Review

Cancer Research

Epstein–Barr Virus Infection as an Epigenetic Driver of Tumorigenesis

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Abstract

Epstein–Barr virus (EBV) establishes latent infection and is associated with tumors, such as Burkitt lymphoma, nasopharyngeal carcinoma, and gastric cancers. We recently reported that EBV^+ gastric cancer shows an EBV^+/extensively high-methylation epigenotype, and *in vitro* EBV infection induces extensive DNA methylation with gene repression within 18 weeks. On the basis of the absence of both EBV and high-methylation accumulation in the surrounding mucosa of EBV^+ gastric cancer, it is suggested that an EBV-infected cell acquires extensive methylation to silence multiple tumor suppressor genes in a short time period and transforms into cancer cells, not forming a precancerous field with EBV infection or methylation accumulation. The methylation mechanism induced by EBV infection has not been fully clarified. Differences in EBV genome methylation that are dependent on a different latency status or other epigenomic alterations, such as 3-dimensional conformation and histone modification, may affect host genome methylation. Expressions of viral proteins and small RNAs are also different depending on latency status, and some viral proteins might trigger DNA methylation by inducing DNA methyltransferase overexpression. In this review, we discuss these roles of EBV infection in driving tumorigenesis and their possible association with aberrant DNA methylation. *Cancer Res; 72(14); 3445–50. ©2012 AACR.*

Introduction

Epstein–Barr virus (EBV) is a gamma-herpes virus consisting of 184 kb of double-stranded DNA, and it is the first virus discovered from human neoplastic cells. EBV is the etiologic agent of infectious mononucleosis, and more than 90% of adults become EBV carriers. EBV causes opportunistic lymphomas in immunocompromised hosts, and in individuals without immunologic suppression, EBV may cause other malignancies, such as Burkitt lymphoma, nasopharyngeal carcinoma, Hodgkin lymphoma, peripheral natural killer/T-cell lymphoma, smooth muscle tumors, and gastric cancers (1).

We recently reported on a specific epigenotype with extensive DNA methylation in EBV^+ gastric cancer (2). Mechanisms of EBV-related tumorigenesis other than DNA methylation may include (i) viral proteins that regulate host gene expressions and signal pathways; (ii) viral small RNAs that can target host genes; (iii) altered expression of microRNAs (miRNA) of host cells; and (iv) other epigenetic alterations, for example, chromatin conformation and histone modification. Here, in the context of our recent study, we review these mechanisms of aberrant gene regulation and discuss their possible association.

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DNA Methylation in Gastric Cancer

Several reports previously showed that promoter methylation was observed more frequently in EBV^+ than EBV^- gastric cancers, but the analysis was limited to known cancer-associated genes (3, 4). Ryan and colleagues analyzed the expression of 96 genes in the gastric cancer cell line AGS, with and without EBV infection, and showed 25 genes down- or upregulated by EBV (5). For 11 of those genes, 5-aza-2′-deoxycytidine treatment reversed the EBV-mediated dysregulation, suggesting that the dysregulation is associated with DNA methylation directly or indirectly. Most of the analyzed genes, however, were already densely methylated in AGS before EBV infection; therefore, any additional methylation was not observed after EBV infection. The exception was *TFF1*, which was 50% to 64% methylated in AGS and 100% methylated after EBV infection, with strong repression.

In our recent study, we did a comprehensive analysis of DNA methylation in promoter regions in gastric cancer, using Infinium HumanMethylation27 BeadChip (Illumina), and identified 3 distinct epigenotypes: EBV^-/low-methylation, EBV^-/high-methylation, and EBV^+/extensively high-methylation. The EBV^+-specific aberrant methylation expands not only within polycomb repressive complex (PRC)–target genes in embryonic stem cells, but also to non–PRC-target genes, suggesting methylation mechanism(s) different from the EBV^-/high-methylation epigenotype. Using the low-methylation gastric cancer cell line MKN7, EBV infection was clearly shown to induce new methylation extensively within 18 weeks to acquire the EBV^+-specific methylation epigenotype and

repress gene expressions, including multiple tumor-suppressor genes, suggesting a role in tumorigenesis (2).

AGS is an EBV$^-$ cell line, but it has an EBV$^+$/extensively high-methylation epigenotype, suggesting that the host cells themselves possess the mechanism for the extensive methylation and that methylation can be triggered by causes other than EBV infection (2). Because AGS was already extensively methylated, a methylation increase by EBV infection was barely discernible. However, some genes that were not yet methylated in AGS, for example, *HIC1* and *SEMA3B*, showed *de novo* methylation by EBV infection. *TFF1* is a low-CpG promoter gene, which was generally methylated in normal gastric mucosa and, thus, excluded in our recent analysis (2). Our Infinium data (GSE31789, GEO data sets) show that *TFF1* and several other low-CpG promoter genes (*AIF1*, *CDH17*, *CTSE*, *LGALS4*, *MMP20*, *NR1H4*, *PLEKHA4*, *PNPLA2*, *REG4*, and *TCP1*) were aberrantly hypomethylated in AGS, and methylation was induced in all 3 EBV-infected AGS clones. Methylation targets by EBV infection may include not only CpG islands (2) but also low-CpG regions.

In EBV$^+$ gastric cancer, monoclonal EBV is detected in nearly all cancer cells in every case, suggesting the establishment of infection in the early stage of gastric carcinogenesis (6). Whereas >90% of adults are EBV carriers, EBV infection is rarely seen in noncancerous gastric epithelium (2), and positive signals were infrequently detected only in a single cell at the surface of gastric pits (6). High methylation did not accumulate in the surrounding noncancerous mucosa of EBV$^+$ gastric cancer (3, 4), whereas all EBV$^+$ gastric cancer cases show markedly high methylation, with no exceptions (2). Early development of an EBV$^+$ gastric cancer after hematopoietic stem cell transplantation was reported: gastritis without EBV or *Helicobacter pylori* at posttransplantation day 100; gastric dysplasia with EBV and without *CDH1* methylation at day 130; and EBV$^+$ gastric adenocarcinoma invasive to submucosa with *CDH1* methylation at day 150 (7). On the basis of these reports, we suggest that EBV infection to the gastric epithelium is a rare event, or if it is not rare, EBV infection seldom causes methylation or cellular growth, resulting in the difficult detection of infected noncancerous epithelium. In either case, once methylation is induced, extensive methylation could be completed in a short time period with good reproducibility, including multiple tumor-suppressor genes. The infected epithelial cells will transform into cancer cells, not forming a precancerous field of epithelium with EBV infection and methylation accumulation.

Atrophic gastritis may be considered a lesion to increase the chance of contact between infiltrated EBV-carrying lymphocytes and epithelial cells. EBV-carrying lymphocytes were often observed in atrophic gastritis, in which one or a few gastric glands with EBV were very rarely observed (6).

Latent Epstein–Barr Virus Infection

Infection of primary B cells leads to latent infection, in which only a subset of viral genes are expressed, for example, *LMPs* (*1*, *2A*, *2B*), *EBNAs* (*1*, *2*, *3A*, *3B*, *3C*, *LP*), *EBERs*, and the transcripts from BamHI A region. This expression program is called type III latency and drives the indefinite proliferation of primary B cells and the lymphoblastoid cell line (LCL). Burkitt lymphoma shows type I latency, with the expression of *EBNA1*, *EBER1/2*, and *BARTs* only. Type II latency is seen in EBV-associated Hodgkin lymphoma, peripheral natural killer/T-cell lymphoma, and nasopharyngeal carcinoma, in which *LMP1* and *LMP2* are expressed in addition to latency I genes. Gastric cancer shows latency I (or II) and expresses *EBNA1*, *EBER1/2*, *BARTs*, and *LMP2A* (1, 6).

In latent infection, the viral genome is silenced by host-driven DNA methylation, which allows viruses to escape from the host immune system. Fernandez and colleagues analyzed the methylation status of 94 EBV genes and *EBER1/2* by bisulfite sequencing. The free viral particle is devoid of DNA methylation. The EBV genome in benign diseases, such as infectious mononucleosis, showed scattered DNA methylation only. LCLs also showed this occasional methylation. In tumors, including Burkitt lymphoma and nasopharyngeal carcinoma, extensive methylation throughout the EBV genome was observed, except *EBER1/2*, Q promoter (Qp), *BZLF1*, and *LMP2B*/*LMP1* (8). Our methylated-DNA immunoprecipitation (MeDIP)–sequencing data of EBV$^+$ gastric cancer also showed a similar extensive methylation pattern of the EBV genome (Fig. 1A).

While EBV$^+$ gastric cancer with type I and/or II latency showed extensive methylation in both the EBV genome (Fig. 1A) and the host genome (2), Burkitt lymphoma cell lines with type I latency, Raji and Akata, also showed extensive methylation in the EBV genome (8) and host genome (Fig. 1B). LCL with latent III infection did not show high methylation in the EBV genome (8) or in the host genome compared with peripheral blood cells (Fig. 1B). On the basis of the similarity between the methylation status of the viral and host genome, it was suggested that the methylation mechanism in host cells might be uniquely and excessively driven in latent I infection and that the host-driven extensive methylation of viral genome may trigger host genome methylation.

Three-dimensional conformations of EBV genomes were also different depending on EBV latency types. Tempera and colleagues (9) reported CTCF binding upstream of the Qp and C promoter (Cp). Although Qp is essential in type I latency, mutation in the Qp CTCF site resulted in loss of Qp transcription and alternative activation of Cp, because of conformation change and the increase of trimethylation of lysine 9 of histone H3 (H3K9me3) and DNA methylation at the Qp initiation site (9, 10). Chromatin insulation by CTCF and 3-dimensional conformation may affect DNA methylation in the EBV genome, which suggests that host genome methylation may also be affected because the episomal EBV genome is linked to the host genome through EBNA1 and may develop close physical proximity with specific host genomic regions as described below.

Roles of Epstein–Barr Virus Latent Genes

Latent genes can cause aberrant regulation of the signaling pathway and gene expression to drive tumorigenesis and may affect DNA methylation. LMP1 is an integral transmembrane

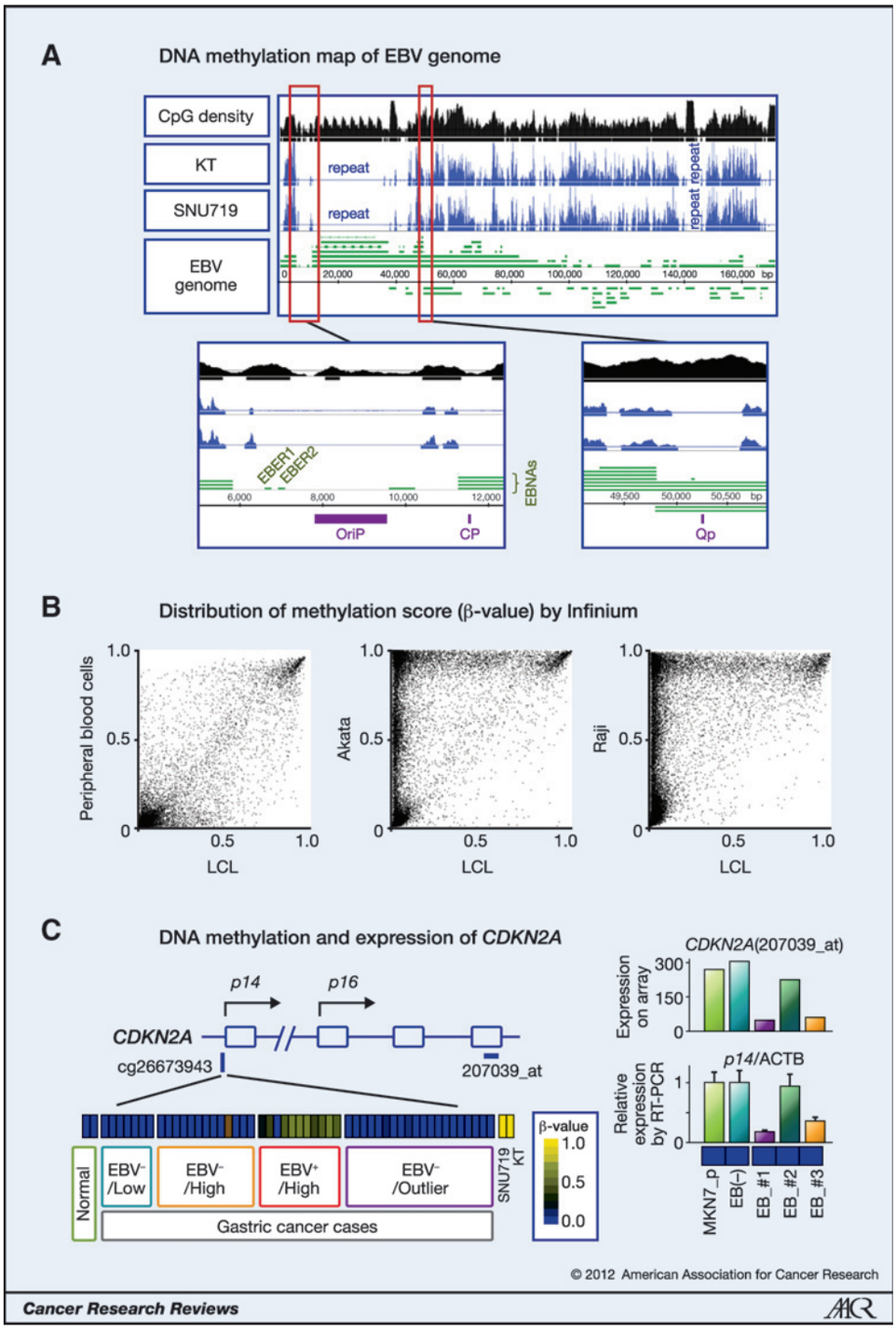

Figure 1. A, MeDIP-seq analysis of EBV$^+$ gastric cancer cell line (SNU719) and xenograft tumor (KT) showed that the EBV genome is mostly methylated, including Cp, which is necessary for *EBNA* expression in latency III, but it is unmethylated in *EBER1/2*, OriP, and Qp, which is necessary for *EBNA1* expression in latency I/II. B, by Infinium analysis in which β-values 1.0 and 0 correspond to 100% and 0% methylation, LCLs in latency III did not show a clear methylation difference compared with peripheral blood cells (left), but Burkitt lymphoma cell lines Akata and Raji in latency I showed extensive methylation (middle and right). C, the Infinium 27k probe *cg26673943* showed specific *p14*^{ARF} methylation in EBV$^+$ gastric cancers (left), whereas *p14*^{ARF} methylation was not induced within 18 weeks after EBV infection (right). EBV$^-$/Outliers, EBV$^-$ cases not clearly classified into EBV$^-$/low-methylation or EBV$^-$/high-methylation epigenotype (2). Expression microarray (Affymetrix probe *207039_at*) showed repression of *CDKN2A* in 2 of the 3 EBV-infected clones (EB_#1 and EB_#3) compared with parental MKN7 cells (MKN7_p) or mock infection [EB(−)], and the repression of *p14*^{ARF} was validated by real-time reverse-transcription PCR.

protein expressed in latency II/III and potentiates a variety of signaling pathways, including NF-κB, mitogen-activated protein kinase, and phosphoinositide 3-kinase/Akt pathways, and LMP1 introduction is sufficient for immortalization of rodent fibroblasts (11). *EBER*s are abundantly transcribed in all forms of latency; the functions of these noncoding, nonpolyadenylated RNAs are largely unknown, but they may play roles in efficient B-cell transformation (12).

EBNAs target the nucleus and affect gene expression. EBNA2 is a transcriptional coactivator that upregulates expression of both viral and host genes necessary for transformation and interacts with transcription factors in the Notch signaling pathway (13). EBNA3A and EBNA3C are necessary for B-cell transformation *in vitro*. EBNA1 is a sequence-specific DNA-binding protein that binds the origin of plasmid replication (OriP) of the EBV genome and host cell chromosomes and is necessary for maintenance and replication of EBV episome. Dresang and colleagues identified EBNA1-binding sites by chromatin immunoprecipitation in human promoters (14). Host genomic regions near EBNA1-binding sites could be close to the extensively methylated EBV genome via EBNA1 binding, although the methylation status of those neighboring regions has not been investigated.

Tsai and colleagues reported that LMP1 downregulates *CDH1* 0.2-fold through upregulation of DNA methyltransferase 1 (DNMT1), DNMT3A, and DNMT3B, and 3- to 8-fold in nasopharyngeal carcinoma cell line NPC076 (15). The LMP1-mediated *CDH1* repression in NPC076 was restored by 5-aza-2′-deoxycytidine treatment, suggesting the possible association of DNA methylation. They also reported that LMP1 directly activated the DNMT1-P1 promoter via the JNK-AP-1 pathway (16). However, the simultaneous induction of dense *CDH1* methylation was unclear, whereas partial methylation was shown by methylation-specific PCR or sequencing of the methylation-specific PCR product using breast cancer cells instead of NPC076 (15, 16). In gastric cancer, LMP2A was reported to induce DNMT1 overexpression 5-fold through phosphorylation of STAT3, and LMP2A-mediated PTEN inactivation was observed. Quantitative methylation-specific PCR showed a 4-fold increase in *PTEN* methylation within 96 hours (17).

These reports successfully showed that latent gene(s) could activate DNMTs and might trigger promoter methylation in a gene. However, it is unknown whether complete methylation can be induced by expression of a single latent gene after a long time period, and LMPs are not expressed in Burkitt lymphoma with type I latency. Other factors may also be necessary to induce complete and extensive methylation.

MiRNA Encoded by Epstein–Barr Virus

EBV is the first human virus shown to express viral miRNAs, specifically, miR-BHRF1-1, 2, and 3 near *BHRF1*, and miR-BART1 and 2 in introns of *BART*; the subsequent deep-sequencing analyses identified 44 possible BART miRNAs (22 miRNAs in 2 strands) in total (18). EBV miRNAs are also under different latency programs and differentially expressed among tumors. miR-BHRF1-3 is highly expressed in type III latency and EBV-associated AIDS-related diffuse large B-cell lymphoma and targets CXCL-11/I-TAC. This chemokine attracts T cells and activates the chemokine receptor CXCR3, so that repression of CXCL-11/I-TAC leads to inhibition of the host-interferon response on EBV infection (19).

BART miRNAs are mainly expressed in epithelial cells undergoing type II latency. Overexpression of miR-BART5 suppressed *BBC3*/*PUMA*, loss of miR-BART5–mediated *BBC3*/*PUMA* suppression enhanced susceptibility to apoptotic stimuli in a nasopharyngeal cancer cell line, and an inverse correlation exists between *BBC3*/*PUMA* expression and miR-BART5 levels in nasopharyngeal carcinoma (20). The proapoptotic *BCL2L11*/*BIM* was also a target of BART miRNAs, containing miR-BART5 (21). The association of viral miRNAs or other noncoding RNAs to DNA methylation has not been reported.

MiRNAs of Host Cells

Host miRNA expression could be altered by EBV infection, and the altered regulation could contribute to tumorigenesis. In latency III, expressions of 41 host miRNAs were altered, and the most upregulated miRNAs were miR-155 and miR-146a (22). miR-146a has 2 NF-κB response elements in its promoter and was induced by LMP1, possibly through the NF-κB pathway (23). miR-155 contributed to the proliferation and survival of LCLs and AIDS-related diffuse large B-cell lymphoma. Depletion of miR-155 suppressed S-phase progression and induced apoptosis. miR-155 was also reported to target components of the BMP signaling cascade, including SMAD1, SMAD5, HIVEP2, CEBPB, RUNX2, and MYO10 (24). Antitumor effects of BMP signaling (25) could be inhibited by miR-155 through downregulation of these mediators.

In gastric cancer, expression of miR-200a and miR-200b was decreased in EBV^+ gastric cancer, compared with EBV^- gastric cancer and the noncancerous surrounding mucosa. Repressors of *CDH1* transcription, ZEB1 and ZEB2, are targets of the miR-200 family, and EBV infection to the gastric cancer cell line caused a decrease of the miR-200 family, an increase of ZEB1 and ZEB2, and loss of CDH1 (26). Aberrant DNA methylation by EBV infection might cause downregulation of miRNAs, but it has not been reported, and the Infinium 27k beadarray that we used (2) did not include probes for miRNAs. EBV latent genes, *BRAF0*, *EBNA1*, *LMP2A*, and *EBER*, were shown to have synergistic effects on downregulation of the miR-200 family (26). Interestingly, *in vitro* EBV infection induced promoter methylation of *CDH1* by 18 weeks (2). Although *CDH1* is not a direct target of upregulated miRNA, subsequent gene repression may perhaps be related to DNA methylation induction.

Histone Modification

Recent exome-sequencing analysis of gastric cancer revealed frequent inactivating mutation or protein deficiency of ARID1A, a SWI-SNF chromatin-remodeling member, in 83% of microsatellite-unstable gastric cancers and 73% of EBV^+ gastric cancers, but only 11% of microsatellite-stable EBV^- gastric cancers (27). Microsatellite-unstable gastric cancers are considered as EBV^-/high-methylation cancers with *MLH1* methylation (2); *MLH1* methylation and the following

microsatellite instability may cause the *ARID1A* mutation. ARID1A inactivation in EBV$^+$ gastric cancers, however, is yet to be interpreted; our Infinium data showed no *ARID1A* methylation in gastric cancer, and *ARID1A* repression was not induced by EBV infection (GSE31789). ARID1A is reported to recruit p53 for transcriptional regulation of its downstream genes, *CDKN1A* and *SMAD3* (28). The question of whether loss of the SWI/SNF chromatin-remodeling family and subsequent repression of its downstream targets are causally related to methylation induction is to be further investigated.

Trimethylation of lysine 27 of histone H3 (H3K27me3) is catalyzed by PRC, causing transcriptional repression. EBNA3C and EBNA3A were shown to be important in repressing *BCL2L11*/*BIM* and *CDKN2A* by H3K27me3 (29). In the absence of EBNA3C or EBNA3A, LCLs showed growth arrest with the increase of $p16^{INK4A}$ and $p14^{ARF}$, accompanying the reduction of H3K27me3 and the increase of trimethylation of lysine 4 of histone H3 and H3 acetylation without DNA methylation alteration, which are similar alterations in oncogene-induced senescence (25). Activation of EBNA3C or EBNA3A reverses the distribution of these epigenetic marks, repressing $p16^{INK4A}$ to allow cell proliferation. Skalska and colleagues suggested that this PRC-mediated repression may also pave the way for DNA methylation in lymphomagenesis (30).

Although Infinium 27k has no probe for $p16^{INK4A}$ promoter, $p14^{ARF}$ promoter methylation was detected specifically in EBV$^+$ gastric cancer cases (Fig. 1C). EBV infection to gastric cancer cells causes repression of $p14^{ARF}$ expression, though DNA methylation was not increased (Fig. 1C). Although EBNA3s are not expressed in latency I/II infection in EBV$^+$ gastric cancer, it is an interesting question whether histone modification alteration is involved in *CDKN2A* repression in EBV-infected cells and could be a seed for subsequent DNA methylation.

Conclusions

We identified that the EBV$^+$ methylation epigenotype is not a parallel phenomenon to EBV infection, but rather it is caused by EBV infection itself. Host-driven methylation of the EBV genome, overexpression of DNMTs by latent proteins, and epigenomic changes, such as 3-dimensional conformation and histone modification, might be involved in the extensive methylation induction, but the details are unknown. Elucidating the intricacies of the methylation mechanism will help in understanding EBV-related tumorigenesis, especially in gastric cancer.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): A. Kaneda, K. Matsusaka, H. Aburatani, M. Fukayama
Writing, review, and/or revision of the manuscript: A. Kaneda, K. Matsusaka, H. Aburatani, M. Fukayama

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