Human herpes virus: Bacteria and periodontium

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Introduction

Periodontitis is a multifactorial, chronic disease that progresses by the destruction of supporting structures of teeth like cementum, alveolar bone, and periodontal ligament. Before the 1970s, a bacterial plaque was considered the key etiologic factor of periodontal disease, no studies had shown a clear relationship between specific bacterial species and destructive periodontal disease. Following the boom in anaerobic microbiology in the 1970s, it was demonstrated that markedly different microfloras were associated with a healthy periodontium and periodontitis. Aggregatibacter actinomycetemcomitans (AA) became implicated in the etiology of localized aggressive (juvenile) periodontitis and Porphyromonas gingivalis in the etiology of severe periodontitis in adults. Since then, major inroads have been made into the microbiology, immunology, and cause-related treatment of periodontal disease. Various human herpes viruses, including cytomegalovirus (HCMV) and Epstein-Barr virus (EBV), have emerged as putative pathogens in destroying progressive periodontal disease in the past few years.

In various types of periodontal diseases, human herpes viruses have emerged as putative pathogens since mid-1900s. They are the leading cause of human viral diseases. Greek word Herpein from which Herpes name come, which means to creep. Nature of the lesions can be understood, caused by herpes virus from this. In oral pathology, these viruses are most important DNA viruses. Human herpes virus infections are immune impairment. 25 families are there in herpetoviridae, but only 8 of them are known to infect humans [Tables 1 and 2].

The human herpes viruses have 4 significant biological properties:

a) There are specific enzymes involved in the biosynthesis of viral nucleic acids and are genetically distinct from the host enzymes, provide unique therapeutic targets for inhibition by antiviral agents.

<table>
<thead>
<tr>
<th>Table 1: Names of different types of human herpes viruses</th>
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<tbody>
<tr>
<td>Human herpes virus - different types</td>
</tr>
<tr>
<td>HHV - 1 Herpes simplex virus 1</td>
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<tr>
<td>HHV - 2 Herpes simplex virus 2</td>
</tr>
<tr>
<td>HHV - 3 Varicella zoster virus</td>
</tr>
<tr>
<td>HHV - 4 Epstein-Barr virus</td>
</tr>
<tr>
<td>HHV - 5 Human cytomegalovirus</td>
</tr>
<tr>
<td>HHV - 6 Human herpes virus 6</td>
</tr>
<tr>
<td>HHV - 7 Human herpes virus 7</td>
</tr>
<tr>
<td>HHV - 8 Kaposi's sarcoma - associated herpes virus</td>
</tr>
</tbody>
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Table 2: Different types herpes viruses belong to different families[^3]

<table>
<thead>
<tr>
<th>Herpes virus - families</th>
<th>Herpes viruses</th>
<th>Latency</th>
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</thead>
<tbody>
<tr>
<td>Alpha - herpes virus</td>
<td>HSV - 1, HSV - 2, VZV</td>
<td>Sensory ganglia</td>
</tr>
<tr>
<td>Beta - herpes virus</td>
<td>HCMV, HHV - 6, HHV - 7</td>
<td>WBC</td>
</tr>
<tr>
<td>Gamma - herpes virus</td>
<td>EBV, HHV - 8</td>
<td>Lymphoid tissue</td>
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b) Viral DNA is synthesized in the nucleus
c) Progeny virus is released from the infected cell which led to cell death
d) Latent infection within tissues for each virus, are distinct, and for the lifetime.

For survival, herpes viruses minimize antiviral inflammatory responses of the host and exploit macrophages, lymphocytes, or other host cells for replication. In the latent state, DNA of human herpes viruses seems to behave like the host DNA. Throughout the lifetime, survival of the herpes viruses is ensured by its latent state. Latent herpes viruses reactivate and affect the cellular immunity from time to time.

After primary infection, herpes viruses may remain as a latent virus or with limited capacity of replication and expression of the viral gene. Latent EBV remains in B lymphocytes, and latent HCMV, in monocytes and their progenitors. Psychosocial and physical stress, infections, immunosuppressive medication, hormonal changes, and also impaired cellular immunity may lead to reactivation of these latent viruses.[^7]

Herpes Viral: Bacterial Interaction in Periodontal Diseases

Specific types of the Herpes virus have been reported by many studies such as Epstein barr, HCMV, and HSV. Human herpes viruses can infect the PMNs, lymphocytes, and macrophages, and alter their functions and decreased ability to defend against periodontopathogens. This dysfunction of PMNs in periodontal sites can increase the periodontopathic microbiota and progression in the destruction of periodontium.[^6]

Studies have reported that sites with the presence of herpes virus increase level of other microbiota, and mainly affect the periodontopathic bacteria, *P. gingivalis, Prevotella intermedia, Treponema denticola, Tannerella forsythia*, and AA.[^9] Presence of both Bacteria and human herpes viruses with immune responses by the host may lead to the destruction of periodontium.

Pathogenicity of human herpes viruses is complex. It may directly infect virus and or by replication, or by altering the host immune defense. Immunocompromised hosts with periodontitis may predominantly involve cytopathogenic events, in immunocompetent, these may occur secondary to humoral or cellular immune responses.

Effect of Herpes Viruses on Periodontium

Herpes viruses exert a cytopathic effect, which has a direct effect on endothelial cells, inflammatory cells, fibroblasts and keratinocytes including PMNs, lymphocytes, macrophages, and also bone cells. In periodontitis, EBV and HCMV can also infect and alter the activities of defense cells. Perhaps infection of herpes virus in periodontitis, aggressive periodontitis contains fewer viable cells, more T lymphocytes and more B lymphocytes than chronic periodontitis or healthy periodontium. Cytopathic effects of herpes virus may inhibit tissue repair and its turnover.[^5]

Infection with the herpes viruses increases periodontopathic bacteria/microbiota. Herpes viruses proteins on the cells may act as binding sites for bacteria. Studies reported infection with EBV increased AA. in periodontal pockets.[^3]

Herpes viruses may induce abnormalities in the defense mechanism of PMNs, which are a key for the control of periodontopathic bacteria. Herpes viruses exacerbate the disease, and a periodontal dual infection with HCMV and EBV, or with HCMV and simplex virus, occur in different types of periodontal disease.[^5]

Herpes viral infections alter cytokine and inflammatory responses. Cytomegalovirus infection can increase interleukin (IL)-1β and tumor necrosis factor receptor (TNF)-α. EBV remain in B lymphocytes and it increases the level of B lymphocytes also these lymphocytes are prominent in progressive periodontal diseases.[^10]

By altering immunopathological responses, human herpes viruses cause injury to the tissues. Herpes simplex and cytomegaloviruses decrease the cell-mediated immunity and lead to immunosuppression. Furthermore, in lymphocytes and monocytes, cytomegalovirus causes metabolic abnormalities. Cytomegalovirus suppress cytotoxic T-lymphocyte functions, which decreases CD4+ cells and increases suppressor cells CD8+, which impairs cellular immunity. EBV-infected B lymphocytes may shed antigens that produce blocking antibodies, immune complex formation, and activates T-suppressor cell.[^10]

Human Herpes Virus: Bacteria and Host Responses in Periodontitis

The interaction between herpes viruses and bacteria is bidirectional, bacterial products, or other inflammatory mediators have the potential to activate human herpesviruses [Figure 1].[^3,11] In an experimental study on mice infected with cytomegalovirus and *P. gingivalis* exhibited a significantly higher mortality rate than mice infected with cytomegalovirus and *Escherichia coli*.[^12] *P. gingivalis* bacteria has potential to suppress the antiviral host response that explains the increase pathogenicity of cytomegalovirus. Human herpes viruses and periodontopathic bacteria play a causal or a contributory role in the periodontal destruction. Balance between Pro- and anti-
inflammatory mediators controlled by lymphocytes that believe to be crucial in the pathogenesis of periodontal diseases. Elevated pro-inflammatory cytokines in periodontium are associated with increased risk of the destruction of periodontium. The human herpes virus can inhibit the antibacterial host defense by inducing production of pro-inflammatory cytokines and chemokines, stimulate osteoclasts production, elevated MMP level, and decrease tissue inhibitors of metalloproteinase, this increases risk of tissue breakdown in periodontium by inhibiting tissue turnover rate and repair.\textsuperscript{[13]}

In the beginning of infection with periodontopathic bacteria, lead the inflammatory cells into the gingival, also macrophages and in their latent state cytomegalovirus remain in T lymphocytes and EBV in B lymphocytes. Presence of IgA antibodies in gingival crevicular fluid indicates the presence of cytomegalo, Epstein-barr, and herpes simplex virus in Gingiva. During periods of impaired host defense, human herpes viruses may reactivate. It may be the result of immunosuppression, infection, physical trauma, hormonal changes, etc. Activating factors of herpes virus are also known as risk factors indicators for periodontal disease.

Herpes virus activation leads to increased inflammatory mediator in macrophages and connective tissue.\textsuperscript{[14]} When theses human herpes viruses load increases, IL-1β, TNF-α, IL-
6, prostaglandins, and interferons are increased by activated macrophages and lymphocytes, with potential to cause bone resorption. Impairment of immunity, induced by human herpes virus may increase gram-negative anaerobic periodontopathic bacteria, its lipopolysaccharide, with the presence of cytomegalovirus, can induce cytokine and chemokine release from various cells and stimulate gene transcription of IL-1α.\(^{[15]}\) Also in this cycle, triggering of cytokine responses activates inactive herpes viruses, it may cause more destruction of the periodontium.

It is possible that viruses, human herpes viruses may depend on coinfection with periodontopathic bacteria to cause destruction of periodontium and also for the initiation and progression of some types of periodontitis, gram negative anaerobic bacteria may depend on presence of human herpes viruses.

### Viral Diagnostic Methods

Different diagnostic methods are available now to identify viruses in periodontitis. Initially, identification of virus has been based on the culturing method, to detect characteristics cytopathic effects, morphologic determination of intracytoplasmic to identify viral antigens in clinical specimens.\(^{[20]}\) The presence of herpes virus in periodontium is also confirmed using flow cytometry, DNA probes and immunofluorescence staining.

Other popular technique is polymerase chain reaction (PCR), which is becoming the standard technique for detection and quantification of periodontal herpes virus.\(^{[16]}\) Several types of PCR methods are used like Nested PCR, real-time PCR, and multiple PCR. In Nested PCR, it shows more periodontal sites that are positive for HCMV than viral culture or real-time PCR.\(^{[17]}\) Nested PCR technique is more efficient in detecting low viral loads.\(^{[18]}\) In multiple PCRs, multiple organisms can be detected. PCR-based studies of periodontal herpes virus have targeted different genomic regions and used to extract the target nucleic acid with different efficiency. Negative PCR may occur because of the absence of virus at the time of periodontal sampling.\(^{[19]}\) Ultrasensitive PCR techniques help to identify herpes virus in unhealthy control sites. Periodontitis patients with healthy periodontal sites will have more herpes virus than patient of healthy periodontal sites with a healthy periodontium.\(^{[20]}\) Studies reported that EBV and HCMV have been identified by Nested PCR, real time, and reverse transcription PCR.\(^{[21]}\)

### Therapeutic Implications

Many therapeutic methods have been implicated in recent years to eradicate the infection caused by herpes virus in the periodontium. Conventional approach for periodontal disease can reduce the herpesviruses load. Mechanical debridement has also showed suppression of subgingival EBV.\(^{[15]}\) The orally administered and intravenously administered acyclovir are used for a variety of herpes viruses diseases. Still studies are going on to detect whether antiviral drugs are effective in the treatment of herpes virus or other viruses in periodontitis.

### Conclusion

Herpes viruses play a major role in the pathogenesis of periodontitis. Prevention and elimination of the periodontal disease are associated with the complete elimination of periodontopathic bacteria and viruses from the oral environment. Periodontopathogenic bacteria, EBV, and HCMV seemed to act well and result in increased risk for the occurrence and spread of periodontitis. Coinfection of active herpes virus and periodontitis bacteria may constitute major causes of periodontitis. A good understanding of the herpes viral-bacterial interaction in periodontitis helps in achieving a long-lasting state of stable and healthy periodontal condition. Control of herpes virus with vaccination may be the future for the prevention of periodontitis with diminishing role for traditional periodontal therapy of surgery and antibiotics. With future researches of virus in periodontitis can lead to progress in prevention and treatment of periodontal diseases.

### References

13. Page RC, Offenbacher S, Schroeder HE, Seymour GJ,


