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Development of Epstein-Barr virus-associated gastric cancer: Infection, inflammation, and oncogenesis

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Abstract

Epstein-Barr virus (EBV)-associated gastric cancer (EBVaGC) cells originate from a single-cell clone infected with EBV. However, more than 95% of patients with gastric cancer have a history of *Helicobacter pylori* (*H. pylori*) infection, and *H. pylori* is a major causative agent of gastric cancer. Therefore, it has long been argued that *H. pylori* infection may affect the development of EBVaGC, a subtype of gastric cancer. Atrophic gastrointestinal inflammation, a symptom of *H. pylori* infection, is observed in the gastric mucosa of EBVaGC. Therefore, it remains unclear whether *H. pylori* infection is a cofactor for gastric carcinogenesis caused by EBV infection or whether *H. pylori* and EBV infections act independently on gastric cancer formation. It has been reported that EBV infection assists in the oncogenesis of gastric cancer caused by *H. pylori* infection. In contrast, several studies have reported that *H. pylori* infection accelerates tumorigenesis initiated by EBV infection. By reviewing both clinical epidemiological and experimental data, we reorganized the role of *H. pylori* and EBV infections in gastric cancer formation.

Key Words: *Helicobacter pylori*; Epstein-Barr virus; Epstein-Barr virus-associated gastric cancer; Coreceptor; Inflammation; Oncogenesis

Core Tip: Epstein-Barr virus (EBV)-associated gastric cancer (EBVaGC) tumor cells originate from a single cell clone infected with EBV. In contrast, it is reported that more than 95% of patients with gastric cancer have a history of *Helicobacter pylori* (*H. pylori*) infection. Accordingly, it has long been argued that *H. pylori* infection may have some effect on the development of EBVaGC, a subtype of gastric cancer. It is also a mystery that the number of gastric cancer patients is higher in Asia, South America, and the Middle East. We will reorganize the role of *H. pylori* and EBV infections in gastric cancer formation.

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INTRODUCTION

Epstein-Barr virus (EBV)-associated gastric cancer (EBVaGC) accounts for 10% of all gastric cancers. At the same time, more than 95% of patients with gastric cancer have a history of *Helicobacter pylori* (*H. pylori*) infection. Thus, the question arises as to whether *H. pylori* and EBV infections promote gastric cancer formation in a dependent or independent manner. The high prevalence of gastric cancer in Asia, South America, and the Middle East is also intriguing.

EBV IS AN ONCOGENIC HUMAN HERPESVIRUS

EBV infects B lymphocytes and epithelial cells and is an oncogenic virus that assists in the proliferation of latently infected cells, resulting in the development of Burkitt lymphoma, Hodgkin lymphoma, nasopharyngeal carcinoma, and EBVaGC[1].

More than 90% of adults are latently infected with EBV; however, cytotoxic T lymphocytes that recognize EBV antigens suppress the proliferation of viral antigen-positive cells. When the local or systemic immune function is compromised, EBV-positive cells begin to proliferate. B lymphocytes that migrate to local areas where immune surveillance is weak often transition to lytic infection, resulting in viral production. Under such conditions, EBV appears to be transmitted to and infects gastric epithelial cells. The expression of EBV genes causes epithelial cells to acquire proliferative properties and resist apoptosis, and cells that escape immunological elimination may begin proliferating[2].

EBV-ASSOCIATED GASTRIC CANCER

Molecular features

Classification of gastric cancer by molecular mechanism was performed through an exhaustive analysis of next-generation sequencing data from numerous cases. The results divided gastric cancer into the following four molecular subtypes: Microsatellite instability (MSI), chromosomal instability (CIN), genomically stable (GS), and EBV[3]. These classifications have facilitated the identification of specific therapeutic candidates for each subtype of gastric cancer, and have revealed that each of these four subtypes is driven by a specific developmental mechanism that needs to be clarified individually. In particular, the molecular biology of EBVaGC is characterized by frequent and extensive methylation of the promoter regions of tumor cell genes[4]. *De novo* EBV infection induces DNA methylation in more than 3000 gene promoter regions within 4 wk[4]. However, methylation of the promoter of the mismatch repair gene *MLH1*, which is frequently observed in MSI, is not observed in EBVaGC[5]. In addition to inactivation by DNA methylation, the EBV genome binds to heterochromatin, a region of inactivation that causes aberrant activation of the region (enhancer infestation) and increases the expression of surrounding proto-oncogenes[6].

Clinical features

In EBVaGC, which accounts for 5%–10% of all gastric cancers, all tumor cells are infected with EBV. Endoscopy is the most informative method for diagnosing gastric cancer. EBVaGC is observed as a superficial depressed lesion in the upper part of the stomach. Using endoscopic biopsy specimens, EBV-

encoded RNA *in situ* hybridization (EBER-ISH), stains all gastric cancer cells positive for EBER, even in the intramucosal cancer stage[7]. The histological hallmark of EBVaGC is lymphoepithelioma-like carcinoma, in which a diffuse lymphocytic infiltrate is observed around EBER-positive epithelial tumor cells[8]. Furthermore, EBVaGC tumor cells are derived from the proliferation of a single EBV-infected epithelial cell[8,9].

Many studies have shown a male predominance (2-fold) of EBVaGC, suggesting that the risk may exist in male lifestyle and occupational factors[10]. The percentage of patients with EBVaGC to those with total gastric cancer is higher in younger patients. In men, the proportion of EBVaGC decreases with increasing age, especially in patients with pyloric gastric cancer. In women, the decrease in the proportion of EBVaGC with increasing age is unclear. Consumption of salty foods that cause mechanical damage to the gastric epithelium as well as exposure to wood and iron filings are associated with a higher EBVaGC risk[11].

EBVaGC is a gastric cancer with a relatively good prognosis. A Dutch study reported that EBVaGC is characterized by fewer lymph node metastases, less residual disease, and younger patient age, which results in longer disease-free survival[12]. Cohort study data from TCGA also reported that EBVaGC has the best recurrence-free period and overall survival compared to MSI, GS, and CIN subtypes[13].

EBVaGC tumors are frequently found in non-antral parts of the stomach[10,14]. In contrast, *H. pylori*-associated gastric cancer mostly occurs in the antral region[10]. Because moderate to severe atrophic gastric mucosa due to *H. pylori* infection was characteristically observed surrounding early gastric cancers, gastritis may play an important role in the tumorigenesis of EBVaGC[14]. Development of gastric cancer is supposed to follow the "infection, inflammation, and carcinogenesis" route, which consists of *H. pylori* infection followed by chronic gastritis, intestinal metaplasia, and cancer. In contrast, in the case of EBVaGC, it is controversial whether tumor formation is initiated by EBV-infected normal mucosal cells or promoted by EBV-infected cells in precancerous lesions[15]. Abe *et al*[16] performed EBER-ISH on 1110 sections of non-neoplastic gastric mucosal tissue from 300 cases and found 2 (0.18%) ductal-level EBER-positive lesions.

The mutual contribution of EBV and *H. pylori* in the carcinogenesis will be discussed later in the chapter "Inflammation and carcinogenesis".

EBV INFECTION OF EPITHELIAL CELLS

EBV infects B lymphocytes through the binding of the viral glycoprotein gp350 to the high-affinity receptor CD21, followed by binding of gp42 to HLA class II molecules, resulting in membrane fusion [17]. In contrast, when low-affinity co-receptors are used to infect CD21-negative epithelial cells, the infection efficiency is extremely low (Figure 1).

The CD21-independent routes of epithelial cell infection include the following: (1) The viral envelope glycoprotein gp350/220 binds to CD35; (2) Integrins $\alpha V\beta 5$, $\alpha V\beta 6$, and $\alpha V\beta 8$ interact with the viral envelope glycoprotein gH/gL complex to fuse the viral envelope with the epithelial cell membrane; (3) The BMRF2 membrane protein expressed during EBV lytic infection binds to $\alpha 3$, $\alpha 5$, αV , and $\beta 1$ integrins; and (4) EphA2 and NMHC-IIA bind to gH/gL produced by many herpesviruses and enhance infection efficiency.

A previous study reported that a boy with X-linked agammaglobulinemia who did not have mature B lymphocytes due to a genetic enzymatic deficiency did not develop an EBV infection[18]. EBV infection of epithelial cells was considered to occur after EBV infection of B lymphocytes because the epithelial cells of the affected boy were intact. EBV-infected B lymphocytes are believed to carry and deliver EBV to the epithelial cells *via* cell-to-cell transfer. In the case of CD21-independent infection, the efficiency of epithelial cell infection by cell-to-cell transfer is more than 1000 times higher than that of direct epithelial cell infection by EBV particles[19]. It is speculated that infection of epithelial cells *via* B lymphocytes is promoted when viral activation and lymphocyte infiltration are accompanied by inflammation (Figure 1).

EBV-associated gastric cancer-derived cell lines

In EBVaGC, all tumor cells are infected with EBV. However, cell lines established from gastric cancer tissues, similar to those in nasopharyngeal carcinoma, are almost entirely EBV-negative[20]. The EBV genome in EBVaGC tumor cells exists as a plasmid-like episome that does not integrate into the host chromosomes. However, the presence of the virus does not appear to favor cell growth *in vitro*. Rather, it may be more convenient for *in vitro* cell growth to avoid the use of extra energy to maintain the episomes. Alternatively, the expression of viral genes such as microRNAs may be crucial for tumor cells to evade elimination by the *in vivo* immune system. In fact, EBV-positive KT cells established from EBVaGC can only be passaged by transplantation into SCID mice and cannot be expanded in an *in vitro* culture system[21]. SNU-719, YCCCELL1, and NCC-24 are rare cells established from EBVaGC and can be propagated *in vitro*. These cell lines appear to be unique because the presence of EBV episomes is essential for their growth. Experiments with hydroxyurea and EBNA1 siRNAs were not successful in shedding the EBV episome from SNU-719 cells[22].

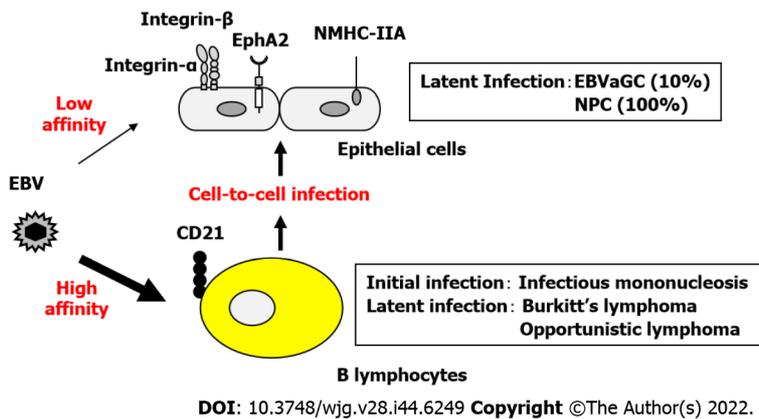


Figure 1 Epstein-Barr virus infects B lymphocytes and epithelial cells to form tumors. Epstein-Barr virus (EBV) infects B lymphocytes and epithelial cells via the CD21 receptor and co-receptors, respectively. Although the efficiency of epithelial cell infection is extremely low, approximately 1000000 times lower than that of B lymphocytes, cell-to-cell EBV infection by B lymphocytes increased the efficiency of EBV infection by more than 1000-fold. The squares show the EBV infection status and disease names that are established differently depending on the cell type. EBV: Epstein-Barr virus; EBVaGC: Epstein-Barr virus-associated gastric cancer; NPC: Nasopharyngeal carcinoma.

Gastric epithelial cell lines infected with recombinant EBV

We established gastric epithelial cells infected with recombinant EBV, where a drug-resistant gene was inserted into the nonessential *BXLF1* (thymidine kinase) gene (Figure 2). It is possible to elucidate the oncogenic molecular mechanism of EBV-infected epithelial cells by comparing EBV-positive cells with EBV-negative cells. EBV infection markedly promotes the proliferation of gastric epithelial cells[23].

EBV-infected gastric epithelial cells also exhibit type I latent infection that expresses EBNA1 and LMP2A, similar to that in EBVaGC *in vivo*. EBNA1 promotes tumorigenesis via p53 ubiquitination, suppresses transforming growth factor- β signaling, and enhances the transcription of the anti-apoptotic protein survivin[24]. In contrast, LMP2A activates PI3K/Akt signaling similar to that activated by B-cell receptor stimulation, increases survivin expression, and resists apoptosis[25]. LMP2A also induces DNA methyltransferases, resulting in epigenetic changes in infected cells[26]. *BARF1* is strongly expressed as a latent gene in EBV-associated epithelial tumors[27]. Nasopharyngeal carcinoma-derived cells infected with recombinant EBV constitutively expressing *BARF1* exhibit resistance to apoptosis[28].

In addition to the oncogenic activity of EBV proteins expressed in type I latent infections, non-coding RNAs (miRNAs and EBERs) that are not translated into proteins have been investigated. Multiple BART miRNAs cooperatively repress lytic replication[29]. BART miRNAs also downregulate pro- and anti-apoptotic mediators such as caspase 3[30]. EBERs bind to protein kinase R and disrupt innate immune function[31]. Elimination of EBER2 from the EBV genome reduces the efficiency of B lymphocyte transformation[32].

INFLAMMATION AND CARCINOGENESIS

Clinical observation

It is very difficult to collect EBVaGC cases without *H. pylori* infection, because most patients with gastric cancer are infected with *H. pylori*[33,34]. However, a clinical study was conducted to investigate the relationship between EBV infection, *H. pylori* infection, and atrophic gastritis in 468 patients with chronic gastritis[35]. This study confirmed that patients who were EBV-positive had a lower pepsinogen I/pepsinogen II ratio than patients who were EBV-negative. EBV infection significantly increases the risk of atrophic gastritis, especially in *H. pylori*-negative patients. However, a report from Mexico mentioned that EBER1 *in situ* hybridization showed that EBV infection of epithelial cells could be detected in gastric cancers as well as in one-third of non-atrophic gastritis samples[36]. This study showed that EBV infection affected early cancer precursor lesions. However, it is difficult to determine whether EBV causes cancer directly or indirectly by triggering inflammation.

Inflammation and initiation of innate immune mechanisms promote EBV activation, although it is difficult to assess the extent to which these mechanisms are involved in tumorigenesis of EBV-infected cells (Figure 3). EBV proliferation occurs at the early stage of EBVaGC formation because early antigens-immunoglobulin G (IgG) and viral capsid antigen-IgG antibodies against early viral antigens and capsids are elevated in the sera of patients with EBVaGC. In addition, while the incidence of EBVaGC is approximately 10% worldwide, the incidence of gastric cancer after surgical invasion by gastric anastomosis increases by three times (30%)[8].

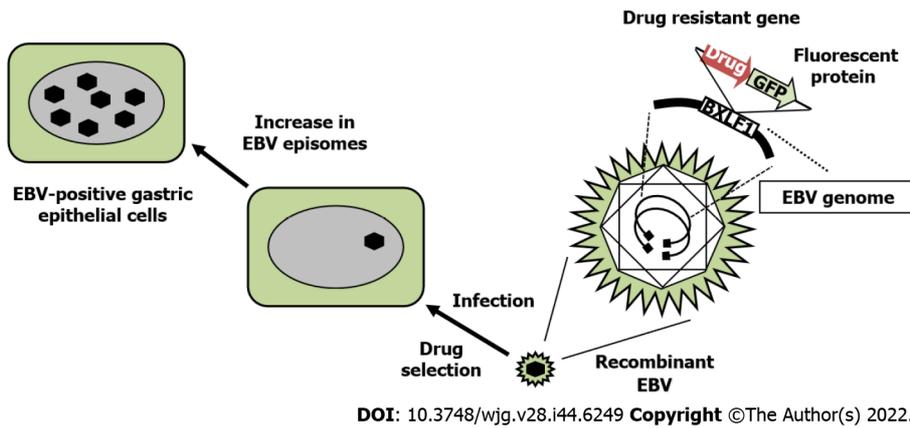


Figure 2 Isolation of recombinant Epstein-Barr virus-infected gastric epithelial cells. A drug resistant gene and fluorescent protein gene were inserted into the viral genome (*BXLF1*) using gene recombination technique. *BXLF1* is an EBV gene that does not affect viral production or infectivity by disruption through the insertion of marker genes. It is possible to isolate only recombinant virus-infected cells by infecting cells with a recombinant virus and selecting them for a drug. When recombinant virus-infected cells are cultured in the presence of the drug, the viral plasmid copy number in the nucleus of infected cells increases[52]. EBV: Epstein-Barr virus; GFP: Green fluorescent protein.

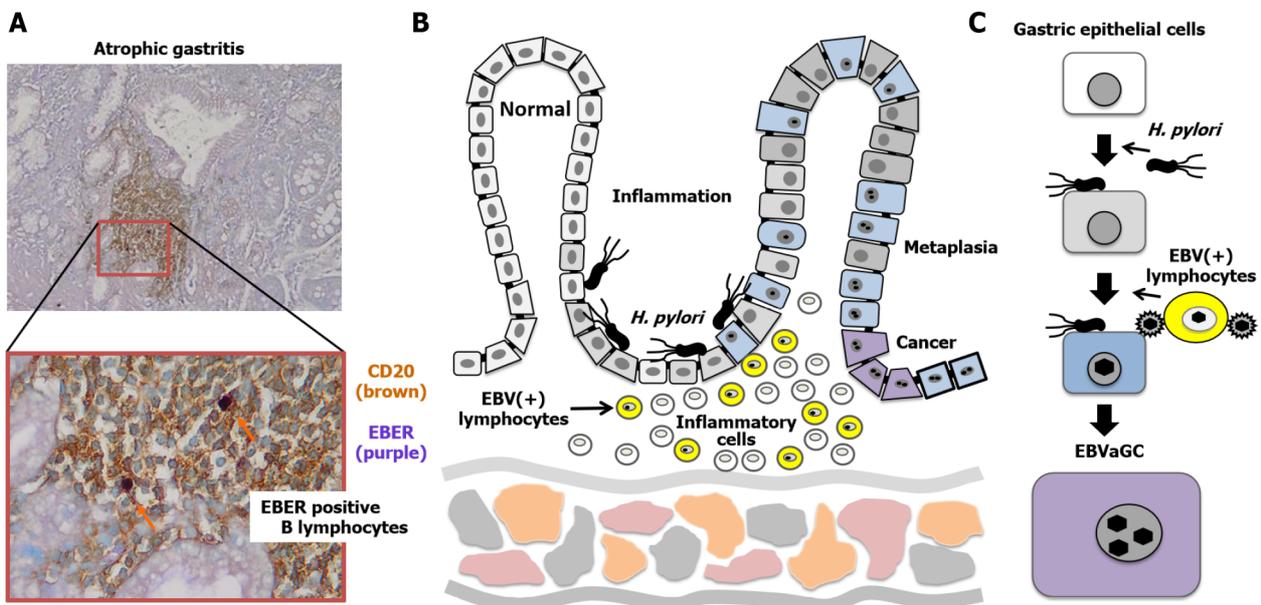


Figure 3 Interaction of *Helicobacter pylori* and Epstein-Barr virus in the formation of Epstein-Barr virus-associated gastric cancer. A: Infiltration of Epstein-Barr virus (EBV)-infected B lymphocytes in non-tumor areas of EBV-associated gastric cancer. Numerous CD20-positive B lymphocytes infiltrate the submucosal lesions of atrophic gastritis. CD20 is stained brown and EBV-encoded RNA (EBER) is stained purple. EBER-positive B lymphocytes are indicated by arrows. Chronic gastritis in the background is counterstained by Hematoxylin-Eosin staining; B: Induction of inflammatory cytokine production by bacterial adhesion to epithelial cells and tumorigenesis of EBV-infected epithelial cells. *Helicobacter pylori* adhesion induces production of inflammatory cytokines from gastric epithelial cells. Inflammation of gastric mucosa leads to an accumulation of various immune cells. EBV-positive B lymphocytes localized in the submucosa are activated by inflammation and transition from latent to lytic EBV infection. The viral particles produced are transferred to gastric epithelial cells, and the infected epithelial cells eventually form tumors; C: EBV transfer infection and tumorigenesis of epithelial cells via activated EBV-positive B lymphocytes. Infectious viral particles produced during inflammation adhere to CD21-positive B lymphocytes and transferred to epithelial cells expressing EBV coreceptors. Thus, gastric epithelial cells infected with EBV form Epstein-Barr virus-associated gastric cancers over time. EBV: Epstein-Barr virus; EBVaGC: Epstein-Barr virus-associated gastric cancer; *Helicobacter pylori*: *H. pylori*; EBER: EBV-encoded RNA.

Here, we investigated the relationship between *H. pylori*-associated gastritis and EBV propagation in the stomach. Gastric biopsy specimens were collected from patients with chronic atrophic gastritis and categorized into three histopathological stages: Mild, moderate, and severe. The specimens were subjected to DNA extraction and quantitative polymerase chain reaction to quantify EBV genome copy numbers[37]. More than 900 copies of the EBV genome have been frequently detected in patients with moderate atrophic gastritis. In other words, EBV frequently activates proliferation in patients with *H. pylori* infection with moderate chronic atrophic gastritis and strong histological inflammation.

In contrast, EBVaGC is significantly associated with marked mucosal atrophy and moderate to marked lymphocytic infiltration, but there is no direct association with intestinal metaplasia[7]. Although this appears to indicate that EBVaGC is not directly associated with *H. pylori* infection, this result is consistent with our findings. This is because the intestinal metaplastic epithelium resulting from prolonged gastritis is an unsuitable mucosal environment for the growth of both *H. pylori* and EBV [38].

Experimental observation

Several studies have been investigated the interaction between EBV and *H. pylori* in gastric epithelial cell lines. Because it is difficult to infect the epithelial cells with the two microorganisms simultaneously, experiments have been conducted on sequential infection with EBV first and *H. pylori* second, or vice versa.

Persistent infection of the gastric mucosa by CagA-positive *H. pylori* strains causes gastric cancer. This is because the tyrosine-phosphorylated CagA protein binds to the tyrosine phosphatase SHP2 in gastric epithelial cells, activating *Ras* oncogene. In contrast, SHP1, which competes with SHP2 weakens the oncogenic activity of SHP2. Saju *et al*[39] showed that EBV infection of gastric epithelial cells activates host cell promoter methylation and decreases SHP1 expression[39]. In other words, SHP2 activity is relatively higher and EBV infection promotes carcinogenesis of *H. pylori* associated gastric carcinoma. The induction of DNA methylase by EBV infection in gastric epithelial cells also decreases the expression of tumor suppressor genes such as *APC*, *breast cancer susceptibility gene 1*, and *phosphatase and tensin homolog deleted from chromosome 10 (PTEN)*[40].

Furthermore, activation of innate immune signals by *H. pylori* attachment enhances the expression of the EBV co-receptor EPHA2 in gastric epithelial cells, thereby increasing the frequency of EBV infection in epithelial cells[41]. Another study demonstrated that organoids derived from gastric cancer cells were infected with EBV but did not infect those derived from the normal gastric epithelium[42]. The probable reason for this is that gastric organoids maintain cell polarity and express EPHA2 only between cells. Therefore, the localization of EPHA2 might change due to gastric epithelial cell injury caused by *H. pylori* infection or by a prior gene mutation, which subsequently facilitates EBV infection.

TUMORIGENIC MECHANISM OF EBV-INFECTED EPITHELIAL CELLS

At present, it is difficult to infect primary gastric epithelial cells with EBV and immortalize them. Instead, gastric epithelial cell lines persistently infected with EBV have been used to elucidate the tumorigenic mechanisms of EBV genes during latent infections.

EBV genes that encode untranslational RNA

The EBV genome contains two miRNA clusters, consisting of four BHRF1 miRNAs and 40 BART miRNAs. Although BHRF1 miRNA is poorly expressed in epithelial cells, BART miRNAs are highly expressed in latently infected epithelial cells and play a substantial role in tumorigenesis[43].

Epigenetic changes of gene expression in EBV-infected epithelial cells

Modification of gene expression *via* methylation is frequently observed in patients with EBVaGC. Tumor suppressor genes, such as *p14*, *p16*, *p73*, *PTEN*, *APC*, *RASSF1A*, and *CXXC4*, are repressed by promoter methylation. And the expression of molecules important for cell invasion, including THBS1, E-cadherin (CDH1), and TIMP2, is also repressed by promoter methylation. The decreased expression of these molecules may be involved in carcinogenic processes[44].

Multiple EBV episomal DNAs have been shown to approach enhancer sites in the genome, alter the surrounding chromatin structure (enhancer infestation), and activate genes such as transcription factors [6]. Although epigenetic analyses have been conducted to understand tumorigenesis, the overall mechanism remains unclear.

Model of tumorigenesis for epithelial EBV infection

Viral gene products transcribed in cells latently infected with EBV confer resistance to apoptosis. EBV gene products also accumulate mutations in the genes of the infected cells. Genetic changes in infected cells further affect EBV gene expression and alter intercellular communication, including the cross-talk between EBV-infected epithelial cells and immune cells[45] or epithelial-mesenchymal transition[46]. In other words, changes induced by persistent EBV infection in host cell signaling and host immune responses advance the tumorigenic stage[47].

FUTURE PROSPECTS

With the progress in research on EBER, miRNA, and long non-coding RNA, the functions of these

molecules in latent EBV-infected cells are being elucidated. A highly tumorigenic B81 EBV strain was isolated from a patient with nasopharyngeal carcinoma[48]; however, an EBV strain unique to gastric cancer has not yet been isolated.

Host gene mutations frequently observed in EBVaGC, including changes in *PIK3CA*, *ARID1A*, *PD-L1*, and *PD-L2*[3] are considered to affect histological characteristics, clinical course, and response to treatment. EBV-induced tumorigenesis is believed to be affected by environmental factors such as previous infections; however, the molecular basis that characterizes EBVaGC remains to be elucidated.

Considering that EBVaGC most strongly expresses *PD-L1* and *PD-L2* among the four molecular subtypes of gastric cancer, immune checkpoint inhibitors are expected to be effective therapeutic agents for EBVaGC[49,50]. *PIK3CA* mutations and *JAK2* amplification are frequently observed in EBVaGC. Therefore, PI3K and JAK2 inhibitors may be effective. Other EBNA-1 inhibitors are also expected to be EBV-specific therapeutic agents[51].

CONCLUSION

Several clinical and experimental data support the etiological role of *H. pylori* in EBV-associated gastric cancer.

FOOTNOTES

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