ROLE OF VIRUSES IN PERIODONTAL DISEASE

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ABSTRACT

Periodontitis is a chronic inflammatory disease that leads to progressive destruction of the connective tissues and bone with subsequent tooth mobility and eventual exfoliation. It is known to be episodic in nature, consisting of periods of exacerbation, and remission. For a long time, bacteria and host response have been considered the determinants for periodontal disease and health. In addition to the above, the role of other microorganisms is still being debated. Thus, the etiology of the disease is now thought to be multiple infectious agents, and interconnected cellular and humoral host immune responses. However, it is difficult to unravel the precise role of various putative pathogens, and host responses in the etiopathogenesis of periodontitis. This led to speculation and research, to discover a new aspect to the pathogenesis of periodontitis. This review article aims to widen the horizon of knowledge with regard to viruses and the pivotal role they play in periodontal destruction.

KEYWORDS: Humoral, putative

INTRODUCTION

We were gifted with the knowledge of the minuscule creatures like bacteria, fungi way back by Antony Van Leeuwenhoek in 1676. This led to discovery of plethora

of microbes including few whose existence is still doubtful. In the thick of microbes, a totally distinct living organism was espied by Dmitry Ivanovsky (1892) with peculiar characteristics of their absence of growth, mobility and metabolism in non-living environment. These were the submicroscopic obligate intracellular parasites named as **"VIRUS"** by Martinus Beijerinck (1898)[1]. Oral cavity, being the hub of microbes, is known to be affected by several diseases like "Riggs disease" which is currently known as periodontitis *(First introduced in AAP,1966)*[2].

Since time immemorial, bacteria are and till now have been, in limelight for periodontal disease and health. Leaders in the field who gathered at the 1996 World Workshop in Periodontics agreed that bacteria like *Actinobacillus actinomycetemcomitans* (now known as *Aggregatibacteractinomycetemcomitans), Porphyromonasgingivalis*, *Bacteroids forsythus (*now known as*Tannerella forsythia)*and *Treponema denticola* are most commonly associated with periodontitis[3]. On further exploration, host response was found to play a pivotal role in pathogenesis[4,5]. Thus, the etiology of the disease is now known to be 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 (Figure-

1) In spite of wide literature on pathogenesis of periodontitis, still some queries plague our minds as to:

- In some cases heavy plaque causes no periodontitis and neither of the same converts gingivitis to periodontitis…*peculiar isn't it*?
- Why does periodontitis of many subjects affect relatively few teeth despite the omnipresence of periodontopathic bacteria??
- Why does the disease tend to develop in a bilaterally symmetrical pattern across the midline?
- Why can alveolar bone destruction advance close to the apex of one tooth, while barely affecting the periodontium of a neighboring tooth sharing the same interproximal space?
- Why do we get deep pocket on a specific localized area of the same tooth?
- **And the most important, factors responsible for conversion of quiescent stage of disease to active one?**

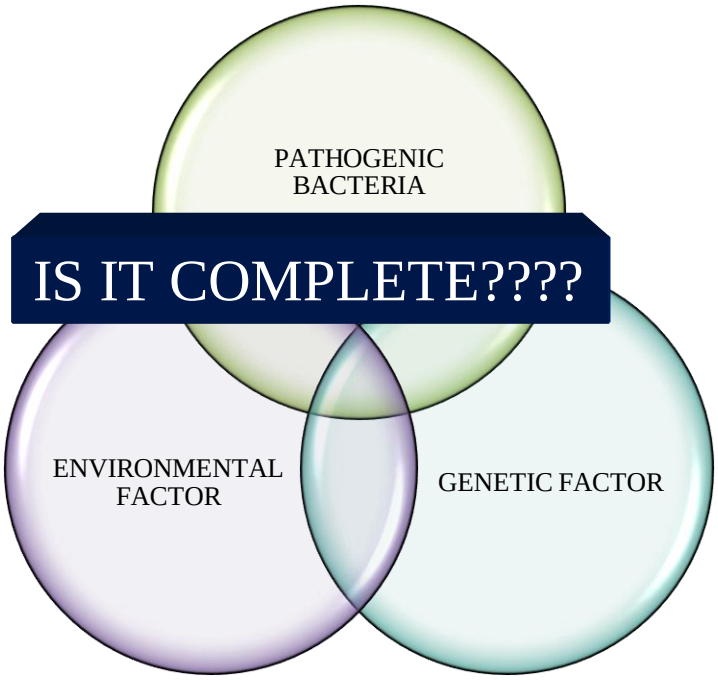


FIGURE 1- THE DIFFERENT ETIOLOGICAL AND CONTRIBUTING FACTORS ARE UNFIT TO EXPLAIN ALL THE CASES OF PERIODONTITIS.

This led to speculation and research to find out any other give away to the pathogenesis of periodontitis. So various scouts like Jorgen Slots[6], Conteras and Slots[7], Ling *et al.*[8], Grande *et al.*[9], Sunde *et al.*[10], Wu *et al.*[11], Li *et al.*[12] and so on ,worked diligently to **REVEAL THE UNREVEALED- VIRUSES "THE UNDERDOG".**

PREPONDERANCE OF VIRUSES

Different landmark studies have been done to correlate viruses with periodontitis (Table-1).

In localized Aggressive Periodontitis, Cytomegalovirus (CMV) and Porphyromonasgingivalis were detected in Afro-caribbean adolescents[13].

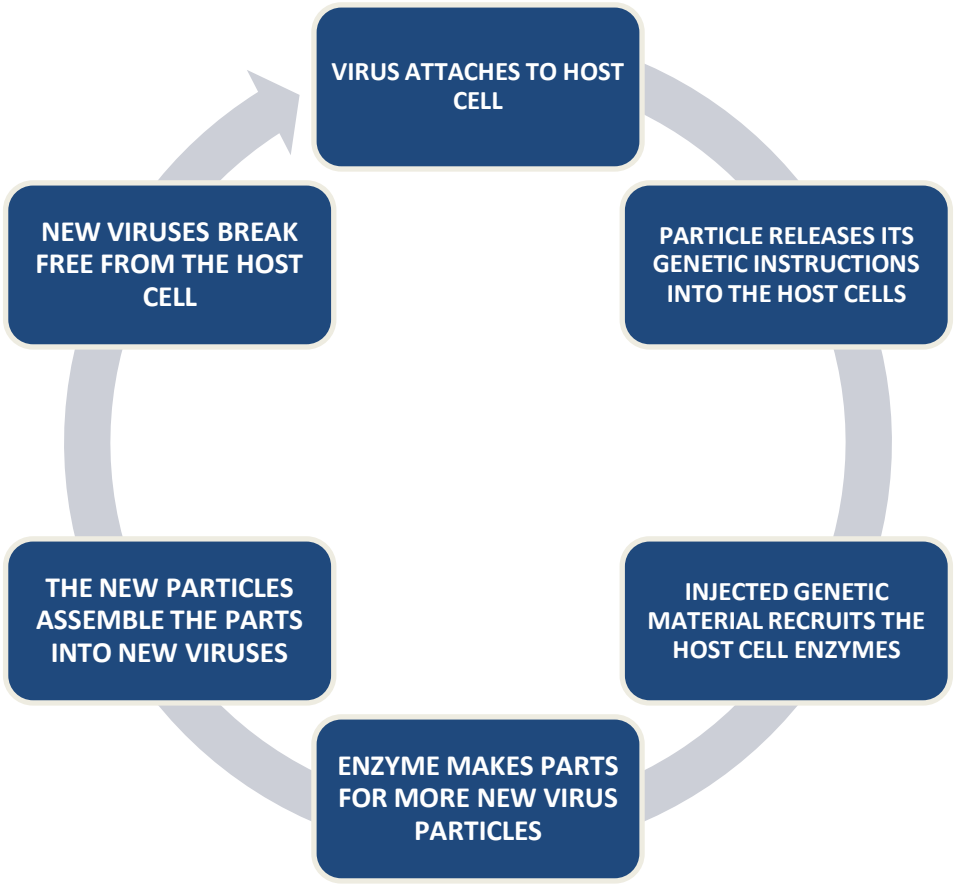
In Chronic periodontitis CMV,Epstein Barr virus (EBV1),Herpes simplex virus1(HSV1)are the main herpes viruses seen. The latent form of CMVis seen in the majority of chronic periodontitis sites, which might account for the slow progression of the disease[14]. CMVandHuman herpes virus (HHV7) are common in periodontitis affected sites and less common in healthy sites[13,14]. Hence, to understand their role in pathogenesis, it is important to know their life-cycle.

TABLE-1- PIONEER WORKS OF DIFFERENT SCIENTISTS ON VIRUSES

VIRUS	AGGRESSIVE PERIODONTITIS (% OF POSITIVE SAMPLES)	CHRONIC PERIODONTITIS (% OF POSITIVE SAMPLES)	AMANUENSIS
HHV-1	57	100	Bilichodmath et al[15]
	87	40	Imbronito et al[16]
	78	No data	Saygun et al[17]
HHV-2	0	16	Bilichodmath et al[15]
	17	0	Saygun et al[17]
EBV	33	47	Imbronito et al[16]
	29	79	Bilichodmath et al[15]
	89	46	Kubar et al[18]
	58	23	Li et al[12]
CMV	No data	0.3	Dawson et al[19]
	No data	35	Grenier et al[20]

LIFE-CYCLE OF VIRUS

Regardless of the type of host cell, all viruses follow the same basic steps, known as “lytic cycle”.



After having a lytic cycle, viral may remain in latent form throughout the life of host.

ROLE OF VIRUSES IN PERIODONTAL PATHOGENESIS

Periodontal tissue breakdown occurs more frequently and expeditiously in HHV infected periodontal sites. HHV 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. In addition, it may exert periodontopathic potential through various mechanisms, operating alone or in combination, as follows-

- CYTOPATHIC EVENTS-

  Cytopathic effect, also termed as CYTOPATHOGENIC EFFECT (CPE), refers to structural changes in the host cells that are caused by viral invasion. HHV causes similar effects on fibroblasts, keratinocytes, endothelialcells and on inflammatory cells such as polymorphonuclear leukocytes, lymphocytes, macrophages and possibly on bone cells[21]. Moreover, it may hamper tissue turnover and repair[21, 22].

- IMMUNOPATHOGENIC EVENTS-

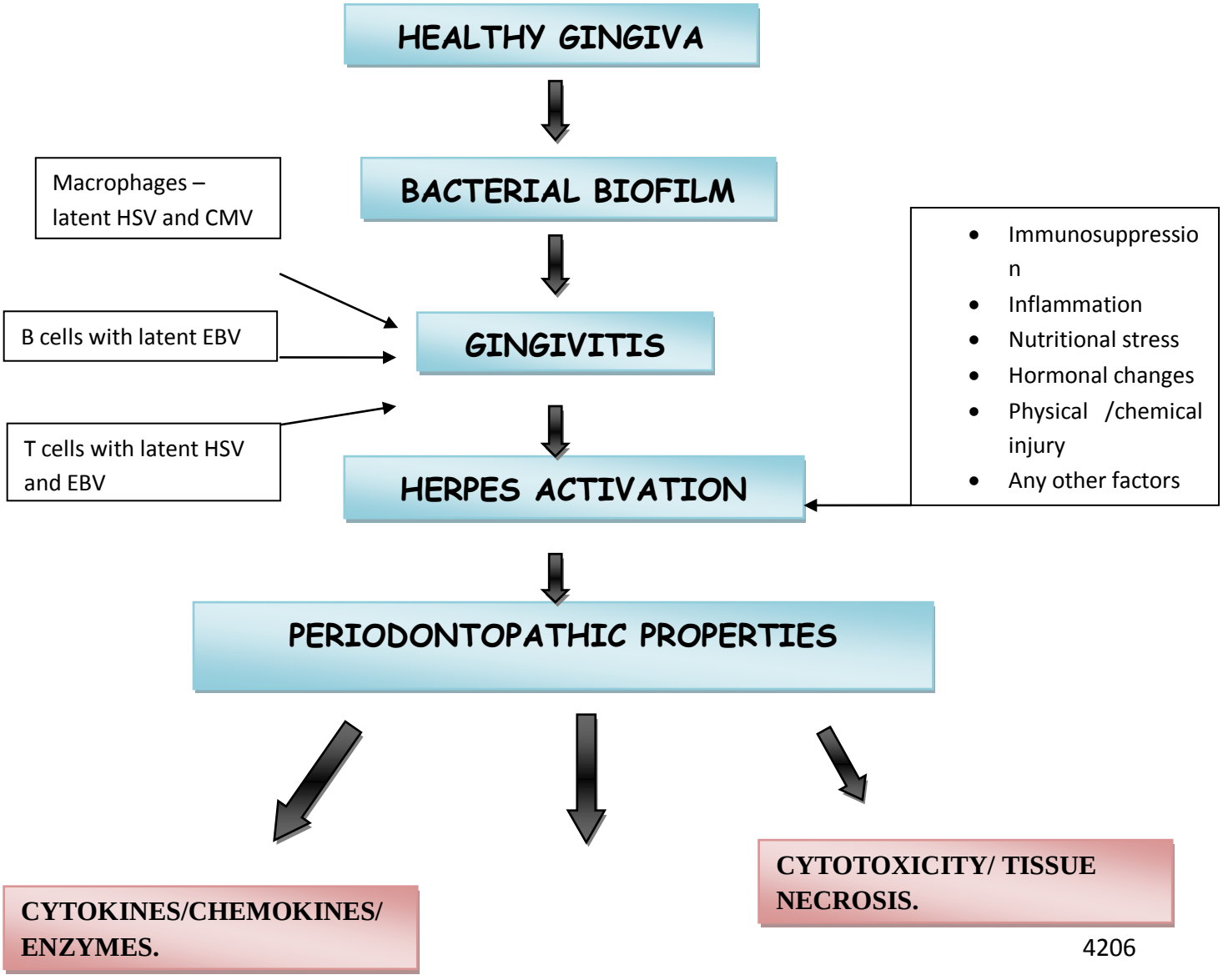
  The term "immunopathogenic" refers to a process of development of a disease in which an immune response or the products of immune

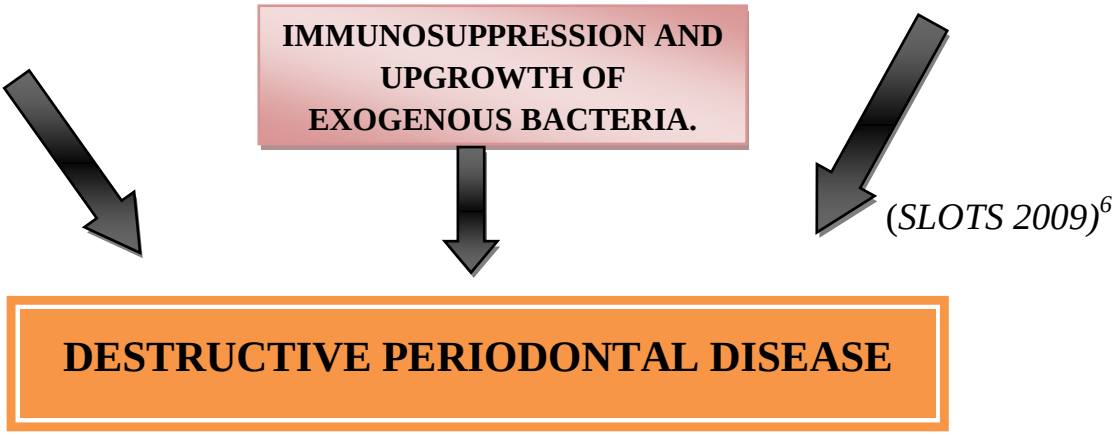
reactions are involved. Similarly, viruses like, HCMV and EBV-1 can infect or alter functions of immune cells mainly monocytes, macrophages and lymphocytes.

Additionally, HHV infections give rise to reformed inflammatory mediators and cytokine responses. Up-regulation of interleukin 1-beta (IL-1β) and tumor necrosis factor-alpha (TNF-α), and gene expression of monocytes and macrophages has been reported in case of HCMV which further lead to enhanced susceptibility to destructive periodontal disease. This may also lead to up-regulation of matrix metalloproteinases, down-regulation of tissue inhibitors of metalloproteinases which mediates periodontal bone destruction. HCMV and HHV further incite cell-mediated immunosuppression by reducing the cell surface expression of Major Histocompatibility Complex (MHC) class I molecules, thereby, interfering with T-lymphocyte recognition. In addition, HCMV suppresses antigen-specific cytotoxic T-lymphocyte functions, resulting in decrease circulating CD4+ cells and increased CD8+ suppressor cells, which in turn may lead to global impairment of cell-mediated immunity (23,24,25,26)

The early phases of periodontitis in immunologically naive hosts may predominantly involve cytopathogenic events, whereas most clinical manifestations in immunocompetent individuals are secondary to cellular or humoral immune responses. After understanding the key role viruses play in destruction of the host cells, let us have a deep insight to interaction between hexagonal and unicellular miniature.

HERPESVIRAL- BACTERIAL PARAGON





(SLOTS 2009)[6]

STUDIES SUPPORTING THE PIVOTAL ROLE OF VIRUSES IN DIFFERENT PERIODONTAL DISEASES

In accordance with, *International Workshop for classification of Periodontal disease and conditions 1999*, periodontal disease was classified into chronic and aggressive. So, researchers have started segregating the role of viruses in periodontal diseases (Tables 2-6).

TABLE 2- DIFFERENT STUDIES ON AGGRESSIVE PERIODONTITIS

STUDY	**AUTHOR**	**YEAR**
Relationship between CMV activation and	Ting M, Conteras A, Slots J[26]	2000

disease active vs. disease –stable periodontitis sites was studied in 11 patients with localized aggressive (juvenile) periodontitis, who were 10–23 years of age and living in Los Angeles		
Hypothesized that a primary CMV infection at the time of root formation of permanent incisors and first molars can give rise to a defective periodontium.	Ting et al[26]	2000
An active cytomegalovirus infection can change the morphology of developing teeth.	Stagno S[27] Jaskoll T[28]	1982 2008

Perhaps, because of a cytomegalovirus infection early in life, teeth affected by localized aggressive periodontitis often show cemental hypoplasia.		

Even **co-habitation** of viruses with bacteria can result in aggressive periodontitis and it is proved by the following studies-

- In a Hopi American–Indianpopulation of 75 adolescents, a single individual wasfound to have generalized aggressive periodontitis and was the only study which demonstrated a periodontal dual infection with EBV-1 and CMV[29].

TABLE 3- DEMONSTRATING SIGNIFICANT STUDIES ONCHRONIC PERIODONTITIS

STUDY	**AUTHOR**	**YEAR**

Antibodies against EBV in 32%and against cytomegalovirus in 71%, of gingival crevice fluid samples from 34 study sites were detected.	Hotchman *et al.*[30]	1998
Identified CMV in 79% patients with chronic periodontitis and also found CMVgB-I genotype in 20% and CMVgB-II genotype in 87%.	Wu *et al.*[31]	2008

Co-infection of viruseswith bacteria takes place in chronic periodontitis as well.

- Co-infection with EBV-1 and the CMV m gB-II genotype was associated with periodontitis with an odds ratio of 28.9, compared to an odds ratio of 11.0 for a co-infection with all genotypes of EBV and CMV[31].

TABLE 4- ASSOCIATION OF VIRUSES IN PERIODONTAL ABSCESS

STUDY	AUTHOR	YEAR
EBV linked toextraoral abscess in children and young adults.	Stenfors LE[32] and Takoudes TG[33]	2000, 1998
CMV implicated in periodontal and extraoral abscesses of HIV infected individuals.	Boudreau[34], Tucker RM[35]	1998,1989
EBV (72%), CMV(67%), herpes virus were not identified in healthy periodontium or after treatment of periodontal abscess	Saygun J[17]	2004

TABLE 5- ROLE OF VIRUSES IN PERIODONTAL DISEASE IN IMMUNOCOMPROMISED INDIVIDUALS

STUDY	AUTHOR	YEAR
In HIV infected individuals, CMV implicated in acute periodontitis.	Dodd CL[36]	1993
CMV is implicated in periodontal abscess, mandibular osteomyelitis and in refractory chronic sinusitis	Berman S[37] Upadhyay S[38]	1990,1995
EBV type 2 found in HIV –infected subjects.	Sculley TB[39], Yao QY[40]	1990,1996
EBV type 2 was detected in 57% of biopsies from	Conteras A[41]	2001

HIV-associated periodontitis		

TABLE-6- SYNDROMES ENCOMPASSING TWAIN PERIODONTAL HERPES VIRUSES AND PERIODONTITIS

PATHOSIS	**PERIODONTAL VIRUSES**	**CITATION**
Guillian- Barre syndrome	CMV	Tabanella and Nowzari[42],
Kostmann syndrome	EBV	Yildirimn*et al.*[43]
Fanconi's anemia	HSV, CMV	Nowzari *et al.*[44]
Papillon-Leferve syndrome	EBV,CMV	Velazco *et al.*[45]
Down syndrome	HSV (26%), EBV type 1 (37%), CMV (37%)	Hanookai *et al.*[46]

These studies prove the cardinal role viruses play in periodontal tissue destruction.

CONCLUSION

"Ignorance is not bliss" always. Turning blind eye to the role of viruses in periodontal destruction can be detrimental. However a quick retrospect of the above text clarifies all these queries that viruses are not merely the bystanders but they are participants in periodontal destruction.

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