Chapter 2

Epstein-Barr Virus–Associated Gastric Carcinoma: The Americas' Perspective

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Abstract

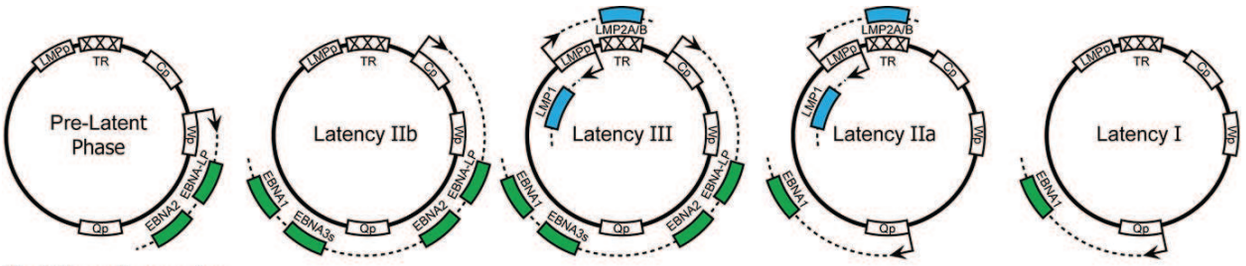
Epstein-Barr virus (EBV) infection has been associated with different malignancies, and compelling evidence has shown that it may have a causative or at least contributing role in gastric carcinogenesis. EBV-associated gastric cancers have a unique molecular signature, which has defined this group of tumors as a distinctive molecular subtype of gastric cancer. This subtype has shown a greater incidence in the Americas than in the Asian countries. This chapter discusses about possible factors underlying these differences and the emerging roles of epigenetics in the pathogenesis of Epstein-Barr virus–associated gastric cancer.

Keywords: gastric cancer, Epstein-Barr virus, strains, phylogeographic diversity, epigenetic abnormalities

1. Introduction: an overview of the Epstein-Barr virus

Epstein-Barr virus (EBV) belongs to the human gammaherpesvirus and is a 175 kbp double-stranded linear DNA virus. EBV infection is associated with the development of different malignancies, including several lymphoid neoplasms like Burkitt's lymphoma, Hodgkin's lymphoma, and immunosuppression-related B-cell lymphoma; in addition, epithelial malignancies like nasopharyngeal carcinomas (NPC) and gastric carcinomas have also been associated with the EBV [1]. Primary EBV infection is most of the time asymptomatic, and like other members of the herpesvirus family, the EBV maintains its

genome as extrachromosomal circular episomes with repression of genes involved in virus replication. If latent persistent infection is established, viral reactivation may occur with the expression of specific EBV genes defining the type of latency in the infected cell. Genes involved in these patterns are shown in **Figure 1** and include the EBV-encoded RNAs (EBERs), the EBV nuclear antigens (EBNAs), the BamH1-A rightward transcripts (BARTs) and the latent membrane protein (LMP)-1, 2A and 2B [3]. These latency-associated patterns have been associated with specific malignancies and in the case of gastric cancer, the virus shows a latency type I/IIab. The EBERs 1 and 2 genes are the most abundant small noncoding RNAs that interact with proteins of the host and are the standard target for EBV detection by in situ hybridization (ISH) [4]. The EBNA-1 and -2 genes are exclusive nuclear proteins expressed in latent infected gastric carcinoma cells and related to the disruption of promyelocytic leukemia nuclear bodies [5]. EBNA-1 is a DNA-binding protein that lacks enzymatic activity although it can interact with some cellular proteins such as CK2 and P32/TAP [6]. Interestingly, EBNA-1 is expressed in all of the EBV-associated tumors and is involved in viral DNA replication, mitotic segregation and transcriptional activation [7]. BART genes encode highly expressed multispliced RNAs whose protein-coding function is controversial [8]. Although some BARTs open reading frames (ORFs) have been predicted, currently it is not clear if any of them can be endogenously translated. In addition, BART genes, small as well as long noncoding RNAs, are highly expressed and associated with oncogenic transformation and immune evasion



Viral Gene Expression:

Pre-Latent Phase	Latency IIb	Latency III	Latency IIa	Latency I
Noncoding RNA: EBERs BHRF1 miRNAs BART miRNAs	**Noncoding RNA:** EBERs BHRF1 miRNAs BART miRNAs	**Noncoding RNA:** EBERs BHRF1 miRNAs BART miRNAs	**Noncoding RNA:** EBERs BART miRNAs	**Noncoding RNA:** EBERs BART miRNAs
mRNAs: EBNA-LP EBNA2 Wp-BHRF1 (vBcl2)	**mRNAs:** EBNA-LP EBNA2 EBNA3s EBNA1 Wp-BHRF1 (vBcl2)	**mRNAs:** EBNA-LP EBNA2 EBNA3s EBNA1 LMP1 LMP2A LMP2B Wp-BHRF1 (vBcl2)	**mRNAs:** EBNA1 LMP1 LMP2A LMP2B	**mRNAs:** EBNA1
Restricted Lytic Genes: (e.g., ZTA, RTA, vBcl2, vIL10)				

Figure 1. Gene expression patterns at different stages of EBV latency states. The theoretical progression of EBV latency gene expression from initial infection to true latency is described from left to right. The EBV genome is shown in episomal form closed at the terminal repeats (TR). Promoters are shown as white boxes and include the EBNA promoters Cp, Wp and Qp as well as the bidirectional LMPp. Primary mRNA transcripts are shown as dotted lines, while coding regions have been simplified as colored boxes. An expanded list of viral genes expressed in each latency state is listed directly underneath the representative schematic. Taken from [2] with permission.

functions [9, 10] (for review, see [3, 11]). The LMP-1 and -2 encode for transmembrane proteins with a plethora of oncogenic functions with conflicted results in gastric carcinoma (for review, see [12]). It has been proposed that variations in its sequences might be related to phylogeographic diversity of EBV-associated gastric carcinoma (EBVaGC) strains worldwide [13]. Taken together, EBV latent genes not only define the type of latency but also are associated with oncogenic transformation, immune evasion and the genetic diversity of EBVaGC.

2. Gastric cancer: novel molecular classifications

The molecular bases of gastric cancer have begun to be unraveled by a comprehensive molecular evaluation of primary tumors [14–20]. As shown in **Figure 2**, the Cancer Genome Atlas (TCGA) network has proposed a novel molecular classification of gastric carcinoma that recognized for the first time a subtype of tumor positive for Epstein-Barr virus, the EBV-associated gastric carcinoma (EBVaGC). This novel subtype of gastric cancer is characterized by frequent PIK3CA gene mutations, amplification of JAK2, CD274 (PD-L1) and PDCD1LG2 (PD-L2), and a unique CpG island methylator phenotype (CIMP) [14, 21].

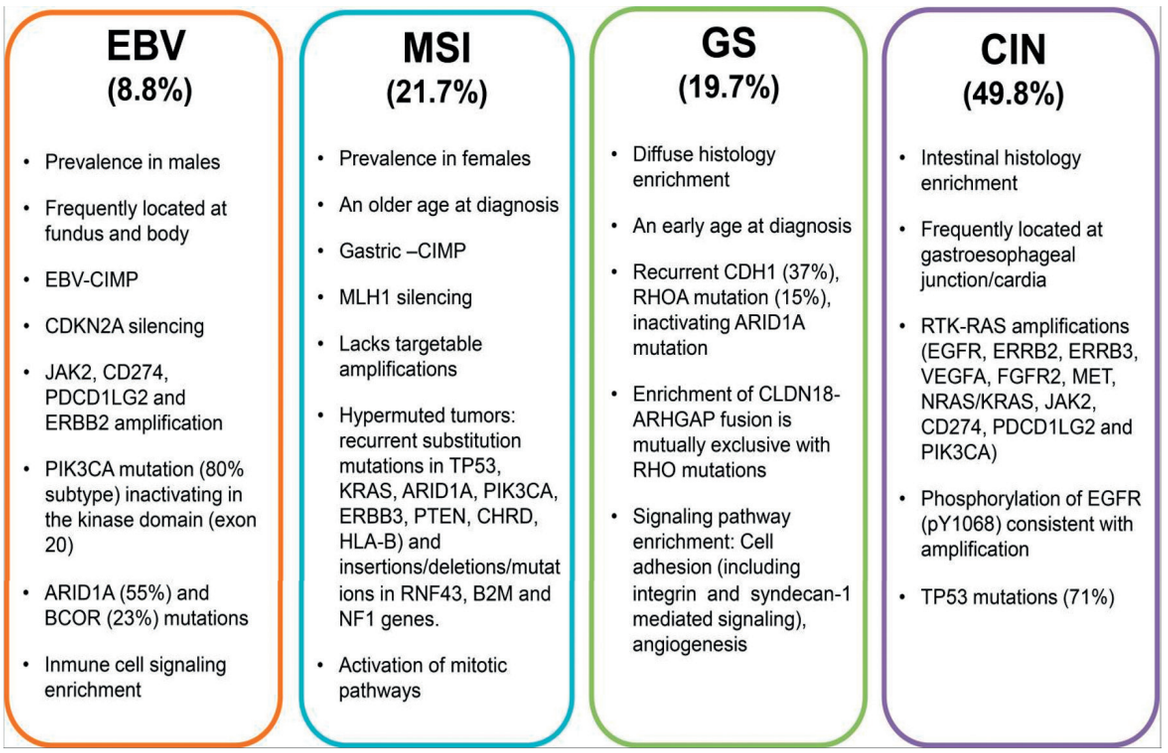


Figure 2. Major features of molecular classification of gastric cancer as proposed by the tumor cancer genome atlas (TCGA) are CIMP: CpG island methylator phenotype, EBV: Epstein-Barr virus, MSI: microsatellite instability, GS: genomically stable and CIN: chromosomal instability. Taken from [20] with permission.

3. EBV-associated gastric carcinoma: the Americas' perspective

Worldwide studies show higher EBVaGC prevalence in the Americas than in Asia [22]. These observations suggest a phylogeographic diversity of Epstein-Barr virus strains along with host and environmental associations [13]. In the Americas, the first report of gastric tumors positive for Epstein-Barr virus comes from Shibata and coworkers [23] (**Figure 3**). These authors, based on the histological resemblance between rare variant of undifferentiated gastric carcinomas with intense lymphoid infiltration (so-called lymphoepithelioma-like carcinoma [LELC]) and nasopharyngeal lymphoepithelioma, a well-established EBV-associated disease, detected EBV sequences in seven of eight LELC cases. EBV genomes were uniformly present only in carcinoma cells but not in reactive lymphoid infiltrate or normal gastric mucosa. Furthermore, the presence of a single genotype in each LELC cell was consistent with a clonal process, suggesting that EBV infection occurs before malignant transformation. Later, the same group expanded these findings to conventional gastric cancer, detecting EBV sequences in 22 of 138 (16%) cases [24]. In all these cases, the EBV genome was expressed, exclusively in gastric tumor cells. No EBV sequences were detected in surrounding lymphocytes, or precancerous lesions such as intestinal metaplasia and chronic gastritis. In addition, EBVaGC cases were most often detected in males than in females (p = 0.007). To define the clinicopathological characteristics of this novel molecular

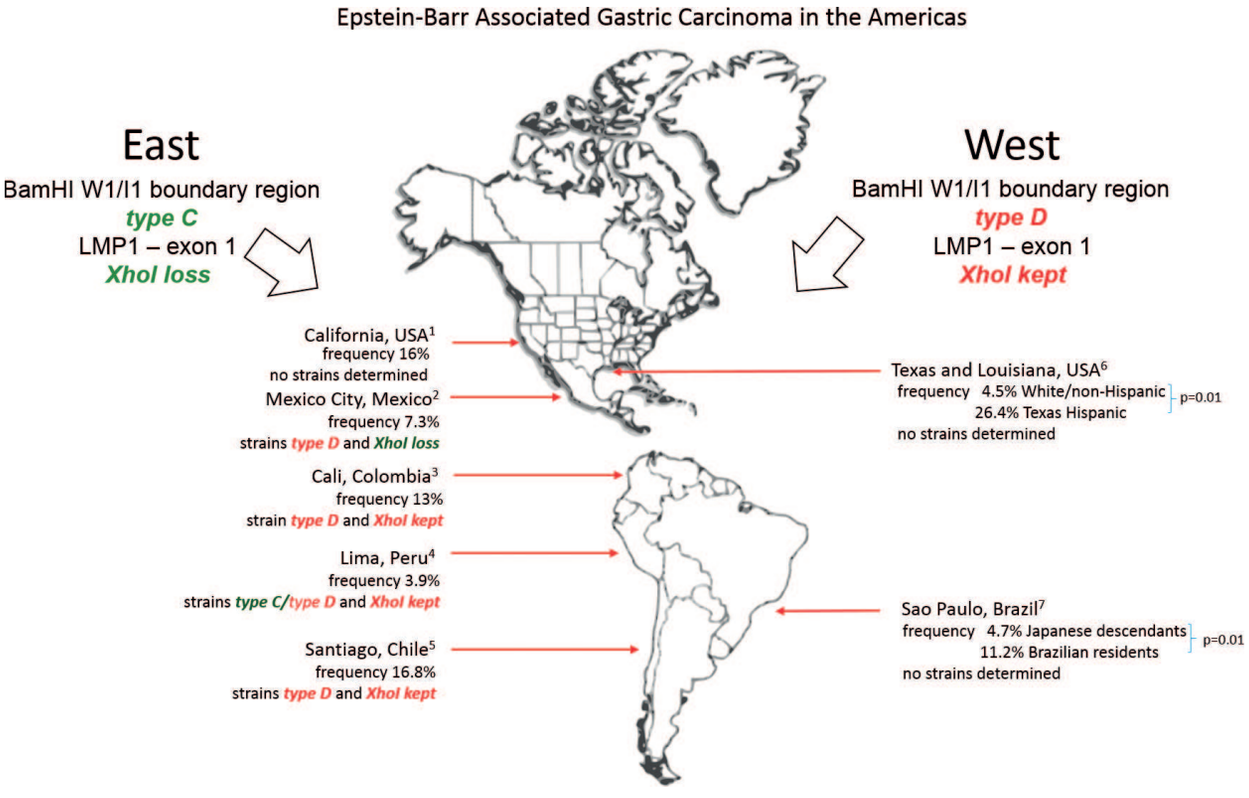


Figure 3. A consolidated overview of EBVaGC in the Americas. Phylogeographic diversity of EBV strains along with host and environmental associations might explain the high incidence of EBVaGC in the Americas [24–31].

subtype of gastric cancer, a long-term, well-characterized cohort of Japanese-Americans living in Hawaii [32, 33] was evaluated. Unfortunately, beyond male predominance, no other clinicopathological characteristic, including survival, was found [32]. A high incidence of EBVaGC has been reported in Santiago, Chile, with 31 (16.8%) EBV-positive cases identified among 185 consecutive gastric cancer patients [25]. In this series, associations with the diffuse-type histology ($p < 0.001$) and nonantrum location ($p = 0.01$) were the most significant findings. Among Mexican descendants living in the USA, Gulley and coworkers and Vo and coworkers have reported 20 out of 138 (14.5%) EBVaGC cases [26, 27]. Interestingly, prevalence of EBV was 26.4% among Mexican descendants in comparison with 4.5% among white/non-Hispanic cases. In addition, male predominance was found exclusively in those with Hispanic ancestry ($p = 0.01$) [27]. Koriyama et al. [28] examined 151 non–Japanese-Brazilian and 149 Japanese-Brazilian gastric carcinoma cases to identify an 11.2% prevalence among non–Japanese-Brazilian but only 4.7% among Japanese-Brazilian residents ($p = 0.01$). EBV-associated gastric carcinoma was predominant in males only in the non–Japanese-Brazilian cases ($p = 0.047$). Taken together, these findings suggest human phylogeographic diversity in the prevalence of EBVaGC.

Among other countries in Latin America, Carrascal et al. [29], in Cali, Colombia, examined 178 consecutive gastric carcinoma cases identifying 23 (13%) cases of EBVaGCs. In this series, EBVaGC also revealed a male ($p = 0.004$) and nonantrum ($p = 0.009$) predominance. Herrera-Goepfert et al. [30] identified 24 of 330 (7.3%) cases in Mexico City. In this series, no male predominance was confirmed, although all cases were of diffuse-type histology. The lowest frequency reported in Latin America was in Peru, where 254 gastric cancer cases from Japanese descendants were evaluated by Yoshiwara et al. [31]. In this analysis, only 3.9% (10 cases) of EBV infection was found, with no male or histological subtype predominance detected. A consolidated overview of EBVaGC in the Americas is shown in **Figure 3**.

A recent meta-analysis estimated a prevalence of 11.49% (95% CI = 8.46–15.43), with high heterogeneity among the aforementioned studies ($I2 = 73.3\%$; $p < 0.001$). Although heterogeneity for predominant sex, location and histology was low ($I2 = 16.5\%$ [$p = 0.35$], 0% [$p = 0.68$] and 33.7% [$p = 0.16$], respectively), these authors showed male predominance ($p < 0.001$) and diffuse-type histology ($p < 0.001$) as the most significant features of EBVaGC in the Americas (**Figures 4** and **5**) [13].

In Asia, low prevalence of EBV-associated gastric carcinoma has been described. The reported prevalence ranges from 6.1% in Northern China [34] to 9.1% in Southern China [35]. In Japan and Korea, the reported prevalence is 6.6 and 6.9%, respectively [35, 36]. Among European countries, Russia and the Republics of the former Soviet Union, 8.7% prevalence has been reported [37]. Interestingly, distribution of EBV-positive GCs by sex, site and histological type was similar to that in Japan. In a study carried out in Holland, EBV was detected in 7.2% of the gastric carcinomas from the Dutch D1D2 trial ($N = 566$; mean follow-up, 9 years) [38]. In France, only 5.8% of 85 cases of gastric adenocarcinomas were EBV-associated adenocarcinomas, from which 4 cases were of the intestinal histological type [39].

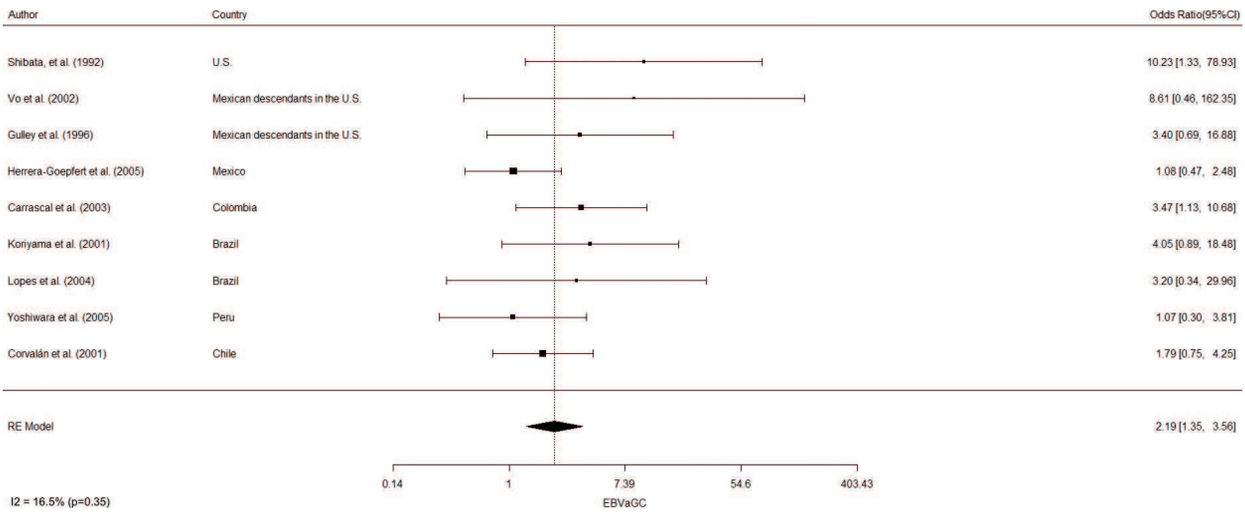


Figure 4. An estimated odds ratio (95% CI) for male predominance of EBV-associated gastric cancer in the Americas. Meta-analyses were performed by a random effects model with the inverse variance method, using the DerSimonian-Laird estimator, a logit transformation and the Clopper-Pearson confidence interval for individual studies. The results are shown in a log-scale. Taken from [4] with permission.

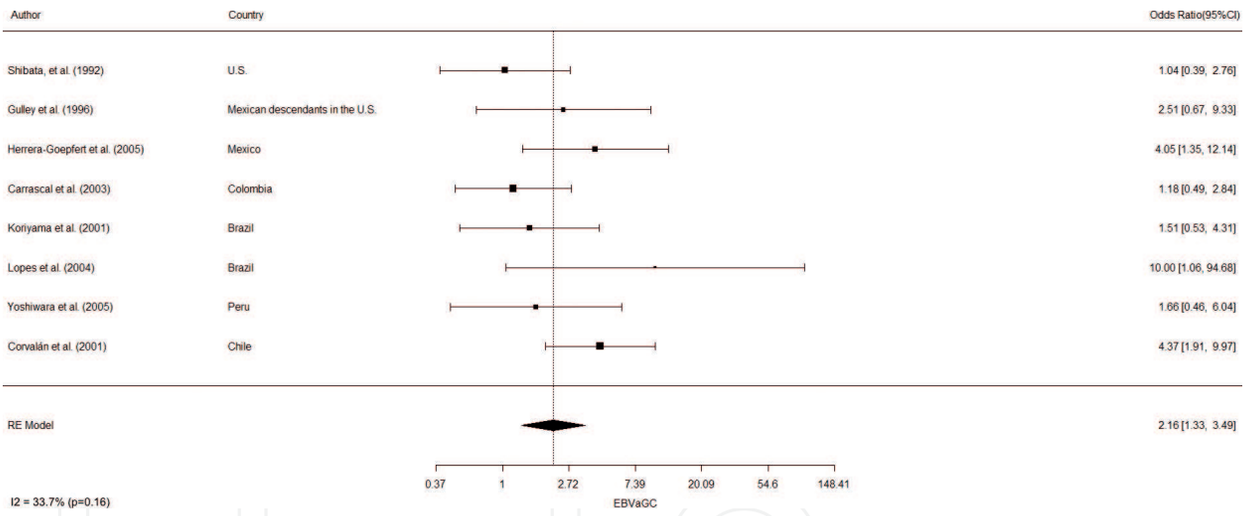


Figure 5. An estimated odds ratio (95% CI) for diffuse-type histology of EBV-associated gastric carcinoma in the Americas. Meta-analyses were performed by a random effects model with the inverse variance method, using the DerSimonian-Laird estimator, a logit transformation and the Clopper-Pearson confidence interval for individual studies. The results are shown in a log-scale. Taken from [13] with permission.

4. EBV strains and EBV-associated gastric carcinoma

Previous restriction fragment length polymorphism (RFLP) studies and the recently completed genome sequencing of 31 viruses head to the first global approach of the diversity of EBV. Seven of these sequences were obtained from healthy donors or benign lesions and twenty-five from strains present in tumors including nine EBVaGC [40–44]. By this approach, the genome diversity of EBV can be classified into five types (A–F). A substitution of 1.8 kb in the C-terminal part of the EBNA-2 gene defines types A and B [45]. Subtype A is the most common strain in the West and in Asia, while subtype B is the most common one in Africa [45, 46]. Polymorphisms at

BamHI W1/I1 boundary region identify C and D subtypes. The lack of the BamHI site defines subtype C that predominates in Asia among healthy people and EBV-associated diseases [47–50]. On the other hand, the presence of the BamHI restriction site defines subtype D that prevails in the West [47, 51]. Lastly, polymorphism at BamHI site identifies subtype F with worldwide distribution. However, the presence of an extra site defines the "f" variant and is found only in cases of nasopharyngeal carcinomas (NPC) [52]. Two more variants of EBV associated with the LMP-1 gene have been described. Polymorphisms at XhoI restriction site in position 169,425 of the LMP-1 gene define Western and Asian strains. Healthy people and EBV-associated diseases in Asia lack the XhoI restriction site [47], while in Western countries, the presence of the XhoI site is frequent [53]. The second variant in the LMP-1 gene is the deletion of 30-base pair at C-terminal (position 168,287–168,256) [54]. This variant confers an aggressive clinical behavior in Hodgkin's disease [55].

In the Americas, both polymorphisms at BamHI W1/I1 boundary region (C and D types) and XhoI RFLPs at exon 1 of the LMP-1 gene are present in healthy donors at similar proportions [56]. These authors also identified two unique novel recombinant strains (C type/kept XhoI site and D type/lack of XhoI site) [56]. As shown in **Figure 3**, these findings might reflect the mixing of different ethnic populations in this continent as has been reported in Texas and Louisiana, USA [26, 27] and Brazil [28]. Conversely of what has been found in Asian and Western countries, this mixing did not reflect in the case of EBVaGC, since almost all EBV strains studied in tumors harbored exclusively the western genotype (D type and kept XhoI site) (OR 16.3 [95% CI 2.5–685]) [56]. **Figure 3** shows a consolidated overview of phylogeographic diversity of Epstein-Barr virus strains in the Americas.

5. Epigenetic abnormalities of EBV-associated gastric carcinoma: DNA methylation

EBV-associated gastric cancer has been reported as the most extensive CpG island methylation at both human and viral genomes, being more extensive than any other tumor type from the TCGA network [14, 21, 57, 58]. CpG island methylation is an epigenetic mechanism of gene expression regulation, affecting all cellular pathways [59]. It consists of methyl groups attached to the 5′ position of cytosines, which are followed by a guanine nucleotide (CpG site) [60] (**Figure 6**). More than 50% of human genes contain CpG site in the promoter region and are known as CpG islands [62]. Methylation of CpG sites within a promoter region may inhibit the binding of transcription factors in their consensus sequence of tumor suppressor genes, thus precluding the transcription of the gene, and resulting in gene silencing [63]. Methylation of tumor suppressor genes is usually seen at early stages of gastric cancer and increases during the stomach carcinogenesis [64]. These observations suggest that the silencing of these genes by DNA methylation mechanisms plays an important role in the gastric carcinogenesis. In addition, aberrant methylation is unusually detected in EBVaGC nonneoplastic surrounding mucosa, which might indicate a critical role of EBV in tumorigenesis mechanisms [65]. Although the extensive CpG island methylation is present in EBVaGC, a distinctive pattern of methylation has been suggested, as promoter methylation of tumor suppressor gene CDKN2A, but not promoter methylation of MLH1,

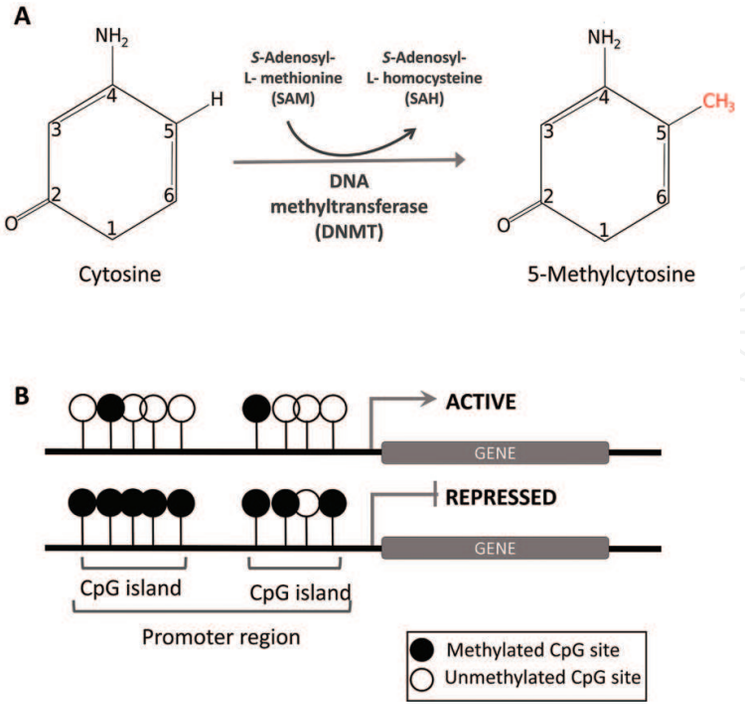


Figure 6. DNA methylation. (A) CpG methylation mechanism is mediated by DNA methyltransferases and consists in the addition of a methyl group to the carbon in the 5th position of cytosines that precedes guanine nucleotides. (B) CpG islands are DNA sequences rich in CpG sites (>50% CpG sites within a 200bp sequence). Methylation of CpG islands inside a promoter region may control gene expression.

characteristic of the microsatellite instability (MSI) GC subtype [21, 27, 66–71]. Individual methylation of p14ARF and p16INK4a, alternative reading frames of CDKN2A locus, has also been described, and many studies have proved a significant association between their methylation and EBV positivity [72, 73]. Ushiku et al. [74] observed a uniform methylation of all CpG sites on promoter regions of both genes in EBVaGC, whereas it was variable in EBV-negative tumors. In addition, methylation frequency of p16INK4a appears to be about three times higher in EBVaGC than in EBV-negative tumors [65, 75]. CDH1, p15 and p73 tumor suppressor genes are also frequently methylated in EBVaGC, representing one of the most common abnormalities described in this tumor [65, 74].

Despite EBV-induced host gene methylation in EBVaGC is well established, the exact underlying mechanisms are not entirely understood. It has been proposed that when the host cell detects the viral genome, it defends itself by starting a host-driven extensive methylation of the foreign genome, which may trigger the subsequent host genome methylation [75–77]. However, based on the specific methylation patterns observed, a possible participation of EBV in maintenance and de novo methylation has been proposed [72, 74]. Several studies have shown that EBV can modulate the expression of DNA methyltransferases (DNMT), which catalyze the transfer of methyl groups to DNA. Specifically, LMP-2A, EBV latent gene, has been shown to upregulate DNMT1 and DNMT3b expression in gastric cancer cell lines, which further induced methylation of several tumor suppressor genes, such as PTEN [78, 79]. Therefore, LMP-2A may play an essential role in the epigenetic abnormalities in host cells and in the development and maintenance of EBV-associated cancer.

6. Epigenetic abnormalities of EBV-associated gastric carcinoma: microRNAs

MicroRNAs (miRNAs) are small (~22 nt) noncoding RNAs and fundamental in posttranscriptional regulation of a broad range of biological processes of different organisms. This fundamental regulation is achieved through specific complementary binding to the 3′ untranslated region (3′UTR) of one or more target mRNAs, allowing regulation of multiple genes simultaneously [80] (**Figure 7**). Increasing evidence has shown that dysregulation of specific miRNAs has a crucial role in tumorigenesis. In fact, microRNAs involved in this process are usually called oncomiRs and anti-oncomiRs, acting similar to onco- and tumor-suppressor genes [11]. Particularly, in gastric cancer, cellular miRNAs have gained special interest because they have shown differential expression between distinct cancer subtypes and have been related to progression and prognosis of the disease (for a review, see [80]). Viral microRNAs were first described in EBV [81]. It is now known that diverse virus families

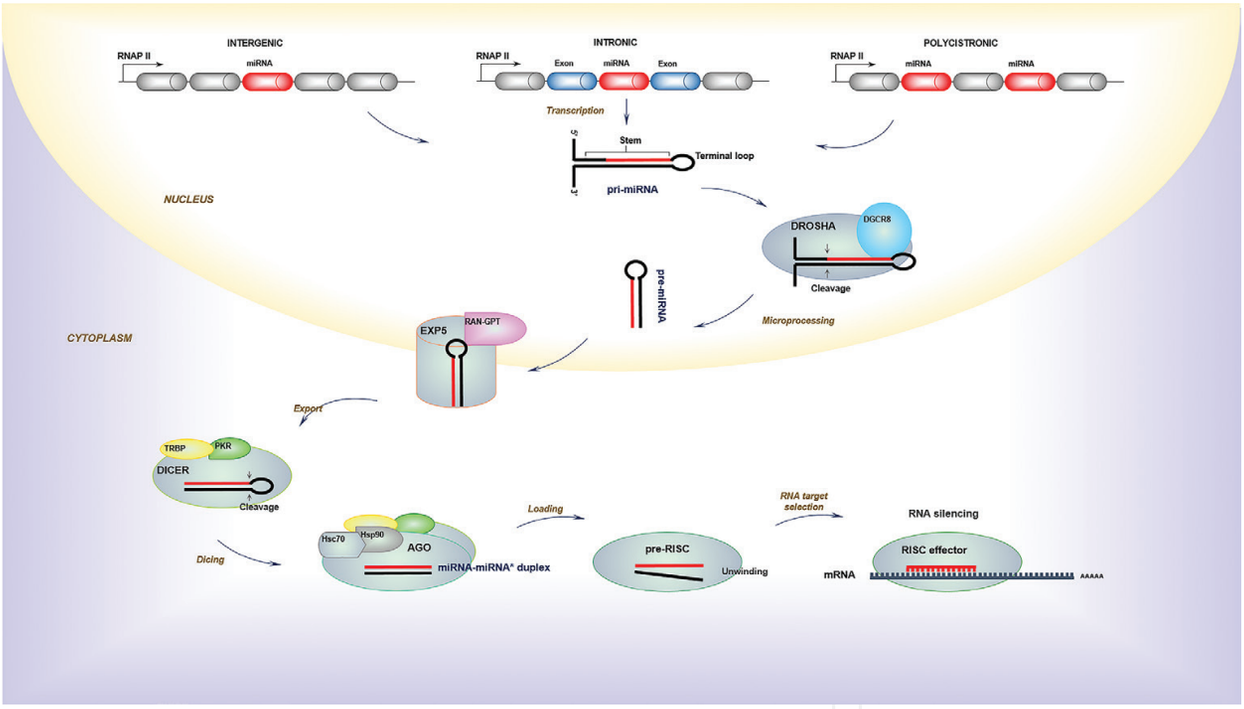


Figure 7. Canonical pathway of miRNA biogenesis in human. miRNAs are transcribed by RNA polymerase II (RNAP II) from intergenic, intronic or polycistronic loci to long primary transcript, called primary miRNA (pri-miRNA), which consists in a stem, a terminal loop and single-stranded RNA segments at both the 5′- and 3′-UTR sides. Microprocessor complex (Drosha and DGCR8 cofactor) cleaves the stem-loop and releases a small hairpin-shaped RNA, called precursor miRNA (pre-miRNA). Following, pre-miRNA is exported into the cytoplasm by the transport complex formed by protein exportin 5 (EXP5) and GTP-binding nuclear protein RAN•GTP. Subsequently, pre-miRNAs are cleaved by a ternary complex formed by dicer, TAR RNA-binding protein (TRBP) and protein activator of PKR (PACT), producing a small RNA duplexes (miRNA-miRNA*). Next, these are loaded onto an Argonaute protein (AGO) to form an immature RNA-induced silencing complex (RISC) or pre-RISC, in a process mediated for heat shock cognate 70 (Hsc70)-heat shock protein (Hsp90) chaperone complex. AGO protein separates the two strands to generate a mature RISC effector. Finally, RISC binds the target mRNA through complementary binding of six to eight base pairs of the miRNA, with a specific sequence of the target resulting in the gene silencing. Taken from [80] with permission.

encode miRNAs and that they are capable of targeting both cellular and viral genes [82]. EBV-miRNA expression is dependent on the host cellular miRNA processing machinery for its biogenesis. EBV miRNAs are encoded in two clusters within the EBV genome. As shown in **Figure 1**, the first cluster is localized in the Bam HI fragment H rightward open reading frame 1 (BHRF1) gene and originates four mature miRNAs, which express only during lytic infection and in latency type IIb/III [83]. The second cluster is localized among the Bam HI-A region rightward transcript (BART) gene, encoding 40 mature miRNAs [84], which are expressed in all EBV latency types [83]. However, variable expression patterns of BART miRNAs have been reported in different EBV-associated malignancies or cell types [83, 85]. Additionally, discrepant reports exist concerning specific BART miRNAs' relative expression within the same cellular context, which could be in part a result of different EBV strains studied [86–89]. Most BART miRNAs host targets, identified so far, are involved in proapoptotic and immune response pathways, suggesting a crucial role in promoting host cell survival [90]. For instance, EBVaGC highly expressed miRBART4-5p and miRBART5-5p that have been shown to target and downregulate the BH3-interacting domain death agonist (BID) protein [91] and the p53-upregulated modulator of apoptosis (PUMA) [92], respectively. Furthermore, EBV not only expresses its own miRNAs but also alters miRNAs' expression of the host cells. Particularly, miR-200 family has been shown to be consistently downregulated both in GC cell lines and in EBVaGC tumor samples compared to normal adjacent mucosa and other GC subtypes [93, 94]. Aberrant DNA methylation following EBV infection and viral proteins such as BRAF0, EBER, and LMP-2A have been proposed as the main mechanisms of downregulation of these miRNAs [93, 95].

7. Summary and conclusions

Novel molecular classifications and meta-analyses identified Epstein-Barr virus (EBV) as a distinct etiological agent for gastric cancer. An important characteristic of EBV-associated gastric carcinoma (EBVaGC) is the difference in incidence in Asia and the Americas. Specific EBV genes such as EBERs, EBNAs, BARTs and LMP are the most actively expressed in EBVaGC, and variations in its sequences might be associated with phylogeographic diversity of EBV strains across the world. Polymorphisms at BamHI W1/I1 boundary region and XhoI RFLPs at exon 1 of the LMP-1 gene have been found in healthy donors reflecting the mixing of different ethnic populations in the Americas. However, this is not the case for gastric cancer, since almost all types of EBVaGC studied harbor exclusively the western genotypes (subtype D and kept XhoI site). These findings propose that a disrupted coevolution between a pathogen and its healthy population might contribute to a phylogeographic origin of disease. DNA methylation and cellular and viral microRNAs play an emerging role in the pathogenesis of EBVaGC.

Disclaimer

The funders had no role in study design, data collection and analysis, decision to publish or preparation of the paper.

Authors' contribution

Alejandra Alarcón: Conception or design of the work, data collection, data analysis and interpretation, drafting the article, critical revision of the article, final approval of the version to be published; Ursula Figueroa: Conception or design of the work, data collection, data analysis and interpretation, drafting the article, critical revision of the article, final approval of the version to be published; Bastian Espinoza: Conception or design of the work, data collection, data analysis and interpretation, drafting the article, critical revision of the article, final approval of the version to be published; Gonzalo Carrasco-Aviño: Conception or design of the work, data collection, data analysis and interpretation, drafting the article, critical revision of the article, final approval of the version to be published; Francisco R. Aguayo: Drafting the article, critical revision of the article, final approval of the version to be published; Alejandro H. Corvalan: Conception or design of the work, data collection, data analysis and interpretation, drafting the article, critical revision of the article, final approval of the version to be published.

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Conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

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