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Molecular mechanisms of Epstein–Barr virus–driven oncogenesis and emerging therapeutic strategies

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Abstract

Epstein–Barr virus (EBV), a ubiquitous human gamma herpesvirus that establishes lifelong latency, was the first virus shown to cause human cancer. It is now causally linked to a diverse group of lymphoid and epithelial malignancies, including Burkitt lymphoma, classic Hodgkin lymphoma, post-transplant lymphoproliferative disorders, extranodal NK/T-cell lymphoma, nasopharyngeal carcinoma, and a distinct molecular subtype of gastric carcinoma. What unifies these otherwise dissimilar tumors is their dependence on the viral latency programs, in which a small set of latent proteins (notably LMP1, LMP2A, and EBNA1) and non-coding RNAs (the EBERs and BART microRNAs) reprogram host signaling, subvert apoptosis, drive genomic instability, and remodel the immune microenvironment. Because these viral products are essential for tumor maintenance yet absent from normal tissue, they present selective therapeutic entry points. This review examines how EBV latency is established and controlled, how latent gene products cooperate to transform the cell, and how the virus evades innate and adaptive immunity. It then surveys therapeutic approaches that exploit these vulnerabilities, from adoptive EBV-specific T-cell therapy and checkpoint blockade to disturbance of virus–host signaling complexes, episome-directed editing, and modulation of regulated cell death. Progress across these fronts is uneven, but together these approaches mark a shift from treating EBV as an incidental marker toward treating it as an actionable driver of disease.

Keywords: Epstein–Barr virus, Viral oncogenesis, latency, LMP1, EBNA1, Immune avoidance, Tumor microenvironment, EBV-associated malignancies, Targeted therapy

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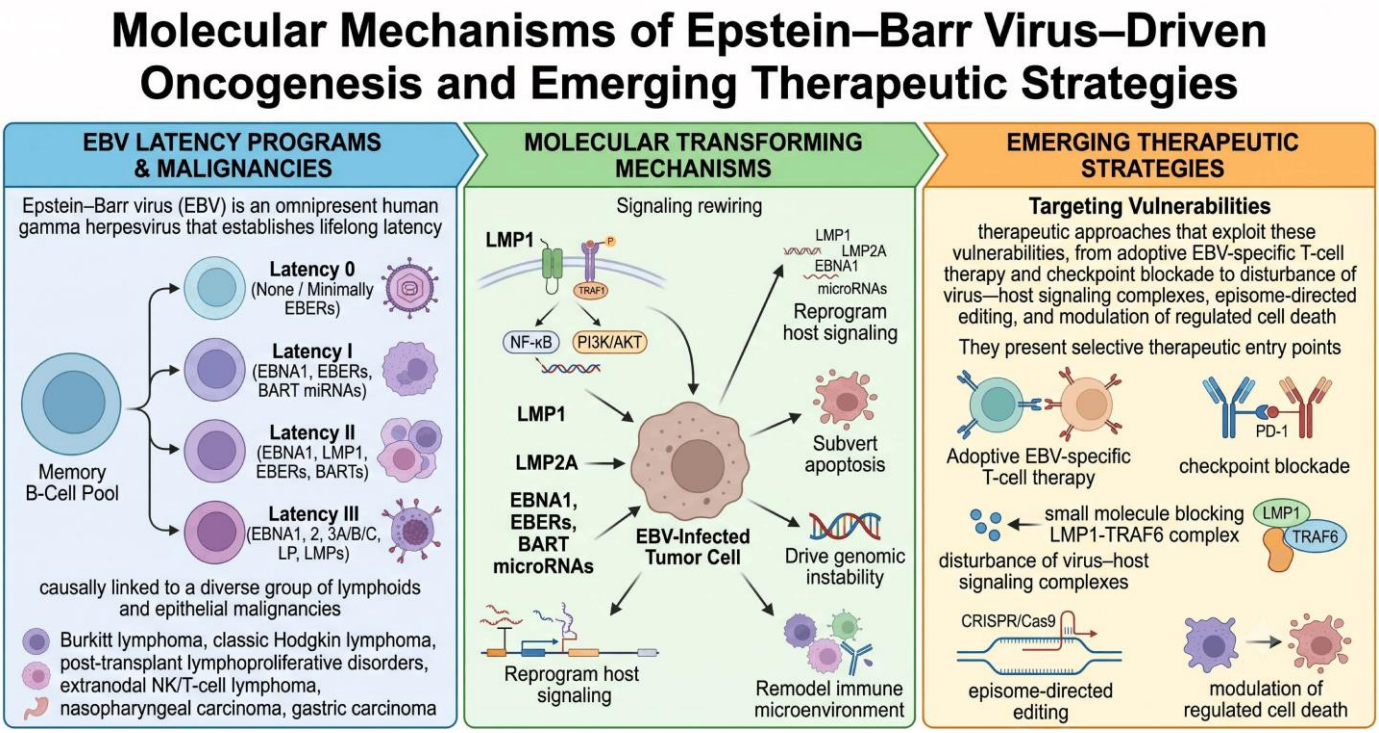
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Graphical abstract



Introduction

Epstein–Barr virus (EBV), or human herpesvirus 4, infects more than 90% of adults worldwide and, in most people, causes no lasting illness (1). Primary infection is typically silent in early childhood and presents as infectious mononucleosis when it is delayed into adolescence or adulthood. After this initial encounter the virus is never cleared; it persists for the life of the host in a latent state within the memory B-cell pool (1,2). This quiet persistence belies the virus's clinical importance. EBV was identified in Burkitt lymphoma in 1964, making it the first human tumor virus, and it remains among the most heavily studied (3).

The malignancies attributed to EBV span two quite different cellular compartments. On the lymphoid side there are Burkitt lymphoma, classic Hodgkin lymphoma, a subset of diffuse large B-cell lymphomas, post-transplant lymphoproliferative disorder (PTLD), and extranodal NK/T-cell lymphoma (4,5). On the epithelial side are nasopharyngeal carcinoma (NPC) and EBV-associated gastric carcinoma (EBVaGC) (6,7). That a single agent contributes to tumors this varied in histology and clinical behavior reflects an ability to manipulate the host cells in a manner that is both tissue-specific and context-dependent, rather than through one fixed transforming lesion.

Latency is the biological core of this behavior. In contrast to lytic replication, which produces virions and eventually destroys the host cell, latency lets EBV retain its genome while presenting almost nothing to the immune system (2,7). During latency the virus expresses a deliberately restricted repertoire—latent membrane proteins, Epstein–Barr nuclear antigens, and non-coding RNAs—that is small in number but disproportionately powerful in effect. These products are not passive markers of an infected cell. They engage the pathways that govern proliferation, survival, metabolism, and immune recognition, converting a normally regulated cell into one that can expand clonally and, when other conditions align, transform (7).

No single viral gene accounts for transformation. LMP1 behaves as a constitutively active receptor and is regarded as the principal EBV oncoprotein (11,12); LMP2A supplies tonic B-cell receptor–like survival signals (8); EBNA1 maintains the viral episome; its built-in immune stealth relies on a glycine-alanine repeat (GAr) domain that severely reduces proteasomal processing (9,10); and the EBERs and BART

microRNAs tune host responses toward survival and immune escape (11-13). Layered onto these direct actions are constitutive activation of NF-κB, PI3K/AKT, JAK/STAT, and MAPK signaling, interference with apoptotic checkpoints, induction of genomic instability, and extensive epigenetic remodeling of both viral and host chromatin. Because these mechanisms operate together and in different combinations, the same virus can produce tumors with distinct pathology in different tissues.

The burden of EBV-associated cancer is unevenly distributed. NPC shows pronounced geographic clustering in parts of East and Southeast Asia and North Africa (14); EBVaGC and several EBV-positive lymphomas are shaped by host genetics, diet, co-infection, and immune status (15,16). In transplantation and advanced HIV infection, loss of T-cell control over EBV can allow aggressive lymphoproliferation to emerge (17). EBV oncogenesis is therefore not a purely virological phenomenon, but a disease process conditioned by host and environmental factors (1).

Two major questions continue to shape the field. First, the sequence of events connecting stable latency to frank malignancy is still only partly resolved, and the relative weight of individual viral and host factors clearly differs between tumor types. Second, EBV is not equally causal in every tumor it inhabits; distinguishing a viral driver that the tumor still depends on from a passenger retained by chance is essential, because only the former is likely to respond to virus-directed therapy. This review addresses these issues by describing how EBV establishes and regulates latency, how its latent products cooperate to transform host cells, and how it reshapes the immune microenvironment. It then examines emerging therapeutic strategies—antiviral, immunological, and molecular—built on these mechanisms, with the aim of providing a coherent framework linking EBV biology to the treatment of EBV-associated cancer.

2. EBV Biology and Latency

EBV owes its evolutionary success to a life cycle finely tuned for persistence. Like other herpesviruses it alternates between lytic replication and latency, but in humans its survival rests chiefly on the latent state, in which it maintains its genome while remaining largely invisible to immune surveillance. Understanding how that state is established and controlled is a prerequisite for understanding how it can go wrong.

2.1. Entry and the fate of the incoming genome

Primary infection begins in the oropharynx, where EBV encounters both epithelial cells and B lymphocytes. Entry into B cells is initiated by binding of the viral glycoprotein gp350 to CD21 (and CD35), with the gHgL–gp42 complex engaging HLA class II to trigger fusion; epithelial entry uses a distinct, gp42-independent route (2). Once the nucleocapsid delivers the linear genome to the nucleus, the DNA circulates and is maintained as an extrachromosomal episome tethered to host chromatin rather than integrated into it.

The differentiation state of the infected cell then biases the outcome:

The germinal center model drives our current understanding of EBV persistence and pathogenesis. The virus crosses the epithelial barrier in the tonsils and directly infects resting, naive B cells. It forces these cells into a hyper-proliferative state by expressing its full arsenal of latent proteins. These activated blasts then migrate into the germinal center. They participate in the standard B-cell maturation reaction. Here, the virus pulls back. It scales down its gene expression to a restricted default program. This mimics the exact survival signals the B cell needs to avoid apoptosis. The infected cell successfully exits the germinal center disguised as a resting memory B cell. This memory pool is the virus's lifelong, silent sanctuary. It expresses virtually no viral proteins. This means roaming T cells simply don't see it.Transformation happens when this cycle breaks down. The germinal center is an intrinsically dangerous place. It requires rapid cell division and heavy DNA mutation. If immune surveillance fails, or if viral survival signals accidentally synergize with host genetic errors, the infected cells stall. They never reach the quiet safety of the memory compartment. Instead, they lock into a permanent, uncontrolled proliferative state. The result is frank malignancy.

2.2. Maintenance of the latent episome

During latency the episome replicates once per cell cycle from the latent origin oriP, using host replication machinery, so that both daughter cells inherit a copy without productive infection. EBNA1 is indispensable here: it binds oriP and concurrently bonds the viral genome to host chromosomes, ensuring faithful partitioning at mitosis (18,19). The episome is not transcriptionally inert. DNA methylation, histone modification, chromatin looping, and differential promoter usage together determine which viral genes are read, and this chromatin-based control—exerted by host machinery as much as by viral factors—dictates whether the virus stays latent or re-enters the lytic cycle.

2.3. The latency programs

EBV deploys several distinct latency programs, conventionally numbered 0 through III, each defined by a characteristic set of expressed genes and each associated with particular cell types and clinical settings (10). In latency 0, found in resting memory B cells, viral protein expression is essentially absent; this is the most immune-evasive state and the principal reservoir of lifelong persistence. Latency I restricts expression largely to EBNA1 (driven from the Qp promoter) and is typical of Burkitt lymphoma, where the virus preserves its genome while minimizing antigenicity. Latency II adds the latent membrane proteins LMP1 and LMP2A to EBNA1 and is characteristic of Hodgkin lymphoma, NPC, and EBVaGC. Latency III, the broadest program, expresses the full complement of EBNA proteins (EBNA1, 2, 3A/B/C, and LP) together with the LMPs from the Wp/Cp promoters; This program efficiently drives B-cell proliferation and immortalization in vitro, generating lymphoblastoid cell lines, and it appears *in vivo* mainly where T-cell surveillance is compromised, as in PTLD. These programs are better viewed as a spectrum than as fixed states, since the virus can move between them in response to the differentiation, immune pressure, and tissue context flexibility that is central to its oncogenic range (Figure 1 and Table 1).

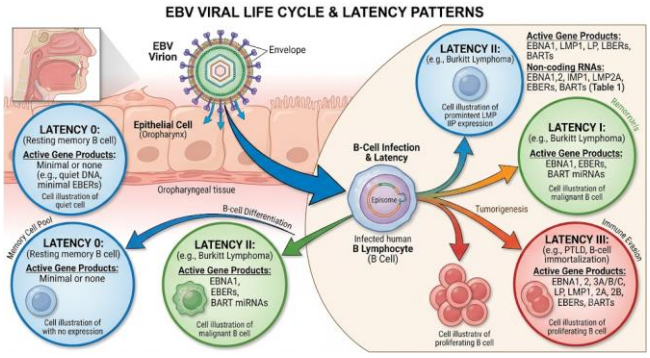


Figure 1. The biphasic is a life cycle of Epstein-Barr Virus. Following primary infection via the oropharyngeal epithelium, EBV enters resting memory B cells to establish distinct latency programs (Latency 0, I, II, and III). Each program features a restricted pattern of viral gene expression that facilitates immune evasion and sets the stage for oncogenic transformation under permissive conditions.

Table 1. EBV Latency Programs and Associated Clinical Settings.

Latency Program	Expressed Viral Gene Products	Associated Cell Types & Malignancies
Latency 0	None / Minimally EBERs	Resting memory B cells (Stealth reservoir)
Latency I	EBNA1, EBERs, BART miRNAs	Burkitt lymphoma, Extranodal NK/T-cell lymphoma
Latency II	EBNA1, LMP1, LMP2A, EBERs, BARTs	Classic Hodgkin lymphoma, Nasopharyngeal carcinoma, EBVaGC
Latency III	EBNA1, 2, 3A/B/C, LP, LMPs	Post-transplant lymphoproliferative disorder (PTLD), Immunocompromised states

2.4. The latent gene products

The latent products are the effectors of both persistence and transformation. EBNA1 balances the episome and additionally influences the cellular transcription, redox balance, and genome stability. EBNA2 is a potent transcriptional activator that, by tethering to the cellular DNA-binding factor RBPJ (CBF1), drives MYC and the LMP promoters and is essential for B-cell immortalization (15-17). LMP1 mimics a constitutively active member of the TNF-receptor family and is the principal viral oncogene, while

LMP2A delivers tonic survival signals in the absence of genuine antigen. Among the non-coding RNAs, the abundant EBERs (EBER1 and EBER2) modulate innate immune sensing and stress responses, and the BART microRNAs—particularly prominent in epithelial tumors—regulate apoptosis, differentiation, immune recognition, and signaling. These factors act as a coordinated network rather than as isolated agents (21,22).

2.5. Reactivation and the lytic cycle

Although latency dominates in vivo, EBV periodically reactivates to produce the virions needed for transmission. The switch is thrown by the immediate-early transactivators BZLF1 (Zta) and BRLF1 (Rta), which are induced by plasma-cell differentiation, cellular stress, and changes in the chromatin landscape, and which then ignite the early and late lytic cascades. Reactivation is not simply the mirror image of latency. Abortive or partial lytic programs, in which some lytic genes are expressed without completion of the replicative cycle, can themselves contribute to pathogenesis by amplifying inflammation and altering survival signaling. EBV-associated cancer biology therefore cannot be read from the latent genes alone; the latent–lytic interplay matters as well.

2.6. Why latency is the bridge to cancer

By expressing only a fraction of its genome, EBV keeps its antigenic profile in low. while still steering host cell behaviors, allowing infected cells to survive, divide, and accumulate additional oncogenic changes over years. Latency is thus not dormancy in the ordinary sense but an active program that facilitates persistent coexistence with the host and, under permissive conditions, transformation. The correspondence between latency program and tumor type is diagnostically and therapeutically consequential, because it determines which viral antigens are available to the immune system and which pathways the tumor has come to depend on. In this sense latency is the conceptual bridge between infection and cancer, and the foundation on which the rest of EBV oncobiology is built.

3. Molecular Mechanisms of Oncogenesis

EBV transforms cells through a layered network of viral–host interactions rather than a single dominant event. After establishing latency, it uses a compact set of latent proteins and non-coding RNAs to rewire signaling, resist cell death, destabilize the genome, and evade immunity(7). The plasticity of this network is what allows one virus to drive tumors as different as B-cell, NK/T-cell, and epithelial cancers (Figure 2).

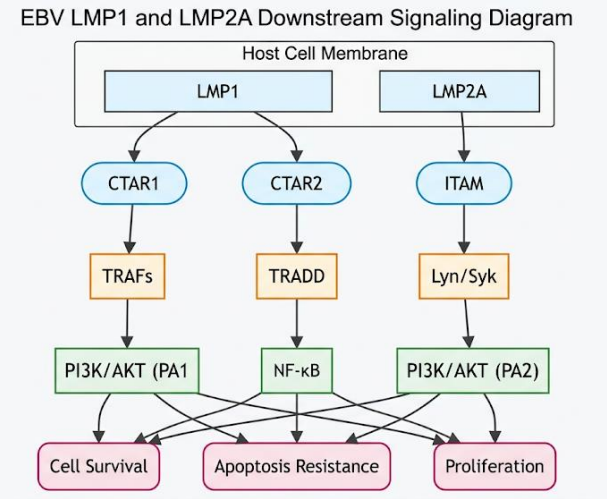


Figure 2. LMP1 and LMP2A Oncogenic Signaling Pathways. LMP1 mimics a constitutively active TNF receptor, driving NF-κB and PI3K/AKT pathways via its CTAR1 and CTAR2 domains. LMP2A mimics a B-cell receptor, utilizing its ITAM domain to activate PI3K/AKT s.

3.1. LMP1

LMP1 is the best-characterized EBV oncoprotein and, in many settings, the dominant transforming factor. Its self-aggregates in the membrane and signals without a ligand, so that its subsequent pathways are switched on continuously. Two cytoplasmic regions carry this signal: CTAR1 recruits TRAF1/2/3/5 to activate the non-canonical NF-κB arm, while CTAR2 engages TRADD and TRAF6 to drive canonical NF-κB and the JNK/AP-1 axis; LMP1 also feeds into PI3K/AKT. The net effect is resistance to apoptosis, accelerated cell-cycle progression, and induction of inflammatory phenotypes. Beyond proliferation and survival, LMP1 promotes invasion, angiogenesis, and epithelial–mesenchymal transition–like changes in carcinoma cells, and it perturbs DNA-damage responses. This breadth—touching transcriptional programs, cytokine output, and stress responses at once—is precisely why LMP1 has remained a central therapeutic target (15).

3.2. LMP2A

LMP2A acts as a surrogate B-cell receptor. Its cytoplasmic ITAM recruits Lyn and Syk and sustains PI3K/AKT signaling, delivering the tonic survival input that B cells normally derive from antigen. Infected cells can therefore persist even when genuine receptor engagement is absent, a property that matters wherever a latently infected cell must survive without normal immune or receptor-derived support. LMP2A also lower signaling thresholds and let cells bypass checkpoints that would otherwise eliminate aberrant clones. It rarely works alone; in EBV-associated malignancies it cooperates with other latent products to stabilize the transformed state, making it a genuine contributor to oncogenic persistence rather than just an accessory (17).

3.3. EBNA1

EBNA1's essential role in episome maintenance is matched by a subtler contribution to transformation. It supports faithful replication and segregation of the viral genome in dividing cells and, in parallel, modulates host transcription, oxidative stress, and genome stability. Its internal glycine–alanine repeat impairs proteasomal processing of the protein, so that EBNA1-derived peptides are inefficiently presented on MHC class I—a form of built-in immune stealth that lets the virus keep expressing EBNA1 in latency without inviting cytotoxic T-cell attack. Because EBNA1 is present in essentially every EBV-positive tumor, it serves both as a near-universal marker of latent infection and as an attractive target for intervention (18,19).

3.4. EBERs

EBER1 and EBER2 are the most abundant EBV transcripts in latently infected cells and among the most reliable markers of infection, yet they encode no protein. They act instead by interacting with host RNA-binding and innate-sensing proteins. Some *in vitro* models suggest they might engage PKR, RIG-I, and related pathways to reshape interferon and stress responses. It isn't a settled fact, though. The extent to which this reliably favors tumor survival over elimination across different human cancers remains highly debated. Much of this proposed mechanism still requires definitive validation in primary tumor tissues (20). Their consistency and abundance make them the standard target for in situ detection (EBER-ISH) in pathology, and functionally they help infected cells tolerate the stresses that accompany oncogenic signaling (21,22).

3.5. BART microRNAs

The BamHI-A rightward transcript (BART) microRNAs form a large viral miRNA family that is especially active in epithelial tumors. By suppressing the transcripts involved in apoptosis, immune recognition, differentiation, and signal transduction, they simultaneously weaken anti-tumor defenses and reinforce the malignant phenotype; individual BARTs have been shown to the arget pro-apoptotic factors such as PUMA and Bim, to dampen immune ligands, and even to fine-tune LMP1 levels. Because a single miRNA can act on many transcripts, the BART family gives EBV an economical means of controlling complex host pathways, and it is a major reason NPC and EBVaGC behave as they do. Their prominence reveals that EBV oncogenesis is driven by RNA-based regulation as much as by proteins (Table 2).

Table 2. Key EBV Latent Gene Products and Their Oncogenic Functions.

Latent Product	Primary Oncogenic Function
LMP1	Master regulator of survival signaling; mimics active TNF-receptor; drives NF-κB and PI3K/AKT.
LMP2A	Surrogate B-cell receptor; sustains tonic survival via Lyn/Syk and PI3K/AKT pathways.
EBNA1	Episome tethering and maintenance; exhibits intrinsic immune stealth (glycine-alanine repeat).
EBERs	Non-coding RNAs; modify host innate immune sensing (PKR/RIG-I) to favor survival.
BART miRNAs	Widespread post-transcriptional suppressors of apoptosis (PUMA/Bim) and immune recognition.

3.6. Oncogenic signaling pathways

The latent proteins converge on specific pathways that supply the infrastructure for proliferation. Canonical

NF-κB activation is the most conspicuous. It's driven directly by LMP1, which mimics CD40 receptor signaling. We see this constitutive activation clearly in primary EBV-positive Hodgkin lymphoma and NPC biopsies, where it sustains anti-apoptotic targets like Bcl-2, Bcl-xL, and Mcl-1. PI3K/AKT, engaged by both LMP1 and LMP2A (functioning as a surrogate B-cell receptor), supports metabolism and growth. We need to be careful here, though. Much of the mechanistic proof for PI3K/AKT and MAPK (ERK, JNK, p38) dependency comes heavily from in vitro lymphoblastoid cell lines. You can't blindly extrapolate those cell-culture findings to complex human tumors. JAK/STAT signaling, particularly STAT3, is frequently hyperactivated in actual human tumor samples like NK/T-cell lymphoma. This happens indirectly through LMP1-induced cytokines (such as IL-6) and receptor crosstalk, entrenching the malignant state. These pathways aren't isolated. Their constant overlap makes EBV-driven signaling notoriously difficult to interrupt with any single agent.

3.7. Cell-cycle dysregulation and apoptosis resistance

Transformation requires both a push toward to proliferation and a brake on cell death, and EBV supplies both. Latent proteins don't just gently nudge the cell cycle; they violently hijack the heavy machinery. Total takeover. EBNA3C physically stabilizes Cyclin D1 while simultaneously ramping up CDK6 kinase activity. This completely neutralizes the Rb tumor suppressor blockade. The cell is shoved aggressively past the G1/S restriction point. It doesn't stop there. EBNA3C also targets the p27 kinase inhibitor for outright ubiquitin-mediated destruction. Meanwhile, LMP1 acts as a massive molecular accelerator by directly forcing the continuous overexpression of Cyclin D1. Hardwired for relentless division. They deliberately disable p53-associated damage checkpoints, so that severely mutated cells aren't culled. At the same time LMP1 and LMP2A drive anti-apoptotic signaling while EBNA1 and the viral miRNAs buffer cells against stress-induced death. The virus can also extend cell lifespan or block terminal differentiation in some contexts, preserving a proliferative pool that is more permissive to transformation. The combined effect is not merely faster growth but a fundamental shift in the control of cell fate.

3.8. Genomic instability and epigenetic reprogramming

EBV fosters an environment prone to genomic instability by disturbing DNA repair, inducing oxidative stress, and promoting micronucleus formation, thereby generating the mutational substrate on which clonal evolution proceeds. Equally important is its epigenetic activity. The viral genome is itself governed by chromatin state, and EBV in turn alters host DNA methylation and histone modification, silencing tumor suppressors and stabilizing latency-associated transcription. In EBVaGC this reaches an extreme, with genome-wide CpG-island hypermethylation (a CpG-island methylator phenotype) that is one of the defining features of the subtype. This regulation runs in both directions: host epigenetic machinery controls EBV latency while EBV products remodel the host epigenome, creating a self-reinforcing loop in which viral persistence and cellular transformation sustain one another.

3.9. An integrated view

EBV oncogenesis is best understood as a system-level process. Latent proteins initiate and maintain pro-survival signaling, non-coding RNAs refine host gene expression, and the NF-κB, PI3K/AKT, JAK/STAT, and MAPK pathways provide the signaling backbone, while genomic instability and epigenetic remodeling allow malignant traits to accumulate and persist. This framework clarifies for a central paradox of the field: EBV-associated cancers are biologically diverse yet mechanistically connected. The virus does not transform through one mutation-like hit but reprograms cell state over time, usually in cooperation with host genetics and environmental cofactors—a view with direct consequences for how targeted therapies and biomarkers should be designed.

4. Immune Evasion and the Tumor Microenvironment

A defining feature of EBV oncogenesis is the virus's ability to persist under intense immune surveillance. Because infection lasts a lifetime, EBV must hold an

equilibrium in which infected cells are neither cleared nor allowed to expand without limit, and it maintains that equilibrium through overlapping strategies operating at innate sensing, antigen presentation, T-cell function, cytokine signaling, and the wider microenvironment.

4.1. Minimizing and masking viral antigen

The economy of the latency program itself is the first line of defense: by expressing few proteins, the virus offers few targets, and in the least of its latency (0) and I the antigenic burden is minimal. Where viral proteins are expressed, EBV limits their visibility—most strikingly through the glycine–alanine repeat of EBNA1, which impairs proteasomal processing and MHC class I presentation. The virus also interferes directly with the presentation machinery: the lytic protein BNLF2a blocks the TAP transporter, and BILF1 promotes MHC class I downregulation, further reducing recognition by CD8+ T cells. Because cytotoxic T cells are the main barrier to EBV-driven transformation, these measures are central to both persistence and malignancy (25) (Table 3).

4.2. Dampening innate immunity

EBV blunts innate defenses that would otherwise eliminate infected cells early. It interferes with pattern-recognition signaling, interferon production, and downstream antiviral programs, and the EBERs contribute by modulating PKR- and RIG-I–associated responses (8). The virus also encodes a homolog of interleukin-10 (vIL-10, BCRF1) that suppresses local immune activation. Since innate responses often decide whether an infection is controlled or allowed to establish latency, this early dampening is decisive; once latency is set, the virus occupies a far more stable and less immunogenic niche (26, 27). Natural killer cells remain relevant later, particularly in epithelial and NK/T-cell tumors, where altered ligand expression can reduce NK-mediated cytotoxicity (Table 3).

Table 3. Mechanisms of EBV Immune Evasion in the Tumor Microenvironment.

Evasion Strategy	Viral Effectors Involved	Mechanism of Action	Consequence for Tumor Survival
Antigen Masking	EBNA1	Glycine-alanine repeat prevents proteasomal degradation.	Evades CD8+ cytotoxic T-cell recognition.
MHC Downregulation	BNLF2a, BILF1	Blocks TAP transporter and downregulates MHC Class I molecules at the cell surface.	Reduces presentation of viral peptides to the immune system.
Innate Immune Dampening	EBERs, vIL-10 (BCRF1)	Modulates PKR/RIG-I sensing and secretes suppressive viral interleukin-10.	Blunts early interferon responses and suppresses local immune activation.
Immune Checkpoint Activation	LMP1 (indirectly)	Up-regulates PD-L1/PD-L2 expression via inflammatory signaling (often compounded by 9p24.1 amplification).	Induces T-cell exhaustion and restrains tumor-reactive lymphocytes.

4.3. Checkpoint activation and T-cell dysfunction

EBV-positive tumors frequently up-regulate immune checkpoints. Elevated PD-L1 is common—sometimes driven by structural amplification of the 9p24.1 locus, as in a fraction of EBV-positive Hodgkin lymphomas and EBVaGC—and additional inhibitory axes including CTLA-4, LAG-3, TIM-3, and others are increasingly recognized. These signals restrain tumor-reactive T cells and help sustain an immunosuppressive microenvironment. The link to viral biology is direct: inflammatory and interferon signals induced by viral products paradoxically up-regulate suppressive pathways, so that chronic inflammation coexists with immune dysfunction. The result is an infiltrate that is often abundant but functionally exhausted—T cells are present, yet qualitatively compromised—which is one reason checkpoint blockade can succeed in selected EBV-driven cancers.

4.4. An inflamed but suppressive microenvironment

EBV-associated tumors are typically rich in tumor-infiltrating lymphocytes yet poorly controlled, a pattern that at first seems contradictory. Immune cells are recruited but then reprogrammed or restrained by checkpoint signaling, suppressive cytokines, and inhibitory stromal interactions, so infiltration does not translate into clearance. EBV shapes many components of this niche—T cells, NK cells, macrophages, dendritic cells, fibroblasts, and endothelium—altering cytokine gradients and antigen-presenting capacity to favor survival, angiogenesis, and metastatic potential. Clinically this explains why some EBV-positive tumors appear immunologically "hot" yet resist elimination: the presence of immune cells matters less than their activation state, spatial organization, and inhibitory constraints (Figure 3).

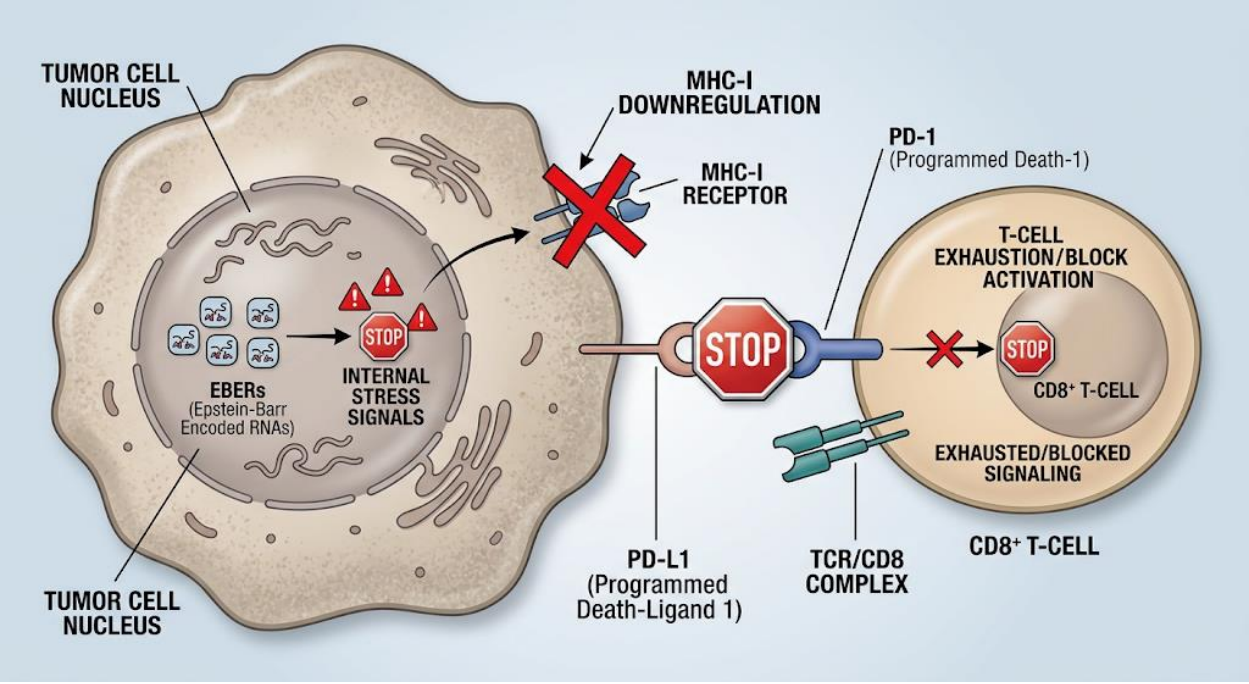


Figure 3. EBV-mediated remodeling of the tumor microenvironment (TME). EBV-positive tumors evade immune clearance through MHC class I down-regulation (via BNLF2a/BILF1), antigen masking (EBNA1 glycine-alanine repeat), and the recruitment of exhausted immune cells.

4.5. Therapeutic implications

Because immune escape is so central to persistence, strategies that reverse it are especially attractive. PD-1/PD-L1 blockade has clear rationale, and CTLA-4-directed and newer approaches against LAG-3 and TIM-3 are under study. Yet responses are unlikely to be uniform: latency pattern, tissue of origin, immune context, and coexisting genomic alterations all shape sensitivity. Immune evasion is therefore best treated not only as a mechanism of pathogenesis but as a framework for stratifying patients—identifying which

tumors have retained targetable antigen, which are dominated by which suppressive pathway, and which are likely to respond to immune-based treatment.

5. EBV-Associated Malignancies

EBV contributes to a spectrum of tumors with different cellular origins, pathology, and clinical behavior (3,4,11). They are unified by dependence on viral latency yet diverge in the specific program employed and the tissue in which it operates, which is why EBV positivity carries a different biological meaning in a lymphoma than in a carcinoma.

5.1. Lymphoid malignancies

The EBV-associated lymphomas include endemic Burkitt lymphoma, classic Hodgkin lymphoma, a subset of diffuse large B-cell lymphomas, PTLD, and extranodal NK/T-cell lymphoma. Endemic Burkitt lymphoma pairs latency I with the hallmark MYC–immunoglobulin translocation; Hodgkin lymphoma exhibits latency II, with LMP1 sustaining the malignant Hodgkin–Reed–Sternberg cells; and PTLD, arising when immunosuppression removes T-cell control, characteristically shows the growth-transforming latency III program. Across these settings the role of EBV tracks with latency-associated expression of EBNA1, LMP1, and LMP2A, which support survival and resistance to apoptosis. The clinical corollary is that EBV-positive lymphomas are often more aggressive or harder to treat in immunocompromised hosts, illustrating how tightly viral oncogenesis is coupled to immune surveillance (11,12). EBV-positive mucocutaneous ulcer (EBVMCU) is a recently recognized, highly indolent B-cell lymphoproliferative disorder. It punches shallow, sharply defined holes in the mucosal lining of the mouth, skin, or gastrointestinal tract. It targets the vulnerable. Patients usually suffer from age-related immune senescence or take heavy immunosuppressive drugs for rheumatoid arthritis and solid organ transplants. The virus exploits this weakened surveillance. It typically runs a Latency II or Latency III program, cranking out LMP1 and often EBNA2 in the lesional cells. But here is the catch. It rarely spreads. If you just taper the patient's immunosuppressive medications, the vicious-looking ulcer often completely vanishes on its own. The host's recovering T-cells simply wake back up and clear the infected clones.

5.2. Nasopharyngeal carcinoma

NPC is the paradigmatic EBV-associated epithelial cancer. EBV is present in essentially all tumor cells of the undifferentiated (non-keratinizing) form, which displays a latency II program. The cancer is notable for its geographic clustering and its strong relationship to inflammatory and immune signaling (13). Mechanistically, latent proteins, BART microRNAs, epigenetic remodeling, and immune-evasive signaling combine to produce a phenotype marked by proliferation, death resistance, and adaptation to an inflamed but immunosuppressive stroma. NPC thus remains a central model for how EBV drives epithelial carcinogenesis and a leading setting for EBV DNA–based monitoring and immunotherapy (8,13).

5.3. EBV-associated gastric carcinoma

EBVaGC is now recognized as a distinct molecular subtype, accounting for roughly a tenth of gastric adenocarcinomas and enriched in lymphoepithelioma-like and certain diffuse-type tumors. It carries a characteristic molecular signature: extensive DNA hypermethylation, recurrent PIK3CA mutations, and amplification of PD-L1/PD-L2, alongside prominent immune-related changes (26). These features distinguish it from EBV-negative gastric cancer and predict a different response to immune checkpoint blockade, which supports its classification as a separate clinicopathologic entity rather than an incidental viral presence (28).

5.4. Extranodal NK/T-cell lymphoma

Extranodal NK/T-cell lymphoma, nasal type, is among the most aggressive EBV-associated malignancies and one of the clearest examples of EBV driving a cytotoxic lymphoid lineage rather than a B-cell one. The tumor typically shows a latency I/II-like program and marked inflammatory and immune-evasive features, often on a background of recurrent genetic lesions. It is difficult to treat and closely tied to EBV serologic and molecular markers, and its biology reflects a tight coupling of viral persistence, immune dysregulation, and lineage-specific oncogenic adaptation.

5.5. Biological and clinical significance

These tumors share a viral requirement but diverge in cell of origin, latency program, immune landscape, and clinical course. EBV is consequently not a simple positive-or-negative marker; its presence means something different in lymphoid and epithelial contexts, and that distinction governs the interpretation of pathology, the choice of biomarkers, and the design of EBV-directed therapy. Viewed as a spectrum—classical lymphomas, epithelial cancers, and aggressive NK/T-cell neoplasms—EBV-associated malignancy is best approached as a set of related but biologically distinct diseases, each of which may respond differently to immune-based, antiviral, or molecularly targeted intervention (Table 4).

Table 4. Clinicopathological Features of Major EBV-Associated Malignancies.

Malignancy	Tissue Origin	Dominant Latency Program	Key Molecular & Clinical Features
Burkitt Lymphoma (Endemic)	B-cell	Latency I	Hallmark MYC–immunoglobulin translocation; minimal viral antigen expression.
Classic Hodgkin Lymphoma	B-cell	Latency II	LMP1 sustains malignant Hodgkin-Reed-Sternberg cells; robust but ineffective immune infiltrate.
EBV-Positive Mucocutaneous Ulcer (EBVMCU)	B-cell (mucosal/cutaneous)	Latency II / III	Shallow, localized ulcers in immunosuppressed patients; highly indolent; typically regresses upon reduction of immunosuppression.
Extranodal NK/T-cell Lymphoma	NK/T-cell	Latency I / II	Highly aggressive; driven by cytotoxic lineage adaptations; strongly tied to EBV viral load.
Nasopharyngeal Carcinoma (NPC)	Epithelial	Latency II	Endemic geographic clustering; rich in BART miRNAs; highly dependent on inflammatory stroma.
EBV-Associated Gastric Carcinoma	Epithelial	Latency I / II	Distinct molecular subtype; features CpG-island hypermethylation (CIMP), PIK3CA mutations, and PD-L1 amplification.

6. Emerging Therapeutic Strategies

Treatment of EBV-associated cancer is shifting from nonspecific cytotoxic therapy toward approaches that exploit viral biology directly. Where EBV functions as a driver rather than a passenger, its latent products create vulnerabilities absent from normal tissue, and several of these are now being tested clinically or in advanced preclinical development (9).

6.1. Targeting latent proteins

The most direct strategy is to disable the latent proteins that sustain the transformed state—LMP1, LMP2A, and EBNA1. Direct small-molecule inhibition is difficult, because these proteins generally lack the enzymatic pockets that drugs usually exploit, but they remain valuable targets for antibody-based approaches, peptide inhibitors, and vaccines. LMP1 is particularly compelling as a master regulator of pro-survival signaling: interfering with its expression, oligomerization, or recruitment of adaptor proteins could attenuate NF-κB–driven tumor maintenance (15,16). EBNA1, expressed across essentially all EBV-positive tumors and required for episome maintenance, is a focus for both immune-based and molecular strategies, including small molecules that block its DNA binding (18).

6.2. Disrupting virus–host signaling complexes

A promising insight is that the interfaces between viral and host proteins may be more druggable than the viral proteins themselves. The LMP1–TRAF6 interaction is a case in point: recruitment of TRAF6 is required for NF-κB activation and the survival of EBV-transformed B cells, and inhibitory peptides that disrupt this contact interfere with the survival of EBV-driven lymphoma

cells, establishing the interface as a validated rather than merely theoretical target. The appeal of this approach is that it dismantles the oncogenic wiring the virus depends on without needing to eliminate the virus outright, and the same logic suggests that systematic mapping of the EBV–host interactome could reveal further actionable nodes (27).

6.3. Targeting the episome

Because EBV persists as an extrachromosomal episome, therapies that destabilize, cleave, or eliminate that DNA could selectively weaken tumor maintenance. CRISPR-based tools are especially interesting here, since they can in principle cut essential regions of the episome, disrupt latent genes, or force loss of the viral genome from tumor cells. The approach remains largely preclinical and faces massive obstacles in delivery and specificity. The EBV episome exists as a distinct, extrachromosomal DNA molecule. It closely tethers itself to host chromosomes to replicate, but it does not physically integrate into the host's genome. Because of this intimate physical association, avoiding off-target CRISPR cuts to the host's actual DNA requires surgical precision. Despite these hurdles, it offers a direct strike on the viral reservoir rather than just managing its downstream consequences.

6.4. Immunotherapy and adoptive T-cell approaches

Immunotherapy is the most clinically mature EBV-directed strategy. Because many EBV-associated tumors retain viral antigens, they can be attacked by virus-specific cellular responses. Adoptive transfer of EBV-specific cytotoxic T lymphocytes has shown meaningful activity in EBV-driven PTLD, and allogeneic “off-the-shelf” products—tabelecleucel being the clearest example—have moved this concept from experimental to clinical use in relapsed or refractory disease. Checkpoint blockade is a complementary pillar, particularly in tumors with an immunosuppressive microenvironment and high PD-L1 expression such as NPC and EBVaGC. Given that immune escape is so central to pathogenesis, immune-based approaches are likely to be most effective when combined with methods that raise antigen visibility or relieve suppressive signaling.

6.5. Modulating regulated cell death

A newer direction is to reverse the cell-death programs EBV suppresses. The virus absolutely uses latent proteins like LMP1 and LMP2A to block standard apoptosis. We know this for a fact. The narrative gets messy when we look at other forms of cell death. Take autophagy. EBV doesn't just restrain it; the virus hijacks the host's autophagic machinery to keep the infected cell alive under starvation and stress. As for ferroptosis, suggesting EBV's non-coding RNAs directly block iron-dependent cell death is a massive leap. It's a fun theory. It isn't proven science in human tumors yet. Therapies designed to strip away these specific survival advantages make sense on a whiteboard but turning them into actual drugs requires us to untangle these chaotic, overlapping pathways first. Apoptosis-restoring agents might counteract LMP1- and LMP2A-mediated survival signaling, autophagy modulation could disrupt stress adaptation, and ferroptosis induction might exploit the altered redox and metabolic state of EBV-driven cells. These remain early-stage concepts, but they are attractive because they hold out the possibility of selectively killing EBV-positive cells while sparing normal tissue (Figure 4 and Table 5).

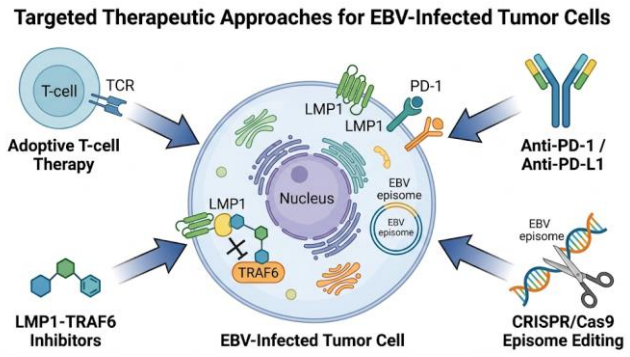


Figure 4. Emerging therapeutic strategies targeting EBV vulnerabilities. Developmental approaches include (1) adoptive cell therapy with EBV-specific cytotoxic T lymphocytes, (2) immune checkpoint blockade targeting the PD-1/PD-L1 axis, (3) pharmacological disruption of viral-host complexes like LMP1-TRAF6, and (4) episome-directed targeting using CRISPR/Cas9 to eradicate the latent viral genome.

Table 5. Emerging Therapeutic Strategies for EBV-Driven Cancers.

Therapeutic Modality	Target / Mechanism	Current Development Status
Adoptive T-Cell Therapy	EBV-specific cytotoxic T lymphocytes (e.g., tabelecleucel).	Clinical use (especially for relapsed/refractory PTLD).
Immune Checkpoint Blockade	PD-1 / PD-L1 axis (and emerging targets like CTLA-4, LAG-3).	Clinical trials/use (effective in tumors with high PD-L1 like NPC and EBVaGC).
Latent Protein Inhibition	Disrupting LMP1–TRAF6 complexes; blocking EBNA1 DNA-binding.	Advanced preclinical / Early clinical trials.
Episome Targeting	CRISPR/Cas9 editing to cleave or destabilize the viral extrachromosomal DNA.	Preclinical (facing delivery and off-target challenges).
Cell Death Modulation	Restoring suppressed apoptotic pathways (counteracting LMP1/2A); inducing ferroptosis.	Early-stage preclinical concepts.

7. Challenges and Future Perspectives

Several obstacles stand between current understanding and routine EBV-directed oncology. The most fundamental is the heterogeneity of latency itself: because EBV persists in several latency states, each with its own transcriptional, epigenetic, and antigenic profile, no single molecular model captures every EBV-associated cancer, and no single target is universal (6,14). Compounding this is the diversity among tumor types—EBV-positive lymphomas, NPC, EBVaGC, and NK/T-cell lymphoma differ in cell of origin, latency program, microenvironment, and treatment response—so that conclusions from one entity rarely generalize to another.

A second, closely related problem is distinguishing genuine viral dependence from secondary association. In some tumors EBV clearly drives transformation; in others its continued functional importance is uncertain. This matters because virus-directed therapy will work best where the tumor still depends on viral persistence or signaling, and resolving the question will require better experimental models and longitudinal analyses that track viral dependency over the course of disease.

Translational hurdles follow from these biological ones. Gene- and genome-editing strategies against the episome face delivery, specificity, and off-target concerns that are magnified by the virus's intimacy with host chromatin, so therapeutic selectivity must be very high to avoid collateral toxicity. And the field still lacks fully validated biomarkers for patient selection. Current markers—EBER in situ hybridization, plasma EBV DNA load, and selected viral transcripts—are useful but do not reliably capture latency state, immune context, or therapeutic vulnerability. In an era of precision oncology, where outcome depends on viral status alongside host genetics, immune phenotype, and coexisting molecular alterations, biomarker panels will likely need to integrate viral, genomic, epigenetic, and immunologic data rather than rely on any single assay.

Progress will also depend on better tools. Single-cell and spatial profiling can resolve how latency is distributed across tumor cells, how immune cells engage infected clones, and how microenvironmental niches sustain persistence, while improved preclinical models are needed to capture the interplay of latency, host immunity, and tissue-specific oncogenesis. The most promising overall direction is not a single universal therapy but integrated, subtype-specific strategies that combine viral targeting, checkpoint modulation, adoptive cell therapy, and biomarker-guided selection—treating EBV-associated cancers as biologically distinct, stratified diseases rather than tumors sharing a common label. Realizing this will determine whether EBV becomes not only a model of viral oncogenesis but a tractable target for personalized therapy.

Conclusion

EBV is among the most instructive models of viral oncogenesis because it shows how a ubiquitous, lifelong infection can be converted into a durable driver of malignant transformation. Rather than acting as a

passive agent, it reprograms infected cells through a coordinated network of latent proteins, non-coding RNAs, signaling pathways, and epigenetic mechanisms that together confer survival, proliferation, immune escape, and genomic adaptation.

A central lesson is that transformation is not governed by any one viral factor but by the cumulative action of latency-associated gene expression on host-cell state. LMP1, LMP2A, and EBNA1, together with the EBERs and BART microRNAs, act in concert to co-opt the control of the cell cycle, apoptosis, inflammatory signaling, and immune recognition. EBV-associated tumors are correspondingly diverse yet share a dependence on viral persistence and host immune context—a shared dependence that provides the rationale for virus-directed therapy, especially where latent antigens or episomal genomes are retained.

From a therapeutic standpoint, EBV is attractive precisely because it offers targets absent from normal cells: latent proteins, episomal DNA, and virus-specific immune vulnerabilities. Adoptive EBV-specific T-cell therapy, checkpoint blockade, episome-directed editing, and disruption of critical complexes such as LMP1–TRAF6 collectively signal a move from descriptive virology toward actionable molecular oncology. These strategies remain uneven in maturity, and their successful translation will require sharper definitions of latency heterogeneity, clearer evidence of tumor-specific viral dependence, and biomarkers capable of identifying the patients most likely to benefit. Integrating molecular pathology, immune profiling, and longitudinal virological assessment into a single precision-oncology framework is the path toward using EBV not merely as a model of viral carcinogenesis but as a clinically tractable target for prevention and treatment.

Author contribution

AA and **DD** wrote the main manuscript and **AAh** edits the text structure and prepared figures and tables.

Conflicts of interest

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References

1. Kang MS, Kieff E. Epstein-Barr virus latent genes. Exp Mol Med. 2015; 47(1): e131.

2. Murata T, Sato Y, Kimura H. Modes of infection and oncogenesis by the Epstein-Barr virus. Rev Med Virol. 2014; 24(4): 242-253.

3. Young LS, Rickinson AB. Epstein-Barr virus: 40 years on. Nat Rev Cancer. 2004; 4(10): 757-768.

4. Marques-Piubelli ML, Salas YI, Pachas C, et al. Epstein-Barr virus-associated B-cell lymphoproliferative disorders and lymphomas: a review. Pathology. 2020; 52(1): 40-52.

5. Shannon-Lowe C, Rickinson A. The Global Landscape of EBV-Associated Tumors. Front Oncol. 2019; 9: 713.

6. Tsao SW, Tsang CM, To KF, Kang H. The role of Epstein-Barr virus in epithelial malignancies. Nat Rev Clin Oncol. 2017; 14(5): 269-282.

7. Dawson CW, Port RJ, Young LS. The role of the EBV-encoded latent membrane proteins LMP1 and LMP2 in the pathogenesis of nasopharyngeal carcinoma (NPC). Semin Cancer Biol. 2012; 22(2): 144-153.

8. Farrell PJ. Epstein-Barr Virus and Cancer. Cold Spring Harb Perspect Med. 2019; 9(4): a023663.

9. Lo AK, To KF, Lo KW, et al. Modulation of LMP1 protein expression by EBV-encoded microRNAs. Proc Natl Acad Sci U S A. 2007; 104(41): 16164-16169.

10. El-Sharkawy A, Al Zaidan L, Malki A. Epstein-Barr Virus-Associated Malignancies: Roles of Viral Oncoproteins in Carcinogenesis. Front Oncol. 2018; 8: 265.

11. Kieser A, Sterz KR. The Latent Membrane Protein 1 (LMP1). Curr Top Microbiol Immunol. 2015; 391: 119-149.

12. Fang W, Zhang J, Hong S, et al. EBV-driven LMP1 and IFN-gamma up-regulate PD-L1 in nasopharyngeal carcinoma: Implications for oncotargeted therapy. Oncotarget. 2014; 5(23): 12189-12202.

13. Cen O, Longnecker R. Latent Membrane Protein 2 (LMP2). Curr Top Microbiol Immunol. 2015; 391: 151-180.

14. Chen CJ, Lin ML, Chen MC, et al. Cryo-EM Structure and Functional Studies of EBNA1 Binding to the Family of Repeats and Dyad Symmetry Elements of Epstein-Barr Virus oriP. J Virol. 2022; 96(23): e0094922.

15. Frappier L. EBNA1. Curr Top Microbiol Immunol. 2025.

16. Nanbo A, Inoue K, Adachi-Takasawa K, Takada K. Epstein-Barr virus RNA confers resistance to interferon-alpha-induced apoptosis in Burkitt's lymphoma. EMBO J. 2002; 21(5): 954-965.

17. Marquitz AR, Raab-Traub N. The role of miRNAs in Epstein-Barr virus pathogenesis. Curr Opin Virol. 2012; 2(4): 492-497.

18. Zheng P, Dong W, Li Q, et al. Epstein-Barr virus-associated gastric carcinoma: a distinct molecular subtype. Cancer Med. 2020; 9(11): 3798-3806.

19. Chen MR. Epstein-Barr Virus, the Immune System, and Associated Diseases. Front Microbiol. 2011; 2: 5.

20. Rowe M, Zuo J. Immune responses to Epstein-Barr virus: molecular interactions in the virus evasion of CD8+ T cell immunity. Microbes Infect. 2010; 12(2): 173-181.

21. Chen JN, Ding YG. Clinical Importance of Epstein-Barr Virus-Associated Gastric Cancer. MDPI Cancers. 2018; 10(6): 167.

22. Thorley-Lawson DA, Hawkins JB, Tracy SI, Shapiro M. The pathogenesis of Epstein-Barr virus persistent infection. Curr Opin Virol. 2013; 3(3): 227-232.

23. Saha A, Halder S, Upadhyay SK, et al. Epstein-Barr virus nuclear antigen 3C facilitates G1-S transition by stabilizing and enhancing the function of cyclin D1. PLoS Pathog. 2011; 7(2): e1001275.

24. Taheri M, Abdullah SR, Saber AF, Hussen BM. Amplification and Overexpression of Cyclin D1 in Epstein-Barr Virus-Positive Inflammatory Follicular Dendritic Cell Sarcoma. Int J Biol Macromol. 2026.

25. Mahajan S, Bongaerts M, Hardillo J, et al. Transcriptomics of Epstein-Barr virus aids to the classification of T-cell evasion in nasopharyngeal carcinoma. Curr Opin Immunol. 2023; 83: 102335.

26. Derks S, Liao X, Chiaravalli AM, et al. Abundant PD-L1 expression in Epstein-Barr Virus-infected gastric cancers. Oncotarget. 2016; 7(22): 32925-32932.

27. Tellam J, Connolly G, Green KJ, et al. Endogenous presentation of CD8+ T cell epitopes from Epstein-Barr virus-encoded nuclear antigen 1. J Exp Med. 2004; 199(10): 1421-1431.

28. Dojcinov CG, Venkataraman G, Raffeld M, Pittaluga S, Jaffe ES. EBV positive mucocutaneous ulcer—a study of 26 cases associated with various sources of immunosuppression. Am J Surg Pathol. 2010; 34(3): 405-417.

29. Bollard CM, Heslop HE. T cells for viral infections after allogeneic hematopoietic stem cell transplant. Blood. 2016; 127(26): 3331-3340.

30. Cohen JI, Fauci AS, Varmus H, Nabel GJ. Epstein-Barr virus: an important vaccine target for cancer prevention. Sci Transl Med. 2011; 3(107): 107fs7.

31. Iizasa H, Nanbo A, Nishikawa J, Jinushi M, Yoshiyama H. Epstein-Barr Virus (EBV)-associated Gastric Carcinoma. Viruses. 2012; 4(12): 3420-3439.