Review Article

Viruses: A forerunner in the periodontal diseases.

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ABSTRACT

The oral cavity present itself as a home to a rich flora of bacteria; more than 500 distinct microbial species are found in dental plaque. Mycoplasma, yeast, protozoa and viruses are found in the plaque as the non-bacterial microorganism. Viruses are known to be immunosuppressive and facilitate establishment of subgingival pathogens and have been detected in the gingival crevicular fluid. Viruses infect the inflammatory cells of the periodontium; they are present more frequently in diseased sites than in healthy sites. Traditional methods such as in vitro cultivation presents difficulty in detecting viruses. The field of virology has advanced greatly over the past two decades because of the introduction of sophisticated molecular tools, such as monoclonal antibodies, polymerase chain reaction based amplification, DNA sequencing, DNA and protein micro array chip assays, rapid diagnostic tests. These technologies identify the viral bodies, proteins and nucleic acids in body fluids and tissue samples.

Key Words: *Herpes virus, PCR, periodontal diseases, sub gingival plaque*

INTRODUCTION

Within the uterus the human fetus is sterile, but acquisition of vaginal & fecal microorganisms occur after passing through the birth canal. The colonization of the oral cavity also starts about the time of birth. The sterile oral cavity becomes colonized by low number of mainly facultative and aerobic bacteria within hours after birth.

The oral cavity present itself as a home to a rich flora of bacteria; more than 500 distinct microbial species are found in dental plaque. Mycoplasma species, yeast, protozoa and viruses are found in the plaque as the non-bacterial microorganism.[1] 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.[2]

Traditional methods such as in vitro cultivation presents difficulty in detecting viruses.[3] The field of virology has advanced greatly over the past two decades, because of the introduction of sophisticated molecular tools, such as monoclonal antibodies, polymerase chain reaction (PCR) based amplification, DNA sequencing, DNA and protein micro array chip assays, rapid diagnostic tests. These technologies identify the viral bodies, proteins and nucleic acids in body fluids and tissue samples and in determining the host response to viral infections.

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Replication of virus occurs only when present within eukaryotic (animals, plants, protists and fungi) or prokaryotic (bacteria and archaea) cells, not on their own. Size of extracellular virion particle ranges from 20-300nm and consists of either DNA or RNA contained within a protective protein capsid.

Taxonomically, according to the presence of DNA or RNA, viruses are classified as single stranded or double stranded nucleic acid and an enveloped or non-enveloped nucleo-capsid. Additional taxonomical criteria include mode of replication, type of host capsid shape, immunological properties and disease association. Recognition of infecting virus by host occurs by innate and adaptive immune responses. Activation of inflammatory cell types by viruses occurs to release antiviral cytokines and cytotoxic agents and to induce lymphocyte mediated adaptive immunity.

Virally derived proteins, which are presented by major histocompatibility complex molecules on the surface of infected cells, serve as epitopes for specific host immune cells. Humoral adaptive immunity mainly control the non enveloped viruses whereas enveloped viruses are controlled by the cellular immunity through the action of natural killer cells and cytotoxic CD8+ T lymphocytes. After recognizing viral surface antigens on infected cells, cytotoxic T lymphocytes inhibit virus replication by cytolytic killing and by releasing interferons, chemokines, tumor necrosis factor-A or other pro-inflammatory mediators. Viral disease may be a direct result of cell destruction or a secondary consequence of host immune reactions against viral proteins. Viral diseases of the oral mucosa and the perioral region are often encountered in dental practice, but received only limited research interest. An important future goal of oral and microbiology would be to determine the diversity, frequency, magnitude, pathogenecity and treatment of oral viruses and their diseases.[4]

The uncertainty about the infectious and clinical events of periodontal breakdown has given rise to a number of hypotheses about the etiology of periodontitis. Some researchers suggest that specific infectious agents are key to periodontal breakdown. Others emphasize the importance of host immune factors and genetic characteristics in the acquisition of periodontitis. It is assumed that periodontitis debuts in genetically or environmentally predisposed individuals, who are infected with virulent infectious agents and reveal persistent gingival inflammation and distinct immune responses. Fitting that concept, various herpes viruses have been associated with severe types of periodontal disease. Studies on a viral cause for periodontitis mark a turning point in periodontal research, which until recently was centered almost exclusively on a bacterial etiology. Epstein–Barr virus and cytomegalovirus are the most commonly researched viruses in periodontology, and more than one million herpes virus genome-copies can be present in a single periodontitis site. The abundance of herpes viruses in aggressive periodontitis lesions suggests a role of the virus in the development of the disease.[5]

Recent findings have begun to provide a basis for a causal link between herpes viruses and aggressive periodontitis. One theory is that herpes viruses cooperate with specific bacteria in the etio-pathogenesis of the disease. Namely, periodontal herpes viruses comprise an important source for triggering periodontal tissue destruction. In cross sectional studies, viruses in Herpes family have been isolated from the lesions of periodontitis patients. Their genomes have been found in chronic periodontal disease, aggressive Periodontal disease and periodontal disease associated with systemic diseases. Herpes virus productive infection may initiate or accelerate periodontal tissue destruction due to a virally mediated release of cytokines and chemokines from inflammatory and non-inflammatory host cells, or a virally induced impairment of the periodontal defense resulting in a heightened virulence of resident pathogenic bacteria.[6]

Of the approximately 120 identified different herpesviruses, eight major types are known to infect humans, namely, herpes simplex virus (HSV) type 1 and 2, varicella-zoster virus, EBV, HCMV, human herpesvirus (HHV)-6, HHV-7, and HHV-8 (Kaposi's sarcoma virus). Research has identified more than 5000 different strains of herpesviruses. Humans are the only source of infection for these eight herpesviruses. Human herpesviruses are classified into three groups (a, b, c) based upon details of tissue tropism, pathogenicity, and behavior under conditions of culture in the laboratory. Because herpesvirus co-infection as well as *P. gingivalis* and *D. pneumosintes* were associated with actively progressing periodontitis, the interrelationship between these infectious agents was investigated. Periodontitis sites revealing herpesviruses co-infections yielded more frequently *P. gingivalis* and *D.pneumosintes* dual infection than sites with no detectable herpes viruses.[7]

Herpes virus-infected inflammatory cells elicit tissue-destroying cytokines and may exert diminished ability to defend against bacterial challenge. 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 Actinobacillus actinomycetemcomitans.[8]

The positive association between an active cytomegalovirus infection and aggressive periodontitis suggests involvement of the virus in the disease, but alone cannot differentiate between the possibilities of an active cytomegalovirus infection causing destructive disease, an active cytomegalovirus infection arising secondarily to the pathological changes of disease active periodontitis, or a combination of these two possibilities in the mode of a vicious cycle. Ting et al. 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 odontogenic cells of developing hamster teeth can disrupt normal cell differentiation, and an active cytomegalovirus 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.[5]

Epstein–Barr virus exhibits more genotypic variability than recognized previously, which may help to explain specific disease patterns in different geographic areas. The Epstein–Barr virus nuclear antigen 2 (EBNA2) genotype1 occurs more frequently in periodontitis lesions than the EBNA2 genotype. Patients who were dually infected with the Epstein–Barr virus type 1 and the cytomegalovirus gB-II genotype tended to have deeper periodontal pocket depths and increased attachment loss.[6]

Studies have confirmed the frequent presence of HCMV, EBV, and HSV in crevicular samples of chronic periodontitis lesions and suggested a strong relationship between the presence of these viruses and measurement of probing depth, clinical attachment loss, and the severity of the disease. Evidence from studies also indicate the subgingival presence of EBV-1 and HCMV is strongly associated with aggressive periodontitis, and co-infection with HCMV and EBV appears to be particularly deleterious to periodontal health.[9]

Periodontal diseases have long been associated with defects in the immune system. In as much as individuals infected with HIV have an impaired

immune system, the common presence of periodontal diseases and alterations in the periodontium is not surprising. On initial examination, we observed bleeding and painful lesions that resembled acute necrotizing ulcerative gingivitis superimposed on rapidly progressive periodontitis. Severe attachment loss was a consistent finding, with the lesions often extending beyond the attached gingiva into the contiguous mucosal tissues and frequently resulting in the exposure of bone.[10]

Periodontitis lesions can also harbor papillomavirus, human immunodeficiency virus (HIV), human T-lymphotropic virus type 1, hepatitis B virus, hepatitis C virus and torqueteno virus. Linkages have been established between human T-lymphotropic virus type 1 infection and gingivitis and periodontitis between hepatitis B and C viruses and periodontal disease, and between torqueteno virus in gingival biopsies and periodontitis. The employment of proficient met genomic pyro sequencing techniques will undoubtedly lead to the identification of several additional periodontal viruses.

Detection of viruses in the oral cavity

Viral diagnostics have become more relevant in clinical dentistry. This is partly because of an increased awareness that viruses are possible etiological agents, and partly because the methods of viral detection have become considerably easier. The preferred methods are based on variants of real-time PCR, which not only offer a test for the viral presence, but also yield quantitative data. A high viral load in a sample taken from affected tissues may, however, as a rule of thumb, suggest direct involvement in the underlying condition. Again, a clinical role is suspected if the titer is particularly high, and even more so if the condition improves upon antiviral treatment. In order to take samples for detection of viral nucleic acids, whether by PCR or other methods, it is preferable to immediately transfer the sample to a small tube containing lysis buffer. Upon arrival in an analytical laboratory, RNA and/or DNA are extracted from the samples, and aliquots added to a reaction mix for PCR Standardization of sampling is a challenge in connection with oral disease. Whether the samples consist of saliva, brush scrapings from mucosa, dental plaque or sub gingival plaque, both the actual amount of sample and the content, e.g. contaminants from blood, can vary considerably. Theoretically, one might correlate the presence of virus with other markers in the sample such as bacterial 16S rRNA or human genes, but that does not offer a convincing standardization. A main limitation of PCR-based methods is that they only detect the viruses they are designed to detect. Several novel human viruses have appeared during the last decade, and most likely the human body is the host to a range of viruses that are yet to be described. Moreover, the cost of the methods restricts analyses to a few viral species; thus the total spectrum of potentially relevant viruses is rarely tested. Two recent strategies compensate for this limitation: microarrays and pyro sequencing. In microarrays, probes detecting different viruses (or other agents) can be applied to a slide and the sample DNA or RNA hybridized onto the slide, thus offering the possible detection of all known viruses. In pyro sequencing, the complete nucleic acids present in the sample are sequenced to look for recognizable viral sequences by searching relevant databases. Both these methods have the same, two fold limitations: one, they are less sensitive than PCR; and two, they are considerably more expensive, although the costs for pyro sequencing is becoming more cost efficient. Thus, these techniques are not useful for routine diagnostics, but they may be valuable when investigating a possible viral cause of unknown conditions. Although various viruses have been implicated by the association, it seems unlikely that the true viral culprit, if any, is yet to be found.[3]

The goal of therapy of oral ulcers is to limit the severity and duration of pain and to accelerate healing. Management of oral ulcers is mainly supportive and consists of a short course of treatment. Scully et al. recently reviewed common over the counter medications for oral ulcers. Medications used in the management of oral ulcers include benzydamine- HCl analgesic topical rinse; lidocaine or benzocaine anesthetic ointments or sprays; anti-inflammatory topical corticosteroids; chlorhexidine, triclosan or sodium hypochlorite mouthwashes; nystatin or miconazole gel for candida infections; fusidic acid cream for Staphylococcus aureus angular cheilitis; and topical acyclovir or pencyclovir cream for herpes virus infections. Treatment of herpes labialis may involve intermittent episodic therapy, intermittent suppressive therapy or chronic suppressive therapy based on defined clinical characteristics and patient preference. Initial primary herpes labialis may be treated with valacyclovir hydrochloride (1 g twice daily for 7 days) or famcyclovir (500 mg twice daily for 7 days). Recurrent episodes of herpes labialis may be managed by early intervention (during the prodrome or erythema stages) using short-course, high-dose systemic antiviral therapy, such as famcyclovir (three 500-mg tablets as a single dose or 500 mg three times daily for 5 days) or valacyclovir (2000 mg twice daily for 1 day) (41, 80). Herpes labialis may also respond to topical medication, such as 10% docosanol cream, 1% pencyclovir cream, 5% acyclovir ointment or 15% idoxuridine solution. However, immune-compromised / HIV-infected patients generally show a poor response to topical antiviral therapy and often require systemic acyclovir, gancyclovir, valgancyclovir, foscarnet, cydofovir or fomivirsen to treat acute herpes virus infections.[4]

CONCLUSION

Human viruses are involved in the development of various types of oral ulcers, oral tumors, classical oral infectious diseases and periodontitis. Herpes simplex virus-1 and Cytomegalovirus are linked to oral ulcers; Ebstein-Bar virus, Herpesvirus-8 and Papillomaviruses to oral tumors; and Ebstein-Bar viruses and Cytomegalovirus to aggressive periodontitis. Rapid advances in medical virology may also help to uncover the pathogenesis and treatments of viral diseases of mouth. Research is encouraged on the topics on antiviral chemotherapeutic agents and augmentation of host defences by means of vaccination. Prevention and therapy based upon antiviral approaches may avert the debut of periodontitis or result in long lasting arrest and ultimate cure of existing periodontitis, as well as of other virally related diseases of the human mouth.

REFERENCES

1. Marc Quirynen, Wim Teughels, Susan Kinder Haake, Michael G. Newman. Microbiology of Periodontal Diseases. In: Newman MG, Takei HH, Klokkevold PR, Carranza FA, editor. Carranza's Clinical Periodontology 10th edition. Philadelphhia: WB Saunders.2006;12:134-69.
2. Pushpa S P, Soumya B G, Herpesviruses in Human Periodontal disease. Reality or Myth…? J. Int Oral Health 2010;14:125-28
3. Bjørn G, and Ingar O. The role of viruses in oral disease; 12 February 2010: Journal of Oral Microbiology 2010; 21:129-34.
4. Jørgen S. Oral viral infections of adults; Periodontology 2000; 49: 60–86.
5. Jørgen S. Human viruses in periodontitis; Periodontology 2000; 53: 89–110.
6. Ljiljana K, Jelena M, Marija I, Radmila O. Microbial etiology of periodontal disease mini review.Medicine and Biology.2008; 15(1): 1 – 6.
7. Kamma JJ, Contreras A, Slots J: Herpes viruses and periodontopathic bacteria in early-onset periodontitis. J Clin Periodontol. 2001; 28: 879–885.
8. Jørgen S. Herpes virus in periodontal disease; Periodontology 2000; 38: 33–62.
9. Das S, Krithiga SP, Gopalakrishnan S Detection of human herpes viruses in patients with chronic and aggressive periodontitis and relationship between viruses and clinical parameters Periodontology 2012; 21: 156-61.
10. Patriciaa M. Periodontal diseases in patients infected by immune deficiency virus, Periodontology 2000; 6: 50-67.

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