European Journal of Medical and Health Sciences
Vol 6 | Issue 6 | December 2024
ISSN 2593-8339

REVIEW

Epstein Barr Virus-Encoded MicroRNAs' and CircularRNAs' Relation with Epstein Barr Virus-Associated Gastric Cancer

Priyam Karmakar[1] and Abhijeet Roy[2,*]

ABSTRACT

Epstein-Barr virus (EBV) is a herpes virus linked to various cancers, including EBV-associated gastric cancer (EBV-aGC). EBV is the first that was identified to produce several kinds of non-coding ribonucleic acids (RNAs) including micro RNAs (miRNAs) and circular RNAs (circRNAs). In EBV-aGC, EBV encodes several miRNAs that play crucial roles in altering the host's gene expression to promote tumorigenesis. EBV miRNAs can suppress host immune responses and regulate cell proliferation, apoptosis, and metastasis, aiding cancer progression. circRNAs often dysregulated in EBV-aGC, interact with EBV miRNAs by acting as sponges, which modulate the availability of miRNAs to their targets. This interplay between EBV miRNAs and circRNAs contributes to the complexity of underlying mechanisms of EBV-aGC development and progression.

Keywords: CircularRNAs, Epstein-Barr virus, Epstein-Barr virus-associated gastric cancer, microRNAs.

Submitted: October 17, 2024

Published: December 17, 2024

10.24018/ejmed.2024.6.6.2224

[1] *District Hospital, Gaibandha Sadar, Gaibandha, Bangladesh.*
[2] *Institute for Biomedical Sciences, Georgia State University, Georgia, USA.*

***Corresponding Author:**
e-mail: aroy9@gsu.edu

1. Introduction

1.1. Epstein-Barr Virus Epidemiology

Epstein-Barr Virus (EBV) is a lymphotropic herpesvirus that is also referred to as human herpesvirus-4. Although it was initially discovered in Burkitt's lymphoma cells in 1964, additional investigation showed that it is highly prevalent [1]. Epidemiological research suggests that more than 90% of the global population is infected with EBV [2]. The majority of EBV infections start in childhood and persist throughout life. The initial childhood infection is still asymptomatic. But, if the infection strikes an adult, it could result in infectious mononucleosis [3]. Like other herpesviruses, EBV enters a latency phase following primary infection in epithelial cells, infects circulating B lymphocytes, and then goes into dormancy for the remainder of its natural life [3]. EBV shares significant similarities with viruses that infect Old World nonhuman primates, such as chimpanzees and rhesus monkeys. For example, EBV and the rhesus monkey virus share genetic sequences and cause chronic infection in the oropharynx and B cells, respectively. It is probable that EBV originated from a virus that afflicted nonhuman primates [4]. The oral route is the primary means of spreading EBV. That being said, there is evidence that organ transplants and blood transfusions can spread EBV [5].

1.2. Structure and Life Cycle of EBV

EBV has a double-stranded genomic DNA which is encased in a toroid-shaped protein core, surrounded by an outer envelope with glycoprotein spikes, a nucleocapsid containing 162 capsomeres, and a protein tegument between the envelope and nucleocapsid (Fig. 1A) [6]. Purified enveloped virus capsids are made up of the EBV homolog of the 68-kD portal protein, 30-kD minor capsid protein, 18-kD small capsid protein, 40-kD minor capsid protein-binding protein, and 155-kD major capsid protein [7]. The EBV tegument is composed of several proteins, which are common components of herpesvirus tegument. A linear double-stranded DNA molecule with a length of around 172 kilobase pairs (kb) makes up the EBV genome. EBV's genome is segmented into short and lengthy, mostly distinct sequence domains by a set of 0.5 kb internal repeat sequences and terminal direct repeats [7]. More than 100 proteins are encoded by the viral genomic DNA. These proteins play a crucial role in the regulation of viral gene expression, replication of viral DNA, formation of the structural elements of the virion, and control of the host

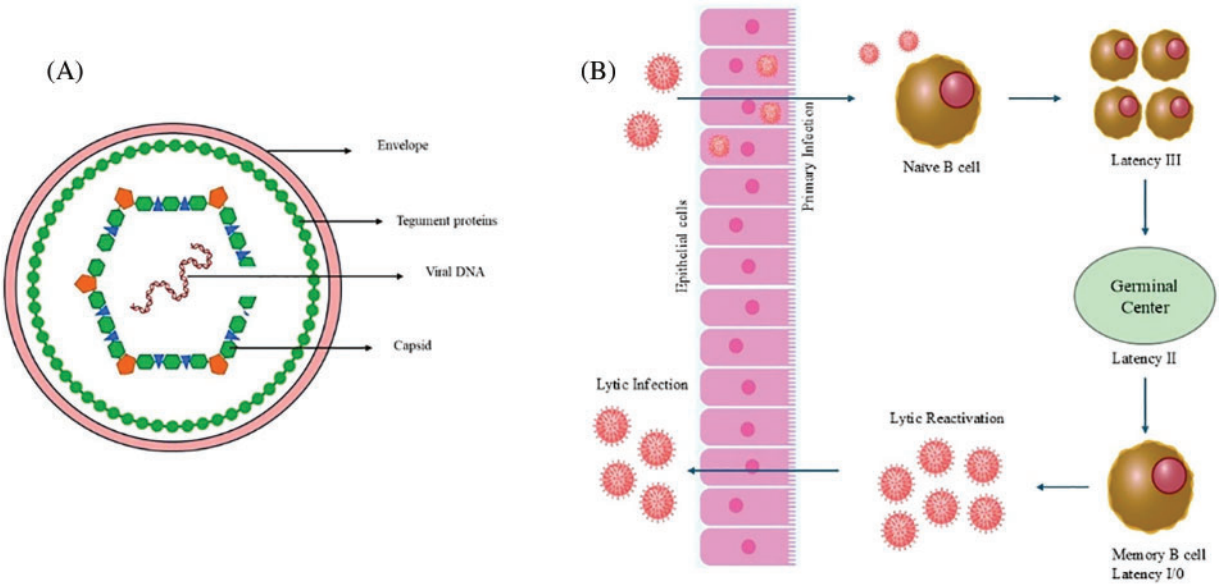

Fig. 1. Structure (A) and latency steps (B) throughout the life cycle of EBV.

immune response during viral replication [7]. Epithelial cells infected with EBV replicate rapidly and produce viruses. On the other hand, EBV infection of B cells results in latent infection and immortality of the cells. After infecting B cells and generating an episome, the linear EBV genome rotates around, staying dormant in these B cells for a long time. Just a small number of latently infected B cells spontaneously reactivate the virus [8], [9].

The viral genome enters the cell and is then discharged into the nucleus, where it undergoes circularization. This keeps the EBV genome as an easily replicable extrachromosomal episome that can be used as a viral clonality marker [10]. The nucleosome structure of the EBV genome is similar to that of the host genome, which causes it to associate with histones and become methylated despite having few epigenetic marks [11]. Viral life cycle completion depends on the regulation of gene expression through crucial epigenetic mechanisms such as DNA methylation and histone modification [12]. EBV enters the latency phase, which silences part of its genes and ensures its persistence in infected B cells. This is an essential step in avoiding host cell immunity [11]. During latency, the circular episome that makes up the EBV genome replicates by enlisting the aid of the cellular replication machinery [13].

EBV has a biphasic life cycle with latent and lytic phases in infected cells [14]. The entire viral gene repertoire is expressed, and progeny viruses are created during the lytic cycle. The lytic cycle makes it possible for virions to spread throughout host cells [14]. EBV expresses a small number of viral genes necessary for the upkeep of its genome while it is in latency. The latent infection of EBV promotes the virus's survival and pathogenesis because it produces very few proteins that the host immune system can target [15]. There are four distinct types of EBV latency based on the expression of latent genes (Fig. 1B) [15]. Only in healthy carriers does latency 0 occur, in which B cells express low amounts of latent membrane protein 2A (LMP2A) and EBV nuclear antigen 1 (EBNA1), or no viral proteins are produced. In type I latency, EBV is primarily found in B cells and only EBNA1 is expressed. During latency II, together with EBNA1, three LMPs (LMP1, LMP2A, and LMP2B) are expressed [14], [16]. Furthermore, Hodgkin's lymphoma, natural killer (NK)/T cell lymphoma, and carcinoma are closely linked to latency II. All EBV nuclear proteins (EBNA1, 2, 3A, 3B, 3C, and LP), the three LMPs, and viral non-coding RNAs are expressed during the latency III. Latency III is frequently observed in lymphomas linked to immunodeficiency, including AIDS-related lymphoma and post-transplant lymphoproliferative disease [14], [16].

1.3. EBV and Cancers

Nearly 1.4 million annual global cancer cases are linked to oncogenic viruses, such as EBV, human T lymphotropic virus type 1, human papillomaviruses, hepatitis B and hepatitis C viruses, Kaposi sarcoma-associated herpesvirus, and others [17]. These oncogenic viruses qualities are closely linked to their capacity to trigger mechanisms required for immune evasion, migration, cellular proliferation, and survival [17]. EBV is linked to nasopharyngeal carcinoma, post-transplant lymphoproliferative disorders, Hodgkin's lymphoma, and gastric cancer [18]. Currently, it is estimated that 15%–20% of all human cancers are caused by viral infections [19]. EBV, which is known to infect the great majority of people worldwide, was the first herpes virus linked to human cancers [18]. The majority of EBV-infected tumors are made up of latently infected cells where the virus is still in the nuclear episome form and is being replicated by the host cell's DNA polymerase [20].

Globally, gastric cancer is the second cancer in terms of cancer-related deaths and is the sixth most common malignant tumor. As our knowledge of gastric cancer has increased, we have been able to identify a subset of individuals suffering from EBV infection. A particular type of gastric tumor, known as EBV-positive gastric cancer, has remarkable clinicopathological features and distinct genomic abnormalities [21]. EBV-associated gastric cancer (EBV-aGC) represents 10% of all gastric cancers [22].

1.4. Gastric Epithelial Cells Infection and Cancer by EBV

EBV is primarily transmitted through saliva [23]. When an uninfected person comes into contact with the virus, the primary infection occurs in the B cells located in the tonsil crypts of the throat. Alternatively, the virus can also infect the epithelial cells of the tonsils. The epithelial cells can then produce more viruses that infect the B cells [23]. After the initial infection, EBV establishes the latency phage in B cells. Occasionally the virus reactivates from the latent state and replicates. These new progeny viruses can infect the epithelial cells in the mouth and release many viruses into saliva [24]. An interesting point is that viruses released by infected B cells tend to infect epithelial cells more easily. On the other hand, viruses released from infected epithelial cells are better able to infect B cells. When the virus comes from B cells, it has a different set of glycoproteins than when it comes from epithelial cells. This change helps the virus move effectively between these two cell types, ensuring it can spread further [24]. Gastric epithelial cells could be infected directly by swallowing infected saliva from the infected oral mucosa. Alternatively, reactivated EBV from infected B cells could migrate to the gastric mucosa, release the virus, and infect neighboring gastric epithelial cells. In certain cases, EBV infection is also associated with adenocarcinomas of the gastroesophageal junction, but not esophageal adenocarcinomas, indicating that specific features of the epithelial cells found only in the proximal stomach and the gastroesophageal junction are crucial for long-term EBV infection [25].

1.5. EBV-Encoded microRNAs and circularRNAs

microRNAs (miRNAs) are a special class of non-coding RNAs with a length of 21–23 nucleotides [26]. miRNAs are typically produced from the exons or introns of transcripts that are processed by RNA polymerase II and contain both protein-coding and non-coding information. miRNAs degrade the target mRNAs to post-transcriptionally regulate gene expression [26]. miRNAs are implicated in a variety of biological processes, including metabolism, development, and cancer. Most significantly, miRNAs have significant roles in the tumorigenesis and progression [27]. miRNAs have also been found in other organisms including algae, worms, plants, and mammals [28]. Interestingly, viruses have been found to encode miRNAs. In 2004, Tuschl *et al*. discovered the first virus-encoded miRNAs in EBV [29]. To date, EBV has been reported to encode 44 miRNAs that target cellular or viral mRNAs [30]. The regulatory roles of EBV-encoded miRNAs in the development and progression of EBV-associated malignancies are proven. Moreover, EBV miRNAs have the ability to directly target immune-related genes, which helps infected cells avoid immune system eradication [31]. Circular RNAs (circRNAs) are covalently jointed, single-stranded RNA molecules, and conduct several biological activities by serving as protein templates, miRNA sponges, and transcriptional regulators [32]. Recently, it has been discovered that circRNAs are also expressed by EBV [33]. EBV circRNAs may act as human miRNA sponges during viral infection, the cell cycle, and oncogenesis. It has been identified that the level of EBV infection has an impact on the quantity of EBV circRNAs [33].

1.6. EBV-Encoded miRNAs are Involved in Gastric Cancer Progression

miRNAs are involved in numerous biological pathways and mechanisms. Moreover, their small size, non-immunogenicity, and ability for post-transcriptional modification make them good candidates for viral immune-evasion functions. Accumulating data highlights the association between the expression of EBV miRNAs and tumorigenesis in EBV-associated gastric cancer [34].

EBV has around 25 pre-miRNAs and 44 mature miRNAs, which play a role in maintaining latent infections in EBV-associated tumors [35]. EBV-aGC is linked to type I or II latency. The BHRF1 gene produces a few miRNAs, but the BART miRNAs are more active and important in EBV-aGC, influencing various cellular functions [35]. miRNA BARTs affect processes like cell movement, growth, death, immune response, and recycling within cells. They are involved in many different activities within cells, creating a complex network of interactions. However, scientists still don't fully understand how these miRNAs contribute to the cancer process, which shows that more research is needed. Some miRNAs can affect many different genes at once. For example, two specific miRNAs, BART2-5p and BART11-5p, are known to target specific genes like *p21* and *RB* genes. They can influence the gene's behavior, which can impact cancer development. For instance, BART2-5p and BART11-5p induce p21 and RB genes that promote cell proliferation [36].

EBV-aGC exhibits high levels of BART14-3p expression [37]. BART22 expression is high in other tumors in type I EBV latency, but it is low in EBV-aGC. EBV miRNAs have been shown to target multiple points in the apoptotic cascade in EBV-aGC. For example, it was discovered that BART4-5p reduced the activity of the pro-apoptotic protein Bid, which in turn reduced apoptosis in gastric cancer cell lines [37]. In EBV-aGC, BART5-3p also suppresses p53 expression [38]. BART1, BART3, BART9, BART11, and BART12 are among the BART-miRNAs that can decrease the expression of pro-apoptotic gene Bcl-2-interacting mediator of cell death in EBV-aGC cells [39].

Tumor immune evasion is necessary for tumor survival and development. Tumor cells proliferate and spread through defense mechanisms that shield them from immune system detection and destruction. In EBV-associated cancers, tumor immune escape is highly correlated with EBV infection [40]. The Programmed cell death protein 1 (PD-1) and programmed death-ligand 1 (PD-L1) can be regulated by EBV protein products such as LMP1, EBNA1, and EBNA2 [41]. For tumor immune evasion and immunotherapy, the PD-1 receptor expressed on activated T cells and its ligand PD-L1 are essential. Immune evasion is promoted by PD-L1 expression. High levels of PD-L1 expression are found in many tumor cells, which exploit PD-L1/PD-1 signaling to evade T-cell response [42]. PD-L1 can facilitate the creation of a barrier on surface of tumor cells by interacting with the T-cell surface receptor PD-1 and blocking T-cell anti-tumor activity [43]. In 2022, Wang *et al*., have identified

that EBV BART11 and BART17-3p miRNAs enhance immune escape in EBV-associated gastric cancer by regulating the PD-1 and PD-L1 pathways [44]. miRNAs present on the BART gene cluster of the EBV genome are highly upregulated in EBV-associated epithelial tumor cells. In their study, firstly, to evaluate the role of PD-L1 in epithelial cancer, they analyzed the genome-wide gene expression profile data for gastric cancer and nasopharyngeal cancer. The expression of PD-L1 was significantly higher in tumor tissues compared to normal tissue. Further analysis between the correlation of PD-L1 expression and EBV infection, and it was revealed that PD-L1 was highly expressed in EBV-positive gastric cancer tissue than in EBV-negative gastric cancer. After analyzing 40 EBV-associated gastric cancer clinical samples compared with 20 normal gastric mucosa tissues, authors found that PD-L1 demonstrated substantially high expression and was positively associated with EBV infection [44]. In EBV-aGC, EBNA1 enhances NF-κB activation, which promotes tumor growth, and it also helps downregulate transforming growth factor-beta (TGF-β) signaling and p53 [45], [46].

1.7. EBV circRNA Promotes Tumor Progression and Tumor Stemness in EBV-Associated Gastric Cancer

Recently, it has been found that EBV generates several circRNAs [33]. EBV circRPMS1 is a circRNA produced by EBV that is derived from the RPMS1 gene and was found to be expressed in EBV-GC and other cancers like Nasopharyngeal carcinoma [33]. In 2022, Zhang *et al*. addressed that EBV circRPMS1 is associated with the tumorigenesis of gastric cancer both in vivo and in vitro [47]. Their study found that circRPMS1 promotes cancer progression by recruiting Sam68 to the METTL3 promoter to induce METTL3 expression and is associated with distant metastasis and poor prognosis [47]. Sam68 is a transcriptional activator involved in several cellular processes like alternative splicing, cell cycle regulation, tumorigenesis, and RNA 3′-end formation [48]. METTL3 is a methyltransferase of mRNA and is found associated with cancer cell proliferation and resistance [49].

Cancer stem cells are the source of tumorigenesis. Studies provided evidence for the existence of cancer stem cells in EBV-aGC and the association of EBV-encoded circRNAs in inducing stemness [50]. The study found that EBV-encoded circLMP2A was highly expressed in gastric cancer cell line SNU-4th cells. This molecule acted as a sponge for a miRNA called miR-3908, which led to the activation of a pathway involving two proteins named TRIM59 and p53. This pathway helped to sustain the stemness phenotype of cancer stem cells. Furthermore, the study found that upregulation of EBV circLMP2A in patients was correlated with poor prognosis and metastasis in EBV-aGC [50]. Additionally, the expression of circLMP2A in EBV-associated gastric cancer patients was evaluated by Real-time PCR. It was found that circLMP2A over expression was potentially related with lymph node metastasis and distal metastasis [50].

1.8. EBV miRNAs and circRNAs as Cancer Biomarkers and Therapeutics

miRNAs and circRNAs are being explored as potential therapeutic targets for EBV-associated cancers, including gastric cancer. Since EBV-encoded miRNAs regulate viral and host gene expression to promote cancer progression, targeting these miRNAs with inhibitors could disrupt their oncogenic effects, restoring normal cellular function. Targeting the highly expressed EBV-BART miRNAs in epithelial cell tumors has long been common practice. For example, anti-miRNA oligonucleotide therapeutics "antagomirs" or miRNA sponges have been used to successfully suppress EBV-driven tumors [51]. With the discovery of EBV circRNAs, the spectrum of possible therapeutic viral targets has expanded [52]. Additionally, circRNAs are more stable than their linear counterparts, making them desirable options for biomarkers in liquid biopsy. EBV-circLMP2A is one such possibility; it has been demonstrated to both initiate and sustain stem cell formation in EBV-aGC. Poor prognosis and metastasis were also significantly correlated with elevated EBV circLMP2A expression. circRPMS1 potentially promotes the epithelial-mesenchymal transition that functions as a tumor biomarker by serving as an early indicator of metastasis [53].

2. Conclusion and Prospects

EBV was the first human virus to be found to express miRNAs and circRNAs, there is still a great deal to learn about EBV-aGCs in order to improve treatment options and patient outcomes, even with the abundance of information currently available. Since EBV-encoded miRNAs and circRNAs are involved in several cellular processes, such as immune response, cell cycle, migration, apoptosis, and proliferation, it reflects that they are integral to the carcinogenesis of EBV-aGC. Noncoding RNA biology is a rapidly growing field that offers many opportunities to understand the pathophysiology of cancers, develop novel disease biomarkers, find new therapeutic targets, and even develop alternative treatments, but obstacles need to be addressed before targeting EBV-encoded miRNAs or circRNAs in therapeutic settings.

Conflict of Interest

The authors declare that there is no conflict of interest.

References

[1] Rowe M, Fitzsimmons L, Bell AI. Epstein-Barr virus and burkitt lymphoma. *Chin J Cancer*. 2014;Dec;33(12):609–19.

[2] Hoover K, Higginbotham K. Epstein-Barr virus. In *StatPearls [Internet]*. Treasure Island (FL): StatPearls Publishing, 2024 [cited 2024 Jul 5]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK559285/.

[3] Tzellos S, Farrell PJ. Epstein-Barr virus sequence variation-biology and disease. *Pathog Basel Switz*. 2012 Nov 8;1(2):156–74.

[4] Mühe J, Wang F. Host range restriction of Epstein-Barr virus and related lymphocryptoviruses. *J Virol*. 2015;Sep;89(17):9133–6.

[5] 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.
[6] Santpere G, Darre F, Blanco S, Alcami A, Villoslada P, Mar Albà M, *et al.* Genome-wide analysis of wild-type Epstein-Barr virus genomes derived from healthy individuals of the 1,000 Genomes Project. *Genome Biol Evol*. 2014 Apr;6(4):846–60.
[7] van Grunsven WM, Nabbe A, Middeldorp JM. Identification and molecular characterization of two diagnostically relevant marker proteins of the Epstein-Barr virus capsid antigen complex. *J Med Virol*. 1993 Jun;40(2):1619.
[8] Tracy SI, Kakalacheva K, Lünemann JD, Luzuriaga K, Middeldorp J, Thorley-Lawson DA. Persistence of epstein-barr virus in self-reactive memory B cells. *J Virol*. 2012 Nov 15;86(22):12330–40.
[9] Babcock GJ, Decker LL, Volk M, Thorley-Lawson DA. EBV persistence in memory B cells in vivo. *Immunity*. 1998 Sep 1;9(3):395–404.
[10] Lee CP, Chen MR. Conquering the nuclear envelope barriers by EBV lytic replication. *Viruses*. 2021 Apr 18;13(4):702.
[11] Buschle A, Hammerschmidt W. Epigenetic lifestyle of epstein-barr virus. *Semin Immunopathol*. 2020;42(2):131–42.
[12] Rehman UU, Ghafoor D, Ullah A, Ahmad R, Hanif S. Epigenetics regulation during virus-host interaction and their effects on the virus and host cell. *Microb Pathog*. 2023 Sep 1;182:106271.
[13] Dheekollu J, Chen HS, Kaye KM, Lieberman PM. Timeless-dependent DNA replication-coupled recombination promotes Kaposi's sarcoma-associated herpesvirus episome maintenance and terminal repeat stability. *J Virol*. 2013 Apr;87(7):3699–709.
[14] Murata T, Sugimoto A, Inagaki T, Yanagi Y, Watanabe T, Sato Y, *et al.* Molecular basis of Epstein-Barr virus latency establishment and lytic reactivation. *Viruses*. 2021 Dec;13(12):2344.
[15] Houldcroft CJ, Kellam P. Host genetics of Epstein-Barr virus infection, latency and disease. *Rev Med Virol*. 2015;Mar;25(2): 71–84.
[16] Kempkes B, Robertson ES. Epstein-Barr virus latency: current and future perspectives. *Curr Opin Virol*. 2015 Oct 1;14:138–44.
[17] Schiller JT, Lowy DR. An introduction to virus infections and human cancer. *Recent Results Cancer Res Fortschritte Krebsforsch Progres Dans Rech Sur Cancer*. 2021;217:1–11.
[18] El-Sharkawy A, Al Zaidan L, Malki A. Epstein-Barr virus-associated malignancies: roles of viral oncoproteins in carcinogenesis. *Front Oncol*. 2018;8:265.
[19] McLaughlin-Drubin ME, Munger K. Viruses associated with human cancer. *Biochim Biophys Acta BBA-Mol Basis Dis*. 2008 Mar 1;1782(3):127–50.
[20] El-Sharkawy A, Al Zaidan L, Malki A. Epstein-Barr virus-associated malignancies: roles of viral oncoproteins in carcinogenesis. *Front Oncol*. 2018 Aug 2;8:265.
[21] Sun K, Jia K, Lv H, Wang SQ, Wu Y, Lei H, *et al.* EBV-positive gastric cancer: current knowledge and future perspectives. *Front Oncol*. 2020 Dec 14;10:583463.
[22] Iizasa H, Kartika AV, Fekadu S, Okada S, Onomura D, Wadi AFAA, *et al.* Development of Epstein-Barr virus-associated gastric cancer: infection, inflammation, and oncogenesis. *World J Gastroenterol*. 2022 Nov 28;28(44):6249–57.
[23] Dunmire SK, Verghese PS, Balfour HH. Primary Epstein-Barr virus infection. *J Clin Virol*. 2018 May 1;102:84–92.
[24] Hutt-Fletcher LM. The long and complicated relationship between Epstein-Barr virus and epithelial cells. *J Virol*. 2016 Dec 16;91(1):e01677–16. doi: 10.1128/jvi.01677-16.
[25] Genitsch V, Novotny A, Seiler CA, Kröll D, Walch A, Langer R. Epstein-Barr virus in gastro-esophageal adenocarcinomas—single center experiences in the context of current literature. *Front Oncol*. 2015;5:1–6.
[26] Dozmorov MG, Giles CB, Koelsch KA, Wren JD. Systematic classification of non-coding RNAs by epigenomic similarity. *BMC Bioinform*. 2013;14(14):S2.
[27] Peng Y, Croce CM. The role of MicroRNAs in human cancer. *Signal Transduct Target Ther*. 2016;1(1):15004.
[28] Moran Y, Agron M, Praher D, Technau U. The evolutionary origin of plant and animal microRNAs. *Nat Ecol Evol*. 2017 Feb 21;1:0027.
[29] Pfeffer S, Zavolan M, Grässer FA, Chien M, Russo JJ, Ju J, *et al.* Identification of virus-encoded microRNAs. *Science*. 2004 Apr 30;304(5671):734–6.
[30] Barth S, Meister G, Grässer FA. EBV-encoded miRNAs. *Biochim Biophys Acta BBA—Gene Regul Mech*. 2011 Nov 1;1809(11): 631–40.
[31] Wang M, Gu B, Chen X, Wang Y, Li P, Wang K. The function and therapeutic potential of Epstein-Barr virus-encoded MicroRNAs in cancer. *Mol Ther Nucleic Acids*. 2019 Jul 15;17:657–68.
[32] Xiao J, Joseph S, Xia M, Teng F, Chen X, Huang R, *et al.* Circular RNAs acting as miRNAs' sponges and their roles in stem cells. *J Clin Med*. 2022 May 20;11(10):2909.
[33] Tan KE, Ng WL, Marinov GK, Yu KHO, Tan LP, Liau ES, *et al.* Identification and characterization of a novel Epstein-Barr virus-encoded circular RNA from LMP-2 Gene. *Sci Rep*. 2021 Jul 13;11(1):14392.
[34] Boss IW, Renne R. Viral miRNAs and immune evasion. *Biochim Biophys Acta BBA-Gene Regul Mech*. 2011 Nov 1;1809(11): 708–14.
[35] Liu T, Zhou X, Zhang Z, Qin Y, Wang R, Qin Y, *et al.* The role of EBV-encoded miRNA in EBV-associated gastric cancer. *Front Oncol*. 2023 Jun 14;13:1204030.
[36] Zhao MH, Liu W, Zhang X, Zhang Y, Luo B. Epstein-Barr virus miR-BART2-5p and miR-BART11-5p regulate cell proliferation, apoptosis, and migration by targeting RB and p21 in gastric carcinoma. *J Med Virol*. 2023 Jan;95(1):e28338.
[37] Shinozaki-Ushiku A, Kunita A, Isogai M, Hibiya T, Ushiku T, Takada K, *et al.* Profiling of virus-encoded microRNAs in Epstein-Barr virus-associated gastric carcinoma and their roles in gastric carcinogenesis. *J Virol*. 2015 Apr 21;89(10):5581–91.
[38] Zheng X, Wang J, Wei L, Peng Q, Gao Y, Fu Y, *et al.* Epstein-Barr virus microRNA miR-BART5-3p inhibits p53 expression. *J Virol*. 2018;92(23):e01022–18. doi: 10.1128/jvi.01022-18.
[39] Marquitz AR, Mathur A, Nam CS, Raab-Traub N. The Epstein-Barr virus BART microRNAs target the pro-apoptotic protein Bim. *Virology*. 2011 Apr 10;412(2):392–400.
[40] Bauer M, Jasinski-Bergner S, Mandelboim O, Wickenhauser C, Seliger B. Epstein-Barr virus—associated malignancies and immune escape: the role of the tumor microenvironment and tumor cell evasion strategies. *Cancers*. 2021 Oct 16;13(20):5189.
[41] Chakravorty S, Afzali B, Kazemian M. EBV-associated diseases: current therapeutics and emerging technologies. *Front Immunol*. 2022;13:1059133.
[42] Cha JH, Chan LC, Li CW, Hsu JL, Hung MC. Mechanisms controlling PD-L1 expression in cancer. *Mol Cell*. 2019 Nov 7;76(3):359–70.
[43] Han Y, Liu D, Li L. PD-1/PD-L1 pathway: current researches in cancer. *Am J Cancer Res*. 2020 Mar 1;10(3):727–42.
[44] 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 Feb 14;13(1):866.
[45] Wood VHJ, O'Neil JD, Wei W, Stewart SE, Dawson CW, Young LS. Epstein-Barr virus-encoded EBNA1 regulates cellular gene transcription and modulates the STAT1 and TGFβ signaling pathways. *Oncogene*. 2007;Jun;26(28):4135–47.
[46] Chung GTY, Lou WPK, Chow C, To KF, Choy KW, Leung AWC, *et al.* Constitutive activation of distinct NF-κB signals in EBV-associated nasopharyngeal carcinoma. *J Pathol*. 2013;231(3):311–22.
[47] Zhang JY, Du Y, Gong LP, Shao YT, Pan LJ, Feng ZY, *et al.* ebv-circRPMS1 promotes the progression of EBV-associated gastric carcinoma via Sam68-dependent activation of METTL3. *Cancer Lett*. 2022 Jun 1;535:215646.
[48] Frisone P, Pradella D, Di Matteo A, Belloni E, Ghigna C, Paronetto MP. SAM68: signal transduction and RNA metabolism in human cancer. *BioMed Res Int*. 2015;2015:528954.
[49] Esteva-Socias M, Aguilo F. METTL3 as a master regulator of translation in cancer: mechanisms and implications. *NAR Cancer*. 2024 Mar 1;6(1):zcae009.
[50] Gong L, Chen J, Dong M, Xiao Z, Feng Z, Pan Y, *et al.* Epstein-Barr virus-derived circular RNA LMP2A induces stemness in EBV-associated gastric cancer. *EMBO Rep*. 2020 Oct 5;21(10):e49689.
[51] Cai L, Li J, Zhang X, Lu Y, Wang J, Lyu X, *et al.* Gold nano-particles (AuNPs) carrying anti-EBV-miR-BART7-3p inhibit growth of EBV-positive nasopharyngeal carcinoma. *Oncotarget*. 2015 Feb 19;6(10):7838–50.
[52] Ungerleider N, Concha M, Lin Z, Roberts C, Wang X, Cao S, *et al.* The Epstein Barr virus circRNAome. *PLOS Pathog*. 2018 Aug 6;14(8):e1007206.
[53] Liu Q, Shuai M, Xia Y. Knockdown of EBV-encoded circRNA circRPMS1 suppresses nasopharyngeal carcinoma cell proliferation and metastasis through sponging multiple miRNAs. *Cancer Manag Res*. 2019 Aug 27;11:8023–31.