· Review ·

Epstein–Barr virus-associated gastric cancer: pathogenesis, molecular characterization, and emerging therapies

Yiqian Wang[1,2], Dachuan Zhang1, Yue Zhang[1,2], Meihua Wang[2*], Qing Li[1*]

[1]Department of Pathology, The Third Affiliated Hospital of Soochow University (Changzhou First People's Hospital), Changzhou 213004, Jiangsu, China.
[2]Department of Pathology, Changzhou Cancer Hospital, Changzhou 213032, Jiangsu, China.

Abstract

Gastric cancer is the fifth most common malignant tumor in the world in terms of morbidity and mortality, with a high prevalence of gastric cancer in Asia, especially in China, Japan, and South Korea. Gastric cancer is strongly associated with Epstein–Barr virus, and gastric cancer cases positive for Epstein–Barr virus are referred to as Epstein–Barr virus-associated gastric cancer (EBVaGC). EBVaGC has unique clinicopathological features and molecular characteristics, and the study of EBVaGC provides new perspectives for the early diagnosis and personalized treatment of gastric cancer. Here, we present a review of the research progress in the epidemiology, pathogenesis, clinicopathologic features and prognosis, molecular features, diagnosis, and treatment of EBVaGC.

Keywords: EBV, EBVaGC, pathogenesis, immunotherapy

Epidemiology

Epstein–Barr virus (EBV), also known as human herpesvirus type 4, is a double-stranded DNA virus that belongs to the γ-herpesviridae family. More than 90% of the world's population are infected by EBV [1]. EBV is primarily transmitted through saliva, and the virus can also be transmitted through breast milk, body fluids, and transplants of EBV-positive organs. EBV was first discovered in Burkitt's lymphoma in 1964, a landmark event in the history of medical virology [2]. EBV is also associated with epithelial tumors, including nasopharyngeal and gastric cancers.

In situ hybridization (ISH) using anti-sense probe for EBV-encoded small RNA(EBER) is a highly sensitive method for detecting EBV-infected cells. In 1993, Tokunaga et al. used ISH to detect EBER-confirmed EBV infection in gastric cancer and defined these EBV-positive gastric cancer cases as EBV-associated gastric cancer (EBVaGC); the cases negative for EBV were defined as EBV-negative gastric carcinomas [3].

M. W. and Q. L. were co-corresponding authors.
***Correspondence:**
Meihua Wang; Email: wangmeihua1234@suda.edu.cn.
Qing Li; Email:liqblk@163.com.

Despite the high rate of EBV infection, only a small percentage of EBV-infected individuals develop EBVaGC. According to the meta-analysis, the proportion of EBVaGC in total gastric carcinoma is around 7.5% to 10.4% [4-6].

Initial EBV infection through the oral route results in lifelong carriage of the virus, known as latent infection. EBV is mostly in a state of latent infection in humans. EBV carriers have a more than 18-fold increased risk of EBVaGC compared with those negative for EBV infection [5].

Mechanisms of EBVaGC occurrence and molecular characterization

Mechanisms of EBV infection

The initial site of replication of EBV is the oropharynx, where it infects B lymphocytes through its envelope proteins (e.g., gp350) that bind to CR2/CD21 receptors on the surface of the host cell, thereby establishing lifelong latency. At least 11 EBV genes are expressed in latent infections, and their products include two small polyadenylated RNAs (EBER1, EBER2), six nuclear proteins (EBNA1, EBNA2, EBNA3A, EBNA3B, EBNA3C, EBNALP), and three integral membrane proteins (LMP1, LMP2A, LMP2B) [7]. EBV latency is divided into three types by the expression of latent proteins: type I latency, expression of nuclear antigen EBNA1 protein, EBERs, and miRNAs (predominantly miR-BARTs); latency type II, expression of latent membrane protein 1 (LMP1), LMP2A, EBNA1, and EBERs and high expression levels of miR-BARTs; and latency type III, expression of all latent genes [8]. The latent EBV infection pattern in EBVaGC is type I latency or between types I and II. The most frequently expressed EBV latent proteins in EBVaGC are EBNA1 (98.1%) and LMP2A (53.8%), whereas LMP1 and LMP2B are present in only 10% of cases [9]. LMP2A activates cellular autophagy and maintains latent EBV infection by promoting CXCR4 transcription through the PI3K/AKT-NRF1 pathway and upregulating ATG7 synthesis by promoting ZEB1 expression [10].

EBVaGC is characterized by the monoclonal growth of virus-infected cells, and the clonality of the viral genome suggests that EBV infection is an early stage of tumorigenesis [11]. The pathway by which EBV infects epithelial cells (ECs) has not been fully elucidated. One study reported that EBV enters ECs via ephrin receptor A2 (EphA2), conferring susceptibility of ECs to EBV [12]. Interferon-induced transmembrane protein-1 (IFITM1), an important member of the IFITM family, plays a crucial role in host defense against various viruses by inhibiting viral entry and replication. IFITM1 was found to competitively block EphA2-mediated EBV entry into ECs, and IFITM1 deficiency increased EBV infection [13]. BBRF2 and BSRF1 are two EBV tegument proteins that form a hetero-complex and mediate viral envelopment. Hui-Ping et al. reported the crystal structure of BBRF2 alone and in complex with BSRF; this complex binds the EBV nuclear capsid to glycoprotein-rich Golgi membranes and facilitates secondary envelopment [14].

Molecular abnormalities in EBVaGC

In 2014, The Cancer Genome Atlas classified gastric cancer into four subtypes: EBV-infected tumors; microsatellite instability (MSI) tumors; genomically stable tumors; and chromosomally unstable tumors [15]. EBVaGC has unique molecular features, mainly including DNA hypermethylation, PIK3CA gene mutation, and high programmed death ligand-1 (PD-L1) expression.

Hypermethylated DNA

EBVaGC exhibits the most extreme DNA hypermeth-

ylation among all human malignancies and leads to silencing of oncogenes (e.g., CDKN2A, PTEN), which promotes gastric carcinogenesis. The common hypermethylated regions in EBVaGC include promoters of tumor suppressor genes such as the CDKN2A and RASSF1A genes [16]. Silencing of these genes promotes cancer cell proliferation and growth by inhibiting cell cycle regulation, DNA repair, and apoptosis [15]. EBV-induced hypermethylation is partially driven by LMP2A, which phosphorylates transcription activator 3, activates transcriptional up-regulation of DNA methyltransferase 1, and in turn down-regulates the key demethylating enzyme TET2 [17-19].

PIK3CA mutation

The mutation rate of the PIK3CA gene in EBVaGC is high, with approximately 40%–80% of EBVaGC patients carrying PIK3CA mutations, a rate higher than that in other gastric cancer subtypes [20, 21]. The PIK3CA gene encodes PI3K, a key enzyme of the PI3K/Akt pathway. Mutations in PIK3CA activate the PI3K/Akt signaling pathway, which not only contributes to tumor cell proliferation, but also supports tumor growth and metastasis through mechanisms such as inhibiting apoptosis and promoting neoangiogenesis and is closely associated with invasiveness and drug resistance in gastric cancer. Thus, PIK3CA mutations and activation of the downstream pathways have become potential targets for EBVaGC therapy. Approximately 14% of EBVaGC cases show intratumoral heterogeneity involving 3–5 different PIK3CA genotypes (including the wild-type gene) coexisting within the same primary tumor [22]. This suggests that evaluating EBV status in tissue biopsies may be prone to sampling errors. In addition to PIK3CA mutations, EBV-positive tumors frequently show ARID1A (55%) and BCOR (23%) mutations, while TP53 mutations are rare [15].

High expression of PD-L1 and immune escape mechanisms

PD-L1 is an immune checkpoint molecule expressed on the surface of tumor cells. PD-L1 binds to the PD-1 receptor on the surface of T cells and inhibits the anti-tumor immune response of T cells, thus allowing tumor cells to evade immune surveillance [23]. A single-center investigation including 3,241 gastric cancer patients suggested that down-regulation of the invasion/metastasis gene SALL4 and up-regulation of the immune checkpoint gene PD-L1 are important molecular features of EBVaGC [24]. Nakano et al. reported a unique dual mechanism underlying PD-L1 overexpression in EBVaGC: high focal amplification of CD274 and IFN-γ-mediated signaling through activation of IRF3 [25]. Young-Bae et al. showed that loss of ARID1A is tightly associated with high PD-L1 expression in gastric cancer [26]. EBV immune evasion relies on complex molecular mechanisms, many of which involve manipulating the interactions between the virus and its host at the molecular level, establishing an environment conducive to EBV survival and replication.

EBV miRNAs also mediate PD-L1 transcription in tumor cells. For example, EBV-miR-BART11 and EBV-miR-BART17-3p inhibit FOXP1 and PBRM1, respectively, and promote immunosurveillance escape by enhancing the transcription of PD-L1 [27]. Platelet activation by EBV infection-induced up-regulation of F3 expression allows EBVaGC to escape NK cell-mediated immune surveillance [28].

MiRNA regulation of EBVaGC

EBV was the first virus found to encode its own miRNAs, and miRNAs play an important role in the development of EBVaGC. EBV-encoded miRNAs are categorized into two major clusters, BHRF and miR-

BARTs, which regulate the expression of host genes and influence cell proliferation, apoptosis, and immune responses. MiR-BART9-5p directly targets MUS81 and down-regulates its expression, and overexpression of MUS81 in EBVaGC cells suppresses EBNA1 expression. Reducing MUS81 expression may thus be a mechanism by which EBV maintains latent infection [29]. Down-regulation of the miR-200 family by all latent type I genes of EBV had a synergistic effect on the down-regulation of the miR-200 family, leading to a decrease in the expression of E-cadherin, which is considered to be a key step in the development of EBVaGC [30]. In EBVaGC, miR-BARTs function to inhibit apoptosis in infected cells, but some miR-BARTs also target anti-apoptotic proteins. These results suggest a complex system of interactions and feedback between miR-BARTs and their target mRNAs.

Clinicopathologic features and prognosis

Clinical symptoms and endoscopic manifestations

EBVaGC is more common in younger patients, especially in men under 60 years of age [31]. An international pooled analysis including 4,599 gastric cancer patients from 13 studies in Asia, Europe, and Latin America revealed that tumor EBV positivity was high in early gastric cancer patients [32]. The symptoms of EBVaGC are not as clinically typical as those of microsatellite-unstable gastric cancer and usually do not become apparent until the disease has progressed to a more advanced stage. Clinical symptoms of EBVaGC usually include upper abdominal discomfort, loss of appetite, weight loss, nausea, and vomiting, like those observed in gastric cancer. EBVaGC is commonly found in the proximal and remnant stomach, which may be related to the route of EBV infection and the local immune response of the gastric mucosa [33].

Studies have shown that Helicobacter pylori (Hp)-associated gastritis and mucosal atrophic changes are often present in the vicinity of EBVaGC lesions, and the anti-Hp antibody positivity rate in EBVaGC is 95% [34]. A recent study showed that in Hp-associated gastritis, EBV enters ECs via EphA2 receptors on endothelial cells [35]. Fukayama et al. named the molecular process of EBVaGC carcinogenesis from Hp-related gastritis the “gastritis-infection-cancer sequence of Epstein–Barr-virus-associated gastric cancer” [36].

EBVaGC typically presents as a depressed lesion, with some cases showing submucosal tumor-like protrusions, and hypoechoic masses are observed on endoscopic ultrasonography [37]. As a result of the more pronounced lymphocytic infiltration, some patients may exhibit thickening of the gastric wall.

Pathological features and prognosis

The microscopic presentation of EBVaGC is characterized by moderately to poorly differentiated adenocarcinoma. The main difference from other gastric carcinomas is the significant lymphocytic infiltration and the common “lace-like” histology, in which the tumor cells are surrounded by many lymphocytes. EBVaGC needs to be differentiated from, for example, mucosa-associated lymphoma in small biopsy tissues. EBVaGC has a better prognosis compared with EBV-negative gastric carcinomas, with a low rate of lymph node metastasis [6, 32]. Mature tertiary lymphoid structures within the tumor are associated with a good prognosis and good treatment response in patients with EBVaGC [38]. Notably, BART-encoded miRNAs are abundantly expressed in EBVaGC, and a meta-analysis revealed that higher EBV miRNA expression in gastric cancer may lead to a poorer prognosis [39].

Treatment of EBVaGC

Early-stage intramucosal EBVaGC has a low rate of lymph node metastasis and is amenable to endoscopic and ultrasound endoscopic mucosal dissection [37]. Unlike lymphoma, there is limited evidence of the clinical benefit of chemotherapy alone in EBVaGC. Surgery and chemotherapy remain the first line of treatment for patients with EBVaGC, but patient response to chemotherapy is inconsistent [40-42]. Immunotherapy can be employed in advanced or metastatic EBVaGC, particularly in patients with PD-L1-positive tumors. Immune checkpoint inhibitors such as nivolumab and pembrolizumab have demonstrated efficacy, often used in combination with chemotherapy [43].

PD-1/PD-L1 immunotherapy

Pembrolizumab is an anti-PD-1 antibody approved for the treatment of many cancers. The NCT02589496 trial enrolled 61 patients with metastatic gastric cancer, including six cases of EBVaGC and six cases of MSI-high gastric carcinoma, who had previously received first- or second-line chemotherapy. The overall responsive rate was 50.0%, 85.7% and 100% in PD-L1-positive, MSI-high, and EBV-positive gastric cancer patients, respectively. The predictive value of EBV positivity for efficacy was independent of tumor mutational load, PD-L1, and MSI status. The results suggest that the presence of EBV, rather than PD-L1 status, is a biomarker for pembrolizumab monotherapy in addition to MSI status [44].

Pembrolizumab did not significantly improve overall survival compared with paclitaxel as second-line therapy for advanced gastric or gastro-esophageal junction cancer with PD-L1 combined positive score of 1 or higher. Pembrolizumab had a better safety profile than paclitaxel. Additional trials of pembrolizumab in gastric and gastro-esophageal cancer are ongoing [45].

Near-infrared photoimmunotherapy (NIR-PIT) is a new type of cancer therapy. NIR-PIT is based on the injection of a conjugate of an antibody, which binds a cell surface marker on the cancer, and a photoactivating chemical [46]. αPD-L1-PIT showed a significant therapeutic effect on tumor models with high PD-L1 expression, inducing abscopal effects and immune memory. The combination with PEGylated IFNγ enhances PD-L1 expression and improves treatment efficacy [47]. There are few prospective clinical trials of immunotherapy for EBVaGC, and its efficacy and safety are still controversial.

CLDN18.2 monoclonal antibody and chimeric antigen receptor (CAR) T-cell therapy

Claudin-18 isoform 2 (CLDN18.2) is highly expressed in digestive system tumors and an ideal antibody target and potential immunotherapy target for gastric cancer. One study showed that more than 80% of EBVaGC patient tumor tissues stained positive for CLDN18.2, and high CLDN18.2 expression was significantly correlated with EBV positivity [48]. CLDN18.2 expression correlated with mucin phenotype, EBV status, the αvβ5 integrin, the EpEX extracellular domain of EpCAM, and lysozyme [49]. Activating antibody-dependent cellular cytotoxicity by targeting CLDN18.2 using zolbetuximab, a monoclonal antibody against CLDN18.2, has been considered a promising novel therapeutic strategy for gastric cancer. Matsuishi et al. demonstrated the effectiveness of zolbetuximab in CLDN18.2-positive gastric cancer, and offer a novel insight into the treatment of this cancer type, highlighting its potential effectiveness for CLDN18.2-positive/EBV-associated gastric cancer [50].

CAR T-cell therapy is currently the most explored

immune cell therapy in the treatment of malignancies. CAR T-cell therapy is based on the principle of assembling a CAR molecule on T cells that specifically recognizes tumor antigens and activates T cells. CLDN18.2 is an emerging target in the field of solid tumor cell therapy, and more than 20 cell therapy products targeting CLDN18.2 are currently in preclinical or early clinical studies. The main CLDN18.2-targeted CAR T-cell product with available clinical data is CT041, which is also the world's first CLDN18.2-targeted cell therapy product to enter confirmatory phase II clinical trials. The NCT02370498 trial treated 37 patients with one of three CT041 doses: 2.5 × 108, 3.75 × 108 or 5.0 × 108 cells. In patients with gastric cancer, the overall response rate and disease control rate reached 57.1% and 75.0%, respectively, and the 6-month overall survival rate was 81.2%. These initial results suggest that CT041 has promising efficacy with an acceptable safety profile in patients with heavily pretreated, CLDN18.2-positive digestive system cancers, particularly in those with gastric cancer [51].

EBV vaccine

Like most virus-associated diseases, one of the most promising approaches for preventing and treating EBVaGC is the development of an EBV vaccine. The development of EBV vaccines primarily involves two directions: 1) preventive vaccines for EBV infection, and 2) therapeutic vaccines for EBV-associated tumors.

Prophylactic vaccines are developed to build up immune memory within the body so that the body can generate a rapid and effective immune response after exposure to the virus. EBV envelope proteins including gH/gL, gB, and gp350 play key roles in EBV entry and the infection of target cells and are therefore relevant immunogens for vaccine development [52]. Transfer of vaccine-elicited IgG protected humanized mice from EBV-driven tumor formation and death following high-dose viral challenge. Kristina et al. demonstrated that LION/repRNA-gH/gL is an ideal candidate vaccine for preventing EBV infection and/or related malignancies in humans [53].

Therapeutic vaccines are designed to enhance existing or induce new antiviral adaptive immune responses in patients with EBV-associated tumors. EBNA1 and LMP1/LMP2, which stimulate specific cellular immune responses in the body, are targets for therapeutic vaccines [54, 55]. One study showed that DHT enhances the immune response against EBVaGC by upregulating MICA and activating NK and T cells. These findings suggest potential therapeutic strategies targeting androgen signaling to improve anti-tumor immunity in EBVaGC [56]. Nanoparticle-based vaccines and mRNA delivery systems are also emerging as innovative platforms for EBV vaccine development [57, 58].

BPLF1, encoded by EBV, is a lytic cycle protein with deubiquitinating activity that participates in disrupting the repair of DNA damage. Hantao et al. [59] demonstrated BPLF1 may lead to the accumulation of DNA double strand breaks by two pathways, reducing H2B ubiquitination and blocking homologous recombination; these results may provide new ideas for the treatment of EBVaGC.

Conclusion and Future Perspectives

EBVaGC is a subtype of gastric cancer with unique molecular characteristics and immune microenvironment. While the molecular mechanisms, immune evasion, and treatment responses of EBVaGC have been extensively studied, challenges remain. Future research should focus on uncovering the early pathological changes associated with EBV infection and

enhance subtype classification based on big data and multi-omics approaches, aiming for more precise personalized treatment. EBV-specific immunotherapy and vaccine development will be key areas of focus for future studies.

Acknowledgements

We thank Gabrielle White Wolf, PhD, from Liwen Bianji (Edanz) (www.liwenbianji.cn) for editing the English text of a draft of this manuscript.

Fundings

Research on the key technology of injectable hydrogel drug delivery system and its application in tumor therapy (CJ20245007).

Author Contributions

Q. L. outlined the content of the manuscript. Y. W., D. Z. and Y. Z. wrote the draft. M. W. reviewed the manuscript.

Conflicts of Interests

The authors declare they have no conflicts of interest regarding publication of this case report.

References

[1] Smatti MK, Al-Sadeq DW, Ali NH, Pintus G, Abou-Saleh H, Nasrallah GK. Epstein-Barr Virus Epidemiology, Serology, and Genetic Variability of LMP-1 Oncogene Among Healthy Population: An Update. Front Oncol. 2018 (8):211.

[2] Epstein MA, Achong BG, Barr YM. Virus Particles in cultured lymphoblasts from Burkitt's lymphoma. Lancet. 1964 (1):702-703.

[3] Tokunaga M, Land CE, Uemura Y, Tokudome T, Tanaka S, Sato E. Epstein-Barr virus in gastric carcinoma. Am J Pathol. 1993 (143):1250-1254.

[4] Hirabayashi M, Georges D, Clifford GM, de Martel C. Estimating the Global Burden of Epstein-Barr Virus-Associated Gastric Cancer: A Systematic Review and Meta-Analysis. Clin Gastroenterol Hepatol. 2023 (21):922-930.e921.

[5] Tavakoli A, Monavari SH, Solaymani Mohammadi F, Kiani SJ, Armat S, Farahmand M. Association between Epstein-Barr virus infection and gastric cancer: a systematic review and meta-analysis. BMC Cancer. 2020 (20):493.

[6] Pyo JS, Kim NY, Kang DW. Prognostic Implication of EBV Infection in Gastric Carcinomas: A Systematic Review and Meta-Analysis. Medicina (Kaunas). 2023 (59): 834.

[7] Zhong LY, Xie C, Zhang LL, Yang YL, Liu YT, Zhao GX, et al. Research landmarks on the 60th anniversary of Epstein-Barr virus. Sci China Life Sci. 2024.

[8] Damania B, Kenney SC, Raab-Traub N. Epstein-Barr virus: Biology and clinical disease. Cell. 2022 (185):3652-3670.

[9] Ribeiro J, Oliveira C, Malta M, Sousa H. Epstein-Barr virus gene expression and latency pattern in gastric carcinomas: a systematic review. Future Oncol. 2017 (13):567-579.

[10] Wang W, Zhang Y, Liu W, Zhang X, Xiao H, Zhao M, et al. CXCR4 induces cell autophagy and maintains EBV latent infection in EBVaGC. Theranostics. 2020 (10):11549-11561.

[11] Ignatova E, Seriak D, Fedyanin M, Tryakin A, Pokataev I, Menshikova S, et al. Epstein-Barr virus-associated gastric cancer: disease that requires special approach. Gastric Cancer. 2020 (23):951-960.

[12] Zhang H, Li Y, Wang HB, Zhang A, Chen ML, Fang ZX, et al. Ephrin receptor A2 is an epithelial

cell receptor for Epstein-Barr virus entry. Nat Microbiol. 2018 (3):1-8.

[13] Yang Y, Ding T, Cong Y, Luo X, Liu C, Gong T, et al. Interferon-induced transmembrane protein-1 competitively blocks Ephrin receptor A2-mediated Epstein-Barr virus entry into epithelial cells. Nat Microbiol. 2024 (9):1256-1270.

[14] He HP, Luo M, Cao YL, Lin YX, Zhang H, Zhang X, et al. Structure of Epstein-Barr virus tegument protein complex BBRF2-BSRF1 reveals its potential role in viral envelopment. Nat Commun. 2020 (11):5405.

[15] Cancer Genome Atlas Research Network. Comprehensive molecular characterization of gastric adenocarcinoma. Nature. 2014 (513):202-209.

[16] Stanland LJ, Luftig MA. The Role of EBV-Induced Hypermethylation in Gastric Cancer Tumorigenesis. Viruses. 2020 (12):1222.

[17] Namba-Fukuyo H, Funata S, Matsusaka K, Fukuyo M, Rahmutulla B, Mano Y, et al. TET2 functions as a resistance factor against DNA methylation acquisition during Epstein-Barr virus infection. Oncotarget. 2016 (7):81512-81526.

[18] Saito M, Kono K. Landscape of EBV-positive gastric cancer. Gastric Cancer. 2021 (24):983-989.

[19] Li W, Okabe A, Usui G, Fukuyo M, Matsusaka K, Rahmutulla B, et al. Activation of EHF via STAT3 phosphorylation by LMP2A in Epstein-Barr virus-positive gastric cancer. Cancer Sci. 2021 (112):3349-3362.

[20] Cristescu R, Lee J, Nebozhyn M, Kim KM, Ting JC, Wong SS, et al. Molecular analysis of gastric cancer identifies subtypes associated with distinct clinical outcomes. Nat Med. 2015 (21):449-456.

[21] Gulley ML. Genomic assays for Epstein-Barr virus-positive gastric adenocarcinoma. Exp Mol Med. 2015 (47):e134.

[22] Böger C, Krüger S, Behrens HM, Bock S, Haag J, Kalthoff H, et al. Epstein-Barr virus-associated gastric cancer reveals intratumoral heterogeneity of PIK3CA mutations. Ann Oncol. 2017 (28):1005-1014.

[23] Zak KM, Grudnik P, Magiera K, Dömling A, Dubin G, Holak TA. Structural Biology of the Immune Checkpoint Receptor PD-1 and Its Ligands PD-L1/PD-L2. Structure. 2017 (25):1163-1174.

[24] Yang Y, Liu YQ, Wang XH, Ji K, Li ZW, Bai J, et al. [Clinicopathological and molecular characteristics of Epstein-Barr virus associated gastric cancer: a single center large sample case investigation]. Beijing Da Xue Xue Bao Yi Xue Ban. 2019 (51):451-458. In Chinese.

[25] Nakano H, Saito M, Nakajima S, Saito K, Nakayama Y, Kase K, et al. PD-L1 overexpression in EBV-positive gastric cancer is caused by unique genomic or epigenomic mechanisms. Sci Rep. 2021 (11):1982.

[26] Kim YB, Ahn JM, Bae WJ, Sung CO, Lee D. Functional loss of ARID1A is tightly associated with high PD-L1 expression in gastric cancer. Int J Cancer. 2019 (145):916-926.

[27] Wang J, Ge J, Wang Y, Xiong F, Guo J, Jiang X, et al. EBV miRNAs BART11 and BART17-3p promote immune escape through the enhancer-mediated transcription of PD-L1. Nat Commun. 2022 (13):866.

[28] Duan X, Chen H, Zhou X, Liu P, Zhang X, Zhu Q, et al. EBV Infection in Epithelial Malignancies Induces Resistance to Antitumor Natural Killer Cells via F3-Mediated Platelet Aggregation. Cancer Res. 2022 (82):1070-1083.

[29] Zhang Y, Shi D, Zhang X, Wu S, Liu W, Luo B. Downregulation of MUS81 expression inhibits cell migration and maintains EBV latent infection through miR-BART9-5p in EBV-associated gastric cancer. J Med Virol. 2023 (95):e28725.

[30] Shinozaki A, Sakatani T, Ushiku T, Hino R, Isogai M, Ishikawa S, et al. Downregulation of microR-

NA-200 in EBV-associated gastric carcinoma. Cancer Res. 2010 (70):4719-4727.

[31] Kim JH, Kim N, Song DH, Choi Y, Jeon EB, Kim S, et al. Sex-dependent different clinicopathological characterization of Epstein-Barr virus-associated gastric carcinoma: a large-scale study. Gastric Cancer. 2024 (27):221-234.

[32] Camargo MC, Kim WH, Chiaravalli AM, Kim KM, Corvalan AH, Matsuo K, et al. Improved survival of gastric cancer with tumour Epstein-Barr virus positivity: an international pooled analysis. Gut. 2014 (63):236-243.

[33] van Beek J, zur Hausen A, Klein Kranenbarg E, van de Velde CJ, Middeldorp JM, van den Brule AJ, et al. EBV-positive gastric adenocarcinomas: a distinct clinicopathologic entity with a low frequency of lymph node involvement. J Clin Oncol. 2004 (22):664-670.

[34] Singh S, Jha HC. Status of Epstein-Barr Virus Coinfection with Helicobacter pylori in Gastric Cancer. J Oncol. 2017 (4):1-17.

[35] Chen J, Sathiyamoorthy K, Zhang X, Schaller S, Perez White BE, Jardetzky TS, et al. Ephrin receptor A2 is a functional entry receptor for Epstein-Barr virus. Nat Microbiol. 2018 (3):172-180.

[36] Fukayama M, Abe H, Kunita A, Shinozaki-Ushiku A, Matsusaka K, Ushiku T, et al. Thirty years of Epstein-Barr virus-associated gastric carcinoma. Virchows Arch. 2020 (476):353-365.

[37] Yanai H, Fujiwara J, Toyama E, Okuda H, Miura O, Kaino S, et al. Endoscopic Diagnosis and Therapy for Epstein-Barr Virus-Associated Gastric Cancer. Microorganisms. 2023 (11).

[38] Yin YX, Ling YH, Wei XL, He CY, Wang BZ, Hu CF, et al. Impact of mature tertiary lymphoid structures on prognosis and therapeutic response of Epstein-Barr virus-associated gastric cancer patients. Front Immunol. 2022 (13):973085.

[39] Abusalah MAH, Irekeola AA, Hanim Shueb R, Jarrar M, Yean Yean C. Prognostic Epstein-Barr Virus (EBV) miRNA biomarkers for survival outcome in EBV-associated epithelial malignancies: Systematic review and meta-analysis. PLoS One. 2022 (17):e0266893.

[40] Qiu MZ, He CY, Yang DJ, Zhou DL, Zhao BW, Wang XJ, et al. Observational cohort study of clinical outcome in Epstein-Barr virus associated gastric cancer patients. Ther Adv Med Oncol. 2020 (12):1758835920937434.

[41] Xie T, Peng Z, Liu Y, Zhang Z, Zhang X, Li J, et al. Clinicopathological Characteristics and Response to Chemotherapy in Treatment-Naive Epstein-Barr Virus Associated Gastric Cancer: A Retrospective Study. Front Oncol. 2021 (11):611676.

[42] Corallo S, Fucà G, Morano F, Salati M, Spallanzani A, Gloghini A, et al. Clinical Behavior and Treatment Response of Epstein-Barr Virus-Positive Metastatic Gastric Cancer: Implications for the Development of Future Trials. Oncologist. 2020 (25):780-786.

[43] Alsina M, Arrazubi V, Diez M, Tabernero J. Current developments in gastric cancer: from molecular profiling to treatment strategy. Nat Rev Gastroenterol Hepatol. 2023 (20):155-170.

[44] Kim ST, Cristescu R, Bass AJ, Kim KM, Odegaard JI, Kim K, et al. Comprehensive molecular characterization of clinical responses to PD-1 inhibition in metastatic gastric cancer. Nat Med. 2018 (24):1449-1458.

[45] Shitara K, Özgüroğlu M, Bang YJ, Di Bartolomeo M, Mandalà M, Ryu MH, et al. Pembrolizumab versus paclitaxel for previously treated, advanced gastric or gastro-oesophageal junction cancer (KEYNOTE-061): a randomised, open-label, controlled, phase 3 trial. Lancet. 2018 (392):123-133.

[46] Kobayashi H, Choyke PL. Near-Infrared Photoimmunotherapy of Cancer. Acc Chem Res. 2019 (52):2332-2339.

[47] Inagaki FF, Kano M, Furusawa A, Kato T, Okada R, Fukushima H, et al. Near-infrared photoimmunotherapy targeting PD-L1: Improved efficacy by preconditioning the tumor microenvironment. Cancer Sci. 2024 (115):2396-2409.

[48] Jia K, Chen Y, Sun Y, Hu Y, Jiao L, Ma J, et al. Multiplex immunohistochemistry defines the tumor immune microenvironment and immunotherapeutic outcome in CLDN18.2-positive gastric cancer. BMC Med. 2022 (20):223.

[49] Dottermusch M, Krüger S, Behrens HM, Halske C, Röcken C. Expression of the potential therapeutic target claudin-18.2 is frequently decreased in gastric cancer: results from a large Caucasian cohort study. Virchows Arch. 2019 (475):563-571.

[50] Matsuishi A, Nakajima S, Saito M, Saito K, Fukai S, Tsumuraya H, et al. The impact of CLDN18.2 expression on effector cells mediating antibody-dependent cellular cytotoxicity in gastric cancer. Sci Rep. 2024 (14):17916.

[51] Qi C, Gong J, Li J, Liu D, Qin Y, Ge S, et al. Claudin18.2-specific CAR T cells in gastrointestinal cancers: phase 1 trial interim results. Nat Med. 2022 (28):1189-1198.

[52] Cui X, Snapper CM. Epstein Barr Virus: Development of Vaccines and Immune Cell Therapy for EBV-Associated Diseases. Front Immunol. 2021 (12):734471.

[53] Edwards KR, Malhi H, Schmidt K, Davis AR, Homad LJ, Warner NL, et al. A gH/gL-encoding replicon vaccine elicits neutralizing antibodies that protect humanized mice against EBV challenge. NPJ Vaccines. 2024 (9):120.

[54] Tellam J, Connolly G, Green KJ, Miles JJ, Moss DJ, Burrows SR, et al. Endogenous presentation of CD8+ T cell epitopes from Epstein-Barr virus-encoded nuclear antigen 1. J Exp Med. 2004 (199):1421-1431.

[55] Brooks L, Yao QY, Rickinson AB, Young LS. Epstein-Barr virus latent gene transcription in nasopharyngeal carcinoma cells: coexpression of EBNA1, LMP1, and LMP2 transcripts. J Virol. 1992 (66):2689-2697.

[56] Seo D, Byun H, Cho M, Lee SH, Youn S, Lee J, et al. Dihydrotestosterone Enhances MICA-Mediated Immune Responses to Epstein-Barr Virus-Associated Gastric Carcinoma. Cancers (Basel). 2024 (16).

[57] Kanekiyo M, Bu W, Joyce MG, Meng G, Whittle JR, Baxa U, et al. Rational Design of an Epstein-Barr Virus Vaccine Targeting the Receptor-Binding Site. Cell. 2015 (162):1090-1100.

[58] Malhi H, Homad LJ, Wan YH, Poudel B, Fiala B, Borst AJ, et al. Immunization with a self-assembling nanoparticle vaccine displaying EBV gH/gL protects humanized mice against lethal viral challenge. Cell Rep Med. 2022 (3):100658.

[59] Wu H, Han BW, Liu T, Zhang M, Wu Y, Nie J. Epstein-Barr virus deubiquitinating enzyme BPLF1 is involved in EBV carcinogenesis by affecting cellular genomic stability. Neoplasia. 2024 (55):101012.