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REVIEW

Epstein-Barr Virus MicroRNAs as Key Regulators of Lymphoma Pathogenesis: Immune Evasion Mechanisms and Therapeutic Opportunities

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ABSTRACT

The ubiquitous human gamma-herpesvirus Epstein–Barr virus (EBV) infects over 90% of adults globally and was the first human virus identified with oncogenic potential. EBV enters a lifelong persistence in the host via a finely regulated life-cycle comprising primary infection, latency and lytic reactivation. Within infected B-cells and epithelial cells, EBV encodes a distinct repertoire of microRNAs (miRNAs), primarily from the BART (BamHI A rightward transcript) and BHRF1 (BamHI H rightward open reading frame) clusters, which play pivotal roles in modulating both viral and host gene expression. These viral miRNAs contribute to key oncogenic processes: by dampening apoptotic responses (e.g., via targeting PUMA, Bim, and PTEN), promoting proliferation of latently-infected B-cells, inhibiting host immune responses (e.g., via down-regulation of CXCL-11 by miR-BHRF1-3), and promoting epithelial-mesenchymal transition (EMT) and metastasis through modulation of E-cadherin and other adhesion molecules. In human lymphomas, such as Burkitt lymphoma, Hodgkin lymphoma, and EBV-positive diffuse large B-cell lymphoma, the interplay of latent viral gene expression, miRNA-mediated regulatory networks, and host microenvironmental factors underlies malignant transformation and disease progression. Emerging evidence also supports the utility of EBV-encoded miRNAs as diagnostic and prognostic biomarkers in EBV-associated cancers. Importantly, therapeutic strategies aimed at interrupting viral miRNA function, restoring host tumor-suppressor pathways, and re-sensitizing tumor cells to immune surveillance hold promise. This review synthesizes current mechanistic insights into EBV-encoded miRNAs in oncogenesis, elaborates on their roles in lymphoma pathogenesis, and evaluates the translational potential of miRNA-targeted therapies in EBV-associated malignancies.

1 | Introduction

Epstein–Barr virus (EBV) is a spherical DNA virus belonging to the herpesvirus family, notable for being one of the most widespread human pathogens. It holds the historical distinction of being the first virus identified as oncogenic, based on a biopsy of a patient with Burkitt lymphoma. The global prevalence of EBV is remarkably high, infecting approximately 95% of the adult population [1, 2]. EBV is primarily transmitted through saliva, though it can also spread via other bodily fluids, including breast milk [1, 3]. Structurally, EBV, like other herpesviruses, is characterized by a toroidal protein core containing its viral DNA, enclosed by a nucleocapsid composed of 162 capsomers. This is further surrounded by a proteinaceous tegument layer and an outer lipid envelope adorned with glycoprotein spikes, which are essential for host cell recognition and entry [4].

EBV exists in two primary genotypic forms, type 1 and type 2, which are distinguished mainly by sequence polymorphisms in genes encoding specific nuclear proteins, particularly EBV nuclear antigen 2 (EBNA-2) and EBNA-3A. These genetic differences can lead to amino acid substitutions that may impact the host's immune response to infection [5].

EBV infection progresses through three distinct phases: the initial phase of primary infection and viral replication, a subsequent latency stage, and eventual lytic reactivation [1, 6]. The virus has a distinct tropism for B lymphocytes expressing the CD21 receptor and for oropharyngeal epithelial cells. Viral attachment is mediated by the gp350/220 glycoprotein binding to the complement receptor type 2 (CR2/CD21) on B cell surfaces. Following this initial contact, the viral glycoprotein gp42 interacts with HLA class II molecules on B lymphocytes to facilitate viral entry. Interestingly, EBV can also infect CD21-negative cells, such as T lymphocytes, highlighting its adaptability and complex host interactions [1, 3, 5].

MicroRNAs (miRNAs) are small non-coding RNA molecules, typically 18–24 nucleotides in length, that play a critical role in gene regulation by suppressing translation or promoting the degradation of target messenger RNAs (mRNAs) [7–13]. The EBV, a highly prevalent human herpesvirus, has evolved to encode its own set of miRNAs that are fundamentally important for its lifecycle, contributing to the survival of latently infected cells and playing a vital role during the early stages of infection. These viral miRNAs are derived from two major genomic loci: the BamHI fragment A rightward transcript (BART) and the BamHI fragment H rightward open reading frame (BHRF1). The expression of these miRNAs is an early and rapid event following infection of B cells, with levels steadily increasing over the first week post-infection [14, 15].

Interestingly, EBV variants lacking BHRF1 miRNAs exhibit impaired growth and reduced efficiency in spreading within infected cells compared to wild-type strains [14, 16]. Furthermore, in vivo studies using mouse models of EBV infection and oncogenesis have demonstrated that infection with EBV variants lacking the BHRF1 miRNA cluster results in delayed onset of viremia [14, 16].

B lymphocytes are naturally susceptible to undergoing apoptosis in vivo; however, EBV infection alters this cell death through various mechanisms, notably involving its encoded miRNAs [14, 17]. Research using EBV-derived mutant strains has shown that BHRF1 miRNAs prevent apoptosis in primary B cells during the early infection and promote their proliferation [14, 17]. BART miRNAs support the persistence of Burkitt lymphoma by inhibiting the activity of caspase 3 [14, 18]. In addition, BART miRNAs have been demonstrated to target pro-apoptotic proteins such as p53-upregulated modulator of apoptosis (PUMA) and Bim (BCL2L11), thereby contributing to the suppression of apoptosis [14, 19].

EBV has a lifelong latency in B cells through different viral immune evasion mechanisms. Although it infects the majority of the adult population, it's typically asymptomatic [14]. Recent research indicates that EBV-encoded miRNAs play a role in modulating the host's antiviral immune response [14]. CXCL-11, a chemokine induced by interferons that attracts T cells via interaction with the CXCR3 receptor, has recently been identified as a key target of miR-BHRF1-3 [14]. These findings suggest that EBV-encoded miRNAs can modulate host cytokine networks, thereby facilitating the virus's evasion of the host immune response [14].

EBV is known to induce many human cancers, notably including Burkitt and Hodgkin lymphomas [20]. Both lytic and latent gene expressions of EBV can drive oncogenesis. EBV has a complex life cycle that alternates between B lymphocytes and epithelial cells, a process that is tightly regulated by the host immune system [21]. This regulation is important for maintaining persistent infection, and the absence of this balance can result in uncontrolled proliferation of EBV-infected cells, ultimately contributing to malignant transformation [22]. EBV induces oncogenesis using different viral proteins, RNAs, and miRNAs. The EBV-encoded nuclear antigen 1 (EBNA1) promotes DNA damage by enhancing the production of reactive oxygen species (ROS) and limiting p53 expression [23].

BART2-5p, the first known EBV miRNA shown to support the maintenance of viral latency by altering the expression of the viral DNA polymerase BALF5 [24, 25]. This results in impeding the transition from latent to lytic replication. BART18-5p has been found to reinforce latency by altering the activity of a critical regulator of viral replication known as MAP kinase 2 (MAP3K2) [24, 26]. Furthermore, BART6-5p targets Dicer, causing a downregulation in the production of various mature miRNAs, including those that typically suppress the expression of viral proteins during the lytic phase [24].

In the early phase of EBV infection, the BHRF1 protein is abundantly expressed, and the miRNA miR-BHRF1-3 from this region suppresses the host tumor suppressor protein PTEN, thereby reducing apoptosis and facilitating viral replication. As the infection progresses, miR-BHRF1-2 downregulates BHRF1 protein expression, a shift that supports the transition to and maintenance of long-term viral latency within host cells [24, 27]. Additionally, miR-BHRF1-2 contributes to apoptosis inhibition by targeting the tumor suppressor protein PRDM1/Blimp1. This interaction may promote the proliferation of EBV-infected B cells and facilitate the development of B-cell lymphoma [24, 28]. Some EBV-encoded miRNAs promote tumor progression and metastasis. BART9 can induce epithelial-mesenchymal transition (EMT), a process in which cells acquire enhanced motility and invasiveness, by directly targeting and downregulating E-cadherin, a key cell adhesion molecule [24, 29]. Additionally,

BART7-3p and BART1-5p can bind specifically to the 3′ untranslated region (UTR) of the tumor suppressor gene PTEN, resulting in reduced PTEN expression and metastatic progression [24, 30].

This review provides a comprehensive and critical overview of the emerging roles of EBV-encoded miRNAs as central regulators of viral persistence, immune evasion, and lymphoma pathogenesis. Particular emphasis is placed on the mechanistic contributions of EBV miRNAs to the molecular landscape of EBV-associated lymphomagenesis. The review is structured into key thematic sections covering the biogenesis and expression profiles of EBV miRNAs, their regulatory functions in host and viral signaling networks, and their roles in modulating oncogenic pathways involved in tumor initiation, progression, invasion, metastasis, and immune escape. In addition, the clinical and translational relevance of EBV miRNAs is examined, highlighting their potential utility as diagnostic and prognostic biomarkers, as well as promising therapeutic targets. Current therapeutic strategies and emerging approaches for targeting EBV miRNAs in EBV-driven malignancies are also critically discussed. Collectively, this review integrates recent mechanistic and translational evidence, underscoring the pivotal role of EBV miRNAs in lymphoma biology and their potential application in precision oncology and targeted immunotherapeutic interventions.

2 | EBV Life Cycle and Latency Types

EBV infects over 90% of people globally. Its ability to switch between lytic and latent phases is key to establishing lifelong persistence. This tightly regulated cycle allows EBV to evade immune surveillance, maintain chronic infection, and drive oncogenesis [31].

During the lytic phase, EBV actively replicates, producing new virions that are released through cell lysis. This process is generally brief due to a strong immune response that clears infected cells. In contrast, the latent phase is characterized by minimal viral gene expression and limited replication. Here, the EBV genome is maintained as a circular episome within B lymphocytes, allowing it to remain hidden from the immune system. This key ability to switch between lytic and latent cycles is essential for the virus's lifelong persistence and its link to malignancies [32, 33].

EBV establishes three major latency types: Latency I, II, and III, each defined by distinct patterns of viral protein expression and associated with specific cancer types, as outlined in (Table 1 and Figure 1). These latency types reflect the virus's strategic adaptations for long-term persistence in the host, playing critical roles in immune evasion and the promotion of oncogenesis [33].

Latency I associated with Burkitt lymphoma. During this latency type, EBV expresses only one protein, Epstein–Barr nuclear antigen 1 (EBNA1), which plays a crucial role in maintaining the viral genome within infected cells and ensuring its stable replication while other immunogenic or cell proliferation-inducing viral proteins are absent, thereby minimizing immune detection. This restricted gene expression

TABLE 1 | EBV latency types with their related viral proteins and their role in various cancer types.

Latency type	Characteristics	Associated cancers	Key viral proteins	Function in cancer pathogenesis	References
Latency I	Minimal viral gene expression (EBNA1 only), the virus maintains its genome in an episomal form.	Burkitt lymphoma	EBNA1	Virus evades immunity. Contributes to Burkitt lymphoma development.	[34, 35]
Latency II	Expression of EBNA1, LMP1, LMP2. Oncogenic potential via LMP1 activation of cell survival and proliferation pathways.	Hodgkin lymphoma, NPC, gastric carcinoma	EBNA1, LMP1, LMP2	LMP1 induces tumorigenesis by activating NF-κB and MAPK pathways. LMP1 plays a critical role in promoting gastric carcinoma, immune evasion, and tumor progression.	[33, 36–38]
Latency III	Expression of all latent genes (EBNA1, EBNA2, LMP1, LMP2A, LMP2B) and active viral replication promote cell proliferation and survival.	PTLD, T-cell lymphomas	EBNA1, EBNA2, LMP1, LMP2A, LMP2B	EBNA2 and LMP1 induce cellular dysregulation, contributing to lymphoproliferative disorders and malignancy.	[36, 39, 40]

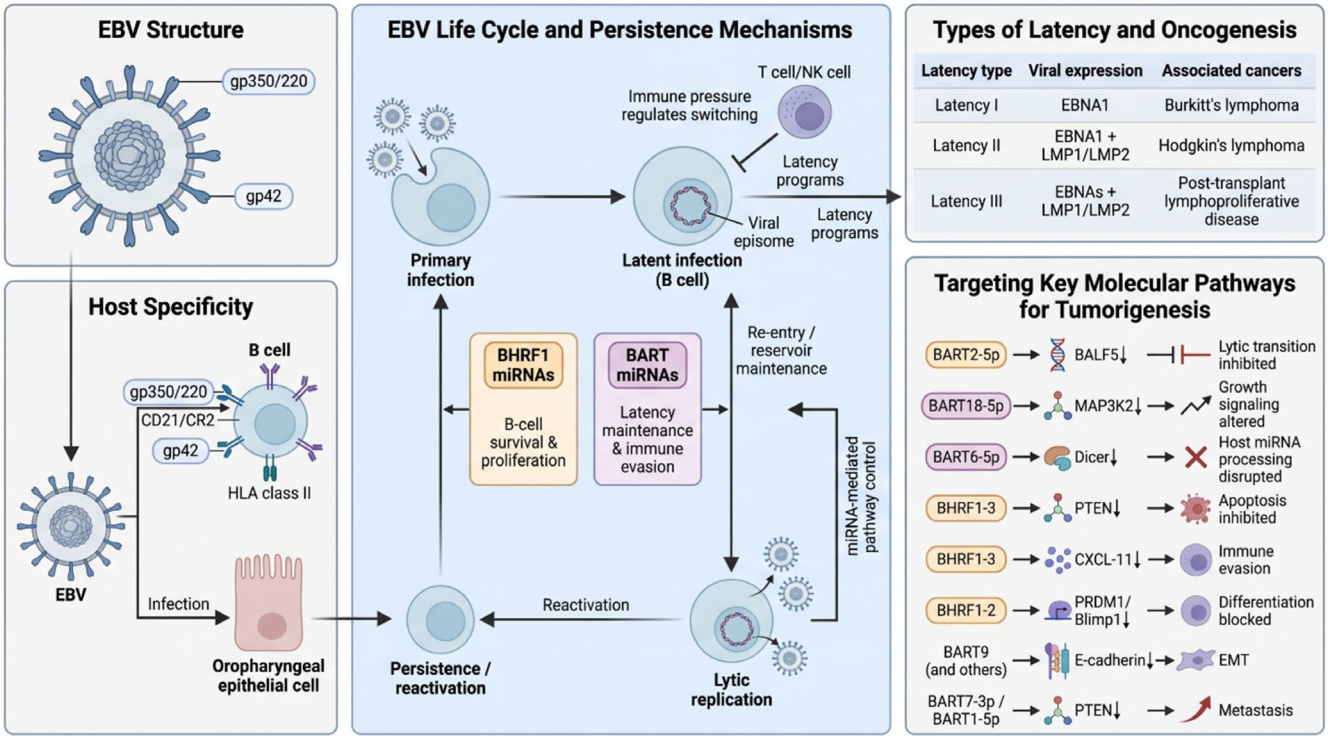

FIGURE 1 | EBV structure, host tropism, latency programs, and oncogenic mechanisms. The figure summarizes Epstein–Barr virus (EBV) infection, beginning with viral attachment to B cells through gp350/220–CD21/CR2 and gp42–HLA class II interactions, followed by infection of oropharyngeal epithelial cells. After primary infection, EBV establishes latency in B cells as a viral episome, with periodic reactivation into lytic replication that supports long-term persistence. Different latency programs show distinct viral gene-expression patterns and are associated with EBV-related cancers, including Burkitt lymphoma, Hodgkin lymphoma, and post-transplant lymphoproliferative disease. EBV-encoded miRNAs, including BHRF1 and BART miRNAs, promote tumorigenesis by altering apoptosis, immune evasion, differentiation, epithelial–mesenchymal transition, and metastasis-related pathways.

allows EBV to persist in a dormant state. This persistent latency contributes to the development of Burkitt lymphoma [41, 42].

Latency II is characteristic of Hodgkin lymphoma. EBV expresses a limited set of latent proteins: EBNA1, LMP1, and LMP2. LMP1 is a key oncoprotein that activates cellular pathways like NF-κB, MAPK, and PI3K/AKT, which promote cell survival and proliferation. While less characterized, LMP2 helps maintain latency and modulate immune responses [33, 43].

Latency III represents the most transcriptionally active state, with the expression of a broad set of latent genes, including EBNA1, EBNA2, EBNA3A, EBNA3B, EBNA3C, LMP1, and LMP2. This latency type is typically found in infected lymphoblastoid cell lines and is associated with certain B-cell lymphomas. The extensive expression of these viral proteins drives cellular proliferation, promotes resistance to apoptosis, and facilitates malignant transformation, as observed in conditions such as post-transplant lymphoproliferative disorder (PTLD) involves the expression of a complete set of EBV latent genes. This robust viral activity alters the behavior of host cells. For example, EBNA2 enhances cell proliferation by activating cell cycle pathways, while LMP1 promotes cell survival by inhibiting apoptosis and activating key signaling cascades. The synergistic effects of these viral proteins and latent gene expression make Latency III a highly oncogenic state, driving the malignant transformation of infected cells [44, 45]. Understanding the mechanisms underlying EBV latency types and their role in disease progression is essential for identifying novel therapeutic targets. Ongoing research into EBV-specific antigens and immune evasion strategies continues to inform the development of novel treatments [36, 46].

3 | EBV-Encoded miRNAs: Biogenesis and Functions

EBV is recognized for encoding miRNAs and possesses 25 miRNA precursors that produce 44 mature miRNAs, classified as BHRF1 and BART miRNAs. The BHRF1 region encodes four miRNAs, whereas the BART region generates 40 miRNAs [47]. Viral miRNA biogenesis mirrors that of the host. Transcription produces primary miRNAs (pri-miRNAs), which are processed by Drosha into precursor miRNAs (pre-miRNAs). These are then exported to the cytoplasm by the exportin-5/Ran GTPase route [48, 49], where Dicer cleaves them into mature miRNAs. The mature miRNAs are then loaded into the RISC complex to regulate gene expression [50].

EBV-encoded miRNAs show distinct expression patterns based on cell type and latency phase. BART miRNAs are highly expressed in epithelial cells, while BHRF1 miRNAs are abundant in B cells, particularly during Latency III [51, 52]. This

differential expression signifies varied functional roles. During lytic replication, specific miRNAs like miR-BHRF1-2 and miR-BHRF1-3 are induced to directly suppress the viral transcription activator Zta, regulating viral gene expression. Crucial for immune evasion and oncogenesis, EBV miRNAs are highly expressed in associated cancers such as Burkitt lymphoma, influencing tumor invasion, metastasis, and apoptosis [53].

In Burkitt lymphoma, EBV-encoded miRNAs, especially from the BART region, influence cell differentiation, proliferation, apoptosis, and the cell cycle, functioning as positive regulators of oncogenesis [54] certain viral miRNAs may negatively affect oncogenesis, as indicated by the recurrent deletions in BART miRNA clusters in EBV-positive lymphomas [54]. Specifically, miR-BHRF1-3 diminishes EBV lytic gene expression, hence reducing lytic replication through direct suppression of Zta expression [55]. Viral miRNAs are highly expressed in EBV-associated lymphomas, including Burkitt and Hodgkin. They bind to their targets with higher efficacy than host miRNAs. In Burkitt lymphoma, miR-BART6-3P and miR-BART17-5P are the most commonly evaluated viral miRNAs [56]. In classical Hodgkin lymphoma, EBV miRNAs facilitate the persistent activation of the NFκB pathway, a defining characteristic of Hodgkin and Reed-Sternberg (HRS) cells [57]. This activation transpires via many methods, encompassing genetic modifications, EBV infection, and interactions with the microenvironment [57].

4 | Mechanisms of EBV miRNA-Mediated Carcinogenesis

4.1 | The Impact of EBV miRNAs on Host Immune Evasion

EBV miRNAs play a crucial role in evading innate as well as adaptive immune mechanisms, as shown in (Table 2 and Figure 2). They suppress the expression of pattern-recognition receptors (PRRs) such as RIG-I, impairing immune activation, and also disrupt inflammasome activation, including targeting the NLRP3 inflammasome and IL-1 receptor signaling, which impedes immune responses [53]. Additionally, EBV miRNAs, such as miR-BART20-5p and miR-BART8, suppress STAT1, a key component of the IFN-γ signaling cascade, enabling the virus to escape antiviral immune responses [61]. In terms of natural killer (NK) cell response, EBV miRNAs like miR-BART7 reduce TGF-β1, impairing NK cell recognition of virus-infected cells [67], while others, including miR-BART1 and miR-BART2, inhibit cytokines essential for immune activation, such as IL-12 [68]. Furthermore, EBV miRNAs weaken antigen presentation by targeting enzymes and transporters involved in antigen processing and MHC presentation [69].

In adaptive immunity, EBV miRNAs also affect MHC I presentation by targeting TAP2, with miR-BHRF1-3 and miR-BART17 playing crucial roles. Additionally, miR-BART1 influences the enzyme IFI30, while miR-BART2 regulates LGMN production, and both miR-BART2 and miR-BHRF1-2 target CTSB, impairing antigen presentation on MHC II for T helper cells. Moreover, miR-BHRF1-3 reduces CXCL-11, a ligand for NK cells, and multiple EBV miRNAs suppress Th1 cell development by binding to IL-12, IL-12B, and IL-23 mRNAs. Other inflammatory cytokines, like IL-6, are also downregulated [68]. Yoon et al. reveal that miR-BART5-5p plays a critical role in the progression of EBV-associated gastric carcinoma (EBVaGC) by targeting PIAS3, leading to STAT3 activation and the upregulation of PD-L1. This process promotes immune evasion, inhibits apoptosis, and augments tumor proliferation, migration, and invasion [70].

TABLE 2 | Epstein–Barr virus miRNAs causing immune evasion.

MiRNAs	Target genes	References
(A) EBV miRNAs causing innate defense evasion		
miR-BART6-3p	RIG-I	[58]
miR-BART15-3p	NLRP3	[59]
miR-BART16-5p	CREBBP	[60]
miR-BART20-5p, miR-BART8	IFNG- STAT1	[61]
miR-BHRF1-3-5p	CXCL-11	[62]
miR-BHRF1	IL-1R1	[63]
(B) EBV miRNAs causing adaptive defense evasion		
miR-BART1-3p, miR-BART10-3p, miR-BART22-3p	IL12B	[64]
miR-BART1-5p	LY75	[65]
miR-BART17-5p	TAP2	[66]
miR-BHRF1-2-3p	IL12B, CSTB, TAP2	[64, 66]

4.2 | EBV-Encoded miRNAs Regulating Cellular Proliferation and Apoptosis

EBV-encoded miRNAs significantly influence cancer progression by governing cellular proliferation and apoptosis as shown in Figure 3. Research indicates that BART miRNAs enhance the initiation and growth of EBVaGC in vivo [71, 72]. Specifically, certain BART miRNAs, such as miR-BART3 and miR-BART5, have been linked to the regulation of the p53, TGF-β, and Wnt signaling pathways [73]. Furthermore, miR-BART7 promotes NPC cell proliferation by affecting oncogenic pathways, including TGF signaling [74].

One of the primary mechanisms behind the oncogenic potential of EBV miRNAs is their ability to regulate tumor suppressor genes. For instance, miR-BART10 suppresses β-TrCP, which may lead to the stabilization of oncogenic proteins like Snail and β-catenin [75]. Similarly, miR-BART7-3p enhances tumor growth by activating the PTEN/PI3K/Akt pathway and promoting oncogenic transcription factors such as c-Myc and c-Jun [76]. Another key miRNA, miR-BART3*, facilitates NPC cell proliferation by targeting and downregulating the tumor suppressor DICE1 [77]. Zhang et al. identified the oncogenic role of miR-BART19-3p in EBV-linked illnesses. Its overexpression promoted cell proliferation and inhibited apoptosis, with adenomatous polyposis coli (APC) confirmed as a direct target, and showed an inverse correlation with miR-BART19-3p in chronic active EBV samples. These findings highlight miR-BART19-3p's

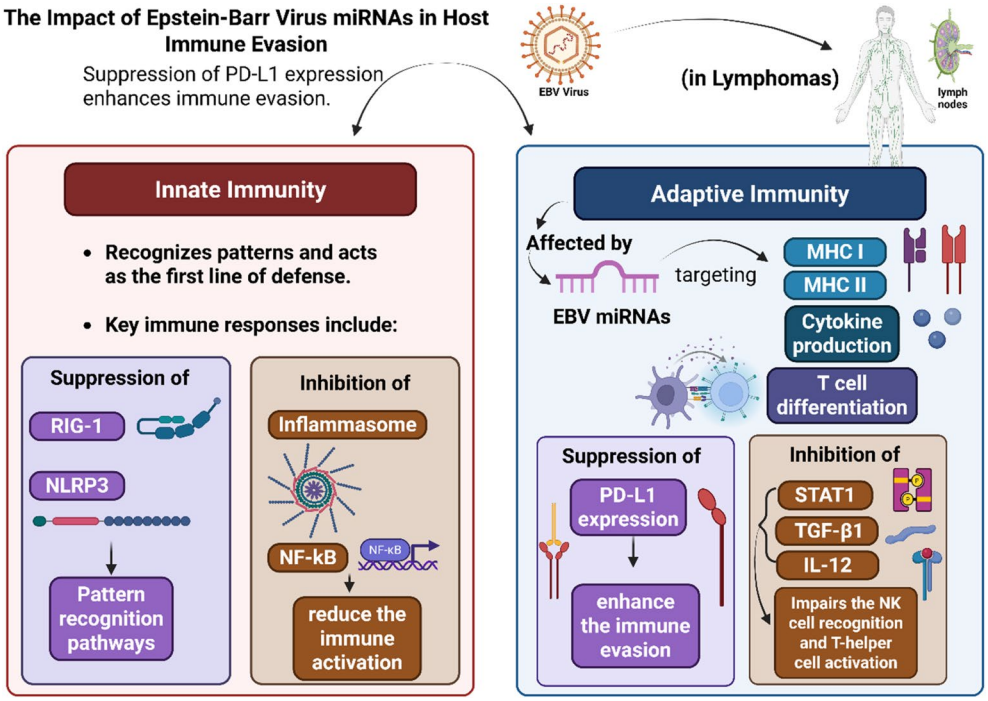

FIGURE 2 | Impact of Epstein–Barr virus miRNAs in host immune evasion in lymphomas. This figure illustrates the role of Epstein–Barr virus (EBV) miRNAs in suppressing both innate and adaptive immune responses in lymphoma. On the left, the innate immune system is depicted, showing how EBV miRNAs interfere with pattern recognition receptors (PRRs) such as RIG-I, inflammasomes (e.g., NLRP3), and NF-κB signaling, thereby impairing immune activation. On the right, the adaptive immune system is shown, with EBV miRNAs targeting key immune processes, including antigen presentation via MHC I and II, cytokine production (e.g., IL-12), and T-cell activation, all of which contribute to immune evasion. This suppression facilitates the persistence and progression of EBV-associated lymphomas.

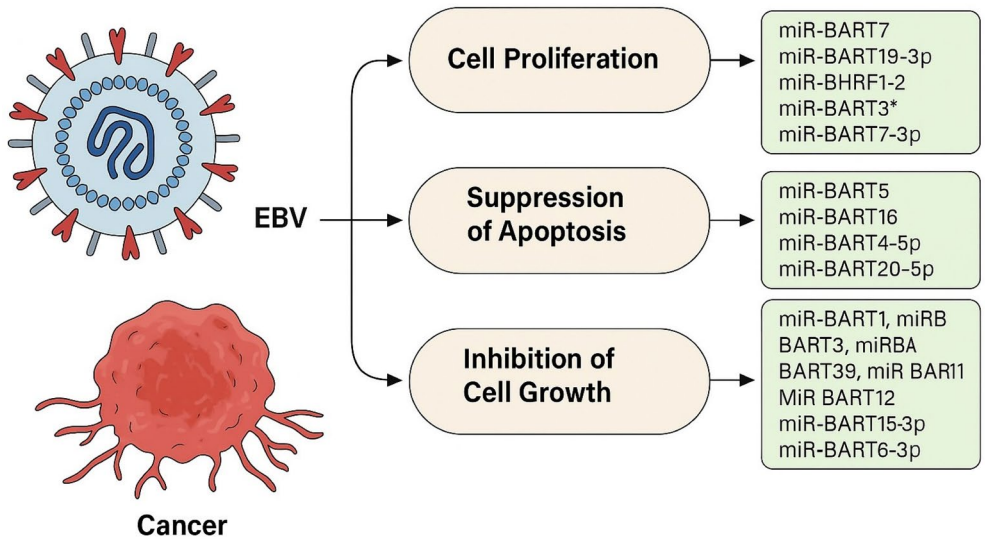

FIGURE 3 | The oncogenic functions of Epstein–Barr virus (EBV)–encoded miRNAs in cancer. The diagram illustrates how EBV produces specific miRNAs that modulate key cellular processes, enhancing cell proliferation, suppressing apoptosis, and influencing cell growth regulation. Individual miRNAs, including miR-BART7, miR-BART19-3p, miR-BART5, miR-BART16, miR-BART4-5p, miR-BART20-5p, miR-BART15-3p, and miR-BART6-3p, are shown in association with their respective functions. Collectively, these miRNAs promote tumorigenesis and survival of EBV-associated cancer cells, such as nasopharyngeal carcinoma (NPC) and EBV-associated gastric carcinoma (EBVaGC).

role in tumorigenesis and its potential as a therapeutic target [78].

Additional studies have shown that miR-BART19-3p suppresses Wnt inhibitory factor 1 (WIF1) and tumor suppressors like Nemo-like kinase (NLK) and APC, thereby enhancing EBVaGC cell proliferation [79]. Similarly, miR-BART6-3p decreases the production of IL-6R and PTEN, stimulating EBV-positive Burkitt lymphoma cell proliferation. These miRNAs impact key pathways, including NF-κB and PI3K/Akt, making them

potential therapeutic targets for EBV-associated lymphomas. Another significant finding is that miR-BHRF1-2 promotes cell cycle progression and inhibits apoptosis in LCLs by suppressing PRDM1/Blimp1 [28].

EBV BART miRNAs actively suppress apoptosis, allowing cancer cells to persist and proliferate [72]. For instance, miR-BART4-5p has been shown to reduce apoptosis in EBVaGC cells by inhibiting the pro-apoptotic protein BH3-interacting domain death agonist (BID) [80]. Similarly, miR-BART16 interacts with translocase of outer mitochondrial membrane 22 (TOMM22), which disrupts the mitochondrial localization of Bcl-2-associated X protein (BAX), ultimately preventing BAX-induced apoptosis [81]. Additionally, Zhang et al. investigate the impact of miR-BART16 on EBVaGC. While the oncogenic LMP1 was absent in EBVaGC samples, miRNA-BART16 was highly expressed in primary tissues. Since miRNA-BART16 suppresses LMP1, altering its levels in cell lines affects LMP1 expression. Inhibition of miRNA-BART16 led to increased cell proliferation and G2/M phase accumulation but had no significant effect on apoptosis. These findings indicate that miRNA-BART16 regulates LMP1 expression and plays a role in EBVaGC progression [82].

Another significant miRNA, miR-BART20-5p, promotes EBVaGC cell survival by interacting with Bcl-2-associated death promoter (BAD), further confirming its anti-apoptotic function in EBVaGC [83, 84]. Several other BART miRNAs, including miR-BART1, miR-BART3, miR-BART9, miR-BART11, and miR-BART12, have been identified as regulators that suppress the expression of the Bcl-2-interacting mediator of cell death (BIM) in EBVaGC cells. EBV employs multiple strategies to downregulate BIM, a key factor in triggering apoptosis, suggesting that inhibiting BIM-mediated cell death is essential for the virus to maintain its presence in cancer cells [85]. Additionally, miR-BART5, which is overexpressed in NPC and EBVaGC cells, contributes to tumor cell survival by inhibiting PUMA [19]. Several other BART miRNAs, including miR-BART1, miR-BART2, miR-BART3, miR-BART4, miR-BART7, miR-BART8, and miR-BART22, have been found to significantly suppress caspase-3, a central executioner of apoptosis. Moreover, Min et al. [86] discovered that miR-BART1-3p inhibited the expression of Disabled homolog 2 (DAB2), a tumor suppressor gene linked to apoptosis, in EBVaGC cells, allowing them to evade programmed cell death. Collectively, these EBV miRNAs interfere with apoptotic signaling pathways, ensuring the prolonged survival and persistence of cancer cells [87].

EBV-encoded miRNAs not only promote tumor survival but can also suppress cancer cell growth by regulating anti-apoptotic proteins. For example, miR-BART15-3p has been shown to reduce EBVaGC cell proliferation while promoting apoptosis by lowering the levels of the BIR repeat-containing ubiquitin-conjugating enzyme (BRUCE) [88]. Additionally, this miRNA downregulates Tax1-binding protein 1 (TAX1BP1), further increasing apoptosis in EBVaGC cells [89]. Since caspase-mediated cleavage of viral proteins can enhance viral replication and spread, miR-BART15-3p may contribute to EBV lytic replication by triggering cell death [90]. Additionally, Dan Wang and collaborators found that the miR-BART6-3p/LOC553103/stathmin 1 (STMN1) axis influenced the regulation of cell cycle-related proteins, including p27, Cyclin E1 (CCNE1), Cyclin D1 (CCND1), and cyclin-dependent kinase 4 (CDK4), ultimately suppressing cell proliferation [91].

4.3 | The Role of EBV miRNAs in Tumor Microenvironment Modulation

Beyond apoptosis regulation, EBV miRNAs also influence cancer progression by modulating their own gene expression. For instance, miR-BART9 promotes the proliferation of nasal NK/T cell lymphoma (NNKTL) cells by upregulating the LMP1 [92]. Another viral component, EBV-encoded BHRF1, functions as a Bcl-2-related protein that prevents apoptosis by interacting with BIM. Interestingly, miR-BART10-3p has been found to target BHRF1 directly. However, in Burkitt lymphoma cells, miR-BART10-3p paradoxically inhibits apoptosis, likely by suppressing apoptosis-related proteins [93]. Min and Lee examined the impact of miR-BART10-3p on EBVaGC. Researchers found that miR-BART10-3p directly targets DKK1, significantly reducing its expression. Overexpression of miR-BART10-3p suppressed DKK1, promoting cell proliferation and migration [94]. EBV miRNAs contribute to creating a tumor-supportive microenvironment. Chronic inflammation associated with EBV infection plays a key role in the progression of NPC and EBVaGC. For example, miR-BART11 promotes monocyte differentiation into macrophages by targeting forkhead box P1 (FOXP1). This function enhances the inflammatory reaction in NPC and EBVaGC, facilitating tumor cell proliferation [95].

The tumor microenvironment (TME) in EBV-associated lymphomas is characterized by a distinctive immunosuppressive cell composition, actively shaped by EBV-encoded miRNAs. In classical Hodgkin lymphoma (cHL), the TME is dominated by a reactive infiltrate composed predominantly of CD4+ T cells (including regulatory T cells, Tregs), exhausted CD8+ cytotoxic T cells with elevated PD-1 and LAG-3 expression, and markedly expanded tumor-associated macrophages (TAMs), particularly M2-polarized CD163+ macrophages, all of which are significantly more abundant in EBV-positive compared to EBV-negative cHL cases [96, 97]. Spatial transcriptomic and high-parameter imaging analyses have further revealed that EBV+ cHL tumor cells receive enhanced pro-survival signals from neighboring macrophages while simultaneously being shielded from Treg-mediated suppression, establishing spatially distinct immunosuppressive niches within the tumor [96]. In Burkitt lymphoma, the TME similarly demonstrates M2 macrophage polarization, in which tumor-associated macrophages with a protumor phenotype predominate in cases with the classic "starry sky" histological pattern, particularly in EBV+ cases, while M1-polarized macrophages with an interferon-γ-driven CD8+ T cell response characterize the less common granulomatous variant associated with more favorable outcomes [98]. In EBV-positive diffuse large B-cell lymphoma (EBV + DLBCL), spatial transcriptomics and single-cell RNA sequencing have identified PD-1/PD-L1 signaling as a hallmark immunosuppressive pathway of the TME, with TLR4 identified as a downstream effector that is EBV-status-dependent [99].

EBV-encoded miRNAs are central orchestrators of this immunosuppressive TME architecture. miR-BART11 and miR-BART17-3p upregulate PD-L1 expression in tumor cells by targeting FOXP1 and PBRM1, respectively, transcriptional repressors of the PD-L1 enhancer, thereby establishing a molecular bridge between viral miRNA activity and PD-1/PD-L1-mediated T cell exhaustion within the TME [100]. Furthermore, miR-BART5-5p drives PD-L1 upregulation through PIAS3/pSTAT3 modulation in EBV-associated gastric carcinoma, and parallel mechanisms are operative in EBV+ lymphomas [70]. EBV miRNAs additionally suppress the antigen presentation machinery (by downregulating TAP1, TAP2, and MHC class I/II) and reduce NK cell-activating ligands, such as MICB, thereby remodeling the spatial immune landscape to favor tumor immune escape [101, 102].

The miRNA-sculpted immunosuppressive TME in EBV-associated lymphomas presents both a challenge and a compelling therapeutic opportunity. The documented upregulation of PD-L1 by EBV miRNAs provides a strong rationale for immune checkpoint blockade (ICB). Accordingly, anti-PD-1/PD-L1 therapies have shown clinical efficacy in EBV-positive malignancies: in EBV-driven nasopharyngeal carcinoma, PD-1 blockade combined with chemotherapy has been established as the first-line standard of care for recurrent/metastatic disease [103]. In cHL, pembrolizumab and nivolumab (anti-PD-1 agents) demonstrate remarkable response rates, particularly in EBV+ cases with high PD-L1 expression in HRS cells and macrophages, features associated with adverse outcome if left untreated [97]. Beyond single-agent ICB, combination strategies offer synergistic potential. EBV-specific T cell (EBVST) therapy, including EBV-specific cytotoxic T lymphocytes and CAR-T cells co-expressing EBV antigen receptors (e.g., CD30.CAR on EBV-specific T cells), can reverse CD8+ T cell exhaustion in the TME and show activity in rituximab-refractory EBV-associated lymphomas [104, 105]. LMP2-mRNA lipid nanoparticle vaccines that drive CD8+ central and effector memory T cell expansion have demonstrated synergistic anti-tumor effects when combined with anti-PD-1 therapy in preclinical models of EBV-driven malignancies, providing proof-of-concept that reversing miRNA-mediated T cell exhaustion through targeted vaccination enhances the efficacy of ICB [106]. Collectively, these emerging strategies highlight how a detailed understanding of EBV miRNA-driven TME remodeling, spanning immune cell composition, spatial architecture, and checkpoint upregulation, directly informs the rational design of next-generation immunotherapies for EBV-associated lymphomas.

5 | Crosstalk Between EBV and Burkitt Lymphoma

Burkitt lymphoma is a highly aggressive subtype of non-Hodgkin lymphoma characterized by rapid cellular proliferation and a well-documented association with EBV infection. EBV, a ubiquitous gamma herpes virus infecting over 90% of the global population, has been strongly implicated in Burkitt lymphoma pathogenesis, particularly in endemic variants. Among the molecular tools employed by EBV to modulate host cell biology, viral miRNAs have emerged as pivotal regulators. The EBV genome encodes approximately 44 mature miRNAs, which orchestrate a wide range of cellular functions, including immune evasion, inhibition of apoptosis, and promotion of cellular proliferation. In the context of Burkitt lymphoma, EBV-derived miRNAs contribute to oncogenesis by downregulating tumor suppressor genes, altering key signaling cascades, and promoting viral latency and persistence within the tumor microenvironment, as illustrated in Table 3. These miRNAs also play a role in circumventing host immune surveillance, thereby enhancing viral survival and oncogenic potential. Furthermore, EBV infection may drive genomic instability and provide selective growth advantages to infected B cells [115, 116]. While comprehensive profiling of EBV-encoded miRNAs in Burkitt lymphoma remains incomplete, significant progress has been made, particularly in understanding the roles of the BART and BHRF1 clusters in latency and lymphoma development.

EBV miRNAs contribute significantly to the oncogenic landscape of Burkitt lymphoma by targeting tumor suppressors, enhancing B-cell survival, and facilitating immune evasion. EBV-encoded miRNAs such as EBV-BART-6-3p act in synergy with host miRNAs like hsa-miR-142 to downregulate tumor suppressors, notably PTEN and IL-6R, thereby fostering immune evasion and lymphomagenesis in EBV-positive Burkitt lymphoma. These miRNAs also suppress regulators like PRDM1/Blimp1, which is critical for B-cell differentiation and apoptosis [28, 110, 111]. Furthermore, EBV miRNAs promote B-cell survival and proliferation by disrupting apoptotic pathways and sustaining cell cycle progression, with miR-378a-3p playing a central role in maintaining proliferative capacity, and the BART and BHRF1 miRNA clusters supporting continued growth of infected B cells [55]. They also dysregulate apoptosis and immune checkpoints, as evidenced by miR-BART11 and miR-BART17-3p, which upregulate PD-L1 expression indirectly through the repression of transcriptional inhibitors like FOXP1 and PBRM1 [102, 117, 118]. In terms of immune evasion, EBV miRNAs inhibit antigen presentation by interfering with MHC expression and antigen-processing machinery, thus compromising T-cell recognition of infected B cells [119, 120]. They also modulate cytokine signaling and T-cell responses by downregulating IL-6R and influencing PD-1/PD-L1-mediated exhaustion pathways [102, 110, 111, 121]. Moreover, these viral miRNAs suppress innate immunity by downregulating interferon signaling and inhibiting NK cell activation, enabling viral persistence and tumor immune escape [117, 122, 123]. In parallel with viral miRNA activity, EBV infection alters the expression profile of host miRNAs; for example, hsa-miR-127 is upregulated by EBNA1, thereby impeding B-cell differentiation and fostering malignancy [119, 120]. Host miRNAs may either cooperate with or antagonize EBV miRNA functions. miR-142 collaborates with EBV-BART-6-3p in suppressing PTEN and IL-6R, whereas miR-150 acts as a tumor suppressor by promoting differentiation when reintroduced into EBV-positive Burkitt lymphoma cells [124, 125] (Figure 4). Importantly, oncogenic drivers like MYC and BCL6 are influenced by deregulated host miRNAs; the downregulation of let-7, miR-98, and miR-363 results in unchecked MYC expression, while the absence of miR-155, which normally prevents MYC-IGH translocation, further contributes to the malignant phenotype [121, 123, 126].

TABLE 3 | Epstein–Barr virus-encoded miRNAs implicated in Burkitt lymphoma.

Type	Target	Function	References
BART miRNAs			
miR-BART1	PSAT1, CTSB, LY75	Modulates apoptosis; regulates Th1 cell differentiation and cell cycle	[100]
miR-BART2	BALF5, MICB (NKG2D ligand)	Reduces viral DNA replication; maintains latent state; evades NK cell killing	[107]
miR-BART3	TP53	Downregulates tumor suppressor gene; enhances cell survival	[107]
miR-BART6	HLA class I, IL-6R, PTEN	Promotes proliferation via NF-κB and PI3K/Akt signaling pathways	[72]
miR-BART9	FOXO3	Promotes lytic reactivation in Burkitt lymphoma cells	[108]
miR-BART1-3p	IL-12B	CD4+ T cell response	[64, 66]
	IFI30	CD4+ T cell response	
	CASP3	Apoptosis	
miR-BART1-5p	IFI30	CD4+ T-cell response	[64, 66]
	CASP3	Apoptosis	
miR-BART2-5p	CTSB	CD4+ T-cell response	[64, 66]
	LGMN	CD4+ T-cell response	
	IL-12B	CD4+ T-cell response	
	CASP3	Apoptosis	
	BALF5	Latency regulation	
miR-BART3-3p	IPO7	Innate immunity	[18, 109]
	CASP3	Apoptosis	[87]
miR-BART4-5p	CASP3	Apoptosis	[87]
miR-BART6-3p	PTEN *	Cell proliferation, apoptosis	[28, 110, 111]
	IL-6RB **	Innate immunity	
	RIG-I	Innate immunity	
miR-BART7-3p	CASP3	Apoptosis	[87]
miR-BART8-5p	CASP3	Apoptosis	[87]
miR-BART10-3p	IL-12B	CD4+ T cell response	[64, 66]
miR-BART13-3p	CASP3	Apoptosis	[87]
miR-BART15	*NLRP3*	Innate immunity	[59]
miR-BART16	*S1PR1*	Cell growth/mobility ***	[112]
	CREBBP	Innate immunity	
	IPO7	Innate immunity	
	CASP3	Apoptosis	
	TOMM22	Apoptosis	
miR-BART17	*TAP2*	$CD8^+$ T-cell response	[66]
miR-BART20-5p	*T-bet* ****	Transcription regulation of cytotoxic Nk cells	[113]

(Continues)

TABLE 3 | (Continued)

Type	Target	Function	References
miR-BART22	*CASP3*	Apoptosis	[64, 66, 87]
	IL-12B	$CD4^+$ T cell response	
BHRF miRNAs			
miR-BHRF1-1	CXCL11, PUMA	Modulates immune response; promotes immune evasion and lymphoma progression	[114]
miR-BHRF1-2	PRDM1	Promotes EBV lymphomagenesis	[28]
miR-BHRF1-3	BZLF1 (3′UTR)	Promotes tumor growth and metastasis; maintains EBV latency	[55]
miR-BHRF1-2-5p	IL-1 receptor	Innate immunity	[63]

6 | Crosstalk Between EBV and Hodgkin Lymphoma

Hodgkin lymphoma is a malignancy derived from unique neoplastic cells called Hodgkin and Reed-Sternberg (HRS). Those cells are characterized by their large, multinucleated nucleus and neoplastic shape. In addition, HRS are often found in the background of reactive immune cells [127]. Those B cells derived from malignancies were due to mutations in IgH variable-region segments [128]. Classical Hodgkin lymphoma is associated with EBV infections. Those associations are reported to be generated linked to a set of viral proteins and miRNAs that play an important role in immune evasion and tumor development, as shown in Table 4 [132]. EBV utilizes its latency type II program on HRS, which manifests its malignancy. miR-BART2-5p was found to be expressed in EBV-positive Hodgkin lymphoma patients. It was reported to escape NK cells through its targeting of MHC Class I Polypeptide-Related Sequence B (MICB). MICB is a key activator of NK cell NKG2D receptors, which promote immune surveillance. miR-BART2-5p alters the protein expression of MICB rather than its gene expression through targeting the 3′UTR of MICB mRNA [129]. Repression of MICB prevents recognition by NK cells via NKG2D receptors, thereby allowing tumor cells to evade immune surveillance and prolong survival [130]. miR-BART2-5p was also mentioned to interfere with the expression of RND3 (Rho family GTPase 3) [131]. RND3 plays a role in the rho/ROCK signaling pathway. ROCK acts as a downstream effector of the small GTPases RhoA, B, and C, which play a key role in cellular functions as cell movement, motility, and proliferation. This role is due to the modulation of the actin cytoskeleton [133].

Overexpression of ROCK has been reported to be associated with the migration and metastasis of several cancers, such as melanoma and Hepatocellular carcinoma [134]. RND3 acts as an inhibitor of the Rho/ROCK pathway [135]. Therefore, reduced RND3 expression resulting from miR-BART2-5p interaction can promote tumor invasiveness. miR-BART2-5p targets the RND 3 mRNA, reducing its transcriptional levels, consequently activating the Rho/ROCK pathway and enhancing tumor metastasis [131]. Another Latency type II EBV-derived miRNAs were found to contribute to cancer progression as miR-BART5. miR-BART5 was reported to interact with PUMA [19]. PUMA is a BH3-only member of the Bcl2 family and plays a pivotal role in mediating p53-dependent and independent apoptotic pathways. Those pathways are activated through several stimuli as genotoxic stress and oncogene activity [136]. mir-BART5 binds to the 3′UTR of PUMA mRNA, decreasing its expression, thereby allowing the cell to escape apoptosis and promoting tumor cell survival. It was also mentioned that the overexpression of miR-BART5 led to the repression of PUMA and suppression of PUMA-mediated apoptosis [19]. Also, miR-BART3 was found to be involved in tumor progression. DICE1, also known as CIC, is proposed to function as a tumor suppressor [137]. miR-BART5 was found to interact with DICE1 through binding to the 3′UTR of its mRNA. This leads to a repression of the DICE tumor suppression effect and induction of uncontrolled cell proliferation [77]. Another miRNA that might contribute to Hodgkin lymphoma progression in EBV-positive patients is miR-BART1-5p. miR-BART1-5p was found to correlate with PTEN suppression, as its overexpression significantly reduced PTEN abundance [30]. PTEN is a tumor suppressor that negatively regulates the PI3K/AKT pathway. The pathway activation and AKT accumulation contribute to promoting cellular growth and survival by escaping apoptosis [138].

7 | Other EBV-Associated Cancers

In cancer, particularly lymphomas, miRNAs are frequently unregulated, serving as either oncogenes or tumor suppressors and contributing to carcinogenesis and progression, as illustrated in Figure 5 [139–141]. A recent study has shown that miRNAs play a significant role in Diffuse Large B-cell Lymphoma's (DLBCL) etiology and progression by regulating multiple signaling pathways involved in tumor cell proliferation, survival, and immune evasion [142–147].

MicroRNA-21 plays an oncogenic function in DLBCL, as it is commonly elevated. It suppresses tumor suppressor genes like PDCD4 and PTEN, which promote cell survival and tumor growth [142]. Furthermore, it has a therapeutic impact that suppresses proliferation, increases apoptosis, and reduces the invasion of DLBCL cells, making it a promising therapy target [142, 143, 148].

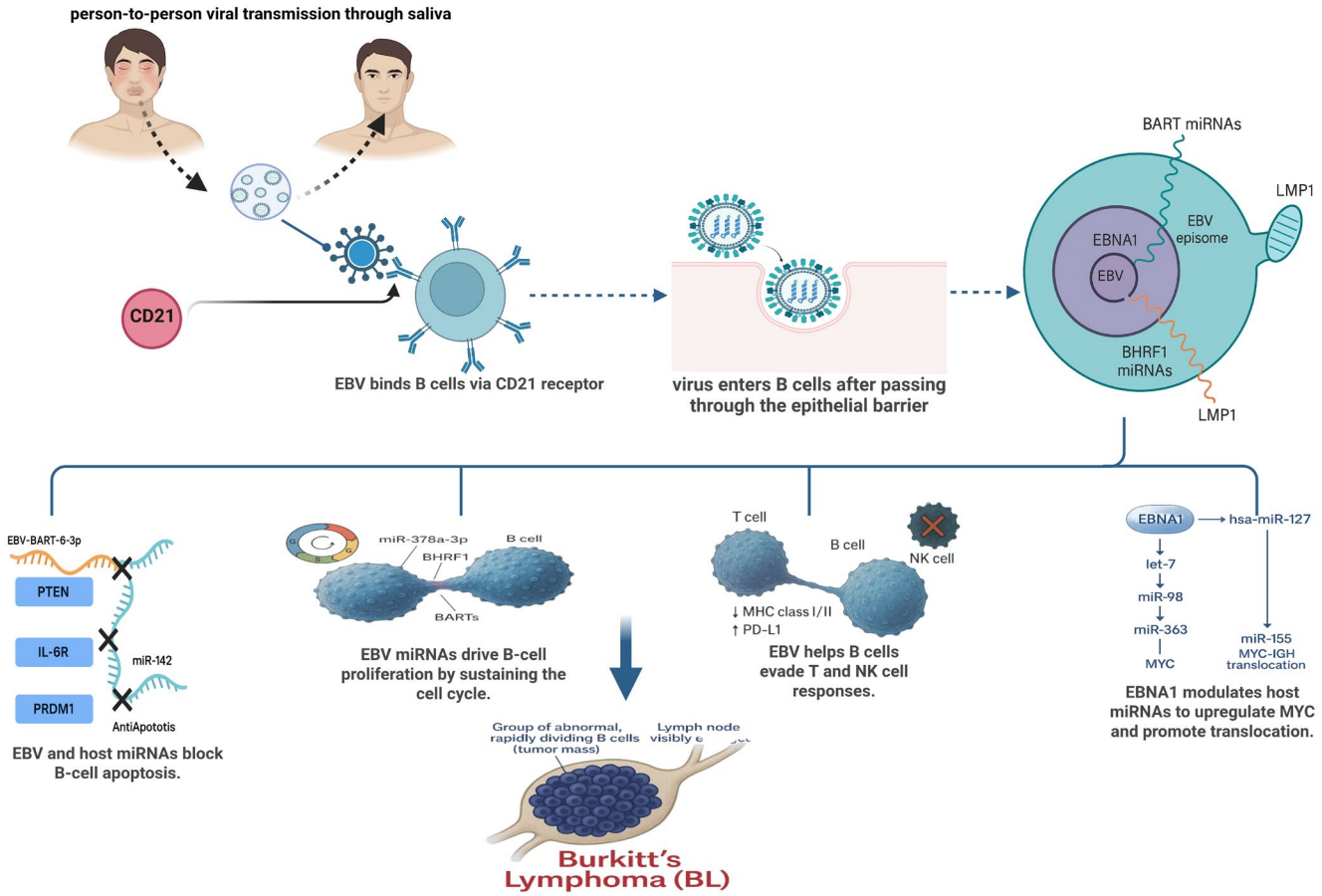

FIGURE 4 | Epstein–Barr virus miRNAs promote immune evasion and B-cell survival in Burkitt lymphoma. This illustration outlines the stepwise progression from EBV infection to the development of Burkitt lymphoma, emphasizing the oncogenic role of EBV-encoded miRNAs. The diagram begins with EBV transmission via saliva and the virus binding to CD21 receptors on B lymphocytes, leading to viral entry and establishment of latency within the host nucleus. During Latency III, EBV expresses latent genes (EBNA1, LMP1) and miRNA clusters (BART, BHRF1), which modulate host gene expression. EBV miRNAs such as EBV-BART-6-3p and host miR-142 downregulate tumor suppressors like PTEN, IL-6R, and PRDM1, preventing apoptosis. miR-378a-3p and BHRF1 miRNAs promote B-cell proliferation, while BART miRNAs mediate immune evasion by reducing MHC class I/II and increasing PD-L1 expression, impairing recognition by T and NK cells. Additionally, EBNA1-driven modulation of host miRNAs (e.g., hsa-miR-127) and suppression of let-7, miR-98, and miR-155 contribute to MYC overexpression and MYC-IGH translocation. These coordinated mechanisms support the survival and clonal expansion of infected B cells, culminating in.

TABLE 4 | Epstein–Barr virus-encoded miRNAs implicated in Hodgkin lymphoma.

miRNA	Target	Mechanism	References
miR-BART2-5p	MICB protein	Downregulates protein expression and evades NK cells' surveillance	[129, 130]
	RND3	Activates Rho/ROCK pathway and promoting metastasis	[131]
miR-BART5	PUMA	Suppresses its expression, leading to suppressed apoptosis	[19]
miR-BART3	DICE1 (CIC)	Reduces its tumor-suppressing activity, leading to tumor cell proliferation	[77]
miR-BART1-5p	PTEN	Causes accumulation of AKT and tumor cell survival	[30]

Another significant miRNA, miR-155, is overexpressed in several B-cell malignancies, including DLBCL [149]. It regulates cell proliferation and death by targeting tumor suppressor genes like SHIP1 and c-Maf, and it is linked to the activation of the PI3K/AKT pathway [149]. Furthermore, it can serve as a prognostic marker, as its expression level correlates with a poor prognosis and aggressive disease [146, 147, 149]. miR-34a is often downregulated in DLBCL, and low expression promotes cell survival and lymphoma progression. miR-34a regulates key mechanisms of apoptosis and cell cycle regulation. Furthermore, miR-34a has a restorative impact, as its expression has been found to cause apoptosis and prevent tumor growth, implying its therapeutic potential [144, 146, 147, 150]. miR-17-92 cluster regulates apoptosis and cell survival in DLBCL. Its overexpression enhances lymphoma progression by inhibiting tumor suppressors such as PTEN and Bim. It is linked to increased tumor development

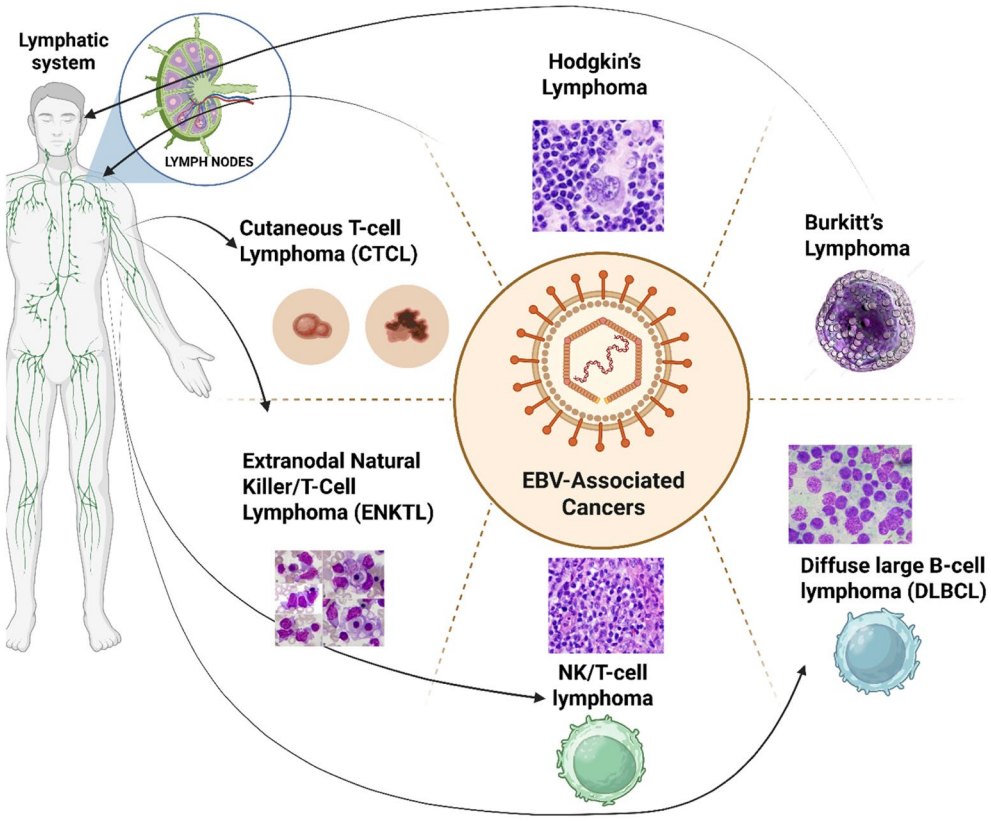

FIGURE 5 | MiRNAs of Epstein–Barr virus-induced cancers. This figure illustrates various cancers associated with EBV infection, affecting multiple components of the lymphatic and epithelial systems. EBV is linked to several lymphomas, including Hodgkin lymphoma, Burkitt lymphoma, DLBCL, NK/T-cell lymphoma, cutaneous T-cell lymphoma (CTCL), and extranodal natural killer/T-cell lymphoma (ENKTL).

and resistance to chemotherapy [146, 147, 150]. miR-21, miR-155, and miR-34a are not only involved in DLBCL pathogenesis but also offer promise as diagnostic, prognostic, and therapeutic biomarkers. Targeting these miRNAs with miRNA mimics or inhibitors has shown potential in preclinical models for treating DLBCL, highlighting their clinical relevance [143, 146, 147, 151].

Extranodal Natural Killer/T-cell lymphoma (NKTCL) is a rare and aggressive type of lymphoma that frequently appears with extranodal involvement. miRNAs have been demonstrated to play essential roles in the course of NKTCL by regulating critical oncogenes and tumor suppressor genes [152]. miR-34a, miR-181c, miR-379, and miR-134 are typically epigenetically suppressed in NKTCL. This silencing is generally caused by DNA methylation, which decreases their tumor-suppressive activity [152]. miR-34a and miR-181c have a crucial role in regulating oncogenes such as PDGFRα, STAT3, and K-RAS, which contribute to cell survival and tumor growth [149, 153].

Few miRNAs are involved, such as miR-155, which is often overexpressed in NKTCL, modulates immune responses, and contributes to cancer by targeting genes including SHIP1 and c-Maf, resulting in uncontrolled cell proliferation and survival [149]. And targeting miR-155 in NKTCL could help reduce tumor progression and improve treatment outcomes, as its inhibition results in a reduction in inflammatory cytokine production [145, 148, 149, 153].

Both miR-20b and miR-143 regulate STAT3, a gene involved in NKTCL's immune evasion and survival. Inhibition of these miRNAs leads to lower STAT3 expression, which slows tumor development [145, 148, 149, 153]. The miRNA regulation network in NKTCL, particularly miR-34a, miR-155, and miR-181c, offers potential therapeutic targets. Restoring the expression of these miRNAs or blocking their targets may be a potential therapy option for people with NKTCL [149, 153].

In addition to DLBCL and NKTCL, miRNAs have important roles in other B- and T-cell cancers, such as Hodgkin lymphoma and Burkitt lymphoma, as previously discussed. In these malignancies, miRNAs such as miR-150, miR-155, and miR-21 play important roles in controlling cell differentiation, apoptosis, and immunological responses [152]. For example, miR-155 plays a critical role in both Hodgkin lymphoma and Burkitt lymphoma by regulating c-Maf, a transcription factor implicated in immune control [149]. Upregulation of miR-155 is associated with aggressive lymphoma behavior and a poor prognosis. miR-21 and miR-34a have comparable roles in lymphoma progression by regulating apoptosis and cell cycle regulation. Targeting these miRNAs may provide therapeutic benefits, especially in lymphomas that are resistant to standard therapy [152].

In addition to the previous table, miR-21 and miR-155 are the most frequently upregulated oncogenic miRNAs in various lymphomas and are associated with poor prognosis and therapy resistance [143, 146, 147, 151]. miR-34a, miR-181c, and other tumor-suppressor miRNAs, such as miR-150, are downregulated in various lymphoma subtypes, and their re-expression could serve as a viable treatment approach [145, 150, 153].

miRNAs in B-cell and T-cell malignancies affect apoptosis, cell survival, proliferation, immunological response, and metastasis by interacting with key pathways like PI3K/AKT, NF-κB, and JAK/STAT signaling [145, 153, 154].

8 | miRNA-Based Therapeutic Potentials of EBV-Induced Cancers

Beyond their mechanistic role in lymphoma pathogenesis, EBV-encoded miRNAs are therapeutically relevant as they also regulate latency, apoptosis, immune recognition, antigen presentation, cytokine signaling, and immune-checkpoint pathways [72]. Hence, EBV miRNAs are promising molecular targets for precision therapy in EBV-associated lymphomas, especially when used to restore apoptosis, enhance immune surveillance, or sensitize malignant cells to immunotherapy [126]. However, the field should be interpreted with caution, as EBV-miRNA-specific therapies are still largely preclinical, whereas EBV-directed cellular immunotherapies and EBV antigen-based vaccines are more clinically advanced [155].

8.1 | Direct Inhibition of Oncogenic EBV miRNAs

One direct therapeutic strategy is the inhibition of oncogenic EBV miRNAs using chemically modified antisense oligonucleotides, including antagomirs, locked nucleic acid anti-miRs, peptide nucleic acid inhibitors, and related anti-miRNA platforms [72]. These inhibitory molecules are designed to bind mature viral miRNAs and prevent them from repressing their target mRNAs, thereby restoring the expression of tumor-suppressive, pro-apoptotic, or immune-stimulatory genes [156].

In EBV-associated lymphomas, anti-EBV-miRNA therapy could theoretically restore the expression of targets involved in apoptosis and immune recognition, such as PUMA, BIM, CASP3, TAP2, MICB, CXCL11, PTEN, and PRDM1/Blimp1 [126]. In Burkitt lymphoma, inhibition of BHRF1 miRNAs may be particularly relevant because BHRF1 miRNAs support B-cell proliferation, inhibit apoptosis, and contribute to early EBV-driven B-cell transformation [116]. Inhibition of miR-BHRF1-2 may restore PRDM1/Blimp1 expression, which is important because PRDM1/Blimp1 promotes plasma-cell differentiation and can restrict malignant B-cell proliferation [28].

Targeting EBV BART miRNAs may also be useful because several BART miRNAs suppress apoptosis by regulating pro-apoptotic mediators such as PUMA, BIM, and caspase-3 [18]. For example, inhibition of miR-BART5 may restore PUMA-mediated apoptosis and increase the sensitivity of EBV-positive tumor cells to cell death [19]. Similarly, blocking BART miRNAs that suppress BIM or caspase-3 could reactivate intrinsic apoptotic signaling in EBV-positive lymphoma cells [85]. Another clinically relevant approach is to inhibit EBV miRNAs involved in immune evasion, especially those that reduce antigen presentation or NK-cell recognition. For instance, inhibition of miRNAs targeting TAP2 could restore antigen processing and improve CD8+ T-cell recognition of EBV-positive lymphoma cells [66].

Inhibition of miR-BART2-5p may also enhance NK-cell-mediated immune surveillance because this viral miRNA suppresses MICB, a stress-induced ligand recognized by the activating NK-cell receptor NKG2D [129]. EBV-miRNA inhibition may also improve chemokine-mediated immune recruitment because miR-BHRF1-3 targets CXCL11, a chemokine involved in T-cell trafficking [62].

8.2 | miRNA Replacement and Activating Strategies

Tumor-suppressive miRNA replacement using synthetic miRNA mimics may restore apoptosis, differentiation, and cell-cycle control in EBV-associated lymphomas [62]. Restoring miRNAs such as miR-34a and miR-150 may help suppress malignant B-cell proliferation, but this approach requires caution because each miRNA can regulate multiple genes and may cause off-target effects [147]. EBV-miRNA inhibition may also be combined with apoptosis-inducing drugs or immune checkpoint inhibitors to enhance lymphoma-cell killing and anti-tumor immunity [155].

8.3 | Delivery Platforms for EBV-miRNA Therapeutics

Efficient delivery remains a major barrier because RNA-based therapeutics are unstable in circulation and may show poor cellular uptake [156]. Lipid nanoparticles, polymeric nanoparticles, antibody-conjugated systems, viral vectors, and engineered exosomes may improve RNA stability, tumor targeting, and intracellular delivery [106]. In lymphoma, delivery systems targeting CD19, CD20, or CD30 may improve selectivity and reduce systemic toxicity [157].

8.4 | Future Directions and Drawbacks

Future studies should identify the most essential EBV miRNAs in each lymphoma subtype because EBV latency pattern, viral miRNA expression, and tumor microenvironment differ among EBV-associated lymphomas [126]. CRISPR-based deletion, single-cell miRNA profiling, and spatial transcriptomics may help define which EBV miRNAs drive lymphoma survival, immune escape, and treatment resistance [54]. Because EBV miRNAs often have overlapping functions, future therapy may require multi-miRNA inhibition rather than targeting a single viral miRNA [14]. EBV-miRNA therapy is promising but still emerging, and its clinical success depends on improving delivery, specificity, safety, biomarker selection, and combination with established lymphoma treatments [155].

9 | Clinical and Translational Significance of EBV miRNAs

Besides their mechanistic roles in tumor initiation, progression, immune evasion and metastasis, EBV-encoded miRNAs are emerging as promising candidates for clinical applications. They exhibit great stability in biological fluids such as plasma,

serum and extracellular vesicles, making them promising non-invasive biomarkers for early detection and monitoring of EBV-associated malignancies [158]. Several EBV miRNAs have shown diagnostic and prognostic value, with expression levels correlating with tumor burden, disease stage, treatment response, and patient survival [159]. Moreover, the unique expression of EBV miRNAs in the virus-associated cancers makes it possible to develop specific therapeutic approaches, such as antisense oligonucleotides, miRNA inhibitors, and RNA-based delivery systems. However, there are still major challenges that remain despite these promising advances, namely the need for large-scale clinical validation studies, standardized detection methodologies, and efficient, safe delivery platforms. Future translational research should focus on bridging these gaps to ease the integration of EBV miRNA-based diagnostics and therapeutics into clinical oncology practice.

10 | Conclusion

This review integrates recent mechanistic insights into the biology of EBV-encoded miRNAs and their involvement in lymphoma development and progression. Collectively, EBV-encoded miRNAs from the BHRF1 and BART clusters function as master regulators of the infected-cell phenotype, simultaneously promoting proliferation, suppressing apoptosis, remodeling the tumor microenvironment, and enabling immune evasion. In Burkitt lymphoma and classical Hodgkin lymphoma, these viral miRNAs establish a profoundly immunosuppressive TME characterized by M2-polarized tumor-associated macrophages, exhausted CD8+ T cells with upregulated PD-1/LAG-3 checkpoint molecules, and spatially organized niches that shield tumor cells from immune surveillance, features now resolvable with single-cell and spatial transcriptomic technologies. The translational significance of EBV miRNA-targeted therapies is underscored by clinical validation of anti-PD-1 agents in EBV-positive malignancies and the emerging synergy between EBV-specific T cell therapies and checkpoint inhibitors. Several critical future directions emerge. First, the functional redundancy of EBV miRNAs across different latency programs and lymphoma subtypes remains incompletely resolved; systematic CRISPR-based deletion studies across Latency I, II, and III models are required to map the precise contributions of individual miRNAs. Second, integration of spatial transcriptomics with single-cell miRNA profiling will be needed to establish causal links between specific viral miRNAs and the immunosuppressive cellular neighborhoods they generate in vivo. Third, combination immunotherapeutic regimens pairing EBV-specific T cell therapy or LMP-targeting mRNA vaccines with PD-1/PD-L1 checkpoint inhibitors warrant well-powered clinical trials in EBV+ lymphoma cohorts. Fourth, the utility of circulating EBV miRNAs as liquid biopsy biomarkers for disease monitoring and immunotherapy response prediction deserves rigorous prospective evaluation. Finally, the crosstalk between EBV miRNAs and host non-coding RNA networks, including ceRNA axes and circular RNAs, represents an underexplored dimension of EBV-driven oncogenesis with potential for novel druggable nodes. Advancing these directions will be essential to translating mechanistic discoveries into clinically meaningful interventions for patients with EBV-associated lymphomas.

Author Contributions

Conception and design: A.S.D., R.S.H., R.M.M., R.A.-K., and N.I.R. Collection and/or assembly of data: H.H.M., O.A.M., S.S.A.M., and M.M.A. Manuscript writing: S.Z.F., H.A.F., A.E., H.N.S., and Y.A. All authors have read and approved the published version of the manuscript.

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Ethics Statement

No animals or human subjects were used in the preparation of this review article. All datasets analyzed are publicly available and anonymized.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Data sharing is not applicable to this article as no new data were created or analysed in this study.

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