Polymicrobial Infection and Bacterium-Mediated Epigenetic Modification of DNA Tumor Viruses Contribute to Pathogenesis

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ABSTRACT The human body plays host to a wide variety of microbes, commensal and pathogenic. In addition to interacting with their host, different microbes, such as bacteria and viruses, interact with each other, sometimes in ways that exacerbate disease. In particular, gene expression of a number of viruses, including Kaposi's sarcoma-associated herpesvirus (KSHV), Epstein-Barr virus (EBV), and human immunodeficiency virus (HIV), is known to be regulated by epigenetic modifications induced by bacteria. These viruses establish latent infection in their host cells and can be reactivated by bacterial products. Viral reactivation has been suggested to contribute to periodontal disease and AIDS. In addition, bacterium-virus interactions may play a role in cancers, such as Kaposi's sarcoma, gastric cancer, and head and neck cancer. It is important to consider the effects of coexisting bacterial infections when studying viral diseases *in vivo*.

Epigenetics refers to biochemical modifications of chromatin that do not change the sequence but regulate gene expression and may be inherited. Several different types of epigenetic modifications exist, such as DNA methylation, histone modification, and nucleosome positioning, and they can regulate a variety of processes, including transcription and protein binding to DNA. DNA methylation occurs mostly in regions containing a high frequency of CpG dinucleotides, called CpG islands. In most cases, DNA methylation is associated with gene silencing and is mediated by a family of enzymes called DNA methyltransferases (DNMTs). DNA is wrapped around eight-member histone complexes called nucleosomes. Histones have unstructured N-terminal tails, which undergo posttranslational modifications, including acetylation, methylation, phosphorylation, ubiquitination, and SUMOylation, at certain positions. There are many enzymes that write or erase these modifications: a few examples are methyltransferases, demethylases, histone acetyltransferases (HATs), and histone deacetylases (HDACs). Some histone marks, such as H3K27ac and H3K9ac are associated with actively transcribed genes, whereas others, like H3K27me3 and H4K27me3, keep genes in an inactive state. In addition, the position of nucleosomes affects transcription by preventing transcription factors or the polymerase complex from binding or inhibiting elongation. There are several complexes that can remove or shift nucleosomes, such as SWI/SNF (1). Epigenetic features have been shown to be predictive of genome-wide gene expression (2).

Epigenetic modifications regulating gene expression can occur on both human and viral genomes. HIV and herpesviruses, including Kaposi's sarcoma-associated herpesvirus (KSHV) and Epstein-Barr virus (EBV), establish lifelong latent infections in their host cells. KSHV, EBV, herpes simplex virus 1 (HSV-1), and HIV latency and reactivation are controlled by epigenetic modifications (3–8). Viruses and bacteria have developed diverse mechanisms to directly affect host cell epigenetics, driving pathogenesis and oncogenesis (3, 9–14). This review will focus on bacterium-promoted epigenetic modifications on viral genomes that regulate the switch between latency and active viral replication and examples of combined bacterial and viral disease.

BACTERIA ACTIVATE VIRUSES VIA EPIGENETIC CHANGES: MECHANISMS

Kaposi's sarcoma: *P. gingivitis* and KSHV. In the oral cavity, active viral replication and shedding occur, indicating that viruses do not remain latent. Kaposi's sarcoma-associated herpesvirus (KSHV) is the causative agent of Kaposi's sarcoma, an AIDS-defining tumor that can be found in the mouth (15, 16). The incidence of oral lesions associated with HIV has decreased since the introduction of highly active antiretroviral therapy (HAART); however, they still cause significant morbidity and are indicative of progression to AIDS (17–19). The transition to viral reactivation or oncogene expression requires epigenetic reprogramming (Fig. 1), illustrated by the hypermethylation of active KSHV promoters (20). Epigenetic reprogramming of both the host and viral genomes can be initiated by oral bacteria. Bacterial infection leads lymphoid cells, which may harbor inactive viruses (e.g., EBV and KSHV), to be recruited to the oral epithelium. This places virus-infected cells and bacteria and their end products in close proximity. Bacteria are present in the oral cavity in abundance, with 20 billion microbes present in our mouths at any given time (21).

One of several bacteria commonly found in the mouth is *Porphyromonas gingivalis*, a widely studied bacterium in the phylum *Bacteroidetes*. The bacteria colonize in a highly site-specific fashion, so the bacterial load can be extremely high at a very discrete site. *P. gingivalis* secretes a number of products, including lipopolysaccharide (LPS), gingipains, outer membrane vesicles (OMVs), and short-chain fatty acids (SCFAs) (22–26). Within gingival pockets, accumulation of SCFAs, including butyrate and LPS, can be detected in association with *P. gingivalis* infection

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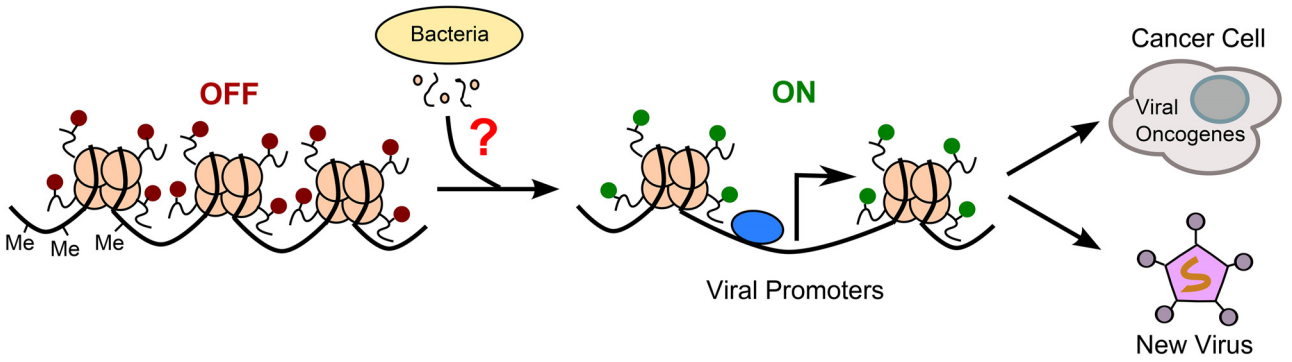

FIG 1 Epigenetic modifications to viral promoters can promote viral production or oncogenesis. Activating epigenetic marks on tumor virus promoters can stimulate the transcription of viral oncogenes, driving cellular transformation, or lead to reactivation of a latent virus and production of new virions.

(27). Bacterial butyric acid levels can be up to 20 mM within the gingival pocket (25, 28, 29). Our group and others have suggested that products secreted by *P. gingivalis*, including butyrate, induce acetylation of histones within neighboring cells (25, 30, 31).

P. gingivalis metabolites, but not those of Gram-positive organisms, were able to enhance KSHV replication. To further explore the mechanism behind these changes, BCBL-1 cells, which are latently infected with KSHV, were treated with *Fusobacterium nucleatum* or *P. gingivalis* culture medium and exposed to specific inhibitors of signal transduction pathways. We determined that bacterium-mediated induction of lytic KSHV infection was not prevented by inhibition of phosphatidylinositol 3-kinase (PI3K) or protein kinase C (PKC) but was significantly reduced by inhibition of the p38 mitogen-activated protein kinase (MAPK) pathway. Bacterium-mediated KSHV reactivation coincided with increased global acetylation of H3 and H4, suggesting the bacterial supernatant contains HDAC inhibition properties. Furthermore, p38 inhibition by multiple inhibitors prevented H3 hyperacetylation and subsequent viral reactivation (31). HDAC inhibition is also critical to the antiviral interferon response (32, 33). The polymicrobial environment may potentiate viral reactivation by decreasing the innate antiviral response and enhancing viral pathogenesis.

Periodontitis: *P. gingivalis* and herpesviruses. Studies linking bacterium-induced epigenetic modifications on viral genomes to human disease are emerging. Periodontitis is highly prevalent in humans, but its etiology is still poorly understood (34). While periodontitis is primarily associated with infection by pathogenic bacteria, such as *Actinobacillus actinomycetemcomitans* and *P. gingivalis*, herpesviruses have also been implicated (35–37). Multiple studies have shown that in patients with periodontal and endodontic disease, herpes group viruses, including human cytomegalovirus (HCMV), EBV, and HSV-1, are readily detected and are associated with the presence of bacteria (38–43). Levels of viral detection were lower in those with less gum disease (44). Moreover, a viral contribution helps explain some symptoms of periodontal disease, such as remission, bilateral symmetry, and why periodontitis often only affects a few teeth, with neighboring teeth exhibiting much less tissue loss (35). Bacterial and viral coinfection was also detected in two-thirds of acute apical abscesses, although the role of the viruses or any interaction between the pathogens in this form of periodontitis is unclear (45). Epigenetic modification of herpesviruses by *P. gingivalis* (discussed below) helps explain the link between viruses and bacteria in the pathogenesis of periodontitis.

Bacterium-induced HDAC inhibition leading to viral reactivation has been observed for EBV. One protein controlling EBV reactivation is ZEBRA, a lytic gene transactivator and the product of the BZLF1 gene. In Daudi cells latently infected with EBV, ZEBRA expression was increased by *P. gingivalis* spent medium, triggering viral reactivation. The virulence factors LPS, fimbriae, or gingipains alone had no effect on ZEBRA expression. Among the various SCFAs produced by *P. gingivalis*, including butyric, isobutyric, propionic, acetic, and valeric acids, only butyric acid treatment led to induction of ZEBRA. After treatment with *P. gingivalis* culture supernatant or butyric acid, binding of H3ac, a mark of active chromatin, to the BZLF1 promoter increased, while binding of HDACS 1, 2, and 7 decreased. ZEBRA expression also requires chromatin remodeling, as treatment with novobiocin, a topoisomerase II inhibitor, blocks *P. gingivalis*-induced ZEBRA production (46, 47).

Butyrate is an HDAC inhibitor and has been implicated in the reactivation of HIV and EBV (46, 48, 49). However, butyrate may not be the only *P. gingivalis* product involved in epigenetic regulation, as differences were found between cellular epigenetic changes induced by *P. gingivalis* and *F. nucleatum*, another *Bacteroidete* anaerobe whose primary end product is butyrate. While global H3K4me3 decreased with *P. gingivalis*, H3K4me3 did not decrease in gingival cells incubated with *F. nucleatum* (50). In addition, *P. gingivalis* produces LPS, and LPS-induced Toll-like receptor (TLR) signaling leads to widespread changes in the epigenetic profiles of TLR-responsive genes (51, 52). Gingipains, OMVs, and other SCFAs, such as propionic and isobutyric acids, are also produced by *P. gingivalis* and may affect epigenetics (23–26).

P. gingivalis also elicits changes in the expression of enzymes that regulate epigenetics, which could lead to global changes in epigenetic profiles for both the virus and the host. For example, exposure of keratinocytes to *P. gingivalis* LPS downregulated expression of DNMT1, HDAC1, and HDAC2, all enzymes that promote epigenetic events (53). *P. gingivalis* uses epigenetic means to modulate the immunoregulatory proteins β-defensin2 and CCL20 and increases promoter methylation for a number of growth control and inflammatory genes (50). In addition, oral bacteria associated with periodontal disease, such as *P. gingivalis*,

induce oxidative stress, a process central to epigenetic modification (54, 55).

HNSCC: periodontitis-associated bacteria and HPV. In addition to tobacco and alcohol use, periodontitis has been associated with oral cancer and premalignant lesions, which in turn are associated with human papillomavirus (HPV). One study found that patients with periodontal disease have an increased risk for oral cancer and premalignant lesions, but only for current smokers (56). A later study from the same group looking at head and neck squamous cell carcinoma (HNSCC) found a significantly increased risk of cancer in patients with alveolar bone loss. An increased risk was found even for nonsmokers with chronic periodontitis, but smokers had a higher risk. In addition, patients with periodontitis were significantly more likely to have poorly differentiated HNSCC (57). HPV, particularly subtype 16, has been associated with HNSCC, as well as cervical cancer (58). In one study, approximately 40% of HNSCCs were positive for HPV16, and alveolar bone loss increased the odds of HPV-positive tumor status, with a stronger association in oropharyngeal SCC than in oral or laryngeal SCC (59). In base of tongue cancer, HPV16 was found in 70% of tumors, and the patients with HPV16-positive tumors had significantly worse periodontitis than patients with HPV-negative tumors, as measured by alveolar bone loss (60). In addition, it has been suggested that streptococci in the oral cavity promote the development of HPV-associated HNSCC through stimulation of the host inflammatory response and production of carcinogenic metabolites, such as acetaldehyde (61).

The bacterial pathogens that cause periodontal disease are known to cause epigenetic modifications to the genomes of EBV, KSHV, and HIV and may modify other viral genomes as well. Another example of a virus that may be affected bacterial epigenetic modulation is HPV16. HPV16 transcription, mediated by the E2 protein, is reduced by CpG methylation of the E2 binding sites in cervical epithelial cells (62). HPV hypomethylation is associated with cervical cancer progression, as progressively less methylation was seen in patients with carcinoma than in patients with precancerous lesions and asymptomatic infection (63). Furthermore, cell lines derived from HPV-associated HNSCCs have increased DNMT3A expression and cellular DNA methylation in regions containing genes and LINE 1 elements compared to cell lines from HPV-negative HNSCCs (64). Taken together, these studies suggest an additional link between bacteria and HPV-associated cancer.

HIV and AIDS: oral, gut, and vaginal bacteria. Several locations in the body are colonized by many microbes that can influence each other as well as their host, sometimes leading to disease. Not only can interactions occur between pathogenic bacteria and viruses, but opportunistic or commensal microbes may also come into play, particularly in immunosuppressed individuals (Fig. 2). It has been suggested that periodontal disease (*P. gingivalis*) and opportunistic bacteria that are associated with HIV immune suppression may in turn contribute to AIDS progression by producing butyric acid and leading to HIV reactivation through HDAC inhibition (65, 66). Furthermore, AIDS-related immune suppression can lead to an increase in opportunistic bacterial load, which could further reactivate HIV, hastening AIDS progression (65) (Fig. 2). The gut is another major site of polymicrobial colonization and infection. In early stages of HIV infection, the composition of the gut microbiota changes, and increased inflammation in the gastrointestinal (GI) tract leads to damage of the mucosal barrier (67). Breakdown of the intestinal barrier allows microbial LPS to enter the blood and results in chronic immune activation, a commonly observed feature of HIV infection and a contributor to the progression to AIDS (68, 69). In the vagina, increased risk of HIV acquisition, transmission, and HIV reactivation have been linked to bacterial vaginosis (70–74). Recent studies indicate the importance of the microbiota in multiple body compartments to the development of AIDS.

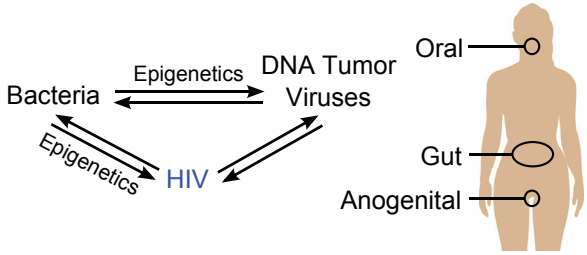

FIG 2 Interactions between multiple pathogens commonly occur at several sites in the body. Bacteria and viruses occupying the same site can work together to enhance pathogenesis. One known mechanism by which bacteria influence viruses is through epigenetic modifications. In HIV-positive individuals, immunosuppression can increase pathogenesis of opportunistic pathogens. Other viruses and bacteria can contribute to AIDS progression. Several body compartments that host polymicrobial communities are shown. The human figure is by Mikael Haggstrom (public domain), via Wikimedia Commons.

In the mouth, *P. gingivalis*-induced histone modifications have been shown to increase transcription of both integrated and nonintegrated HIV (49, 75). Gene expression and replication of nonintegrating HIV-1 were increased *in vitro* upon exposure to histone deacetylase inhibitors in the form of various short-chain fatty acids (SCFAs) known to be endogenously produced by normal microbial gut flora. The increased expression of integrated HIV was attributed particularly to butyric acid produced by the bacteria, not any virulence factor (LPS, fimbriae, or gingipain) or other SCFA (75). Integrated HIV is silenced by a number of repressive epigenetic modifications, including HDAC recruitment, methylated H3 (H3K9me3, H3K27me3, and H3K9me2), and binding of Polycomb Repressive Complex 2 members (7). *P. gingivalis* and butyric acid were found to increase H3 and H4 acetylation and binding of polymerase II to the HIV long terminal repeat (LTR). These treatments also decreased binding of two repressors of gene expression: HDAC1 and AP-4. *P. gingivalis*-mediated HIV transcription was diminished by novobiocin, a topoisomerase II inhibitor, indicating dependence on chromatin remodeling (75). HIV gene expression is stimulated by *P. gingivalis*, and epigenetic changes are critical.

In addition to the oral cavity, several studies have focused on HIV reactivation in the gut and vagina. Gene expression and replication of nonintegrated HIV were notably increased *in vitro* upon exposure to various short-chain fatty acids (SCFAs) endogenously produced by gut bacteria (49). HIV can be reactivated by supernatant from other butyric acid-producing bacteria, including *F. nucleatum*, *Clostridium cochlearium*, *Erythema multiforme*, and *Anaerococcus tetradius*. *F. nucleatum* is commonly found in the mouth and gut, *C. cochlearium* and *E. multiforme* in the gut, and *A. tetradius* in the vagina, indicating that HDAC inhibition caused by bacterial butyric acid may be able to reactivate HIV in multiple body compartments. Both H3ac levels and HIV gene

TABLE 1 Summary of bacterium-mediated epigenetic modifications to viruses

Bacteria	Virus	Interaction	Viral epigenetic modification(s)	Reference(s)
P. gingivalis	KSHV	Direct	Global H3 and H4 acetylation	31
	EBV	Direct	H3 acetylation and HDAC dissociation from BZLF1 promoter	46
Periodontitis-associated bacteria	HPV	Indirect	DNA hypomethylation	56, 57, 62–64
P. gingivalis, *F. nucleatum*, *C. cochlearium*, *E. multiforme*, *A. tetradius*, (Butyrate)	HIV	Direct	Increased H3K4me2, H3ac, and H4ac, decreased H3K9me3, RNAPII binding, HDAC1 dissociation at LTR	48, 49, 69, 70, 75
H. pylori	EBV	Indirect	DNA hypermethylation	76, 81–97

expression were positively correlated with the amount of butyrate produced by these bacterial species. Supernatant from *F. nucleatum*, *C. cochlearium*, and *A. tetradius* cultures reduced binding of HDAC1 and increased binding of RNA polymerase II (RNAPII) to the HIV LTR. These epigenetic changes were not observed when the culture media were heat treated to remove SCFA or when the cells were treated with novobiocin, a topoisomerase II inhibitor (48). NaB treatment led to increases in the activating marks H3K4me2, H3ac, and H4ac and decreases in the repressive mark H3K9me3 on the HIV LTR. In monocyte-derived macrophages, HIV replication that was diminished by the integrase inhibitor raltegravir was partially restored by the SCFAs propionic, valproic, and heptanoic acids (49).

Gastric cancer: *H. pylori* and EBV. Both present in the gut, *Helicobacter pylori* and EBV have each been linked to gastric cancer (76, 77). Although the majority of gastric cancers are associated with *H. pylori*, up to 10% of gastric cancers contain EBV. EBV-associated gastric cancers, *H. pylori*-associated cancers, and coinfected cancers have different characteristics (76, 78). Cancers with only *H. pylori* express Bcl-2, while coinfected or uninfected cancers do not. In addition, c-Myc and Bax expression was detected more often in *H. pylori*-only cancers than in coinfected ones (78), indicating double infection may modulate disease characteristics and possibly outcome. In addition to these two infectious agents, increased CpG methylation has been suggested as an early event in and risk factor for the development of gastric cancer (79, 80).

In the context of gastric cancer, *H. pylori* infection has been linked to CpG hypermethylation of several tumor suppressor genes. One gene frequently observed to be silenced by methylation in gastric cancers is the gene coding for Runx3. Runx3 methylation has been correlated with age, tumor location, and *H. pylori* infection (81). *H. pylori* causes methylation of Runx3 by stimulating nitric oxide production by macrophages (82). Another of these genes is the gene coding for E-cadherin, a transmembrane adhesion protein whose loss is involved in invasion and metastasis (83). E-cadherin mutations have been observed in diffuse gastric cancers, and methylation of the E-cadherin promoter may be a second hit in patients with heterozygous mutation (84, 85). E-cadherin methylation was associated with *H. pylori* infection in patients with dyspepsia and gastric cancer, with loss of E-cadherin protein observed by immunohistochemical staining in gastric cancer biopsy specimens (86). Furthermore, treatment to eliminate *H. pylori* in dyspepsia patients reversed E-cadherin methylation by 6 weeks (87). Hypermethylation of the E-cadherin and two other tumor suppressor promoters, DAPK and p16, was found to be increased in normal gastric mucosa of gastric cancer patients compared to healthy controls and may be a marker for increased risk of cancer (88). Methylation of CpG islands in p16, LOX, FLNc, HRASLS, HAND1, THBD, and p41ARC was also increased in *H. pylori*-positive individuals (89).

EBV-associated transformation and tumorigenesis in gastric and other cancers have been linked to latency (90). Latent EBV is highly methylated, and expression of the EBV-encoded nuclear antigens (EBNAs) is silenced by cell-type-dependent methylation (91, 92). However, ZEBRA, an EBV transactivator that is increased in cells treated with *P. gingivalis* spent medium in association with histone acetylation (46), preferentially binds to the methylated form of its AP-1-like binding sites in the BRLF1 and BRRF1 promoters, increasing transcription (91, 93). ZEBRA and the products of BRLF1 and BRRF1 are all transcription factors involved in the switch to viral lytic replication (93). Like *H. pylori*, EBV has been implicated in high levels of CpG methylation of cellular genes associated with gastric cancer, including those coding for $p14^{ARF}$, $p16^{INK4A}$, PTEN, RASSF1A, GSTP1, MGMT, and MINT2 (94–96). EBV infection was correlated with overexpression of the DNA methyltransferase DNMT1 in gastric cancers, which was in turn correlated with CpG methylation of the hMLH1 and THBS-1 genes (97). Given the documented effects of epigenetic modifications on EBV gene expression, the ability of EBV and gut bacteria such as *H. pylori* to induce epigenetic changes in cells, and the strong link between gastric cancer and CpG methylation, it is plausible that coinfections may heighten gastric cancer risk.

CONCLUDING REMARKS

There is extensive evidence demonstrating the critical role of bacterial products in the modulation of viral epigenomes (summarized in Table 1). Regardless of tumor virus type or cell type, bacteria are associated with enhanced viral replication, and there is significant modulation of processes associated with epigenetic regulation both *in vitro* and *in vivo*. In the case of latent viruses, epigenetic modifications may lead to lytic reactivation of the virus, production of virions, and spread of the virus. Epigenetic modifications to the promoters of virus encoded oncogenes could increase production of these proteins and promote cancer progression (Fig. 1). Recent work has shown that HDAC inhibition activity is central to bacterium-mediated activation of viral epigenomes, including HIV (49) and herpes group viruses (31, 46). In addition, gut bacteria can modulate CpG methylation, an important regulator of EBV gene expression, and the presence of all three is a risk factor for gastric cancer (76, 77, 79, 80). These results suggest that epigenetic modifications are common to bacterium-mediated reactivation, but the rigorous testing needed to understand the exact epigenetic mechanisms has not been done. Several important questions remain. First, what are the mechanisms of chromatin modification on tumor viral promoters, and are these modifications sufficient to drive viral gene activation? Second, what are the bacterium-mediated modifiers that deregulate the

host antiviral response? Third, are there disease-relevant associations between bacterial infection and viral epigenetic modification within various body cavities? Finally, do bacterium-mediated chromatin modifications affect cellular genes that are critical to viral pathogenesis?

There is strong evidence of enhanced pathogenesis in bacterium-virus coinfections. Extensive use of epigenetics to direct viral gene expression and emerging data on epigenetic regulation of HIV and herpesviruses by bacteria suggest epigenetic modification in polymicrobial interactions may be a generalizable principle contributing to a wide variety of diseases. Further studies may provide information on host and viral molecules key to disease progression that can be translated into high-impact novel therapies that consider multiple pathogens. The treatment that may emerge would be highly significant because of the high incidence of polymicrobial diseases, particularly in immunocompromised hosts. Importantly, the implications may be far-reaching, as similar interactions may occur in all mucosally coinfected compartments. Without an understanding of the environmental factors that modulate these critical viral epigenetic modifications, our ability truly to eradicate these virus-associated disorders remains compromised.

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