

WJG 20th Anniversary Special Issues (8): Gastric cancer**Epigenetic dysregulation in Epstein-Barr virus-associated gastric carcinoma: Disease and treatments**

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Core tip: Epstein-Barr virus (EBV)-associated gastric carcinoma (EBVaGC) comprises nearly 10% of gastric carcinoma cases worldwide. In the present review, we critically discuss the role of EBV in gastric carcinogenesis, summarising the role of viral proteins and microRNAs with respect to aberrant methylation in EBVaGC. Given the role of epigenetic dysregulation in tumorigenesis, epigenetic modifiers may represent a novel therapeutic strategy.

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Abstract

Epstein-Barr virus (EBV)-associated gastric carcinoma (EBVaGC) comprises nearly 10% of gastric carcinoma cases worldwide. Recently, it was recognised to have unique clinicopathologic characteristics, including male predominance, lower rates of lymph node involvement, and better prognosis. EBVaGC is further characterised by abnormal hypermethylation of tumour suppressor gene promoter regions, causing down-regulation of their expression. In the present review, we critically discuss the role of EBV in gastric carcinogenesis, summarising the role of viral proteins and microRNAs with respect to aberrant methylation in EBVaGC. Given the role of epigenetic dysregulation in tumorigenesis, epigenetic modifiers may represent a novel therapeutic strategy.

INTRODUCTION

Epstein-Barr virus (EBV) infection is ubiquitous, and is accepted as a causative microorganism for various malignancies including nasopharyngeal carcinoma (NPC), Burkitt's lymphoma, and gastric carcinoma (GC). EBV-associated GC (EBVaGC) accounts for approximately 10% of cases worldwide^[1,2], and is characterised by unique clinicopathologic features including a relatively favourable prognosis (Table 1)^[1-4]. In recent years, the molecular mechanisms underlying EBV-related carcinogenesis have become increasingly understood. EBV may contribute to tumorigenesis through the expression of viral proteins and microRNAs (miRNAs). Previous studies have also reported that promoter methylation was observed more

Table 1 Clinical and pathological features of Epstein-Barr virus-associated gastric carcinoma

Clinical and pathological features	
Age	Younger ¹
Gender	Male predominance
Associations	Smoking
Prevalence	10% of gastric carcinoma cases
Location	Gastric body/cardia Remnant stomach
Clinical	Multiple carcinomas ¹ Thickening of gastric wall Ulcerated (saucer-like) neoplasm Lower rate of lymph node involvement ¹
Histology	Lymphoepithelioma-like Lymphocytic infiltration in various degrees Atrophic gastritis Lace pattern within the mucosa Moderate to poorly differentiated adenocarcinoma
Prognosis	Longer survival ¹

¹Items are controversial and subject to on-going research.

frequently in EBVaGC. Hence another method by which EBV contributes to gastric carcinogenesis is through aberrant DNA methylation and histone modification. Thus EBVaGC is characterised by distinct variations on genomic, epigenomic, and transcriptomic levels^[5]. Here, we review the mechanism by which EBV infection causes aberrant methylation, transformation, cancer development, and its associated therapeutic implications.

MECHANISM OF EBV INFECTION

EBV may infect host gastric epithelial cells directly or indirectly (Figure 1). In direct infection, the viral envelope glycoprotein BMRF-2 interacts with cellular $\beta 1$ integrins. Subsequently, viral protein gH/gL attaches to cellular $\alpha v\beta 6/8$ integrins, and triggers fusion of the viral envelope with the epithelial cell membrane^[6]. EBV preferentially infects B lymphocytes, which then mediates subsequent infection to epithelial cells^[7]. In B cell invasion, EBV envelope glycoproteins gp350/220 bind to B cell receptors CD21 and/or CD35^[8,9]. Simultaneously, viral glycoprotein gp42 interacts with Human Leukocyte Antigen (HLA) class II molecules on the B cell membrane to trigger the core fusion complex, enabling EBV entry into the B cell (Figure 2)^[8,10]. Through direct cell-to-cell contact, EBV-infected B cells may subsequently infect epithelial cells^[11]. The exact mechanism of epithelial cell invasion is unclear, but involves CD21-mediated co-capping of EBV and integrins on B cells, as well as conjugate formation between EBV-infected B cells and epithelial cells *via* the capped adhesion molecules^[11]. Once EBV enters epithelial cells, the viral capsid dissolves and the viral genome is transported to the cell nucleus.

LATENCY, VIRAL PROTEINS, AND CARCINOGENESIS

Following infection, EBV typically persists in a latent

Table 2 Latent gene expression patterns in Epstein-Barr virus infected malignancies

Genes	Latency I a	Latency I b	Latency II	Latency III
<i>EBNA1</i>	+	+	+	+
<i>EBNA2</i>	-	-	-	+
<i>EBNA3a</i>	-	-	-	+
<i>EBNA3b</i>	-	-	-	+
<i>EBNA3c</i>	-	-	-	+
<i>EBNA-LP</i>	-	-	+	+
<i>LMP1</i>	-	-	+	+
<i>LMP2A</i>	-	+	+	+
<i>LMP2B</i>	-	-	+	+
<i>EBER1</i>	+	+	+	+
<i>EBER2</i>	+	+	+	+
<i>BARTs</i>	+	+	+	+
Disease	EBVaGC, Burkitt's lymphoma	EBVaGC	NPC, Hodgkin's lymphoma, NK/T-cell lymphoma	AIDS- associated B-cell lymphomas, Pyothorax- associated lymphoma

EBVaGC: Epstein-Barr virus-associated gastric carcinoma; NPC: Nasopharyngeal carcinoma; AIDS: Acquired-immunodeficiency-syndrome.

stage. During latency, the viral genome is largely silenced by host-driven methylation of CpG island motifs. Based on the subset of viral genes which are expressed, tumours may be classified into four types; latency I a, I b, II, and III (Table 2). EBVaGC belongs to latency type I, where the viral genes EBV nuclear antigen 1 (EBNA1), EBV-encoded small RNA (EBER1/2), BamHI-A rightward transcripts (BARTs), and latent membrane protein 2A (LMP2A) may be expressed^[12,13]. Notably, the expression of latency genes is associated with malignancy. For example, EBER1 up-regulates the expression of insulin-growth factor-1, an autocrine growth factor which accelerates cell proliferation in EBVaGC^[14].

Half of all EBVaGCs also express LMP2A. LMP2A plays a critical role in the oncogenic processes in EBVaGC, and thus EBV latency patterns should be further subdivided into Ia or Ib based on the absence or presence of LMP2A^[12,15]. LMP2A not only inhibits apoptosis through up-regulation of the cellular survivin gene *via* the NF- κ B pathway^[16], but induces expression of phosphorylated signal transducer and activator of transcription 3 (pSTAT3), which causes up-regulation of DNA methyltransferase DNMT1^[16] and DNMT3B^[17] in EBV-infected GC cells. DNA methyltransferases play important roles in controlling DNA methylation. The subsequent overdrive of CpG methylation and silencing of tumour suppressor genes such as PTEN, p16, and p73 leads to the transformation of EBV-infected cells. Hence epigenetic dysregulation plays an important role in gastric carcinogenesis.

EBVaGC AND EPIGENETIC ALTERATIONS

Epigenetics refer to functionally relevant and heritable changes in gene expression that occur without alteration of the underlying DNA sequence. The two primary mechanisms which may produce this change are DNA

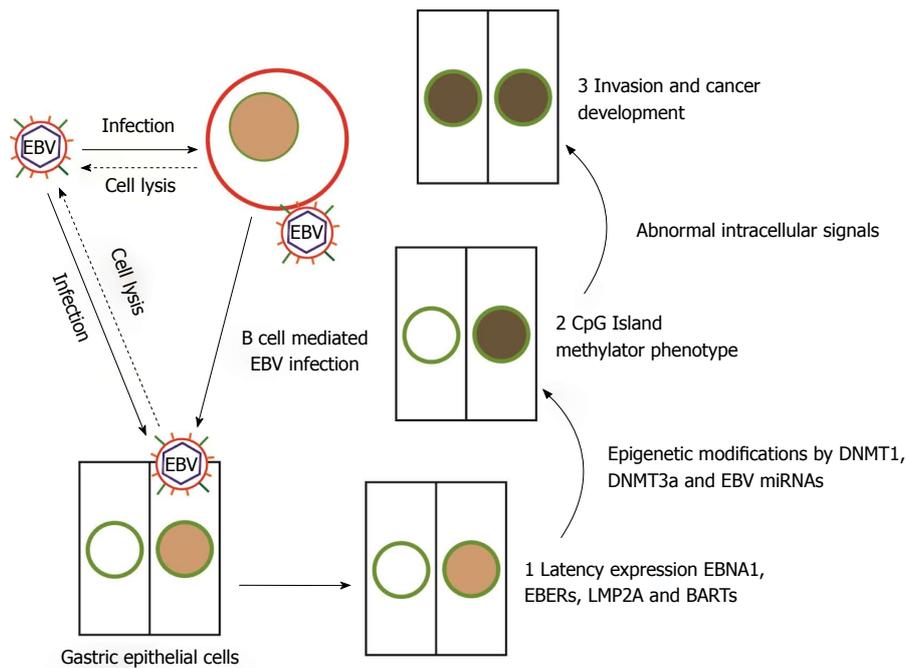


Figure 1 Epstein-Barr virus infects host gastric epithelial cells through direct and indirect mechanisms. Epstein-Barr virus (EBV) preferentially infects B lymphocytes, which subsequently infects gastric epithelial cells through direct cell-to-cell contact. EBV infection causes expression of latency 1a and/or 1b proteins in gastric epithelial cells. EBV infection also up-regulates genes including *EBNA1*, *EBER*, *LMP2A*, and *BART*, altering expression of DNMTs and miRNAs. Collectively, the abnormal intracellular signals lead to carcinogenesis and tumour development.

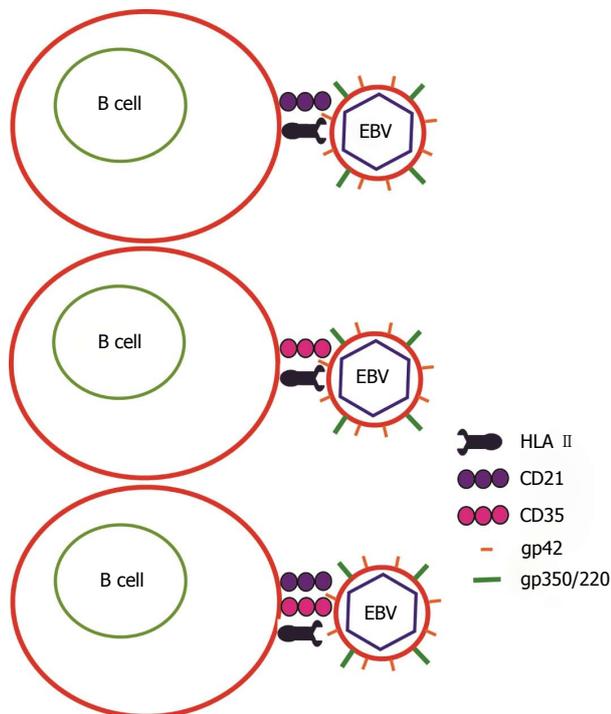


Figure 2 Mechanism of Epstein-Barr virus infection in B lymphocytes. Epstein-Barr virus (EBV) envelope glycoproteins gp350/220 bind to B lymphocyte receptors CD21 and/or CD35. Simultaneously, viral glycoprotein gp42 interacts with HLA II on the B cell membrane to trigger the core fusion complex, enabling EBV entry into the B cell.

methylation, and histone modification. According to the epigenetic progenitor model, tumour-progenitor genes promote the polyclonal epigenetic disruption of stem

cells as a first step in the development of cancer^[18]. This epigenetic plasticity causes genomic instability, and collectively drives tumour progression^[19].

The CpG island methylator phenotype was first observed in EBVaGC in 1999^[20]. EBV infection was shown to induce extensive methylation and repression of tumour suppressor genes over 18 wk in MKN7, a low methylation GC cell line^[21]. Subsequent studies confirmed that EBVaGC has higher rates of aberrant DNA methylation than EBV non-associated GC (EBVnGC)^[21,22]. Nevertheless, the mechanisms by which EBV induces aberrant DNA methylation and histone modification remain poorly understood.

EBV AND microRNA

Viral encoded miRNAs play a pivotal role in alterations to DNA methylation status in host cells. The expression of EBV miRNAs vary under different latency programs (Table 3)^[23]. For example, miR-BART1-5p, 6, and 17-5p suppresses LMP1 expression^[24], whilst miR-BART-22 regulates expression of LMP2A^[25]. EBV miRNAs further repress cellular proteins, including PUMA, DICER1, and BIM. EBV infection may also affect host cell miRNA expression. Specifically, miR-200a and miR-200b are down-regulated in EBVaGC compared to EBVnGC and adjacent mucosa. This down-regulation may be mediated by viral proteins such as BRAF0, EBER, and LMP2A, as well as by aberrant DNA methylation following EBV infection^[26]. More recently, miRNA sequencing studies have revealed that EBV-infection mediates down-regulation of tumour suppressor miRNAs including the Let-7 family.

Table 3 Epstein-Barr virus-driven miRNAs and their target genes

Gene name	Gene targets in EBV	Gene targets in host cell
miR-BHRF1-1	-	<i>GUF1</i> ^[58] , <i>SCRN1</i> ^[58]
miR-BART1-5p	<i>LMP1</i> ^[24]	<i>CLEC2D</i> ^[58,59] , <i>LY75</i> ^[58,59] , <i>SP100</i> ^[58,59] , <i>DICER1</i> ^[58,59] , <i>MICB</i> ^[58,59]
miR-BART1-3	-	<i>CXCL11</i> ^[60]
miR-BART2-5p	<i>BALF5</i> ^[61]	<i>MICB</i> ^[62]
miR-BART3	-	<i>DICER1</i> ^[58] , <i>MICB</i> ^[58]
miR-BART3-3p	-	<i>IPO7</i> ^[63]
miR-BART5	<i>LMP1</i> ^[59]	<i>PUMA</i> ^[66]
miR-BART6	<i>LMP1</i> ^[24]	<i>DICER1</i> ^[65]
miR-BART10	<i>BHRF1</i> ^[59]	-
miR-BART13	-	<i>CAPRN2</i> ^[59]
miR-BART16	<i>LMP1</i> ^[24]	<i>TOMM22</i> ^[63]
miR-BART17-p	<i>LMP1</i> ^[24]	-
miR-BART19	<i>LMP1</i> ^[59]	-
miR-BART22	<i>LMP2A</i> ^[25]	-
miR-BARTs	-	<i>BIM</i> ^[66]

EBV: Epstein-Barr virus.

Further research is required to elucidate their role in tumorigenesis^[27].

ABERRANT DNA METHYLATION IN EBVaGC

Currently, GC is subdivided into three subtypes based on CpG-island methylator phenotype (CIMP). Defined as high (CIMP-H), low (CIMP-L), or none (CIMP-N), the classification is based on the number of methylated loci (≥ 4 , 1-3, and 0 respectively) in the promoter regions of five genes (LOX, HRASLS, FLNC, HAND1, and THBD)^[28]. It was previously shown that promoter methylation of cancer-related genes was seen more frequently in EBVaGC than EBVnGC. EBVaGC is thus classified as CIMP-H^[29].

In a genome-wide study comparing promoter methylation between EBV-infected and EBV non-infected GC cell lines, hundreds of genes involved in cancer pathways such as cell adhesion molecules, wnt signalling pathway, and mitogen-activated protein kinase signalling were observed to be hypermethylated following EBV infection^[17]. Further investigation through epigenomic and transcriptomic sequencing revealed that 216 genes were down-regulated by promoter hypermethylation. Significantly, hypermethylation of tumour suppressor genes, including p14, p15, p16, APC, E-cadherin, and PTEN were noted in EBVaGC, but not EBVnGC^[30,31]. All studies unanimously agreed that p16 was significantly more hypermethylated in EBVaGC^[29-35]. P16 is a tumour suppressor gene which acts in the G1 phase of the cell cycle to phosphorylate the retinoblastoma gene product (pRb). Loss of p16 leads to uncontrolled cell growth^[36], and is thus commonly found in tumours^[37,38].

Another important cellular abnormality in EBVaGC is its resistance to apoptosis. The frequency of apoptosis is significantly lower in EBVaGC than in EBVnGC^[38].

Table 4 Hypermethylated genes verified in Epstein-Barr virus-associated gastric carcinoma tissue

Function	Hypermethylated genes
Apoptosis	<i>DAPK</i> ^[30] , <i>BNIP3</i> ^[29] , <i>FAM3B</i> ^[5] , <i>HRK</i> ^[29] , <i>IL15RA</i> ^[17] , <i>MINT31</i> ^[32] , <i>p16</i> ^[29-35] , <i>p73</i> ^[30,32-34] , <i>PTEN</i> ^[31,67] , <i>RASS-FIA</i> ^[31]
Cell adhesion	<i>EPHB6</i> ^[17] , <i>FLNC</i> ^[30] , <i>FSD1</i> ^[34] , <i>REC8</i> ^[17] , <i>CSPG2</i> ^[29]
Cell-cell interactions	<i>MDGA2</i> ^[17] , <i>THBS1</i> ^[31]
Cell cycle regulation	<i>APC</i> ^[31] , <i>p15</i> ^[30] , <i>p16</i> ^[29-35] , <i>p57</i> ^[29] , <i>p73</i> ^[30,32-34]
Cell invasion	<i>E-Cadherin</i> ^[30,68,69]
Cell migration	<i>EPHB6</i> ^[17]
Cell proliferation	<i>E-Cadherin</i> ^[30,68,69] , <i>HRASLS</i> ^[30] , <i>IL15RA</i> ^[17] , <i>MINT31</i> ^[32] , <i>NKX3.1</i> ^[34] , <i>RUNX3</i> ^[32] , <i>TIMP2</i> ^[21] , <i>TIMP3</i> ^[30]
Cell signalling	<i>14-3-3Sigma</i> ^[31] , <i>CSPG2</i> ^[29] , <i>MINT1</i> ^[31] , <i>MINT2</i> ^[31,32] , <i>PLXND1</i> ^[21]
Differentiation	<i>HAND1</i> ^[30]
Dna repair	<i>hMLH1</i> ^[32,43,53] , <i>MGMT</i> ^[31]
Exocytosis	<i>SCRN1</i> ^[34]
Metastasis	<i>E-Cadherin</i> ^[30,68,69] , <i>LOX</i> ^[30]
Other	<i>BCL7A</i> ^[34] , <i>BLU</i> ^[34] , <i>CHFR</i> ^[29] , <i>CXXC4</i> ^[21] , <i>GSTP1</i> ^[30,31,40] , <i>HLTF</i> ^[29] , <i>HOXA10</i> ^[70] , <i>IHH</i> ^[5] , <i>MARK1</i> ^[34] , <i>MINT25</i> ^[31] , <i>PAX5-β</i> ^[29] , <i>SCARF2</i> ^[17] , <i>SSTR1</i> ^[17,39] , <i>THBD</i> ^[30] , <i>WNT5A</i> ^[71]

It may be caused by hypermethylation of SSTR1 and GSTP1; both genes are frequently hypermethylated in NPC and GC infected EBV tissues, and regulate cell migration, proliferation, and apoptosis^[30,31,39-42]. Notably, EBV infection also up-regulates expression of FAM3B and IHH^[5]. FAM3B is associated with invasion^[43], and Indian Hedgehog (IHH) with increased metastatic potential through angiogenesis and Snail protein expression, as well as a decrease in e-cadherin and tight junctions^[44,45]. Table 4 shows a comprehensive list of hypermethylated genes and their role in carcinogenesis. Hence aberrant DNA methylation plays an important role in gastric carcinogenesis.

IMPLICATIONS FOR TREATMENT

Current treatment guidelines from the National Institute for Health and Clinical Excellence (NICE) for the management of GC depends on the stage of disease. Broadly, the mainstay for cure is surgical excision with clearance of adjacent lymph nodes. Radiotherapy, and chemotherapeutic agents including cisplatin, docetaxel, epirubicin, and 5-fluorouracil (5-FU) may be used as adjuvants or in the palliative setting. Notably, no differentiation is made between the distinct subtypes of GC in the treatment guidelines.

Research has established that EBVaGC represents a distinct entity of GC, characterised not only by unique genomic aberrations, but also by clinicopathologic features such as less lymph node involvement, and significantly better prognosis^[2]. Naturally, there are associated therapeutic implications, as evidenced by resistance to docetaxel and 5-FU in EBV-positive, but not EBVnGC cell lines^[46,47]. The chemoresistance is mediated by EBV-lytic gene expression, which induces expression of Bcl-2

Table 5 Selection of epigenetic therapeutics in cancer chemotherapy

Target	Drug name	Status	Ref.
DNA methylation	Azacitine (5-Aza-CR)	Approved	[72]
	Decitabine (5-Aza-CdR)	Approved	[72]
	Hydralazine	Phase II/III	[73]
	Epigallocatechin-3-gallate (EGCG)	Phase II	[74-76]
	5-Fluoro-deoxycytidine (FdCyd/FDAC)	Phase I/II	[77]
	5-fluoro-2'-deoxycytidine (FCdR)	Phase I/II	[78]
	Procainamide	Phase I	[79]
	Procaine	Phase I	[80]
	Psammaplin A	Phase 0	[81,82]
	RG108	Phase 0	[83-86]
	Zebularine	Phase 0	[87-89]
	Histone deacetylases	Vorinostat	Approved
Romidepsin		Approved	[90]
Panobinostat		Phase II	[91]
SEN196		Phase II	[92]
Phenyl butyrate		Phase I/II	[93-95]
Valporic acid		Phase I	[93-95]
Compound 6J (R = -C ₄ H ₉)		Phase 0	[96]

and survivin whilst simultaneously suppressing p21 to inhibit apoptosis^[48]. In support of this hypothesis, silencing of EBV-lytic gene LMP1 through specific small interfering RNA (siRNA) enhanced chemosensitivity of cancer cells to bleomycin and cisplatin^[49]. Since epigenetic dysregulation is implicated in the expression of EBV-lytic genes and consequent tumour progression, we believe that epigenetic processes are a rational therapeutic target in EBVaGC.

Crucially, aberrant DNA methylation in cancer is reversible. Thus the enzymes which regulate epigenetic modifications are attractive targets for pharmacological intervention. Current epigenetic therapies may be classified into histone acetyltransferase (HAT), histone deacetylase (HDAC), and DNA methyltransferase (DNMT) inhibitors (Table 5). Broadly, they facilitate demethylation and re-expression of epigenetically silenced tumour suppressor genes, lowering the apoptotic threshold to sensitise tumour cells to chemotherapy and radiotherapy. Consequently, there has been an emphasis on investigating the clinical value of epigenetic therapies in combination with conventional cytotoxic agents and radiation.

It was previously reported that the combination of irradiation and 5-aza-CdR significantly decreased growth activity compared with irradiation alone in OCUM-2M, OCUM-12, and MKN-45 GC cell lines ($P < 0.05$). The cell cycle arrest and increased apoptotic rate may be partly mediated by enhanced expression of p53, RASSF1, and DAPK gene families by 5-aza-CdR^[50]. The use of epigenetic therapies in conjunction with targeted therapies such as gefitinib in lung cancer, imatinib in chronic myeloid leukemia, and trastuzumab in breast cancer cell lines and *in vivo* tumour models also had synergistic effects on the induction of apoptosis^[51,52]. More recently,

epigenetic modifiers and ZEB1 inhibitors have been used to induce lytic transformation of EBV-infected gastric cancer cells. Expressed only in the lytic form of infection, virally encoded kinases convert ganciclovir into its active form, potentiating its cytotoxic effects^[53,54]. Hence epigenetic modifiers may be a useful therapeutic strategy in EBVaGC.

However, several problems must be considered. Firstly, methylation is reversible, so re-methylation and re-silencing after cessation of drug therapy may occur^[55]. Moreover, there have been numerous concerns raised regarding the systemic effects of non-specific gene activation in non-cancerous cells by epigenetic therapies. Conflicting evidence exists in the literature regarding the effect of epigenetic therapies on normal cells. Some studies have demonstrated that 5-Aza and decitabine increases mutation frequency, causes chromosomal rearrangements, and decreases fertility in mice. Conversely, no increase in chromosomal integrity was observed following administration of low dose 5-aza-CdR in patients with myelodysplastic syndrome^[56]. Additionally, treatment of 41 leukemia patients with 5-aza-CdR showed only mild effects on global genomic de-methylation, as measured by changes in Alu methylation^[57]. Few adverse effects were observed, and original methylation levels were regained within two weeks after therapy. No development of secondary malignancies were recorded. Consequently, further studies are needed to investigate the long term effects of epigenetic therapies.

CONCLUSION

EBVaGC is a unique type of GC. The characteristic global hypermethylation of the promoter region in tumour-suppressor genes may be due to overexpression of DNMTs by viral latent proteins, miRNAs, and various epigenomic changes. However, the precise role of EBV in the multifactorial etiology of GC is still not fully understood. Further studies are needed to elucidate the intricate relationship between EBV infection, environmental factors, genetic backgrounds, and aberrant DNA methylation in GC. A better understanding of the role of EBV in gastric carcinogenesis will enable discovery of novel therapeutic targets and strategies.

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