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The PD-1/PD-L1 pathway and Epstein–Barr virus

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Abstract

Epstein–Barr virus (EBV) is a gamma-herpesvirus with double-stranded DNA. Primary EBV infection leads to infectious mononucleosis (IM) in 20–50% of children and young adults. EBV establishes latent infection in B lymphocytes and can infect T lymphocytes and NK cells, potentially causing lymphoproliferative disorders (LPD) and malignancies. While the PD-1/PD-L1 pathway's role in chronic viral infections is well-established, its specific functions in EBV infection remain poorly understood. Growing evidence suggests this pathway facilitates EBV immune evasion, yet the effect of PD-1 upregulation on Epstein–Barr virus-specific CD8 + T cell function during acute IM is unclear. Furthermore, the role of PD-1/PD-L1 pathway in cytotoxic T cells and immune regulation during EBV infection is still controversial. This review systematically analyzes current knowledge on PD-1/PD-L1 signaling in EBV infection, focusing on three key aspects: (1) its dual role in maintaining immune homeostasis during acute infection while potentially facilitating viral persistence, (2) its emerging potential as a diagnostic biomarker for disease progression and prognosis, particularly during acute infectious mononucleosis, and (3) the therapeutic implications of pathway modulation. We critically evaluate recent advances that position PD-1/PD-L1 at the intersection of virology and tumor immunology, while highlighting important unanswered questions that require further investigation to optimize EBV-specific immunotherapies.

Keywords Epstein–Barr virus, PD-1/PD-L1 pathway, Infectious mononucleosis, Immune evasion

Introduction

Epstein–Barr virus (EBV), a γ-herpesvirus, infects more than 90% of people worldwide, typically establishing lifelong latent infections in B lymphocytes. Often asymptomatic in healthy individuals, EBV is nonetheless a well-known contributor to the development of several malignancies, including nasopharyngeal carcinoma, Burkitt's lymphoma, and certain gastric carcinomas. Over 90% of adults worldwide are seropositive for EBV, with higher infection rates observed in children from developing countries (> 95%) compared to those from developed nations (50–70%) [1]. Following typically asymptomatic primary infection during childhood or adolescence, the virus establishes lifelong latency in memory B cells [2]. In the natural environment, particularly during early life, primary EBV infection is typically asymptomatic. However, 20–50% of primary infections in children and adolescents manifest as IM [3].

Emerging evidence also suggests a potential link between EBV and tumors, particularly in individuals with immune suppression or a genetic predisposition [4]. EBV-associated malignancies, including nasopharyngeal carcinoma and Burkitt lymphoma, are responsible for an estimated 200,000 deaths per year worldwide [5]. EBV infection demonstrates a significant epidemiological

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association with the development of multiple sclerosis (MS) and systemic lupus erythematosus (SLE) [6]. EBV-linked pathologies, including IM and neoplastic conditions, generate multibillion-dollar healthcare costs yearly. While gp350-targeted vaccines show promise in curtailing IM cases, their widespread deployment has yet to be achieved [7, 8]. Consequently, EBV infection continues to pose a substantial global public health challenge.

It is currently believed that EBV is predominantly transmitted through oral contact, as well as through blood transfusions, organ transplants and other routes [9]. EBV predominantly infects cells within the oropharyngeal lymphoid ring, also known as Waldeyer's ring, including epithelial cells and B cells [10]. Upon successful infection of the host, EBV can circumvent the host's immune surveillance and establish latency within memory B cells, which results in a persistent lifelong latent infection [11]. Latent infection of EBV does not involve integration of its DNA into the host genome but rather persisting as free fragments in the nucleus of the infected cell [12]. EBV continuously expresses two small RNAs (EBER1 and EBER2), both are characterized by their stable structures which are resistant to host nuclease [13]. EBV is capable of establishing latent infection in B lymphocytes, T lymphocytes, and NK (natural killer) cells [14]. Under specific conditions, EBV-infected cells can undergo clonal expansion, resulting in LPD and in some cases, malignant tumors [15, 16].

IM is a prevalent acute upper respiratory tract infection in children, typically benign and self-limiting [17]. The peak incidence of IM in China occurs between the ages of 4 and 6 years. The primary symptoms encompass fever, sore throat, fatigue, lymphadenopathy, and an elevated count of atypical lymphocytes in the peripheral blood. Additional symptoms may involve hepatosplenomegaly, rash, and myalgia. In severe cases, there can be serious complications, including splenic rupture, airway obstruction due to pharyngeal and tonsillar edema, encephalitis, meningitis, myocarditis, hemolytic anemia, thrombocytopenic purpura, and other critical conditions [18]. Rarely, patients may develop severe complications such as hemophagocytic syndrome, which poses a significant health risk to children [19]. Most primary cases of IM end with complete recovery, with acute symptoms resolving within 1–2 weeks [20]. However, fatigue and weakness can persist for several months, and a minority of individuals may develop chronic active persistent infection. During the initial phase of EBV infection, cytotoxic T cells targeting EBV antigens are pivotal in controlling the infection, alongside a significant contribution from NK cells [21]. In the acute phase of IM, there is a marked elevation of atypical lymphocytes in the patient's peripheral blood [22]. This was accompanied by an enhanced EB virus-specific CD4 +and CD8 +T cell response, characterized by a substantial increase in the frequency and proportion of CD8 +T cells, predominantly due to the expansion of CD8 +T cells reactive to EBV antigenic epitopes [23]. Multiple lines of evidence suggest that the cellular immune response is pivotal in limiting the initial EBV infection and managing chronic infections [24–26]. During the acute phase of viral antigen degradation, there is a marked amplification of antigen epitope-specific CD8 +T cell, which diminish during the recovery phase. In IM patients, the characteristic cellular immune response encompasses the proliferation of activated CD8 +T cells and the expression of latent viral antigens by B cells [27]. Symptoms observed in the acute phase of IM, including fever, fatigue, and splenomegaly, reflect excessive immune activation and the overproduction of inflammatory factors by cellular immunity. The distinct symptoms and immune system response of IM patients contribute to its clinical diagnosis [28].

CD8 +T cells are pivotal in regulating EBV infection. During the acute phase of IM, there is a pronounced expansion of CD8 +T cells, which subsequently decline in total count as the disease progresses, ultimately returning to baseline levels. Nonetheless, a significant fraction of EBV-specific memory CD8 +T cells persist, and in some cases, their numbers may even rise, albeit with diminished functionality [28]. Research has demonstrated that in mice harboring recombinant human immune system components, CD8 +T cell depletion results in elevated EBV loads and an increased prevalence of tumors that mimic IM [29, 30]. Furthermore, individuals harboring mutations in perforin or the vesicular fusion proteins responsible for the release of cytotoxic granules are prone to uncontrollable EBV infections [31]. Additionally, primary immunodeficiencies linked to T cell and NK cell function, including those associated with CD27 and SH2D1A genes, can predispose individuals to lymphomas induced by EBV [32]. These findings underscore the critical role of cytotoxicity in managing this oncogenic virus. Previous research has demonstrated that during lupus, the capacity to control EBV is compromised, due to lupus induced exhaustion of T cells, which was characterized by increased expression of programmed cell death receptor-1 (PD-1) [33]. As a co-inhibitory receptor on T cells, PD-1 dampens initial T cell activation by reducing its intensity. It is also important infinite-tuning differentiation and effector functions of T cells and the development of immune memory. It is crucial for the induction and maintenance of central and peripheral immune tolerance [34]. T cell exhaustion is a gradual and dysregulated process of T cell transformation, triggered by continuous activation of T cell by high antigen loads. Initially, T cells lose

their cytotoxic function, and inhibitory and terminal differentiation receptors on the cell surface such as PD-1, Tim-3, and Lag-3 are progressively upregulated [35, 36]. Consequently, exhausted T cells fail to produce IFN-γ and are eliminated from the lymphocyte pool. Research indicates that the PD-1-positive CD8 + T cell population retains both its function and proliferative capacity during the primary symptomatic EBV infection as shown in Fig. 1 [37]. Examination of CD8 + T cells from patients with active IM revealed an increase in the frequency of inhibitory and differentiation molecules on their surface, including PD-1, Tim-3, Lag-3, B-and T-lymphocyte attenuator (BTLA), 2B4, and Killer cell lectin-like receptor subfamily G member 1 (KLRG1). These molecules were positively associated with the elevated EBV load. Consequently, despite the expression of PD-1, these cells continue to produce cytotoxicity-related cytokines, such as degranulation markers (CD107a-positive), and maintain their proliferative function. Furthermore, the study revealed that the post-EBV infection PD-1-positive CD8 + T cell population demonstrates heterogeneity. For instance, CD8 + T cells that express PD-1 continue to exhibit protective T cell functions. PD-1 signaling is crucial for sustaining the functionality of these T cell subsets, as evidenced by the increased viral and tumor loads observed in animals treated with anti-PD-1 antibodies [38]. These findings imply that PD-1 expression during acute EBV infection signifies a functional state of CD8 + T cells, a state that is vital for their self-protective response against the common human oncogenic virus. Consequently, there remains ongoing debate concerning the function of the PD-1/PD-L1 pathway in cytotoxic T cells and immune modulation during the course of EBV infection.

EBV exhibits a preferential affinity for human cells, particularly mucosal B cells, following transmission via saliva. Upon infection with EBV, proliferating B cells exhibit a distinct immunoregulatory phenotype,

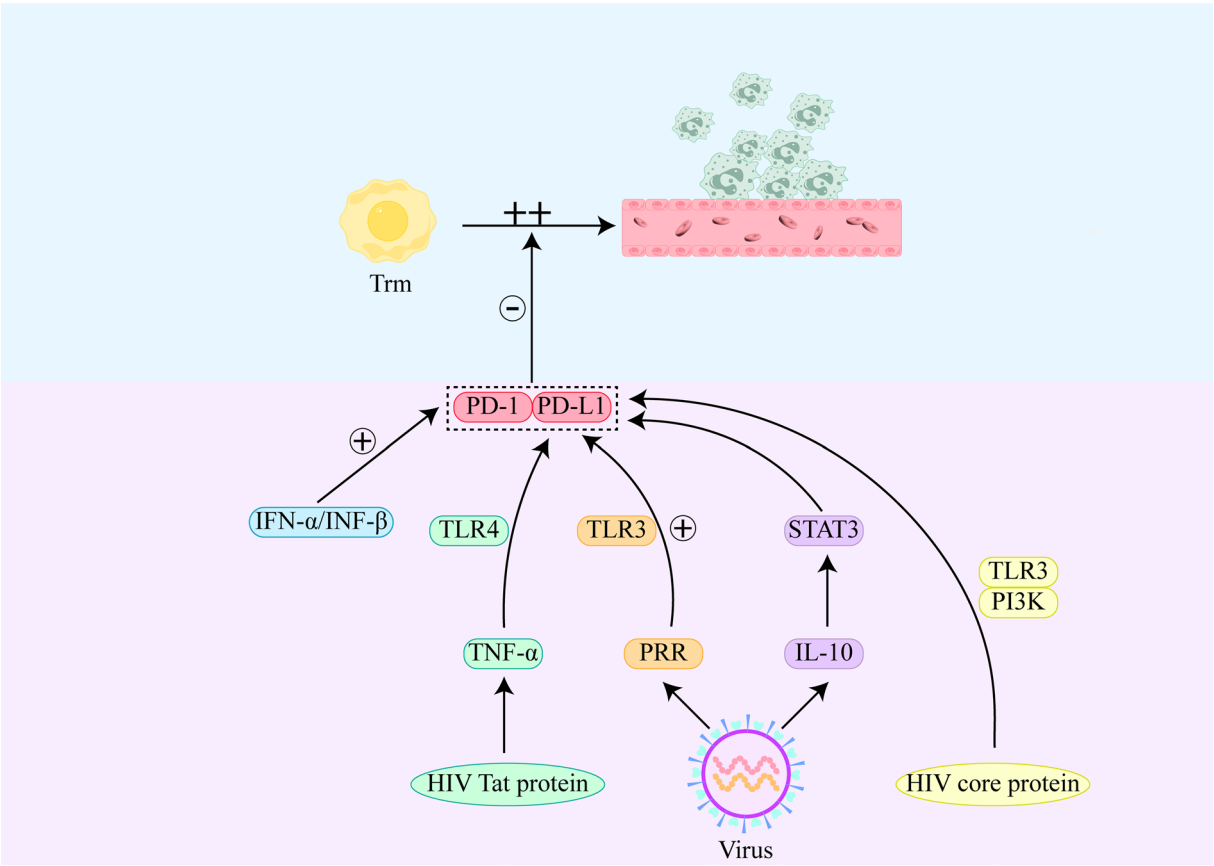

Fig. 1 The Infection and PD-1/PD-L1 pathway PD-1/PD-L1 pathway may prevent uncontrolled activation and excessive inflammation of Trm cells within infected tissues, thereby preventing fatal immunopathological damage. This includes vascular leakage, pulmonary edema, and severe hypotension, which can arise from uncontrolled inflammation. Viruses and viral proteins play a significant role in modulating the PD-1/PD-L1 pathway during viral infections.The HIV Tat protein enhances PD-L1 expression on DCs via TNF-α and TLR4 signaling pathways. The HCV core protein upregulates PD-L1 in a TLR2 and PI3K-dependent signaling pathways.Concurrently, viruses induce the release of pro-inflammatory cytokines, such as IFN, through PRR signaling, leading to increased PD-L1 expression

actively contributing to the expansion of Treg cells through the PD-1/PD-L1 pathway. CD4 +/CD25 + Tregs inhibit activated T cells by engaging their CTLA-4. Tr1 cells secrete IL-10 to inhibit T cell proliferation and differentiation, while Th3 cells produce TGF-β, suppressing effector cell proliferation and differentiation, and dampening cytokine production to limit overall immune activity.

This review comprehensively summarizes the role of the PD-1/PD-L1 pathway in EBV infection and immune evasion, offering novel insights into viral immune escape mechanisms. It aims to provide immunologists and virologists with an enhanced understanding of the PD-1/PD-L1 pathway's significance during EBV infection. The target audience includes researchers in immunology, virology, and oncology, as well as peers in related biomedical disciplines, especially those involved in viral infection studies and drug development targeting the PD-1/PD-L1 pathway.

Survey methodology

For harvesting the articles about researches on the role of PD-1/PD-L1 pathway in EBV infection, the literature research was conducted in the Web of Science and PubMed. We used the following keywords: PD-1, PD-L1, viral infections, Epstein–Barr virus, immune evasion and tumors. The collected articles cover a range of aspects, from basic research to clinical applications. Particular emphasis was given to the most recent advancements, and authoritative baseline studies were conducted within the last decade. Articles were included based on the following criteria: Studies presenting novel data and findings on the role of the PD-1/PD-L1 pathway in EBV infection, with a particular focus on immune evasion mechanisms. Authoritative research articles published within the last decade that established fundamental understandings of the PD-1/PD-L1 pathway and its interactions with EBV infection. Studies exploring the translational aspects and therapeutic potential of targeting the PD-1/PD-L1 pathway in EBV-related diseases, including clinical trials and case series. Clinical literature published more than 15 years ago related to EBV infection and the immune system was excluded to prioritize contemporary understandings and advancements. By meticulously employing these search strategies, inclusion and exclusion criteria, and focusing on both contemporary advancements and foundational studies, we ensured a comprehensive and unbiased understanding of the literature. This approach captured the interplay between EBV infection and the PD-1/PD-L1 pathway, providing valuable insights into this complex field.

The PD-1/PD-L1 pathway

PD-1, also known as CD279, was initially discovered by Tasuku Honjo and his colleagues at Kyoto University in Japan during a gene-screening study on programmed cell death [39]. Encoded by the PDCD1 gene, it consists of five exons. Exon 1 houses the signal sequence, exon 2 encodes a class I Ig-like variable domain, exon 3 contains a stalk and transmembrane region, while exons 4 and 5 are responsible for the cytoplasmic domain, which includes an immunoreceptor tyrosine-based inhibitory motif (ITIM) and an immunoreceptor tyrosine-based switch motif (ITSM). PD-1 expression is induced and regulated swiftly through T-cell receptor (TCR) signaling upon cell activation by cytokines. This receptor is predominantly expressed on activated lymphocytes, including CD4 + and CD8 + T cells, as well as other immune cells such as B cells, natural killer (NK) cells, NKT cells, dendritic cells (DCs), and mononuclear cells (MNCs). A wealth of studies underscores the pivotal role of PD-1, a member of the immunoglobulin superfamily, in modulating the magnitude and intensity of T cell responses [37, 40–43]. PD-1 belongs to a family of structurally diversed surface molecules that function as co-inhibitory receptors in host immune response to pathogens and cancer. These molecules balance function of co-stimulatory receptors like CD28, which can interact with CD80 and CD86 on antigen-presenting cells (APCs) to support T cell activation [44]. CD28, the initial member of the co-stimulatory molecule family, features a variable immunoglobulin-like extracellular domain. CD80 typically exists as dimer on the cell surface, while CD86 is monomeric. CD86 is constitutively expressed on APCs and upregulated upon stimulation, whereas CD80 is induced later in the process. The PD-1 pathway exerts immunosuppressive effects by inhibiting T cell activation. During an acute infection, major histocompatibility complex (MHC) on APC cell presents pathogenic peptides to naive T cells, which leads to T cell activation and differentiation into effector T cells targeting the pathogen. Simultaneously, memory T cells are generated, which provide immunity against recurrent infections [45–47]. During chronic infections, the persistent presence of pathogens results in continuous T cell activation and ultimately T cell exhaustion [36, 48–50]. CD8 + T cell dysfunction is a gradually process. After ceased antigen exposure and resolution of an acute infection, functional T cells could promptly produce inflammatory cytokines such as IFN-γ, TNF-α and IL-2 upon re-exposure to antigens. In contrast, when viral persistence occurs, CD8 + T cells display varying functional states. Initially, functional T cell populations can coexist with the virus if antigen expression is low or encounters are infrequent, as in some latent infections or when antigens are no longer recognized by the immune

system. As antigen encounter persists, T cells progress through stages of exhaustion: Phase I involves loss of effector functions, with reduced IL-2 and TNF-α production, while IFN-γ synthesis remains intact, and cytotoxicity is compromised. In Phase II, IFN-γ production wanes, with some cells retaining the ability to produce it but exhibiting functional inactivity, and was unable to produce IL-2 and TNF-α. Ultimately, complete exhaustion ensues, with the complete loss of effector functions, including cytotoxicity and cytokine synthesis (IL-2 and TNF-α), and the capacity to respond to pathogen stimulation by producing IFN-γ. T cell exhaustion is mediated by upregulation of inhibitory receptors like PD-1, LAG-3, and Tim-3. These receptors dampen T cell function by lowering IL-2 production, T cell proliferation and survival [35, 49, 51, 52]. Typically within 24 h of stimulation PD-1 expression on activated T cells increases in a time-dependent manner, which makes it a marker of T cell activation both in vivo and in vitro. PD-1 expression is dynamic during viral infections. In acute infections, PD-1 expression on antigen-specific T cells is transient, typically observed during the initial immune response. Chronic infections, however, involve sustained stimulation of T cell with antigens and persistent PD-1 expression, which is positively correlated with T cell dysfunction. Exhausted T cells represent a heterogeneous population of antigen-specific T cells, where additional co-inhibitory receptors contribute to their overall functional impairment. In both acute and chronic infections, PD-1 acts in concert with other co-suppressive receptors to regulate T cell function, reflecting the intricate interplay between these mechanisms and the progression of T cell exhaustion.

PD-1 functions through its interaction with its ligands, PD-L1 (Programmed Death Ligand 1) and PD-L2. PD-L1 consists of an Ig-V and Ig-E-like extracellular domain, a transmembrane region, and a short cytoplasmic tail devoid of a typical signaling sequence [53, 54]. Primarily expressed on leukocytes, non-hematopoietic cells, and non-lymphoid tissues, PD-L1 can be induced on tissue cells through the IFN-γ/transforming growth factor-beta signaling pathway. PD-L1 is also found on various tumor cell types, with its expression linked to increased infiltration of tumor-infiltrating lymphocytes. Expression of PD-L1 is observed on endothelial and epithelial cells as well. PD-L2, predominantly expressed on dendritic cells and monocytes, can be induced on other immune and non-immune cells depending on the local microenvironment. Upon binding to PD-1, PD-L1 and PD-L2 inhibit the proliferation, migration, and cytokine production of activated lymphocytes, playing a pivotal role in cell exhaustion, immune tolerance induction, and maintenance. This mechanism significantly influences the development of tumors, transplant immunity, and autoimmune diseases. While PD-L1 and PD-L2 share the function of PD-1 activation, evidence suggests that they independently regulate T cell responses. This highlights the complexity of their interplay in modulating immune responses in various pathological contexts. Research has shown that PD-L2 serves as a primary regulator of CD8 + T cell proliferation [55], while PD-L1 plays a significant role in the induction of peripheral regulatory T cells. Upon interaction with PD-L1/2, PD-1 undergoes conformational changes, which lead to the phosphorylation of the immunoreceptor tyrosine-based inhibitory motifs (ITIMs) in its cytoplasmic tail [56–59]. The phosphorylated tyrosine residues in ITIMs facilitate binding to the SH2 domains of protein tyrosine phosphatases (PTPs), recruiting these enzymes and activating them. This recruitment inhibits signal transduction pathways, exerting a negative regulatory effect. The downstream effects of the PD-1 signaling pathway involve the suppression of key signaling proteins such as Akt, phosphoinositide 3-kinase (PI3K), extracellular signal-regulated kinase (ERK), and phospholipase C-γ (PLC-γ). This leads to modulation of cell cycle progression, resulting in reduced production of IFN-γ and IL-2, and a decline in cell proliferation capacity. Concurrently, an increase in apoptosis occurs. Furthermore, the PD-1 signaling pathway influences T cell metabolism by inhibiting glycolysis and promoting fat breakdown and fatty acid oxidation.

Role of the PD-1/PD-L1 pathway and its inhibitors in tumors

The interaction between PD-1 and PD-L1 inhibits the downstream signaling pathways involved in T-cell activation. This inhibition is mediated through multiple mechanisms, including the suppression of phosphatidylinositol-3-kinase phosphorylation, activation of protein kinase B, stimulation of T-cell stimulatory signaling pathways, and disruption of interferon secretion. By directly binding to PD-L1 through their respective structural features, PD-1/PD-L1 inhibitors disrupt the PD-1/PD-L1 interaction. This obstruction also inhibits the protein interaction between PD-1 and PD-L1, impairing PD-1 signaling transduction. Consequently, these actions lead to the inhibition of T-cell transcription and the suppression of T-cell immunosuppressive function. Blocking the interaction between PD-1 and PD-L1 weakens the inhibitory effect on T-cell activation and stimulates the endogenous anti-tumor immune response [60]. PD-1/PD-L1 monoclonal antibodies function by inhibiting the binding of PD-1 to its ligands (PD-Ls), leading to the reactivation of suppressed T cells within the body. This reactivation enables enhanced recognition of tumor cells and potentiates the body's anti-tumor capabilities. PD-1/

PD-L1 monoclonal antibodies enhance effector T-cell function and provide long-term relief to patients with different malignancies [61]. Within the tumor microenvironment, tumor cells induce aberrant expression of the PD-1/PD-L1 pathway, skewing the immune balance toward immunosuppression. This shift facilitates immune escape, allowing tumor cells to evade the body's immune surveillance. Consequently, the immune system becomes compromised, failing to recognize and eradicate "non-self" tumor cells effectively. Instead, it inadvertently promotes tumor cell growth, metastasis, and immune evasion. These collective dysfunctions ultimately lead to extensive proliferation of tumor cells and the development of tumors. Interferon and other inflammatory factors can rapidly induce PD-L1 expression in a variety of tumor tissues. By binding to PD-1 on activated T cells, it inhibits tumor-specific T cell activation effects. Consequently, disrupting the PD-1/PD-L1 pathway is a key strategy in current anti-cancer drug development, aiming to restore T cell antitumor activity and directly target cancer cells [62–65].

The programmed death receptor and its ligands, collectively known as"immune checkpoints,"form the basis for checkpoint blockade therapies, which enhance host immune system's cytotoxicity by inhibiting the interaction between these molecules. Immune checkpoint inhibitors, such as those targeting PD-1 and PD-L1, are exemplified by monoclonal antibodies. Recent clinical studies have demonstrated the efficacy of targeting the PD-1/PD-L1 pathway in treating various advanced malignancies, such as melanoma, lymphoma, non-small cell lung cancer, head and neck squamous cell carcinoma, and renal cell carcinoma [66–68]. These immunotherapy agents, particularly immune checkpoint inhibitors, boost CD8 + T cell function, offering substantial therapeutic benefits to patients with certain types of cancer. However, it is crucial to note that a subset of patients experiences severe immune-related adverse events, including colitis, hepatitis, and dermatological conditions. This highlights the need for a more comprehensive understanding of why some patients respond favorably while others suffer from severe side effects. The impact of PD-1 blockers on viral and bacterial infections remains uncertain and requires further investigation.

The PD-1/PD-L1 pathway and chronic viral infections

During viral infections, the PD-1/PD-L1 pathway plays a significant role, particularly in chronic infections. PD-1 signaling facilitates pathogens to evade host immune system clearance, thereby sustaining chronic infections. Research efforts have predominantly focused on chronic infections such as HIV, HBV, and HCV, as documented in studies [69–71]. In the context of chronic viral infections, continuous viral antigen exposure drives antigen-specific T cells into a state of exhaustion, characterized by repeated stimulation during the infection process [36, 48]. The phenotypic features of exhausted T cells have been elucidated through a series of mouse studies investigating the disparities in T cell responses between acute and chronic lymphocytic choriomeningitis virus (LCMV) infections. A study revealed that antigen-specific T cells isolated from chronically infected mice with LCMV expressed higher and more sustained levels of PD-1 compared to those from acute infections [35]. PD-1 expression levels reflect distinct functional states of T cells. T cells with intermediate PD-1 expression can regain effector function upon PD-1 blockade, while PD-1 inhibitors are ineffective in restoring function of cells with high PD-1 expression, indicating their terminal exhaustion. Notably, concurrent blockade of PD-1 along with other inhibitory molecules like LAG-3, 2B4, and CTLA-4 has shown better outcomes, supporting the role of additional co-inhibitors in T cell exhaustion [72–74]. The outcomes and effects of PD-1 blockade vary significantly across different studies and pathogens. PD-1 blockade has demonstrated the most significant impact in HBV infection. It enhances T cell proliferation, reduces viral load and induces high level of IFN-γ and IL-2in HBV-specific CD8 + T cells isolated from both peripheral blood and liver of chronic hepatitis B patients [75, 76]. However, differences in viral strain toxicity and host immune function among study populations contribute to variations in T cell exhaustion levels during chronic infection. Some reports suggest that HBV-specific T cells express additional inhibitory receptors, like Tim-3 and LAG-3, which can limit the effectiveness of PD-1 blockade in chronic infections [77]. In mice infected with Norway rat hepatovirus (NrHV), CD4 + T cells play a crucial role in sustaining anti-viral CD8 + T cell responses, mirroring the chronic LCMV model [78]. Early intervention with PD-1/PD-L1 blockade significantly reduces viral load, but no further benefits are observed later in the chronic phase. Although PD-1 pathway blockers can reactivate exhausted T cells in certain infection models, not all PD-1 blockade models elicit this response.

The PD-1/PD-L1 pathway and acute viral infections

The mechanism of the PD-1/PD-L1 pathway in chronic viral infections is relatively well understood, but its role during the acute phase remains less clear. The debate persists over whether the upregulation of host PD-L1/PD-L2 expression in response to viral antigens during acute infection is a selective evolutionary strategy for viral survival or an adaptive response to minimize host immune damage. In acute LCMV-infected mice, PD-1 expression is significantly increased on initial virus-specific CD8 + T

cells, and blocking the PD-1 signaling pathway enhances their functional capacity [79]. This suggests that PD-1 may negatively regulate the terminal differentiation of initial CD8 + T cells during acute infection, thereby reducing the generation of effector CD8 + T cells. Similarly, in mice with acute retroviral infection, the PD-1/PD-L pathway can inhibit the differentiation of CD8 + T lymphocytes into multifunctional cytotoxic T cells, suggesting that the PD-1/PD-L pathway negatively regulates the final differentiation of initial CD8 + T cells into effector CD8 + T lymphocytes during acute viral infection [80]. After viral clearance, PD-1 expression on virus-specific T cells returns to normal levels. Post-acute infection, memory T cells are established, with at least four primary subsets identified to date: central memory T cells (Tcm), effector memory T cells (Tem), terminally differentiated effector memory cells that re-express CD45RA (TEMRA), and the newly characterized tissue-resident memory T cells (Trm). Functionally, Trm cells play a pivotal role in the first line of defense against viruses, establishing an antiviral state, and recruiting circulating memory T cells to the site of infection. Distributed in frontline tissues like the lungs, skin, and gut, Trm cells are indispensable for viral resistance and immune surveillance. The specific function of the PD-1/PD-L1 pathway in CD8 + Trm cells remains unclear, but it may prevent uncontrolled activation and excessive inflammation of Trm cells within infected tissues. In PD-1/PD-L1-deficient mouse models, LCMV infection leads to fatal immunopathological damage, including vascular leakage, pulmonary edema, and severe hypotension due to exacerbated inflammation. Upon blocking the PD-1/PD-L1 pathway, while virus clearance improves, inflammation also escalates. These findings suggest that during acute viral infection, modulating the PD-1/PD-L1 pathway aids in balancing the intensity and quality of cytotoxic CD8 + T cell responses, preventing excessive tissue damage. Furthermore, the PD-1/PD-L1 pathway plays a crucial role in maintaining self-tolerance. Disruption of this pathway in mice, through gene deletion or antibody blockade, increases the risk of autoimmune diseases such as dilated cardiomyopathy and experimental autoimmune encephalomyelitis (EAE) [81]. Additionally, transgenic mice expressing PD-1 with mutated ITIM sequences develop lupus-like autoimmune conditions [82].

Acute and chronic viral infections exhibit distinct pathobiological characteristics. During acute infections, the immune system is intensely activated by viral particles, which are ultimately cleared, and memory cells are generated. Numerous studies have shown that PD-1 expression is significantly upregulated in mice during acute infections with cowpox virus, influenza, rabies, and human infections with hepatitis A virus, hepatitis B virus and hepatitis C virus [35, 83–85]. In the acute phase, virus-specific T cells become activated, with concurrent increases in PD-1 expression and other activation markers. Furthermore, viruses can directly or indirectly stimulate the release of pro-inflammatory cytokines through pattern recognition receptor signaling, leading to upregulation of PD-L1 expression on various cell types. Majority of studies demonstrate that upregulation of the PD-1/PD-L1 pathway during acute viral infections serves as a protective mechanism to prevent severe immunological damage [82, 86]. For instance, PD-1-deficient mice succumb to fatal immune injury within a week of LCMV infection, characterized by systemic cytokine storms and acute lung injury due to endothelial cell damage [87]. In another study, PD-1-deficient mice infected with HAV exhibit more severe airway dysfunction and slower weight recovery compared to wild-type mice [35]. A clinical investigation of acute HBV infection reports that PD-1 expression is significantly upregulated on HBV-specific CD8 + T cells during the early phase of acute infection, which then decreases after viral clearance [77]. Importantly, PD-1 expression levels in patients with acute liver failure are reduced 1–2 weeks after clinical onset, suggesting a positive correlation between PD-1 dysregulation on HBV-specific CD8 + T cells and liver failure. The data not only substantiate the pivotal role of the PD-1/PD-L1 pathway in regulating tissue injury but also suggest that PD-1 expression may serve as a potential biomarker for the clinical outcome of HBV infection. These studies have further revealed that the PD-1-mediated signaling pathway not only impairs the effector function of HBV-specific CD8 + T cells during the acute phase but also positively correlates with the formation of memory CD8 + T cells after disease remission [77, 88]. Given the signaling pathway's involvement in dampening T-cell responses, a therapeutic intervention targeting this pathway could, in theory, enhance effector T-cell function during acute infection. Two key aspects of PD-1 pathway activity during the acute phase are noteworthy: first, some viral strains exploit the immunosuppressive properties of the PD-1 pathway to facilitate the establishment of chronic infection by impairing immune clearance; second, the PD-1/PD-L1 pathway suppresses immune reactions in the acute phase of persistent infection to prevent severe immunopathology. While the exact role of the PD-1/PD-L1 pathway in acute infection remains inconclusive, its expression has been implicated as a significant biomarker for predicting disease outcomes. As a potential indicator of immune cell activation or dysfunction during acute infection, considering PD-1 expression in therapeutic strategies holds notable advantages. In situations where viral antigens persist, T-cell exhaustion ensues, characterized by upregulation

of PD-1 alongside other inhibitory receptors like CTLA-4 and Lag3. This shift in phenotype leads to a gradual loss of CD8 + T cell functionality, with earlier impairments in proliferation, cytotoxicity, and IL-2 secretion, while effector functions like IFN-γ secretion can persist for a longer period. Blocking the PD-1/PD-L1 pathway can restore some CD8 + T cell function, mitigate cell exhaustion, and decrease viral load. Collectively, these studies underscore the role of the PD-1/PD-L1 pathway in regulating the quantity and quality of cytotoxic CD8 + T cell responses during acute infection, thereby preventing excessive immunological damage.

The PD-1/PD-L1 pathway may suppress uncontrolled activation of tissue-resident memory T (Trm) cells in infected tissues, thereby preventing excessive inflammation and fatal immunopathology. This includes vascular leakage, pulmonary edema, and severe hypotension, which can arise from uncontrolled inflammation. Viruses and viral proteins play a significant role in modulating the PD-1/PD-L1 pathway during viral infections. The HIV Tat protein enhances PD-L1 expression on DCs via TNF-α and TLR4 signaling pathways. The HCV core protein upregulates PD-L1 in a TLR2 and PI3K-dependent signaling pathways. Concurrently, viruses induce the release of pro-inflammatory cytokines, such as IFN, through PRR signaling, leading to increased PD-L1 expression.

The infection and PD-L1/2 expression

PD-L1/2 expression is modulated by both pro-inflammatory and anti-inflammatory signals. Type I and III interferons, crucial antiviral cytokines, are induced in primary barrier tissues like lung and intestinal epithelial cells during viral infections, functioning as the first line of defense. IFN-α and IFN-β predominantly induce PD-L1 expression, while IFN-γ and IFN-β mainly drive PD-L2 upregulation. Studies have shown that suppression or deficiency of the type I IFN signaling pathway leads to reduced PD-L1 expression during chronic LCMV infection, despite increased viral replication [89, 90]. Activation of pattern recognition receptors (PRRs), such as TLR3, particularly enhances PD-L1 levels on dendritic cells (DCs) upon viral recognition. Viruses do not directly regulate the PD-1/PD-L1 pathway; instead, they induce PD-1 and PD-L1 expression through intermediaries, like IL-10, which acts on DCs and monocytes via STAT-3-dependent mechanisms, as observed in studies [91, 92]. Recent studies have identified viral proteins capable of inducing PD-L1/PD-L2 expression. For instance, the HIV Tat protein enhances PD-L1 expression on DCs via TNF-α and TLR4 signaling pathways [93]. In vitro, the HCV core protein robustly upregulates PD-L1 on primary Kupffer cells and monocytes in a TLR2 and PI3K-dependent fashion [94, 95]. Circulating monocytes, upon internalizing extracellular vesicles from HBV-infected hepatocytes, display enhanced PD-L1 expression [96]. Furthermore, latent transcripts of herpes simplex virus type 1 (HSV-1) induce an increase in PD-L1 expression on mouse neuroblastoma cells via an uncharacterized mechanism [92]. During the later stages of viral infection, IFN-γ significantly boosts PD-L1 levels, which in turn inhibits the terminal differentiation of CD8 + T cells, thereby preventing excessive tissue damage from uncontrolled cytotoxic responses. PD-L1 expression on hematopoietic and non-hematopoietic cells has distinct roles; enhancing PD-L1 expression can shield virus-infected cells from elimination by cytotoxic CD8 + T cells. Viral-induced PD-L1 expression on antigen-presenting cells (APCs) may facilitate specificity of the antiviral CD8 + T cell on its target cells, and prevent the activation of CD8 + T cells by most weakly immunogenic viral peptides and onset of excessive inflammatory reactions. During the acute phase of viral infection, virus-specific T cells rapidly upregulate the inhibitory receptor PD-1 upon antigen recognition. Concurrently, viruses induce the release of pro-inflammatory cytokines, such as IFN, through PRR signaling. These cytokines lead to increased PD-L1 expression on both hematopoietic and non-hematopoietic cells. Ideally, the optimal state would involve the activation of CD8 + T cells to clear pathogens while minimizing immune damage. However, immune dysregulation often occurs during infection, potentially linked to the timing, intensity, and type of PD-L1 expression induced by the virus. Viruses also exploit the balance of immune co-stimulation and co-inhibition to manipulate the immune system, thereby preventing effective antiviral responses and facilitating persistence within the host, a phenomenon known as immune evasion. CD8 + T cells, with their functionality compromised by heightened PD-1 signaling, exhibit a decline in efficacy and ultimately undergo apoptosis during persistent viral infections [51]. In chronic LCMV infections, blockade of the PD-1/PD-L1 pathway has been shown to reactivate antiviral T cells and reduce viral load [72]. However, it is crucial to note that CD8 + T cell exhaustion can also occur in the absence of PD-1 [49]. Recent data suggest that PD-L1 upregulation is part of a normal innate immune response to IFN and PRR activation, although the underlying mechanism remains unclear [97]. Initially, PD-L1 might exert an as-yet-unexplored immune stimulatory effect during viral infection. Subsequently, it fine-tunes the quantity and quality of antiviral CD8 + T cell responses, minimizing tissue damage during viral clearance.

The PD-1/PD-L1 pathway and Epstein–Barr virus infection

EBV exhibits a preferential affinity for human cells, particularly mucosal B cells, following its transmission via saliva. The virus undergoes a biphasic lifecycle, alternating between lytic and latent phases. During primary infection, when the host's immune system is initially unprepared, EBV causes cell lysis at the site of entry. Subsequently, over days and weeks, cellular and humoral immune responses evolve, allowing the virus to establish latency within memory B cells. This latent state is characterized by immune evasion within the infected cell, as documented in studies [98, 99]. The progression of latency within memory B cells typically involves a transition from Latency III to II, and then to I [100, 101]. The latency patterns, initially observed in cell lines, are intricately linked to the in vivo biology of EBV. Following infection of resting primary B cells, EBV enters Latency III, during which EBERs and all latent viral proteins are expressed, including EBNA1 (EBV nuclear antigen 1), EBNA2, EBNA3A, EBNA3B, EBNA3C, EBNALP, LMP1, LMP2A, and LMP2B. These proteins exhibit a hierarchical immune response in CD8 + T cells, with EBNA3A, EBNA3B, and EBNA3C eliciting the strongest responses. A similar hierarchical pattern is observed in the lytic phase, with the host's response to early antigens BZLF1 and BRLF1 being the most robust. Subsequently, the virus restricts its gene expression, transitioning to Latency II, which further divides into subtypes IIa (with EBERs, EBNA1, and LMP-1) and IIb (EBERs and EBNA1 co-expressed with EBNA2, but not LMP-1). Memory B cell differentiation ensues. Finally, EBV further limits its gene expression, reaching Latency I, where only EBNA1 and EBERs are expressed. EBNA-1 is ubiquitously expressed in all EBV-infected cells and plays a central role in maintaining and replicating the viral genome as shown in Fig. 2. Periodic reactivation of these latent cells may contribute to low-level viral replication. Like other γ-herpesviruses, EBV expresses distinct proteins during the lytic and latent phases: approximately eighty genes are transcribed during the lytic cycle, while only eight

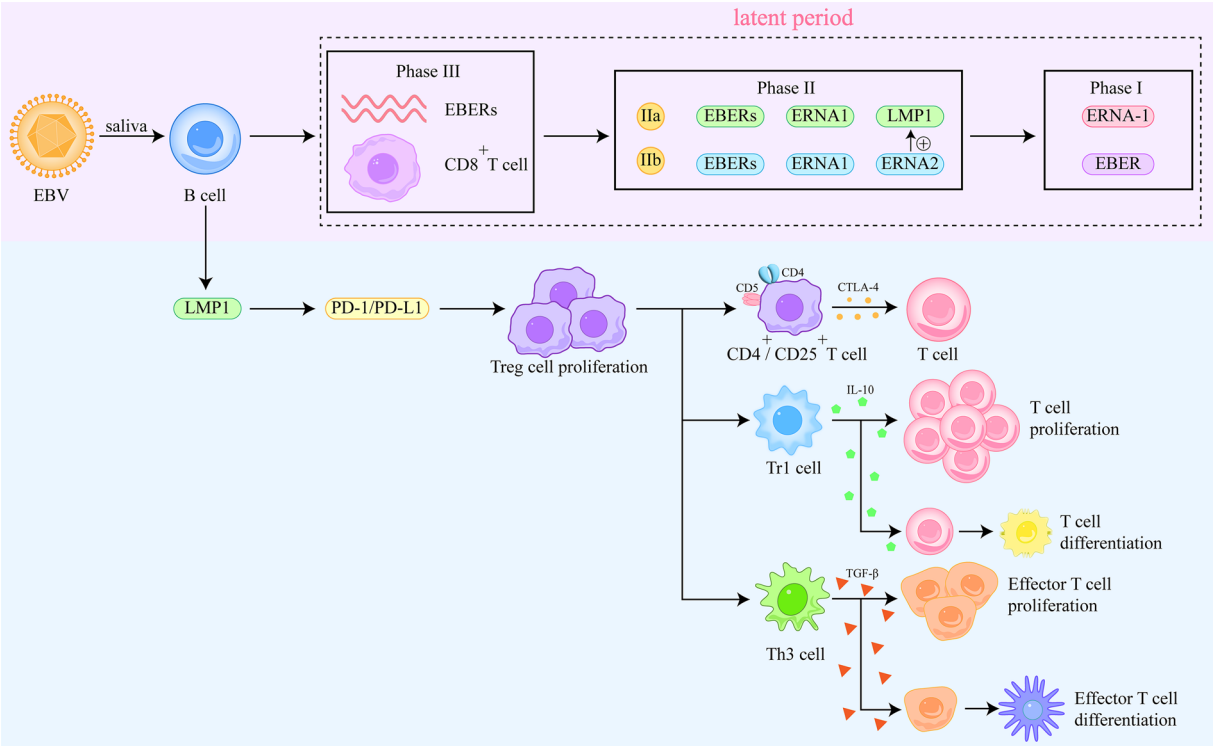

Fig. 2 EBV-Induced Immune Evasion and Regulatory Mechanisms EBV exhibits a preferential affinity for human cells, particularly mucosal B cells, following transmission via saliva. The progression of latency within memory B cells typically involves a transition from Latency III to II, and then to I. Following infection of resting primary B cells, EBV enters Latency III, during which EBERs and all latent viral proteins are expressed. Subsequently, the virus restricts gene expression, transitioning to Latency II, which further divides into subtypes IIa and IIb . Memory B cell differentiation ensues. Finally, EBV further limits gene expression, reaching Latency I, where only EBNA1 and EBERs are expressed. Upon infection with EBV, proliferating B cells exhibit a distinct immunoregulatory phenotype, actively contributing to the expansion of Treg cells through the PD-1/PD-L1 pathway. CD4+/CD25+ Tregs inhibit activated T cells by engaging their CTLA-4. Tr1 cells secrete IL-10 to inhibit T cell proliferation and differentiation, while Th3 cells produce TGF-β, suppressing effector cell proliferation and differentiation, and dampening cytokine production to limit overall immune activity

latent viral antigens are expressed in latency. The hierarchical immune response to EBV is driven by the specific expression patterns of latent and lytic phase genes during initial infection and establishment of persistence. Studies have shown that the latent EBV gene expression program mirrors that observed in malignancies linked to EBV, suggesting that immune regulation is a critical factor in preventing these latent programs from transforming into lymphomas [102, 103]. CD8 + T cells, NK cells, and various cytokines and immune mediators play pivotal roles in this regulatory process.

Upon EBV infection of B cells, the linear dsDNA forms circular structures within the nucleus, where all latent genes are transcribed. Latency III, also known as the proliferative program, is triggered by EBV, which disables key activation pathways of B cells and leads to immortalization of the infected cells. The expression of EBVLMP-1 and −2A, under the control of EBNA2 gene, provides constitutive survival signals mimicking CD40 and BCR interactions [104, 105]. Although primary EBV infection can confer B cell immortalization, it often resolves spontaneously, particularly during the asymptomatic or symptomatic phase, due to robust immune responses. However, host immune systems fail to eradicate the viral fragments completely, which persist in memory B cells' nuclei, resulting in lifelong persistence after primary EBV infection. This phenomenon highlights the ability of EBV-infected proliferative B cells to evade host immune surveillance. Imbalances between the host immune system and the virus can ultimately contribute to the development of EBV-related lymphoproliferative disorders. It has been reported that B cells infected with EBV exhibit an increase in PD-L1/CD274/B7H1 expression, which subsequently impairs the proliferation or disrupts the normal function of cytotoxic T cells [106, 107]. Regulatory B cells (Bregs) play a crucial role in the pathogenesis of a variety of infectious diseases, autoimmune disorders, and neoplastic conditions by facilitating immune suppression. Bregs inhibit effector T cell proliferation and promote the expansion of CD4 + Tregs. IL-10, a key factor in human B cell activation, proliferation, and differentiation, is also a crucial immunosuppressive molecule, particularly in Breg-like cells derived from latent phase III EBV-infected cells, which rely on the PD-L1 signaling pathway. The ability of EBV-proliferating B cells to modulate host immune responses explains their frequent evasion of anti-EBV immune responses.

Upon EBV infection, the proliferating B cells exhibit a pronounced immunoregulatory phenotype. They suppress the proliferation of homologously activated T cells by expressing LMP1 and presenting immune suppressive cytokines and PD-L1. These B cells actively contribute to Treg expansion through the PD-1/PD-L1 pathway, where Tregs, a T cell subset characterized by Foxp3, CD25, and CD4 expression, exert potent immunosuppressive effects [108, 109]. Tregs play a crucial role in the pathogenesis of various immune disorders due to their diverse immunosuppressive mechanisms, including CD4 +/CD25 + Treg cells, Tr1, and Th3. CD4 +/CD25 + Tregs inhibit activated T cells by engaging their CTLA-4, suppressing their immune function. Tr1 cells secrete IL-10 to inhibit T cell proliferation and differentiation, while Th3 cells produce TGF-β, suppressing effector cell proliferation and differentiation, and dampening cytokine production to limit overall immune activity. Bregs, initially characterized as a distinct B cell subset, were found to ameliorate chronic inflammation in mouse gut diseases. Their immunoregulatory properties are linked to their capacity to secrete immunomodulatory cytokines, primarily IL-10, but also TGF-β and IL-35. A widely accepted feature of all Breg subsets is their ability to inhibit self-T cell proliferation and induce IL-10 secretion [110]. Latent phase III EBV-infected B cells drive T cells towards a FoxP3 +/CD25 +/CD4 + Treg lineage, akin to Bregs, steering T cells towards Treg differentiation as shown in Fig. 2 [111]. EBV-proliferating B cells exhibit high immunogenicity and are prone to apoptosis induced by homologous CD95 + T cells. Notably, these latent III B cells express high levels of IL-10, TGF-β1, IL-35, and PD-L1, with PD-L1 expression being Latent III EBV-transformed B cells drive Treg expansion, at least through the PD-1/PD-L1 pathway. PD-L1 modulates the self-cytotoxic response of CD8 + T cells against these immortalized EBV-infected B cells. Aberrant PD-L1 expression is observed in various malignancies, including EBV-negative lymphomas, potentially linked to structural rearrangements of the ninth chromosome in diffuse large B-cell lymphomas, a strong genetic indicator for tumor favoring transformed cells that evade immune surveillance. Enhanced PD-L1 expression is also detected in both EBV-positive and EBV-negative Hodgkin's and non-Hodgkin's lymphomas (HLS). Multiple studies have implicated the PD-1/PD-L1 pathway in the differentiation of Th1 cells into Tregs. The fact that latent III EBV B cells contribute to Treg conversion via this axis suggests a pivotal role for the pathway in EBV immune evasion [112–114]. PD-1/PD-L1 inhibitors have demonstrated significant efficacy in EBV-associated cancers, including Hodgkin lymphoma (HL), NK/T-cell lymphoma (NKTCL), nasopharyngeal carcinoma (NPC), and gastric cancer (GC), with notable response rates in clinical trials [107, 115–117]. EBV upregulates PD-L1 expression through multiple mechanisms, primarily driven by latent membrane protein 1 (LMP1), which activates NF-κB, STAT, and AP-1 pathways in NPC and NKTCL [118]. Despite promising outcomes, resistance remains a challenge due to T-cell exhaustion or compensatory

immune checkpoints. Combination strategies, such as chemotherapy, epigenetic modulators, or EBV-targeted therapies are under investigation to improve efficacy. Future research should focus on biomarkers and novel agents like bispecific antibodies targeting both PD-1 and EBV antigens. Understanding EBV-mediated immune evasion will advance precision immunotherapy for these malignancies.

The expression of PD-1 is predominantly influenced by viral antigens, and the mere presence of PD-1 does not provide a comprehensive reflection of the functional state of CD8 + T cells. Both in vivo and in vitro studies have demonstrated that exposure of epitope-specific CD8 + T cells to high concentrations of its target peptide results in varying degrees of PD-1 upregulation [119, 120]. If antigen presentation is the most critical factor, then unstable pMHCI complexes may be associated with lower PD-1 expression. Therefore, there is a likelihood of a decisive factor for PD-1 upregulation, which is a response made by cells against these specific epitopes. Further research is required to elucidate the factors that regulate PD-1 expression on virus-specific CD8 + T cells and to understand their functional implications. PD-1 expression on these cells serves as a sensitive indicator of slow virus replication. Some studies propose that PD-1 expression may be utilized as a marker of viral activation [36, 121]. Although PD-1 levels are correlated with CD8 + T cell exhaustion, no simple correlation was observed between higher PD-1 levels in EBV-specific CD8 + T cells and patients with IM in the convalescent phase. The functional implications of upregulated PD-1 during the acute phase of IM on EBV-specific CD8 + T cells remain to be elucidated.

The PD-1/PD-L1 pathway and local tissue Epstein–Barr virus infection

The primary infection has been implicated in the development of autoimmune diseases, and understanding events during the IM phase is crucial for identifying factors influencing the risk of EBV-related disorders. Researchers analyzed EBV-infected cells and local immune cells from IM patients, revealing that approximately 50% of B cells in the regional tissue harbor the virus, exhibiting a heterogeneous pattern of latent viral gene expression, which aligns with previous quantitative PCR assessments of peripheral blood [122, 123]. Notably, while the majority of EBV-positive cells were B cells, approximately 9% of that expressed T-cell antigens, and a median of 14% of it displayed PD-L1 expression. Unlike the situation in peripheral blood, this study did not observe a higher proportion of CD8 + cells than CD4 + cells in the IM tissue microenvironment, which may be consistent with the impaired homing of CD8 + cells to the tonsils during the acute phase of IM. Studies have found that the proportion of CD8 + TBET + cells among total CD8 + T cells range from 14 to 72%, and the number of these cells is negatively correlated with viral load. These characteristics suggest that CD8 + TBET + cells contribute to the control of primary EBV infection and support the role of TBET as an activation marker for tonsillar CD8 + T cells during primary EBV infection [124–126]. In non-specific follicular hyperplasia of the tonsils, only a minority of lymphocytes exhibit weak PD-L1 expression. However, in IM patients, a substantial number of cells display high PD-L1 expression [127, 128]. This upregulation of PD-L1 in EBV-positive B cells, possibly mediated by LMP1 and/or EBNA2, might contribute to IM progression. Nevertheless, the majority of PD-L1-positive cells are EBV-negative. Hence, the increased PD-L1 expression in IM compared to non-specific tonsillar hyperplasia may be a result of a Th1/cytotoxic immune response in IM, where the suppressive loop might be activated in a steady state. The expression of PD-L1 in EBV-infected cells varies, with a positive correlation between the number of EBER + PD-L1 + cells and EBER + CD3 + cells per square millimeter. In IM patients, immune synapses involving PD-L1 and PD-1 on T cells in the tonsils might directly or indirectly facilitate EBV infection of T cells, either by creating a window for cell-to-cell transmission or enabling infected T cells to evade immune control [129, 130]. PD-1 exhibits a distinctive expression pattern during acute IM, with upregulation in EBV-specific CD8 + T cells, which is directly linked to the local viral load.

Conclusion

Upon viral infection, the optimal immune response involves the activation of CD8 + T cells to clear the pathogen while minimizing immunological damage. EBV has evolved sophisticated immune evasion strategies, including exploitation of the PD-1/PD-L1 checkpoint pathway, to circumvent host defenses and modulate inflammatory responses. This immunoregulatory axis serves dual functions in EBV pathogenesis: while maintaining immune homeostasis during acute infection, it paradoxically facilitates viral persistence through multiple mechanisms, including LMP1-mediated PD-L1 upregulation and promotion of Treg differentiation. The demonstrated efficacy of PD-1/PD-L1 blockade in EBV-associated malignancies underscores its therapeutic potential, yet critical questions remain regarding its role in primary infection. Specifically, the functional consequences of PD-1 upregulation on EBV-specific CD8 + T cells during acute infectious mononucleosis, and whether this pathway could serve as a reliable biomarker for disease progression, require systematic investigation. Furthermore,

the potential of checkpoint inhibitors to prevent the transition to chronic EBV infection and improve clinical outcomes represents a promising but underexplored therapeutic avenue that warrants rigorous preclinical and clinical evaluation.

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Author contributions
Hui Wang and Ning Zhang conducted an extensive literature search, performed a comprehensive data analysis, and wrote the initial draft of the manuscript. Rongshuang Xu provided assistance in the literature search and contributed to a significant portion of the manuscript writing. Cundong Ji played a crucial role in meticulously revising and editing the manuscript. Youzhen Wei offered valuable guidance and insightful input throughout the writing process, and substantially contributed to the editing of the manuscript. Qing Mi supervised the entire project, designed the structure and framework of the review, determined its scope and focus, performed an additional literature search, and was actively involved in the revision and finalization of the manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable.

Competing interests
The authors declare no competing interests.

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