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EBV-induced T-cell responses in EBV-specific and nonspecific cancers

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Epstein-Barr virus (EBV) is a ubiquitous human tumor virus associated with various malignancies, including B-lymphoma, NK and T-lymphoma, and epithelial carcinoma. It infects B lymphocytes and epithelial cells within the oropharynx and establishes persistent infection in memory B cells. With a balanced virus-host interaction, most individuals carry EBV asymptomatically because of the lifelong surveillance by T cell immunity against EBV. A stable anti-EBV T cell repertoire is maintained in memory at high frequency in the blood throughout persistent EBV infection. Patients with impaired T cell immunity are more likely to develop life-threatening lymphoproliferative disorders, highlighting the critical role of T cells in achieving the EBV-host balance. Recent studies reveal that the EBV protein, LMP1, triggers robust T-cell responses against multiple tumor-associated antigens (TAAs) in B cells. Additionally, EBV-specific T cells have been identified in EBV-unrelated cancers, raising questions about their role in antitumor immunity. Herein, we summarize T-cell responses in EBV-related cancers, considering latency patterns, host immune status, and factors like human leukocyte antigen (HLA) susceptibility, which may affect immune outcomes. We discuss EBV-induced TAA-specific T cell responses and explore the potential roles of EBV-specific T cell subsets in tumor microenvironments. We also describe T-cell immunotherapy strategies that harness EBV antigens, ranging from EBV-specific T cells to T cell receptor-engineered T cells. Lastly, we discuss the involvement of γδ T-cells in EBV infection and associated diseases, aiming to elucidate the comprehensive interplay between EBV and T-cell immunity.

KEYWORDS

Epstein-Barr virus, T-cell immunity, EBV-associated cancer, EBV-specific T cells, CAR-T, γδ T-cells, tumor-associated antigens (TAAs)

1 Introduction

Epstein-Barr virus (EBV), also known as human herpesvirus 4 (HHV-4), is a highly prevalent γ-herpesvirus that infects an overwhelming 90% of the adult population worldwide (1). Since its discovery in 1964 from a Burkitt lymphoma cell line, extensive research has been conducted to investigate its association with cancer (2). In 2020, EBV-

associated cancers accounted for an estimated 239,700 to 357,900 new cases and caused 137,900 to 208,700 deaths globally (3). EBV is considered the primary etiological agent associated with multiple epithelial and lymphoid cancers of variable fractions, including nasopharyngeal carcinoma (NPC), gastric carcinoma (GC), Hodgkin lymphoma (HL), Burkitt lymphoma (BL), Diffuse large B-cell lymphoma (DLBCL) and Extranodal NK/T-cell lymphoma, Nasal type (ENKTL-NT). In addition, EBV reactivation can lead to uncontrolled B-cell proliferation in immunocompromised individuals, including post-transplant lymphoproliferative disease (PTLD) in hematopoietic stem cell transplant (HSCT) or solid organ transplant (SOT) recipients and B-cell lymphoma in AIDS patients (4–6).

Despite its ubiquity, most people remain asymptomatic throughout their lifetime, owing to the potent host immune system, especially its cellular immunity, which keeps the virus at bay. However, when cellular immunity is compromised or dysregulated, the virus can replicate unchecked, leading to EBV-associated B-cell malignancies (7). These malignancies express EBV antigens that T cells can specifically target (8). Over the last two decades, the encouraging outcomes of adoptive cell therapy using EBV-specific T cells in treating PTLD have sparked significant research interest. Many clinical trials have been launched to explore their potential application in treating other EBV-related malignancies (9). Recent studies find that EBV latent membrane protein 1 (LMP1), upon ectopic expression in EBV-unrelated cancers, can upregulate TAAs and induce a robust TAA-specific CD4+ CTL response (10), indicating that beyond its oncogenic implications, EBV also has the potential for therapeutic applications in cancer treatment. This review aims to advance our understanding of the roles of T-cell immunity across both EBV-related and unrelated cancers and provide insights to devise more effective immune-based cancer prevention and treatment strategies.

2 Biology of EBV and EBV-associated cancers

The transmission of EBV occurs through oral means and involves the infection of epithelial cells of the oropharynx, followed by replication and spread to B cells, which are major sites for EBV infection in humans. While EBV predominantly targets B lymphocytes and epithelial cells, it can sporadically infect other human cell types, including T cells and natural killer cells, albeit infrequently (11–13). EBV life cycle is complex and is composed of latent and lytic infections. Only nine proteins contributing to B cell transformation and tumorigenesis are expressed during latent infection. These include six EBV nuclear antigens (EBNA-1, -2, -3A, -3B, -3C, and -LP) and three latent membrane proteins (LMP-1, -2A, and -2B). The latent cycle can be subdivided into four patterns, namely latency III, II, I, and 0, characterized by gradually restricted viral gene expression patterns to evade immune surveillance. Ultimately, EBV establishes persistent residence in memory B cells, characterized by the absence of viral antigen expression (latency 0), thereby evading T-cell recognition and acting as a viral reservoir. The latent-lytic switch is a particularly significant event in the EBV life cycle, but its mechanism remains elusive. EBV can transition to the lytic cycle periodically, resulting in viral replication, shedding, and subsequent transmission (8, 11, 12, 14).

During lytic infection, EBV expresses more than 80 lytic proteins that facilitate the generation of new viral particles (8). The viral lytic cycle is divided into three temporal and functional stages: immediate early (IE), early (E), and late (L). IE gene products are transcription factors in charge of turning on the cascade of expression of lytic genes. Among these proteins, the immediate early proteins BZLF-1 and BRLF-1 act as triggers of the EBV lytic cycle (15). E genes encode enzymes with DNA replication function, and L genes are mostly viral structural proteins.

Several lytic genes are somewhat expressed during latent states. For instance, BHRF1, commonly associated with the virus lytic cycle, remains constitutively expressed as a latent protein *in vitro* within growth-transformed cells and might contribute to virus-associated lymphomagenesis in Wp-restricted BL (16). Additionally, BALF1, expressed with early kinetics during the lytic cycle, is found in latently infected epithelial and B cells (15). While dispensable for lytic replication and B cell transformation, BALF1 might facilitate efficient transformation, potentially *in vivo* (15).

Under specific circumstances (17), such as immunosuppression like HIV or immunosuppressive therapy (18), concurrent infections such as CMV, HPV, or coronavirus (19, 20), disruptions in cellular equilibrium like hypoxia (21), or psychological stressors like familial and socio-economic instability (22), EBV can switch from latency to lytic infection, termed viral reactivation, contributing to the dissemination of the virus and its potential to cause various diseases and complications.

In EBV-associated cancers, latent EBV proteins are crucial for tumor pathogenesis, and their expression can classify tumors into distinct categories (Figure 1). In type III latency cancers, cells infected with EBV express a full array of latent proteins, including six EBV nuclear antigens (EBNA1, 2, 3A, 3B, 3C, LP), two latent membrane proteins (LMP1, 2), BamH1-A right frame 1 (BARF1), several small noncoding RNAs, various micro-RNAs, and EBV-encoded small RNAs. All EBNA3 family proteins are highly immunogenic and can be effectively targeted and cleared by T cells in immunocompetent individuals (8, 23, 24). Consequently, type III latency malignancies can primarily be seen in innate or acquired immunodeficient individuals, such as PTLD of HSCT or SOT recipients and B-cell lymphoma in AIDS patients. Type III latency can also be seen in EBV-transformed B cell lymphoblastoid cell lines (LCLs) cultured *in vitro*.

Type II latency tumors mainly include NPC, GC, some cases of HL, and NKT. These tumors express EBNA1, LMP1, LMP2, and BARF1 and have intermediate immunogenicity.

Type I latency, marked by sole EBNA1 expression, is seen in BL and exhibits constrained immunogenicity.

Apart from latent antigens, some lytic cycle transcripts are also found in certain tumors, which encode molecules known to contribute to tumor growth (25). Among these transcripts, BZLF1

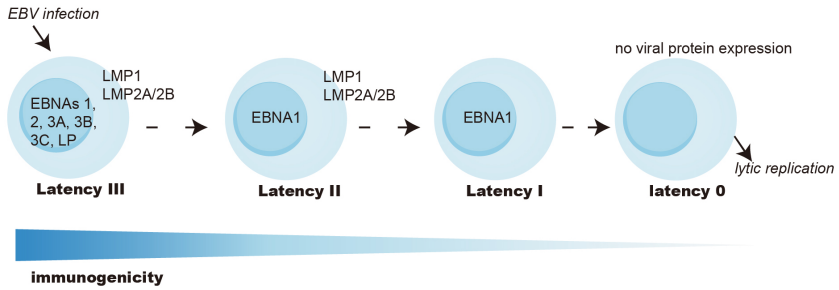

FIGURE 1
EBV latency types. Latency III express all EBV-encoded latent proteins and is the most immunogenic. Latency II expresses EBNA1, LMP1, and LMP2, and has intermediate immunogenicity. Latency I only expresses EBNA1 and is poorly immunogenic. Latency 0 abolishes all antigen expression and is seen in memory B cells as a reservoir of the virus. There can be transition latency states with upregulation of latency and lytic genes. EBNA, EBV nuclear antigen; LP, leader protein; LMP, latent membrane protein.

and BRLF1 are the IE transcription factors that master-regulate EBV reactivation/lytic expression. Notably, the expression of some of the immediate early genes, such as BZLF1, in the absence of other lytic genes, particularly those encoding late structural proteins, thereby precluding the formation of infectious viral particles, is termed the abortive lytic cycle. Specifically, it is known as the pre-latent abortive lytic cycle when it occurs just after infection. The abortive lytic cycle has been well-documented in pre-latent cells (26–30) and established tumors (31–34). Furthermore, evidence derived from mouse models (35, 36) supports the notion that the abortive lytic cycle facilitates cell-to-cell viral dissemination and contributes to viral-induced tumorigenesis.

3 EBV-specific T cell immunity in EBV-related cancers

3.1 EBV-positive lymphoma in immune-deficient host

In the context of immunocompromised SOT or HSCT recipients, PTLD predominantly arises, characterized by the presence of six EBNA and two LMP antigens denoting Type III latency. The EBNA3 antigens within PTLD demonstrate notable immunogenicity, forming a foundation for potential adoptive cell therapies targeting these specific antigens.

Front-line therapies for PTLD post-HSCT or SOT commonly involve reducing immunosuppression, often coupled with rituximab and occasionally augmented by chemotherapy. However, cellular therapy remains the primary option in cases of inadequate response or relapse. The rich diversity of EBV antigens expressed in these tumors facilitates the efficacy of adoptive therapy using virus-specific cytotoxic T cells (CTLs). Clinical trials across global centers have successfully employed CTL preparations, sourced either autologously or from third-party donors, for PTLD treatment or prevention, with a strong record of safety and efficacy. These antigen-specific T cells are primed via *in vitro* exposure to LCLs. The potent immunogenicity of the EBNA3 family proteins makes them the principal targets of CD8 T-cell immunity (8, 23, 24). CD4+ T cells, though less frequent, also contribute to tumor control (10, 37, 38). CD4+ T-cell effectors are crucial in limiting early-stage EBV-induced B-cell proliferation, and some direct target EBV-transformed LCLs (37). Notably, EBV-specific T cell products enriched with CD4+ T cells correlate with improved clinical outcomes (38). Furthermore, the expansion of T cells through LCL generates CD4+ T cells specific to nonviral cellular antigens (39, 40), known as TAAs (10), upregulated by LMP1 in EBV-infected cells.

3.2 EBV-positive tumors in the immunocompetent host

Unlike PTLD, which expresses a full array of EBV latent antigens (latency III), most EBV-associated cancers exhibit limited expression of EBV latent antigens in relatively immunocompetent hosts (Figure 1). Immunodominant proteins such as EBNA2, 3A, 3B, 3C, and -LP are absent, redirecting immune attention towards remaining target antigens, such as EBNA1 in BL, EBNA1, LMP1, and LMP2 in HL, and primarily EBNA1 and LMP2 in NPC, GCa, ENKTL, and DLBCL. Efficient recognition of these EBV antigens by T cells is crucial for targeting and eliminating infected cells.

Traditionally considered immunologically inert, EBNA1 has a glycine-alanine repeat (GAr) region that shields it from proteasome breakdown and MHC I presentation (41). However, studies of CD8 + T cells targeting specific EBNA1 epitopes are also reported (42, 43). These T cells can recognize naturally expressed native EBNA1 protein within EBV-transformed LCLs, inhibiting LCL proliferation (44), suggesting that the GAr domain within EBNA1 does not confer complete protection from MHC class I presentation. *In vitro* models suggest that HL, NPC, and T/NKL cells retain MHC class I antigen processing capabilities and can be recognized by CD8+ T cells specific to LMP2 (45–49).

In contrast, BL is deficient in MHC class I processing (50) but exhibits MHC class II expression (51), allowing recognition by EBNA1-specific CD4+ T cells ex vivo and in murine models (52, 53). Besides MHC molecules, HLA polymorphism, which influences antigen presentation and immune recognition, is strongly associated with disease risk (54–57). For example, the HLA-A01 allele increases the risk of EBV-positive HL, whereas

HLA-A02 has a protective effect (58). Despite EBV-specific T cells being restricted by various HLA alleles, the emergence of EBV-positive tumors cannot be solely attributed to antigen-specific blindness in the T cell repertoire. T-cell population deficiencies and attenuated T-cell responses are plausible contributors (59, 60). This is particularly evident in endemic BL, where Plasmodium falciparum and EBV act as co-factors in cancer development (61). Malaria stimulates the proliferation of latently infected B cells through viral reactivation (53). Meanwhile, T-cell control of EBV-infected B cells is lost during P. falciparum malaria (59, 60), possibly contributing to an increased risk of incidence of BL.

Furthermore, EBV-positive cancers employ diverse strategies to evade immune surveillance. The tumor microenvironment (TME) within EBV-associated malignancies, including HL, NPC, and the majority of EBV-positive gastric cancers, is characterized by an "immune hot" phenotype (58, 62, 63). These tumors display pronounced infiltration of lymphocytes whose specificities and functions remain incompletely elucidated.

EBV-positive HL exhibits distinct characteristics compared to EBV-negative HL. Notably, the signature of EBV+ cHL tissues is enriched in genes characteristic of Th1 and antiviral responses. Furthermore, in pediatric cases of EBV+ cHL, a robust T cell infiltration is evident, exhibiting a cytotoxic/Th1 immune profile (64, 65). However, markers of suppression also increase, including LAG-3 and IL-10 (66). Regulatory T cells (Tregs), both natural and induced, are present in higher frequencies, contributing to immunosuppression (66, 67). EBNA1 may upregulate CCL20 expression, promoting the migration and recruitment of Tregs (68). Additionally, active signaling by LMP1 and LMP2 can induce high-level expression of galectin-1 and PD-L1 (69–71).

Undifferentiated NPC is invariably EBV-positive and exhibits a suppressive TME characterized by dysfunctional lymphocyte infiltration. Regulatory CD4+ T cells are elevated in the blood and consistently detected in tumors (72). CD8+ FoxP3+ lymphocytes with suppressive functions are also present (73). Immune checkpoint molecules such as PD-L1, LAG3, galectin 9-TIM3, TIGIT, and CTLA4 are overexpressed (74–77). Recently, an epithelial-immune dual feature of NPC cells has been identified, characterized by upregulated MHC II gene expression. This dual feature correlates with CD8+ T cell exhaustion and a suppressed TME, ultimately associated with poor prognosis (78).

Approximately 10% of gastric cancers are EBV-positive (79), and patients with EBV-associated gastric cancer (EBVaGC) have a more favorable prognosis compared to their EBV-negative counterparts (80). EBV-positive gastric cancer exhibits pronounced lymphocytic infiltration (81). Many perforin-positive CD8+ T cells are observed within this infiltrate, exhibiting effectiveness in eliminating autologous EBV-transformed cells (82). However, these CD8+ T cells may not recognize known EBV latent antigenic peptides, suggesting the involvement of alternative cellular antigens (82). Nevertheless, these CD8+ T cells can be counteracted by localized immunosuppression, as evidenced by high expression of PD-L1, PD-L2, and indoleamine 2,3-dioxygenase (IDO), which inhibits T and NK cell function through tryptophan depletion (83, 84).

Despite the diverse repertoire of immunomodulatory mechanisms employed by EBV-positive cancers, adoptive transfer of EBV-specific T cells has demonstrated clinical efficacy in patients with PTLD, HL, NPC, and T/NKL (85–88). The therapeutic effect of EBV-specific T cells not only destroys tumor cells and reduces tumor burden but may also induce the release of potentially antigenic debris from tumor cells, thereby stimulating an immune response against nonviral cellular antigens. This phenomenon, known as epitope spreading (85), expands the range of targeted antigens for T-cell recognition and response. However, the origin of these cellular antigens, whether from epitope spreading or as a consequence of LMP1 signaling-induced upregulation of TAAs on B cells (10), warrants further investigation.

3.3 HLA susceptibility

The human leukocyte antigen (HLA) complex, located within the major histocompatibility complex (MHC) on chromosome 6p21.3, plays a vital role in antigen presentation to the immune system. The MHC region encompasses three subregions: HLA class I, crucial for CD8+ T-cell cytotoxicity induction; HLA class II, involved in CD4+ helper T-cell responses; and class III, housing non-HLA genes associated with inflammation, leukocyte maturation, and the complement cascade.

HLA's diversity and polymorphism contribute to its ability to recognize and target various pathogens. Growing evidence suggests that HLA variations can influence genetic susceptibility to EBV-associated cancers. Notably, NPC strongly associates with HLA genes in the MHC region (54–57). In the genomic analysis of NPC patients, a notable frequency of aberrations in MHC class I genes (NLRC5, HLA-A, HLA-B, HLA-C, B2M) has been observed (89). An HLA class I region-specific association suggests the importance of CD8+ T-cell cytotoxicity in NPC etiology (90). HLA associations may vary across racial groups, with specific HLA alleles conferring protective or increased risk effects in different populations. In Southern China and Southeast Asia, where NPC is most prevalent, HLA-A11 and B13 are associated with a protective effect against NPC, whereas HLA-A02 (A0207, A0206), A33, B46, and B58 are linked to an increased risk of NPC (91).

HLA also demonstrates significant links with other EBV-associated cancers, including HL, BL (92), and PTLD (93). For example, the HLA-A01 allele increases the risk of EBV-positive HL, whereas HLA-A02 has a protective effect (58). However, the mechanisms underlying the diverse roles of HLA alleles in cancer susceptibility and immune escape remain incompletely understood.

In addition to classic HLA genes, non-classic HLA genes have been implicated in immune escape. HLA-G, known to inhibit T-cell and NK-cell function, is frequently expressed in NPC tumors and is associated with poor survival outcomes (94).

Due to its strong association with cancer etiology, HLA has potential applications in cancer screening, as demonstrated in improved prediction efficiency for NPC screening when combining HLA class I gene variants with EBV genetic variants and epidemiological risk factors (95).

To advance our understanding of the intricate role of HLA genes and their interplay with T-cell immunity in EBV-associated cancers, larger-scale and comprehensive studies are needed.

4 EBV-induced T cell responses against TAAs

Choi et al. (10) demonstrated in a mouse model that the expression of the EBV signaling protein LMP1 in B cells induces T-cell responses against multiple TAAs. LMP1 signaling enhances the presentation of TAAs on B cells and upregulates the expression of costimulatory ligands CD70 and OX40L, leading to the activation of potent cytotoxic CD4+ and CD8+ T-cell responses against LMP1 (EBV)-transformed B cells (Figure 2). Furthermore, through the ectopic expression of LMP1 on patient-derived tumor B cells to prime T cells, autologous cytotoxic CD4+ T cells can be expanded to target a wide range of endogenous tumor antigens, including TAAs and neoantigens. This innovative approach holds great promise for treating B-cell malignancies and augmenting immune-mediated protection against EBV-unrelated cancers by targeting shared TAAs (96).

Several independent studies have also reported a nonviral, cellular antigen-specific component in the human CD4+ T cell response upon EBV-transformed LCL stimulation *in vitro* (39, 97). However, these cellular antigens have not been identified and their classification as TAAs remains to be established. Furthermore, clinical studies have observed the detection of T cells specific for nonviral TAAs in the peripheral blood following cytotoxic T lymphocyte (CTL) infusion, which is associated with clinical responses (85). Nevertheless, whether these T cells arise through epitope spreading or are derived from the therapeutic T cells through LCL stimulation is unclear. Therefore, further investigations are needed to identify TAAs expressed by EBV-infected or transformed B cells and to determine their recognition by T cells in individuals with EBV infection (96).

In addition to B cells, whether LMP1 or other EBV antigens can induce the upregulation of TAAs in epithelial cells has yet to be examined. Furthermore, the exact roles of MHC II molecules in cancer remain subject to debate and investigation. Accumulating evidence indicates that tumor-specific MHC II expression is linked to positive outcomes in many cancer types (98) (e.g., breast cancer (99), colon cancer (100), melanoma (101)). However, an opposing functional aspect of MHC II has also emerged. In HLA-DR+ melanoma, MHC II lessens CD8+ T cell activity by inducing LAG3+ and FCRL6+ TILs (102) or recruiting CD4+ T cells to the tumor (103). In the TC-1 mouse model of HPV-related carcinoma, the absence of MHC II molecules promotes CD8+ T cell infiltration and activation, curbing tumor growth (104). Moreover, a recent study examining NPC using single-cell transcriptomics has revealed a dual epithelial-immune feature of tumor cells, characterized by the expression of immune-related genes, including MHC II-coding genes (78), which relates to poor prognosis. This distinct trait also links to CD8+ T cell exhaustion and a suppressed tumor environment (78).

5 EBV-specific T cells in TME: bystanders or not?

Humans can experience common viral infections like CMV, EBV, and influenza. Once recovered, antiviral memory T cells are retained throughout the body to sense reinfection or recrudescence (105, 106) and are endowed with the capacity for rapid response, sustained vigilance, and cytotoxic prowess (107). Although such virus-specific T cells are abundant within tumors, they may not target tumor cells and are therefore regarded as “bystander-T cells”

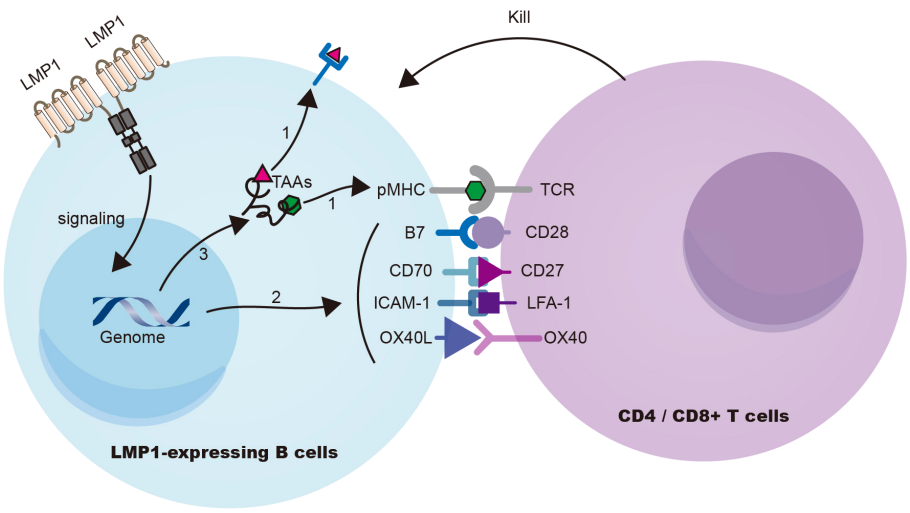

FIGURE 2
LMP1 signaling in B cells triggers cytotoxic T-cell resposes against TAAs. (Choi et al., 2021) LMP1 signaling induces substantial cellular gene expression, leading to (i) upregulation of antigen processing and presentation machinery, (ii) enhanced expression of co-stimulatory ligands (CD70, OX40L, etc.), and (iii) overexpression of cellular antigens known to function as TAAs. Collectively, these mechanisms contribute to the effective eradication of LMP1 (EBV)-transformed B cells. TAA, tumor associated antigens.

(108). However, emerging evidence suggests that these virus-specific T cells can still be harnessed for cancer immunotherapy (107, 109–111).

One strategy involves antibody-mediated delivery of viral epitopes to tumors (110, 111), achieved by conjugating virus-derived epitopes with tumor-targeting antibodies. These antibodies bind to specific tumor cell antigens and release immunogenic virus epitopes when cleaved by tumor-specific proteases. The released peptide then binds to free HLA class I molecules at the tumor cell's surface and can be targeted for destruction by circulating virus-specific CTLs (110, 111).

Another strategy employs viral peptides to mimic a viral reinfection event in memory T cells. Memory T cells can execute a 'sensing and alarm' function upon antigen re-exposure (112), and this form of immunotherapy is termed peptide alarm therapy (PAT) (109). Reactivating virus-specific memory T cells through intratumoral delivery of adjuvant-free virus-derived peptide triggers local immune activation. This delivery translates to antineoplastic effects, which lead to a significant tumor reduction of tumor growth in mouse models of melanoma (107) and improved survival in a murine glioblastoma model (109). This approach can reactivate and attract T-cell infiltration into the tumor and transform the immunosuppressive tumor microenvironment into immune-active sites.

6 EBV-specific T cell-based therapies

6.1 EBVSTs

EBV-specific T cells (EBVSTs) derived from allogeneic or autologous donors can recognize and eliminate cancer cells expressing EBV antigens, highlighting their potential in adoptive cell therapy (Table 1).

Clinical trials in the early stages have demonstrated the effectiveness of adoptive T-cell therapy in treating PTLD, which leverages the restoration of cellular immunity to control EBV-associated PTLD. Initial trials using unmanipulated donor-derived lymphocytes in HSCT patients yielded favorable outcomes, with complete regression observed in all 5 patients (113). However, the alloreactive nature of these T cells also led to the development of graft-versus-host disease (GvHD). Subsequent trials focused on generating allogeneic EBVSTs through *in vitro* stimulation using EBV-transformed LCLs, recombinant viral vectors, or synthetic peptides (86, 114–118). These trials demonstrated efficacy in preventing and treating PTLD in HSCT recipients, with minimal alloreactivity and reduced production pipeline. Similar strategies have been employed in the context of SOT to address PTLD (119–121); however, the response rate and persistence of EBVSTs in SOT patients have been limited, likely attributed to high levels of immunosuppression (9). To overcome this challenge, preclinical studies have attempted genetic modifications of EBVSTs to confer resistance against immunosuppressive agents (122–124).

The success of EBVSTs in PTLD has fostered an interest in treating other EBV-associated malignancies, such as NPC and HL. EBVSTs targeting type II latency antigens (EBNA1, LMP1, and LMP2) have shown promising results in clinical trials (85, 87, 88, 117, 125), with increased response rates and overall survival observed in patients with NPC and HL compared to those who did not receive adoptive cell transfer. However, it should be noted that the best response rate is still observed in PTLD-post HSCT (Table 2). In addition, emerging evidence indicates that immediate early and other lytic transcripts, including BARF1, could broaden specificity and enhance cytotoxicity for EBV-associated diseases. BARF1-specific T cells have demonstrated the ability to efficiently eliminate NPC cell lines *in vitro* (127).

TABLE 1 EBV-associated malignancies and their forms of viral latency.

tumor	subtype	% EBV positive	latency
PTLD	post HSCT	>95%	III
PTLD	post SOT	95% in first year	III
		50-60% after 1 year	I/II
Hodgkin's lymphoma	classical	30-40%	II
	AIDS-related	100%	
Diffuse large B cell lymphoma	late post-transplant DLBCL	>50%	I/II
	Elderly DLBCL	>50%	
	AIDS-related	~50%	
Burkitt's lymphoma	Endemic BL	100%	I
	AIDS-related BL	30-40%	
T/NK cell lymphoma	Extranodal	>95%	I/II
Nasopharygeal carcinoma	Undifferentiated	100%	I/II
Gastric carcinoma		9%	I/II

PTLD, post-transplant lymphoproliferative disease; HSCT, hematopoietic stem cell transplant; SOT, solid organ transplant; AIDS, acquired immunodeficiency syndrome; DLBCL, diffuse large B cell lymphoma; EBV, Epstein-Barr virus; NK, natural killer.

To improve accessibility and expedite treatment, the establishment of third-party EBVST banks is actively being explored for PTLD (38, 126). The use of banked cells from third-party donors has broadened the availability of EBVSTs, and the observed response rates indicate the potential effectiveness of this approach in a wider range of patients. Alternatively, a combination of therapies with other immunomodulatory agents, such as checkpoint inhibitors (135) or vaccines (136) may be necessary to ensure clinical impact.

6.2 EBV specific T cell receptor engineered T cell therapy

TCR (T-cell receptor) engineered T-cell therapy has emerged as a promising strategy for immune-based treatment (Table 1). TCRs specific to EBNA3A, EBNA3B, LMP1, LMP2, BRLF1, and BMLF1 have been generated from CD8+ T cell clones (129, 137, 138). However, recognition of autologous EBV-transformed LCLs by T-cell lines transduced with these TCRs was weak, partly attributed to the limited expression of latent EBV antigens in LCLs. Nevertheless, the adoptive transfer of TCR transgenic T cells significantly attenuated tumor growth induced by the CNE NPC line in nude mice, demonstrating their efficacy *in vivo* (139). The interactions between transgenic TCR α and β chains with the endogenous TCR is another possible factor contributing to the constrained killing efficiency (140). To overcome this, chimeric TCRs have been devised. These chimeric TCRs entail the fusion of constant regions derived from mouse TCR with variable domains derived from EBV-specific T cell clones (141). The stability of these modified receptors was enhanced by introducing an additional disulfide bond between the TCR α and β chain constant domains (128, 142). Transgenic T cells expressing these chimeric TCRs exhibited improved cytotoxicity against co-incubated EBV-positive NPC cells, effectively suppressing tumor growth in immune-compromised mice (128). Similarly, promising outcomes were observed with an LMP1-specific TCR, as T cells transduced with LMP1-specific TCR rendered a twofold increase in the survival of immune-compromised mice challenged with LMP1-expressing tumor cells (129).

Consequently, despite the limited cytotoxicity towards autologous tumor cells, transgenic T-cell therapy remains a promising strategy in combating EBV-associated malignancies.

7 Beyond αβ: accumulating evidence of a role for γδ T-cells

The preceding review primarily focuses on αβ T cells, but it is important to note the unique features of γδ T cells that make them appealing in various cancer settings. These features include tissue tropisms, MHC-independent antigen presentation, antitumor activity regardless of neoantigen burden (143), and a combination of T and natural killer cell properties (144–146). In humans, γδ T cells can be categorized into Vδ1+ and Vδ2+ cells, with distinct distributions in mucosal tissues and blood/lymphoid organs, respectively. They play a crucial role in antiviral immune responses in cytomegalovirus (147–150). Emerging evidence suggests that γδ T cells also play a role in primary EBV infection and EBV-associated cancers.

During primary EBV infection, there is an observed increase in the frequency of γδ T cells in the blood of patients with infectious mononucleosis (IM) (151–153). Pediatric patients have a bimodal innate response to primary EBV infection (154), influenced by a dimorphism in TCRγ-chain repertoires (155). Altered γδ T cells have also been observed in patients with EBV-associated malignancies, such as NPC, where the impaired functional capacity of γδ T cells is observed despite an unchanged frequency (156, 157). In a case involving a cord blood transplant recipient with elevated EBV viremia, the absence of detectable αβ T cells was compensated by expansions of cytotoxic Vδ1+ γδ T cells, resulting in no signs of lymphoproliferative disorder (158). Moreover, early recovery of Vδ2+ T cells has been identified as an independent protective factor against EBV reactivation in recipients of allo-HSCT (159). Interventions that induce early reconstitution of autologous γδ T cells could hold therapeutic benefits. αβ TCR graft depletion (160, 161) has demonstrated efficacy in reducing GVHD by facilitating rapid immune reconstitution of NK cells and γδ T cells (162–164). Additionally, reducing immunosuppressants has led to enhanced recovery of Vδ2+ T cells and decreased risk of EBV-associated lymphoproliferative disorders in HSCT recipients (159). Notably, long-term persistence of donor-derived Vδ1+ T cell clones has been detected in recipients' blood even a decade post-HSCT, with these cells exhibiting expandability *in vitro* and cytotoxicity against autologous EBV-LCL (165).

While extensive research and clinical trials have explored the therapeutic potential of γδ T cells in managing solid tumors and hematopoietic malignancies (166–168), only a limited number of studies have investigated their efficacy in EBV-associated cancers using murine models (Table 1). Adoptive transfer of anti-γδ TCR antibody-expanded γδ T cells to Daudi lymphoma-bearing nude mice significantly prolonged their survival time (130). In addition, the adoptive transfer of pamidronate-expanded Vγ9Vδ2-T cells prevented and inhibited EBV-LPD in mouse models (131). Moreover, co-administration of Vδ2+ T cells and the EBNA1-targeting peptide L2P4 enhanced γδ T cell cytotoxicity against NPC in immunodeficient mouse models (132). Additionally, exosomes derived from Vδ2+ T cells exhibited the ability to eliminate EBV-associated tumor cells (133), and when combined with radiotherapy, γδ-T-Exos demonstrated efficacy in effectively treating NPC by eradicating radioresistant cells (134).

Thus, γδ T cells represent an essential component of cellular immunity in regulating primary EBV infection and hold promise in combating EBV-associated malignancies.

8 Conclusions

Cellular immunity is pivotal in maintaining the delicate equilibrium between the host and EBV. Despite EBV's high prevalence, affecting a significant portion of the global population, most individuals remain asymptomatic throughout their lives,

TABLE 2 Summary of EBV-specific T cell-based therapies.

method	disease, clinical trial/animal model	phase	published year (reference)	results
Adoptive cell therapy				
Donor-derived unmanipulated lymphocytes	PTLD	I	1994 (113)	CR in 5/5 patients, but GVHD developed
gene-modified donor-derived EBVSTs	PTLD, HSCT	I	1995 (114)	CR of immunoblastic lymphoma in 1/1 patients; EBV reactivation controlled in 3/3 patients without lymphoma
Donor-derived EBVSTs	PTLD, HSCT	I	1998 (115)	CR of immunoblastic lymphoma in 2/2 patients; EBV reactivation controlled in 6/6 patients without lymphoma
Multivirus-specific CTLs activated by LCLs genetically modified with an adenoviral vector	PTLD, HSCT	I	2006 (116)	CR in 11/11 individuals with evidence of active CMV, EBV or adenoviral infection, without GVHD
EBV, ADV-specific CTLs activated by monocytes and LCLs transduced with adenoviral vector	PTLD, HSCT	I	2009 (118)	none of 13 receiving EBVSTs as prophylaxis developed PTLD
Peptide-induced multivirus-CTL	PTLD, HSCT	I	2014 (86)	11 recipients: 94% response rate of 8 patients receiving EBVSTs as treatment; 3 patients receiving EBVSTs as prophylaxis did not develop PTLD.
third party-EBVSTs	PTLD	II	2007 (38)	CR or PR in 17/33 patients
third party-EBVSTs	PTLD	I	2019 (126)	CR or PR in 35/59 patients
Autologous EBVSTs	PTLD, SOT	I	1999 (119)	Significant regression of the PTLD in 1/1 patient
Autologous EBVSTs	PTLD, SOT	I	2006 (120)	CR of liver PTLD in 1/1 patient; prevention of PTLD in 12/12 patients
Autologous EBVSTs	SOT	I	2002 (121)	Decrease EBV load, prevention of PTLD in 7/7 patients
Autologous EBVSTs	NPC	I	2005 (125)	CR in 4/10 patients and PR in 2/10 patients
Autologous EBVSTs combined with chemotherapy	NPC	II	2014 (87)	CR in 3/35 patients and PR in 22/35 patients
LMP1/LMP2-specific Autologous EBVSTs	Lymphoma	II	2014 (85)	CR in 11/21 patients and PR 2/21 patients
LMP1 and LMP2a-specific EBVSTs	Extranodal NK/T Cell Lymphoma	I	2015 (88)	CR in 10/10 patients
LMP- EBVST	HSCT	I	2018 (117)	PR in 2/7 post treatment therapy 15/19 remain in remission post prophylaxis therapy
BARF1-EBVST	NPC cell lines		2016 (127)	CTLs generated with doxorubicin-treated LCLs kill T2-A2 cells with exogenous or endogenous BARF1-peptides
EBV Specific TCR engineered T cell therapy				
Autologous CD8 and CD4 Lymphocytes expressing LMP2-specific TCR	NSG mouse, NPC model		2015 (128)	Lysed LMP2+ NPC cells and inhibited tumor growth in a mouse model
LMP1-specific TCR-T	NSG mouse, tumor model		2018 (129)	Doubled the survival time of mice bearing tumor
EBV-Specific γδ T cells				
Anti-γδ TCR antibody-expanded γδ T cells	nude mice, lymphoma model		2012 (130)	adoptive transfer of the expanded γδ T cells to Daudi lymphoma-bearing nude mice significantly prolonged the survival time of the mice and improved their living status
pamidronate-expanded Vγ9Vδ2-T cells	EBV-LPD Model in Humanized and Rag2−/− γc−/− Mice		2014 (131)	prevented and inhibited EBV-LPD in mouse models
adoptive γδ T cells combined with EBV-targeting probe (L2)P4	NPC-bearing NSG mice model		2023 (132)	exerted killing against certain NPC cells, enhanced tumor regression *in vivo* by adoptive transfer of γδ T cells

(Continued)

TABLE 2 Continued

method	disease, clinical trial/animal model	phase	published year (reference)	results
Exosomes derived from Vδ2-T cells	EBV-associated tumors in Rag2−/−δc−/− mice and humanized mice		2020 (133)	Vδ2-T-Exos induce CD4 and CD8 T cell–mediated antitumor immunity and control EBV-associated tumors in Rag2−/−δc−/− mice and humanized mice models.
γδ-T-Exos combined with radiotherapy	NPC tumors in Rag2−/−δc −/− mice		2022 (134)	γδ-T-Exos synergize with radiotherapy to control NPC tumors *in vivo*, and preserve antitumor activities in immunosuppressive NPC microenvironment

this list contains examples.
CR, complete response; PR, partial response.

highlighting the critical role of effective immune control. However, EBV-associated malignancies primarily occur in individuals with apparently intact immune function. This raises intriguing questions about the mechanisms and stages at which these tumors manage to evade the surveillance of virus-specific T cells.

EBV-associated malignancies express distinct EBV latent antigens, triggering diverse T-cell responses while also employing a range of immune evasion mechanisms, rendering a complex interplay with cellular immunity. Encouragingly, promising clinical responses have been observed from adoptive cell transfer of EBV-specific T cells targeting latent antigens. Recent investigations into early lytic EBV antigens in tumorigenesis provide additional potential targets for therapeutic interventions. Additionally, TCR transgenic therapy offers the possibility of redirecting T cells to recognize EBV antigens and the involvement of γδ T cells also merits consideration in EBV-associated diseases.

In cancers not associated with EBV, there usually exists an abundance of EBV-specific memory T cells, which can be leveraged to either activate the immunosuppressive tumor microenvironment or re-directed to target tumor cells. In addition, EBV can activate TAA-specific T-cell responses. These further broaden our understanding of this oncogenic virus and its implications for the fields of cancer biology and therapy. In this regard, a pivotal research goal is to attain a comprehensive grasp of the intricate interplay between cellular immunity and the virus. By harnessing the inherent capabilities of T-cell immunity, we can advance toward more precise and effective interventions in the treatment of EBV-associated and other cancers.

Author contributions

QZ prepared the manuscript draft, MX provided valuable comments to the text and figures, read and approved the final manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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