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Review

Microbial interaction of periodontopathic bacteria and Epstein-Barr virus and their implication of periodontal diseases

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ABSTRACT

Epstein-Barr virus (EBV) is a ubiquitous human gamma herpesvirus that infects more than 90% of the world's population. EBV infection causes several human diseases, including infectious mononucleosis, autoimmune disorders, and a number of malignancies. Interestingly, evidence accumulated over the past 10 years supports the role for EBV as a pathogenic agent of periodontal disease because bacterial activities alone do not explain several of its clinical characteristics. Despite this, it remains unclear how EBV is reactivated in the oral cavity and how activated EBV leads to the progression of periodontal diseases. We focused on the microbial interaction between bacteria and viruses in the etiology of infectious disease and found that the periodontal pathogen *Porphyromonas gingivalis* could induce EBV reactivation via chromatin modification. Our observations provide evidence for a possible microbial interaction between bacteria and EBV that may contribute to the pathogenesis of EBV-related diseases. This review describes the molecular mechanisms involved in the maintenance of EBV latency and its reactivation by periodontopathic bacteria. In addition, we discuss possible mechanisms by which EBV reactivation may facilitate progression of periodontal disease in infected individuals.

Contents

1. Introduction

Epstein-Barr virus (EBV), a gamma-herpesvirus, infects a majority (> 90%) of the adult human population worldwide [1]. EBV infection causes several human diseases, including infectious mononucleosis, autoimmune disorders, and a number of malignancies, including Burkitt's lymphoma, Hodgkin's disease, nasopharyngeal carcinoma, and gastric adenocarcinoma [1,2]. Similar to other herpesvirus, EBV establishes a persistent infection in the human host, and its life cycle has lytic and latent phases [1,3]. EBV is transmitted from person to person via saliva, and the virus passes through the oropharyngeal epithelium to B-lymphocytes, where it establishes a lifelong latent infection [1,3]. Although the elucidation of the molecular mechanism involved in maintaining EBV latency and its reactivation have been a central focus of EBV

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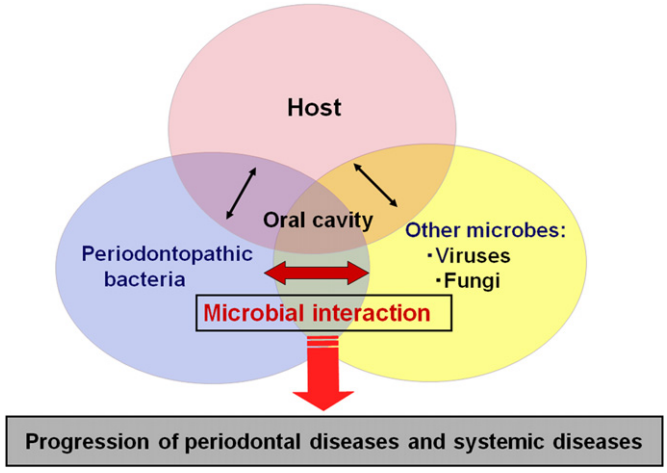

Fig. 1. Interactions between bacteria and viruses in the oral cavity. The oral cavity is colonized by a wide variety of and numerous microbes, including oral bacteria, viruses, and fungi. In addition to host–microbial interactions, the interactions of herpesviruses, such as EBV and HCMV, with periodontopathic bacteria have the potential to contribute to periodontal disease pathogenesis.

research, a causal relationship between co-infection with EBV and bacteria and the disruption of viral latency is not well understood.

Periodontal disease, a complex chronic inflammatory disorder that involves interactions of specific bacteria and cellular host responses, is among the most prevalent microbial diseases in humans [4]. Severe periodontitis can result in loosening of teeth, occasional pain and discomfort, impaired mastication, and eventual tooth loss. Specific bacterial species, mostly gram-negative bacteria such as *Porphyromonas gingivalis*, *Fusobacterium nucleatum*, *Aggregatibacter actinomycetemcomitans*, *Tannerella forsythia*, and *Treponema denticola* show a close association with periodontitis [4,5]. Periodontopathic bacterial infections and their associated bacterial products, such as lipopolysaccharide and fimbriae, stimulate host immune responses and result in the production of inflammatory mediators and matrix metalloproteinases, which leads to connective tissue destruction and bone loss [4,5].

Interestingly, the concept that herpesviruses such as EBV and human cytomegalovirus (HCMV) are involved in the etiology of several types of severe periodontal disease has been proposed [5]. However, the process by which latent EBV is re-activated in the oral cavity, and how activated EBV contributes to the progression of periodontal disease remains unclear. We demonstrated a relationship between microbial interaction and etiology of infectious diseases and found that *P. gingivalis* can induce EBV reactivation via epigenetic regulation (Fig. 1) [6].

In the present review, we describe the current understanding of the relationship between periodontopathic bacteria and the molecular mechanisms of EBV reactivation. In addition, we discuss how this relationship may pertain to the etiology of periodontal diseases.

2. Histone deacetylation and acetylation are involved in the establishment and disruption of viral latency

Previous studies have shown that novel mechanisms of epigenetic regulation, such as histone modification, play an important role in the maintenance and disruption of viral latency [7,8]. It is well known that post-translational modifications of the N-terminal region of each core histone play an important role in the control of the structural organization of chromatin and its transcriptional status [7]. The histone N-terminal tail region protrudes from the center of the nucleosome, where it interacts with other nuclear proteins and is subjected to numerous post-translational modifications, including acetylation, methylation, phosphorylation, and ubiquitination [7]. Particularly, Lys acetylation of histones at lysine residues by histone acetyltransferases (HAT), including cyclic AMP-responsive enhancer binding protein-binding protein (CBP) and p300, and deacetylation by histone deacetylases (HDACs) play a central role in switching between "open" and "closed" chromatin [7,8].

Human immunodeficiency virus-1 (HIV-1) gene expression is regulated by histone modification during the lytic and latent stages of infection [9,10]. Our group and others have reported that transcriptional repressors recruit HDACs to the 5′ long terminal repeat of HIV-1 and consequently maintain HIV-1 latency by repressing transcription of HIV-1 proviruses [9–11]. In contrast, activation of HIV-1 gene expression by cell stimulation induced by mediators such as HDAC inhibitors and tumor necrosis factor-α is correlated with local histone acetylation, which dismisses the negative regulator/HDAC protein complexes, thus initiating transcription [9–11]. In addition, recent studies have shown that a switch between the lytic and latent stages of herpesvirus infection is determined by the viral chromatin status [3,12,13]. Furthermore, hepatitis B virus replication is associated with specific epigenetic marks, such as histone acetylation or deacetylation [14]. In the next section, we describe the role of histone modification during EBV replication.

3. Molecular mechanism of the maintenance of EBV latency at the transcriptional level

Reactivation of latent EBV is associated with progeny virus production and several human diseases [1]. Therefore, elucidation of the molecular mechanisms that promote or disrupt EBV latency will be required to understand the pathobiology of EBV infection and to develop preventive measures or novel therapies. The transition of EBV from latency to the lytic replication cycle is regulated by the master transcription factor, ZEBRA (also known Z, Zta, or EB1), which is encoded by the viral gene BZLF1 (Fig. 2) [3,13]. ZEBRA can transactivate both early and late EBV genes,

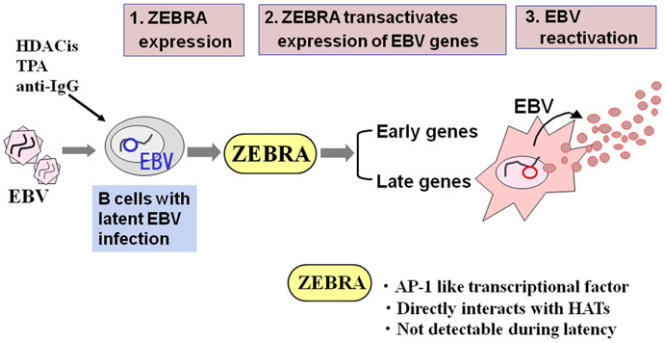

Fig. 2. Induction of the EBV lytic switch transactivator ZEBRA involving epigenetic regulation. The latent form of EBV can be induced to enter the lytic replication cycle by treatment with various inducers such as HDAC inhibitors (e.g., butyric acid and trichostatin A), TPA, and antibodies against immunoglobulins. These inducers lead to increased transcription of the early EBV gene, BZLF1, which encodes ZEBRA, a sequence-specific DNA-binding protein that is a member of the bZIP family of leucine-zipper transcriptional activators. In the latent state, hypoacetylation of histone proteins in the BZLF1 promoter by HDACs is primarily involved in the maintenance of EBV latency. Upon cellular stimulation, local histones are acetylated, the negative regulators are dismissed together with HDAC proteins, and BZLF1 transcription is initiated. ZEBRA can transactivate both early and late EBV genes, thereby inducing the lytic cycle cascade.

thereby inducing the lytic cycle cascade [3,15]. In the latent stage of infection, the ZEBRA protein is not detectable and only a limited group of viral genes are expressed [3,15].

It has become increasingly clear that post-translational modification of DNA-associated histone proteins by HAT and HDAC in the BZLF1 promoter plays an important role in the maintenance and disruption of EBV latency [3,13,15]. For example, the cellular Sp1/Sp3 protein complex and myocyte enhancer binding factor-2 (MEF2D) are associated with HDAC molecules (HDAC1, 2, 4, 5, and 7), and they recruit these molecules to the BZLF1 promoter [16–18]. These complexes lead to hypoacetylation of local histones and establishment of transcriptional latency [16–18]. Although it is known that BZLF1 transactivation is induced by a variety of stimuli, including HDAC inhibitors, 12-*O*-tetradecanoylphorbol-13-acetate, anti-immunoglobulin, and calcium ionophore, a causal relationship between bacterial infection and the disruption of EBV latency has not been established [3,13,15].

4. Positive relationship between EBV and periodontal disease

There is a complex relationship between herpesviruses, such as EBV and HCMV, and severe periodontal disease [5]. Notably, EBV infection, HCMV infection, EBV+HCMV co-infection are frequently detected in various types of periodontal diseases, such as adult periodontitis, juvenile periodontitis, acute necrotizing ulcerative gingivitis, and HIV-associated periodontitis [5,19–21]. Indeed, more EBV DNA was found in gingival crevicular fluid and saliva of periodontal patients than in an otherwise healthy control group [5,19–21]. Slots and his collaborators showed that viral DNA is detected in 60%–80% of aggressive periodontal lesions and 15%–20% of gingival lesions or normal periodontal sites [21]. Our own unpublished data support these previous findings. In addition, many reports indicate that EBV prevalence in periodontitis patients correlated with periodontal pocket depth [21–24]. Furthermore, bacterial and viral co-infections were also reported to be more frequent in deep periodontal pockets. *P. gingivalis*, *T. forsythia*, EBV-1, HCMV, *A. actinomycetemcomitans*, and EBV-2 were detected in 95%, 75%, 72.5%, 50%, 12.5%, and 10% of sites with probing pocket depths deeper than 6 mm, respectively [22]. Higher concentrations of *P. gingivalis* bacilli were found in EBV-positive periodontal patients [21–24]. These observations suggest a relationship between periodontitis and EBV as well as periodontopathic bacteria.

5. Reactivation of latent EBV infection by *P. gingivalis* involves histone acetylation

Butyric acid, a metabolite generated by bacteria during their growth, inhibits HDAC enzymatic activity [25]. We previously reported that butyric acid secreted extracellularly by *P. gingivalis* could be involved in periodontal disease [26,27]. In addition, the presence of high concentrations of butyric acid in periodontal pockets has been demonstrated [28]. Since HDAC contributes to the maintenance of EBV latency and butyric acid is involved in reactivation of the "repressed" chromatin [3,25], we hypothesized that *P. gingivalis* reactivates EBV. We observed that *P. gingivalis* clearly induced ZEBRA expression at the transcriptional level (Fig. 3) [6]. Because no such activity was found with *P. gingivalis* bacteria or bacterial components such as lipopolysaccharide and fimbriae, this activity could be ascribable to bacterial culture supernatant, which can induce Lys acetylation of histone H3 in the BZLF1 promoter. Although *P. gingivalis* produces several short-chain fatty acids (SCFAs), we found that only butyric acid accelerates ZEBRA induction and histone H3 acetylation in EBV-infected cells [6]. In addition, the highest concentration of butyric acid was produced by another periodontogenic bacterium, *F. nucleatum* (Fig. 3). The supernatants from *F. nucleatum* similarly induced ZEBRA expression and lysine acetylation of histone H3. Our findings indicated that H3 histone acetylation and ZEBRA induction is ascribable to butyric acid contained in bacterial culture supernatants. In a chromatin immunoprecipitation assay, we observed that HDAC1, HDAC2, and HDAC7 were present in the core BZLF1 promoter region (from -176 to $+61$) [6], but are dissociated from the promoter concomitantly with acetylated histone H3 upon stimulation with *P. gingivalis* culture supernatant. These observations suggest that *P. gingivalis* acts as an inducer of EBV reactivation by stimulating histone acetylation and HDAC dissociation from the BZLF1 promoter in latently infected cells.

6. Concluding remarks and future perspectives

6.1. Possible mechanisms of EBV reactivation in the oral cavity

The mechanism that regulates the switch between latency and lytic replication is a central problem in EBV pathogenesis, and the trigger responsible for this switch in vivo is not well understood. Previous reports demonstrated that co-infection with EBV and other pathogens, such as malaria and HIV in EBV-infected individuals, is associated with increased EBV replication [29–31]. Evidence over the past decade supports a role for periodontal diseases as a risk factor for several systemic diseases, including heart disease, diabetes, and pre-term birth [4,32,33]. We previously reported that periodontal diseases might contribute to AIDS progression [9,34]. These findings have shown that periodontopathic bacterial infections may be causative factors in numerous systemic diseases. Our observations suggest that periodontopathic bacteria may also be risk factors for EBV reactivation in infected individuals.

We found that *P. gingivalis* can induce ZEBRA expression by stimulating acetylation of histones and HDAC dissociation from the BZLF1 promoter in latently infected cells, and that butyric acid may be responsible for this effect [6]. Previous studies support our hypothesis that the concentrations of butyric acid in affected dental plaques (4.7–13.8 mM) [35,36] and in periodontal pockets of periodontal disease patients (2.6 ± 0.4 mM) are more than sufficient to induce virus re-activation [28]. In contrast, concentrations of butyric acid are below detection limits in healthy sites [28]. In addition, several studies have shown that activation of ZEBRA expression and lytic EBV replication following intraperitoneal injection of butyric acid in some EBV tumors in vivo [37,38]. These observations imply that butyric acid has a role in EBV reactivation in individuals with latent EBV infections, and therefore, may contribute to clinical progression of EBV-related diseases, including periodontal disease.

6.2. Possible causal relationship between bacteria and EBV in periodontitis progression

It has become increasingly clear that herpesviruses are involved in the etiology of severe periodontal diseases, because bacterial activities alone do not explain several clinical characteristics of the diseases. In fact, a pure bacterial cause of aggressive periodontitis cannot explain why the disease tends to develop in a bilaterally symmetrical pattern, and why vertical bone resorption can advance close to the apex at one tooth, while barely affecting the periodontium of an adjacent tooth sharing the same interproximal space [39]. The emerging concept in the etiology of

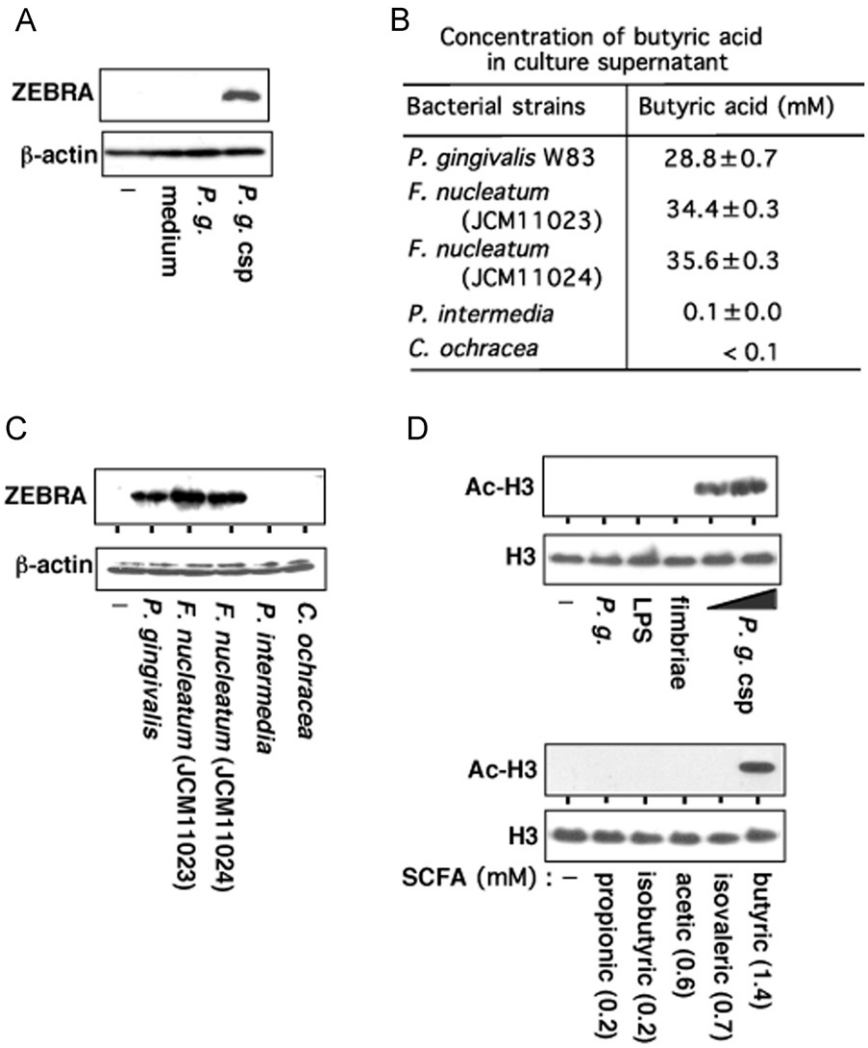

Fig. 3. *Porphyromonas gingivalis* facilitates EBV reactivation via chromatin remodeling. (A) Induction of ZEBRA by the culture supernatants of *P. gingivalis* W83 (*P. g.* csp). EBV-infected Daudi cells were incubated with or without *P. g.* csp (25, 50, or 100 μl/ml), *P. gingivalis* W83 bacilli, or bacterial growth medium alone (medium) for 48 h. The lysates were harvested, and ZEBRA protein levels were assessed by western blotting. (B) Butyric acid concentrations in the culture supernatant of various bacteria were measured by gas chromatography. *P. gingivalis* and *F. nucleatum* produced high concentrations of butyric acid. (C) Effects of culture supernatants of various periodontopathic bacteria on latent EBV reactivation. Daudi cells were incubated with culture supernatant from indicated bacteria (10% v/v) for 48 h, and ZEBRA proteins were detected. Among the bacteria, only butyric-acid producing species could induce ZEBRA expression. (D) Hyperacetylation of histones by *P. gingivalis* and butyric acid. The cells were incubated with *P. g.* csp, *P. g.* bacilli, medium- or short-chain fatty acids, and the concentrations of acetylated histone H3 proteins were determined by western blotting. *P. g.* csp, culture supernatant of *P. gingivalis* W83 (modified from Reference [6]).

periodontal disease such as "periodontopathic virus" is also supported by the following evidence. Antiviral treatment resulted in decreased EBV detection and an improved periodontal condition [5,24]. Although emerging evidence implicated EBV in periodontal disease progression, the underlying mechanisms remain unclear. Our research provides evidence for a possible microbial interaction between EBV and periodontopathic bacteria in periodontal disease pathogenesis. Because the regulation of the switch from latency to reactivation is an initial key step in EBV infection, our observations suggest that butyric acid-producing periodontopathic bacteria have the potential to trigger EBV reactivation in the oral cavity of infected individuals. In addition, inflammatory cytokines such as IL-1, IL-6, and IL-8 play an important role in periodontal disease pathogenesis and increased concentrations of cytokines in sera from EBV-infected patients have been reported [4,5]. The envelope protein and genomic DNA of EBV can stimulate inflammatory cytokines in primary human monocytes [40,41]. We also found that EBV protein, which is produced only during the lytic phase, induced greater activation of nuclear factor-κB and production of IL-6 and IL-8 from human gingival fibroblasts when compared with the stimulation of LPS by *P. gingivalis* (unpublished data). These observations suggest that EBV is intimately interrelated with the various stages of periodontal disease progression.

We assume that microbial synergy by the interaction between periodontopathic bacteria and EBV leads to the following negative chain of pathological events in the oral cavity (Fig. 4): (1) periodontopathic anaerobic bacteria, such as *P. gingivalis* and *F. nucleatum*, produce butyric acid; (2) butyric acid induces EBV reactivation; (3) EBV produces inflammatory cytokines and impairs local host defenses; (4) increased severity of periodontopathic bacterial infection; (5) increased inflammatory cytokine production by the synergistic effects of EBV and periodontopathic bacteria; and (6) periodontal disease escalation.

Although further studies are required, we suggest that an increased understanding of the role that viral infections play in the pathogenesis of periodontal diseases will lead to new treatments and superior prevention methods.

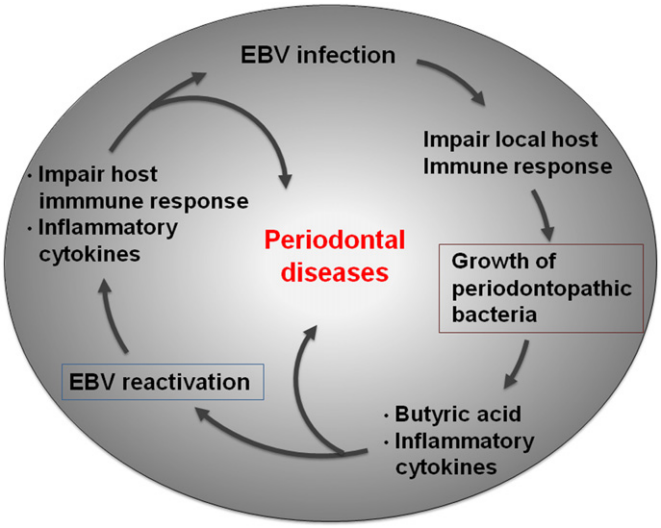

Fig. 4. Microbial synergy by EBV–bacterial interaction in periodontal disease pathogenesis. There is a possibility that a "negative chain reaction" by EBV and periodontopathic bacteria contributes to the etiology of severe periodontitis. It is expected that future basic clinical studies will determine whether the concept of "periodontopathic virus" is applicable to the etiology of periodontitis. We are currently researching the role of viral infections in the progression of periodontal diseases.

Conflict of interest

The authors declare that they have no conflict of interest.

Acknowledgments

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