV was detected in 68.8% of aggressive periodontitis lesions but not in any of the periodontally healthy sites[37]
- Study performed by Saygun *et al*., in 2005 determined the presence of HCMV and EBV-1 in periodontal abscesses and the effect of treatment on these viruses. It was concluded that HCMV and EBV-1 genomes are commonly found in periodontal abscesses. This fact supports that viral infection of the periodontium suppresses the immunity and provide the entry of bacterial pathogens with the subsequent risk of abscess development[38]
- Study was performed by Ling *et al*. 2004 was periodontal status in terms of gingival inflammation, bleeding on probing, probing depth, and clinical attachment loss of 20 participants was evaluated. Nested PCR method was used. This study demonstrated that HSV is related to the severity of periodontal diseases in terms of clinical attachment loss[39]
- Study conducted by Darby *et al*., 2005, was in subgingival plaque samples were taken from chronic periodontitis and generalized aggressive periodontitis patients before and after sulfate-reducing prokaryotes. PCR assay were used to determine the presence of *Aggregatibacter actinomycetomcomitans*, *Porphyromonas gingivalis*, *Tanerella forsythensis*, *Prevotella intermedia,* and *Treponema denticola*. Scaling and root planning was effective in reducing the clinical parameters[40]
- A study was done by Botero *et al*., 2007, to compare the subgingival frequency of HCMV in subjects affected by periodontitis to periodontally healthy subjects and to see interaction of the virus with the bacteria. It was concluded that HCMV detection in periodontal pockets was associated with higher levels of periodontopathic bacteria and increased probing depth and clinical attachment level at sampled sites. HCMV/bacteria interaction may be an important factor in periodontal destruction.[41]

Summary and Conclusion

The causation of periodontal disease depends on the 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.

Clinical significance

Viruses in association with bacteria's such as *P. gingivalis, T. denticola,* and other species may aggravate the periodontal destruction. Synergism among herpesviruses and bacteria may play an important role in the onset and progression of periodontitis.

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