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Role of Programmed Cell Death Receptor-1 and Cytotoxic T Lymphocyte-Associated Antigen 4 in Bovine Leukemia Virus Infection

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ABSTRACT

A cluster of T-cell receptors includes activating and inhibitory stimulatory molecules that favorably or unfavorably control immune responses. Recent studies on chronic bovine infections have revealed that, under severe viral loads and malignant pathologies, stromal and immune cells increase the expression of immune inhibitory molecules. To maintain internal homeostasis, programmed cell death receptor-1 (PD-1) and cytotoxic T lymphocyte-associated antigen-4 (CTLA-4) inhibit T cell activity. In chronic viral infections, the prolonged activation of T cells leads to the continuous production of PD-1 and CTLA-4. Blocking PD-1 and CTLA-4 is a successful therapeutic approach that is actively used in the treatment of oncological diseases. The effectiveness of this approach in the treatment of chronic viral infections, particularly those caused by bovine leukemia virus has been hypothesized. However, uncertainty surrounds these receptors' function in persistent viral infections. This review focused on the functions of PD-1 and CTLA-4 in bovine leukemia virus and discusses disease therapies based on their blockade.

Key words: Programmed cell death receptor-1, Cytotoxic T lymphocyte-associated antigen 4, T cell exhaustion, Chronic virology infection, Checkpoint inhibitor, Bovine leukemia virus.

INTRODUCTION

The oncogenic Bovine Leukemia Virus (BLV) belongs to the genus Deltaretrovirus, family Retroviridae, and subfamily Orthoretrovirinae. The virus is widespread in domestic cattle worldwide, affecting up to 39% of beef breeds and up to100% of dairy breeds. Despite the ability of the virus to infect blood and milk, less than 5% of infected cattle show clinical signs of the disease. The mechanism of BLV transmission to humans is unknown; however, consumption of raw milk can transmit the virus from cattle to humans (Buehring et al. 2019; Khatami et al. 2020; Canova et al. 2021; de Quadros et al. 2023).

Despite ongoing anti-BLV interventions, the widespread prevalence of the disease has increased interest in studying immune checkpoints for the treatment of chronic bovine infections. The programmed cell death receptor-1 (PD-1)/programmed cell death ligand (PD-L1) signaling pathway is associated with BLV infection. Studies have shown that immune suppressive molecules are highly expressed as the BLV infection progresses (Shirai et al. 2011; do Nascimento et al. 2023). The regulatory mechanisms of the immune system under different physiological conditions are based on the opposing activities of various T helper cell subpopulations. T cells are one of the critical cells that protect the organism from pathogenic microbes, maintain tolerance, and reduce tumor progression and metastasis (Jubel et al. 2020; Zou and Chen 2008). Effectors T cells (Teffs), which include regulatory T cells (Tregs), helper T cells (Ths), and cytotoxic T cells (CTL), mediate the antagonistic activity of the T-helper cell subpopulation. The roles of Teffs in acquiring immunity and Tregs in developing tolerance are essential for maintaining effective immunity and internal homeostasis (Bucktrout et al. 2018).

The opposing activities of Teffs and Tregs are regulated by several receptors that activate or inhibit signals. Stimulatory or inhibitory receptor signals are activated upon binding of the T-cell receptor (TCR) to the major histocompatibility complex (MHC). These stimulatory and inhibitory signaling mechanisms provide additional information to T cells concerning local microenvironment and host state (Frauwirth et al. 2002; Parry et al. 2005). One of the receptors regulating T-cell activity is PD-1 and its ligands, PD-L1 and PD-L2, which play essential roles in both the T-cell activity regulated

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negatively and positively. The PD-1 protein reduces T lymphocytes activation, thereby reducing the risk of autoimmunity and immunopathology (Freeman et al. 2000; Latchman et al. 2001; Sharpe and Pauken 2018). Further, the B7 family receptor co-stimulator, cytotoxic T lymphocyte-associated antigen 4 (CTLA-4), exert inhibitory and stimulatory effects on activation. The CTLA-4 receptor is a competitor of the cluster of differentiation (CD28) receptor, thereby inhibiting the formation of the CD28:B7 signaling pathway and reducing immune activation. In addition, the CTLA-4 receptor can disrupt stimulatory TCR and MHC signaling and bind to the B7.1 receptor CD80 on dendritic cells to inhibit antitumor immunity (Buchbinder and Desai 2016; Shen and Zhao 2018; Mayoux et al. 2020). In addition to CTLA-4's ability to inhibit the immune system, increased receptor expression has been observed during the progression of human immunodeficiency virus (HIV) infection. High receptor expression levels have also been observed in liver CD8+ T cells during viral hepatitis (Nakamoto et al. 2009; Zhang et al. 2010). A worse prognosis is linked to increased CTLA-4 expression in nasopharyngeal cancer patients (Zhang et al. 2016). The presented data demonstrates the role of CTLA-4 receptor in aggravating not only cancer but also chronic infections. In addition, dysfunction of antigen-presenting cells (APCs), cells of myeloid origin, Tregs, and stromal and tumor cells with high levels of CTLA-4 expression are essential factors for decreased immunity against chronic infections and cancer (Chen 2004; Curiel et al. 2004; Gabrilovich 2004; Banchereau and Palucka 2005).

Given the regulatory functions of PD-1 and CTLA-4 receptors in inflammatory processes and tumors, chronic infectious agents and transformed cells have evolved mechanisms to evade host immunity (Attanasio and Wherry 2016; LaFleur et al. 2018). Thus, the study of PD-1 and CTLA-4 receptor function during chronic infection or in oncology is an area of intense research. This review presents the structures of PD-1 and CTLA-4 receptors and their functional roles in bovine leukemia. Based on the literature, the therapeutic roles of PD-1 and CTLA-4 receptor blockade involving different mechanisms of immune inhibition in BLV-infected cows have been described.

Structure and Function of PD-1

Under typical physiological conditions, the body uses the PD-1 signaling pathway to induce apoptosis to limit excessive T cell activation in peripheral organs. The same signaling mechanism controls the immune response to bacterial and viral infections. The inhibition of PD-L1 and PD-1 receptors restored cytotoxic T-cell growth and cytokine expression in CD4-deficient and infected virus mice. By eliminating infected cells, cytotoxic T cells can lower the viral burden (Barber et al. 2006; Francisco et al. 2010). Blocking the PD-1/PD-L1 or PD-1/PD-L2 signaling pathways leads to a similar effect in cancer (Dong et al. 2016; Rui et al. 2023) (Fig. 1).

The PD-1 receptor CD279 was isolated from hybrid cells of murine T cells and a progenitor hematopoietic cell line. On chromosome 2 (2q37), the conserved regions (CR)-B and CR-C of the programmed cell death protein 1 (Pdcd1) gene, which codes for the PD-1 receptor, are two Deoxyribonuclease I hypersensitive sites that affect receptor expression. Nuclear factor activating T cell transcription (NFAT) is present in CR-C and is essential in Pdcd1 expression. In addition, NFATc1 binding to CR-C and c-Fos sites in the CR-B region of CD4+ and CD8+ T cells enhances PD-1 production at the initial recognition stage. The receptor is a membrane protein refers to the CD28 family. At the protein's extracellular N terminus, there is an IgV-like fragment, a transmembrane fragment, and a cytoplasmic fragment. The receptor has a molecular weight of 55 kDa and a length of 288 aa. There are two amino acid sequences in the cytoplasmic domain of PD-1, that is, tyrosine-based inhibitory and switch motifs. Tyrosine phosphatases (SHP) 1 and SHP-2, which contain the sarcoma homology 2 domain, are connected to the C-terminal tyrosine sequence (TEYATIVF). Protein tyrosine phosphorylation and dephosphorylation are critical regulatory activities in numerous signaling pathways that result in cell growth, differentiation, and death (Ishida et al. 1992; Shinohara et al. 1994; Starr et al. 1997; Lorenz 2009).

Immune cells that have been activated, such as CD4+ T cells, CD8+ T cells, B cells, T-killer cells, monocytes, dendritic cells, and macrophages, express the Pdcd1 gene. Additionally, Pdcd1 expression is an indicator for eliminated T lymphocytes and cells with reduced effector function and is specifically elevated in T cells exposed to long-term antigens (Agata et al. 1996; Matsuzaki et al. 2010).

The activation of the PD-1 receptor is regulated by several mechanisms. PD-L1 production in cells of tumor and increased PD-1 production in CD8+ T-lymphocytes correlate with soluble factors like interleukins 6 and 10 (IL6, IL-10) (Chen 2004; Curiel et al. 2004). Additionally, there was an indicated association between the production of PD-L1 on monocytes in the blood and that of PD-1 on circulating CD4+ or CD8+ T cells, suggesting that the same mechanisms may be responsible for the increased activity of PD-1 and PD-L1. Furthermore, the production of PD-1 in both CD4+ and CD8+ T lymphocytes was shown to be significantly higher inside tumor tissues when in contrast to cells from samples of blood and healthy stomach mucosa. The findings imply that in gastric tumor, cancer cells influence the production of PD-1 and PD-L1 (Saito et al. 2013).

The transcription factor T-box protein produced by T cells (T-bet) also controls PD-1 expression. An investigation on the stimulation of killer T cells against the virus in persistent infections shed light on the function of T-bet. Depending on the level of immune activity during chronic viral infections, the relationship between PD-1 and T-bet protein may also change. For example, during 15 days of viral infection, no relationship was found between the levels of PD-1 receptor and T-bet protein. Additionally, decreased T-bet expression during acute infection leads to increased PD-1 production in CD8+ T cells. However, for full production of PD-1 at persistent infections, receptor regulation by T-bet is insufficient. Antigenic signals, T-bet, and other transcription factors are expected to control PD-1 and other regulatory receptors (Kao et al. 2011).

The two major PD-1 ligands are PD-L1 and PD-L2. The ligand of PD-1 is a 290 aa long membrane-spanning glycoprotein member of the Ig superfamily B7-CD28 (Kao et al. 2011). The B7 family of proteins includes B7-DC,

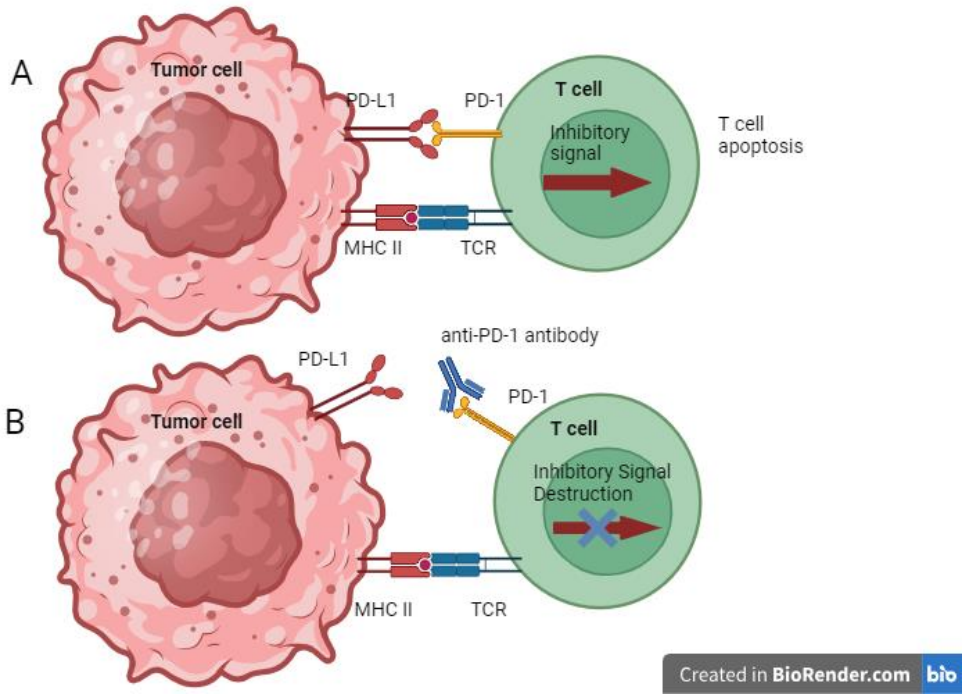

Fig. 1: PD-1-mediated inhibition of T cells. A. Tumor cells evade the immune response by activating PD-1 using PD-L1 ligand. B. Binding of anti-PD-1 antibodies to PD-1 increases T cell activity against tumorigenic cells.

also known as PD-L2, which is the second recognized ligand of the PD-1 receptor. In all healthy human and mouse tissues, PD-L1 messenger ribonucleic acid (mRNA) expression was found. However, it has been noted that the PD-L1 receptor is present on the surface of some macrophage-like cells in internal organs. The disparity between the mRNA and receptor expression on the cell membrane highlights the crucial function of the post-transcriptional systems regulating PD-L1 production (Sanmamed and Chen 2014).

Structure and Function of CTLA-4

CTLA-4 or CD152 belongs to the Ig superfamily and has been identified as a membrane protein with a molecular mass of approximately 41–43 kDa. CTLA-4 generally consists of a leader peptide, extracellular, membrane and intracellular region. Three protein isoforms have been identified as a result of standard and alternative CTLA-4 mRNA splicing. The surface CTLA-4 protein is the first, the second is soluble CTLA-4 (sCTLA-4) protein with the transmembrane fragment removed, and the third is the CTLA-4 independent from ligand (liCTLA-4) protein lacking the extracellular domain (Jakubczik et al. 2016).

The presence of the receptor on the outer layer of T cells during the G1 stage and subsequent phases of the cell lifecycle is suggested by the early occurrence of CTLA-4 mRNA expression during the stimulation of T cells. A lack of protein mRNA expression leads to severe autoimmune diseases and significant tissue damage in many organs (Sutherland et al. 2000; Homann et al. 2006). Various nucleotide substitutions in CTLA-4 gene mapped to human chromosome 2q33 have been associated with susceptibility to various autoimmune and infectious diseases mediated by T cells (Danilovic et al. 2012; Liu et al. 2013). According to Eskandari-Nasab et al. (2014), the CTLA-4 gene C/T polymorphism at position 318 in the Iranian population indicated susceptibility to the risk of brucellosis infection. The leader peptide codon is altered by the CTLA-4 A/G polymorphism at position +49, which causes alanine to be changed to threonine. There are no statistically significant variations between autoimmune illness patients and healthy people in the frequencies of the alleles and genotypes of the CTLA-4 gene variations, according to studies done in patients with autoimmune diseases. For example, CTLA-4 gene polymorphism was not associated with systemic lupus erythematosus (Farivar et al. 2014; Oaks and Hallett 2000; Rochmah et al. 2022).

Activated T cells produce the CTLA-4 receptor, which interacts with APCs via B7-1 and B7-2 (Lindsten et al. 1993; Mulley and Nikolic-Paterson 2008; Wing et al. 2011) (Fig. 2). This receptor was the first immune checkpoint that has become a clinical target for cancer immunotherapy. Monoclonal antibodies against CTLA-4 blocking the CTLA-4-CD80/CD86 signaling pathway activate antitumor immunity and improve the survival of patients with melanoma (Danilovic et al. 2012). One signaling pathway that enhances T-cell activity is the interaction of the CD28 receptor with CD80 and CD86, which significantly enhances the TCR-antigen signaling. In contrast to CD28, CTLA-4 has stronger affinity to CD80 and CD86, and its induction negatively regulates T-cell activation (Freeman et al. 1993; Hathcock et al. 1993; Linsley et al. 1994; Lee et al. 1998; Rudd et al. 2009; Schneider et al. 2006; Fife and Bluestone 2008; Callahan et al. 2010).

The B7-1 and B7-2 receptors play a crucial role in activating T cells by transmitting a signal from CD28 upon specific binding of the TCR receptor to an antigen on the MHC. B7-1 and B7-2 are transmembrane proteins type 1 that have the proximal IgC and distal IgV membrane domains, respectively. Although both proteins interact with CTLA-4 and CD28, differences exist in the strength of the

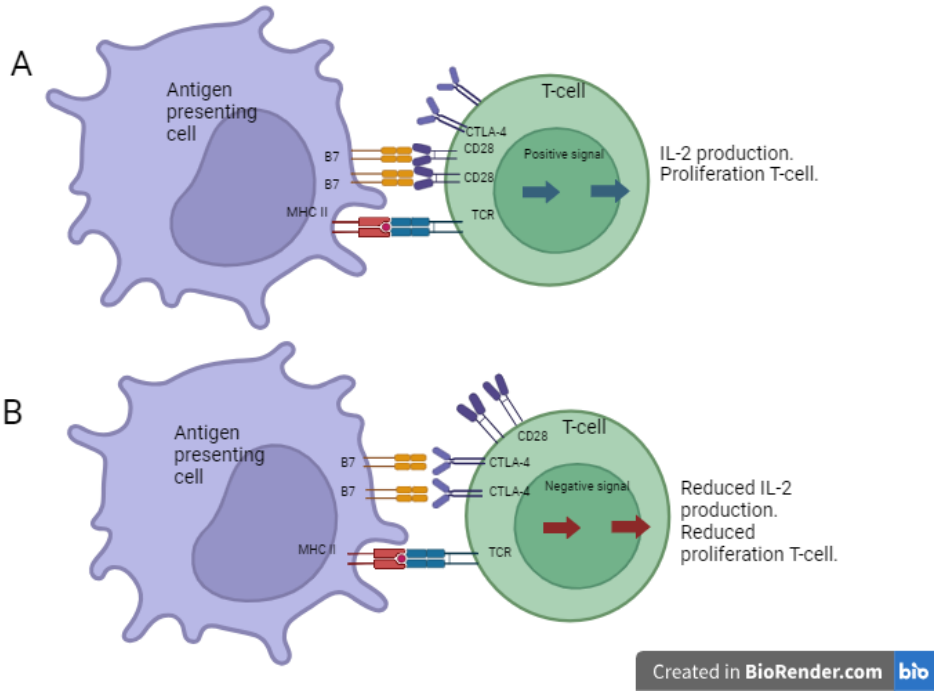

Fig. 2: Inhibition of T lymphocytes by CTLA-4 protein. A. Under weak T-cell receptor (TCR) stimulation, CD28 and B7 receptors are predominantly dissociated, which is a positive signal for interleukin 2 (IL2) productions and T-lymphocytes proliferation. B. Under intense TCR stimulation, there is an increase in CTLA-4 induction and dissociation of CTLA-4 and CD28 receptors, which results in the inhibition of IL-2 and T-cells.

equilibrium dissociation constants between these receptors. The equilibrium dissociation constant of B7-1 with CTLA-4 and CD28 was 5–10 times greater than that of B7-2. The structure of receptors' cytoplasmic tails and the molecules engaged in the signaling pathway are probably related to the differences in the biological functions that exist amongst receptors. B7-1 and B7-2 receptors' extracellular domains' monomeric or dimeric states play a significant role in the development and location of signaling complexes. B7-2 predominantly enhances the overall response of Th2-type T cells, whereas B7-1 promotes the differentiation of Th1-type T cells (Suvas et al. 2002; Bhatia et al. 2005; Greenwald et al. 2005).

Role of Immune Checkpoints in Infectious Diseases

Owing to the widespread use of chronic infectious diseases in animals and the low efficiency of preventive measures, interest in studying animal immune checkpoints has increased. The study of cow immunity in leukemia has revealed an increase in the number of regulatory T cells responsible for the production of transforming growth factor-β (TGF-β). Natural killer (NK) cells, tumor necrosis factor (TNF-α), and interferon γ(IFN-γ) are all suppressed by the rise in TGF-β (Ohira et al. 2016). When studying BLV, a connection was established between the PD-1/PD-L1 receptor signaling pathway and lymphocyte activation gene 3 (LAG-3) (Okagawa et al. 2018). Additionally, elevated CTLA-4+ T cell expression has been reported during the progression of BLV infection (Suzuki et al. 2015). By enhancing the stimulation of macrophages and dendritic cells, T lymphocytes and their secretion of the cytokines IFN-γ and TNF-α play a significant role in developing immunity against bacterial and viral illnesses. However, in the late subclinical stages, T-lymphocyte activity decreases, contributing to an increased viral or bacterial load and progression to clinical diseases (Sohal et al. 2008; Xing et al. 2022; Yang et al. 2023).

According to a recent study, tumors, malignancies, and persistent infections activate CTLA-4, which could compromise the immune system. Conversely, the immune system's defense against these illnesses is restored when antibodies prevent the action of the CTLA-4 receptor with CD80 or CD86 (Kaufmann et al. 2007). The inhibitory action of cattle CTLA-4 was proven in various investigations employing synthesized bovine CTLA-4-Ig. Anti-CTLA-4 antibodies were produced when mice were immunized with synthesized bovine CTLA-4-Ig. Antibodies against CTLA-4 protein significantly boosted both healthy and infected BLV immune system's IFN-γ production. According to the authors, antibodies against CTLA-4 may be useful for developing new therapies against BLV infections (Watari et al. 2019).

Similar effects were observed when the PD-1/PD1-L1 signal was blocked, which stimulates T-cell activation and proliferation in BLV. The progression of viral infection is aided by the association of PD-L1 on B cells, which lowers the number of PD-1+ T cells. Antibodies against PD-L1 or PD-1 were administered to HIV-infected macaques and mice infected with lymphocytic choriomeningitis virus (LCMV) to treat their infections. This restored multiple functions of the previously depleted T cells and eliminated the virus *in vivo*. According to studies, blocking the PD-1/PD-L1 pathway may have clinical uses for boosting host antimicrobial immunity for managing persistent infections (Ikebuchi et al. 2011).

The research of the impact of inhibiting the bovine PD-L1 receptor on the development of chronic ruminant enteritis caused by *Mycobacterium paratuberculosis* showed the possibility of anti-PD-L1 antibody treatment for regulating bacterial excretion. Treatment with anti-PD-

L1 antibodies also activated the production of *M. paratuberculosis*-specific Th1 cytokines in infected cattle (Sajiki et al. 2021; Sun et al. 2021). However, immune checkpoint-based therapies for chronic infectious diseases in animals remain poorly understood (Sun et al. 2021).

Role of PD-1 in BLV

Subsets of the T cell family like Teff, CTL, Th, and Treg are essential for preventing viral illnesses and preserving internal homeostasis. Costimulatory or coinhibitory signaling pathways regulate T-cell subset functions following successful interaction of TCR with MHC. CD4+ T cells that specifically recognize MHC II molecules on B-lymphocytes, macrophages, and NK cells are responsible for forming immunity against bacteria and parasites. CD8+ cells, which recognized MHC I after activation, function as cytotoxic cells in viral infections and malignancies.

However, T cells are depleted in chronic infections and malignant neoplasms owing to constant antigenic stimuli and inflammation. Lack of IL-2 and IFN-γ and diminished cell proliferation prevent depleted T lymphocytes from performing their effector and cytotoxic activities (Wherry and Kurachi 2015; Dyck and Mills 2017). In cases of chronic infections and malignancies, T cells that are exhausted have been seen to show a higher level of induction of PD-1 and CTLA-4 receptors. (Bennett et al. 2003; Qin et al. 2019). Studies related to BLV have shown the inhibitory properties of PD-1 and CTLA-4 receptors during infection. Increased concentration receptors mRNA was observed in CD4+ and CD8+ cells of cows infected BLV. Depleted T cells also showed increased mRNA expression of factors such as LAG-3, T cell Ig and mucin domain-3 (TIM-3). In persistent infections and cancers, elevated PD-1 and TIM-3 mRNA levels aid in developing and maintaining pathogenic conditions. Simultaneously, antibodies blocking these signaling pathways reactivate T-cell depletion and activate immune responses (Ikebuchi et al. 2013; Nakamura et al. 2023).

Studies on depleted T cells from mice with chronic and acute infections caused by the LCMV showed different levels of PD-1 mRNA expression. Moreover, PD-1 blockade in T cells with different expression levels led to different results. PD-1 mRNA expression was significantly higher in mice with chronic viral infections. PD-1 blockade in mice with acute infection and high expression levels in cells did not restore the effector functions of depleted T cells (Yi et al. 2018). The provided data highlight the significant contribution of Teff proliferation to PD-1 blockage in improving the management of persistent viral infections. Moreover, the blocking of PD-1 and LAG-3 yielded good results, confirming the role of additional inhibitory in depleted T cells (Blackburn et al. 2009; Saeidi et al. 2018; Wykes and Lewin 2018).

When specific T lymphocytes are reduced, persistent infections in humans caused by the hepatitis B (HBV) and C (HCV) viruses and HIV also exhibit elevated expression of PD-1 on those cells. Moreover, the higher the level of PD-1 expression, the lower the activity of CD+ T cells (Dong et al. 2019). In BLV-infected cows with B-cell lymphoma, increased induction of PD-1 protein was observed in CD4+ T cells in the blood, and in CD4+ and CD8+ T cells in tumor-containing lymph nodes. Additionally, the number of PD-1+ T cells in lymph nodes containing tumor was higher than that in the blood cells. Examination of other BLV lymph nodes from infected and healthy cows revealed low concentrations of PD+1 T cells. These data suggest that the tumor-bearing lymph nodes contain lymphoma-specific CD+ T cells. The PD-1 signaling pathway, however, enables BLV-induced lymphoma cells to prevent immune system reactions. (Ikebuchi et al. 2013).

In cattle, CD4+ T-cell growth and cytokine induction in response to viral infection are impaired in late-stage leukemia. PD-1 receptor blockade boosted IFN-γ induction in blood mononuclear cells in response to a mixture of glycoprotein gp51 peptides. The increase in IFN-γ was determined to be because of the increased PD-1+ cell levels in the CD4+ T cell population. Simultaneously, the blockade did not boost IL-10 production in mononuclear cells, indicating that PD-1+ T-cells function was not fully restored (Ikebuchi et al. 2013).

PD-1 inhibition is a viable method for reactivating fatigued T cells in BLV. Both cows with BLV infection and healthy cows produced more IFN-γ when exposed to monoclonal antibodies against bovine PD-1. Anti-PD-1 mAb therapy can be employed to treat various bovine infections despite the systemic side effects of immunotherapeutic techniques. Monoclonal antibodies may also expand education in the field of immunology and elucidate the immunosuppression disorder in chronic viral infection.

Role of CTLA-4 Protein in BLV

CTLA-4 is associated with T-cell depletion in several chronic infections. CTLA-4 is selectively induced in HIV-specific CD4+ T cells, whereas no induction of this antigen is in CD8+ T cells obtained from patients infected with HIV. Increased induction of CTLA-4 was observed in patients with HIV with advanced disease in which CD4+ T cells were unable to produce IL-2. CTLA-4 blockade enhances the functional activity of CD4 + T cells *in vitro*. These results demonstrate the potential role of CTLA-4 as a target for increasing CD4+ T-cell activity during immunotherapy in HIV-positive individuals (Kaufmann and Walker 2009; Wu et al. 2023). In CD4+CD25+ Foxp3+ T lymphocytes, CTLA-4 production is positively linked with disease progression. High levels of CTLA-4 have been observed in the leukocytes of HIV-infected macaques with a high viral load. The study demonstrated that CTLA-4 induction was lower in patients with HIV with slow disease progression than in asymptomatic patients with HIV. In addition, CTLA-4 induction was negatively correlated with CD4+ T-cell concentration, proving the significance of low Treg concentration combined with low CTLA-4 induction in slowing HIV progression (Boasso et al. 2007; Zhang et al. 2010).

Studies have shown that CTLA-4 contributes to the immunosuppression of chronic infections and malignancies. In persistent lymphocytosis in BLV-infected cows, T cell dysfunction leads to the dysregulation of Th1 and Th2 cytokines, resulting in disease progression. According to Suzuki et al. (2013), the disease progression in BLV-infected cows was closely related to the concentration of Foxp3+CD4+ T cells. These data suggest that decreased immunity during BLV infection is associated with the induction of CTLA-4 inhibitory molecules on Tregs. Amino acid sequencing of CTLA-4+ T cells revealed a conserved

MYPPPY site, which is characteristic of the CTLA-4 amino acid sequence in other mammals. Additionally, a protein phosphatase 2A binding site for the immunological inhibitory signaling pathway is present in a cytoplasmic domain of CTLA-4 (Suzuki et al. 2015).

In BLV infections, autoimmune diseases, graft rejection, persistent infection, and chronic viral infections, CTLA-4 is induced on CD4+CD25+Foxp3+T cells. Because Foxp3 is a marker of Tregs, studies support the assumption that CTLA-4 induces Tregs. The increase in Foxp3+CD4+cells level coincided with an increase in viral load, while there was a decrease in IFN-γ induction in BLV-infected cattle. These findings suggest that T cell depletion during BLV infection is associated with increased induction of CTLA-4 on Tregs (Suzuki et al. 2013).

The CTLA-4 inhibition has proven to be a successful treatment for malignant diseases and persistent infections, using melanoma and HIV as examples. Monoclonal antibodies against CTLA-4 activated T cells and cytokine production in BLV-infected cows. With T-cell activation, blocking CTLA-4 increased IFN-γ production in BLV antigen-stimulated mononuclear cells of blood (Watari et al. 2022). The opposite effect on IFN-γ increased concentration in mononuclear cells of blood activated by BLV antigens was exerted by bovine CTLA-4-Ig. The findings imply that CTLA-4 causes depletion of the function of CD4+ and CD8+ T cells and disease progression in cattle infected with BLV (Watari et al. 2019; Passariello et al. 2020; Lembo et al. 2022) and that antibodies against bovine CTLA-4 increase lymphocyte function and may be used as a novel treatment for chronic illnesses that have failed to respond to conventional therapies.

Conclusion

Owing to the widespread occurrence of BLV infections and limited studies on the immunosuppressive functions of Tregs, there is a scientific and technological need to obtain new knowledge and methodological approaches for treatment. In the onset and development of chronic infectious illnesses, immune checkpoint receptors and inhibitory cytokines mediate the immunoregulatory actions of Tregs. CTLA-4 and TGF-1 may facilitate t-cell-mediated immunosuppression during the persistent infection stage. The resulting recombinant proteins, monoclonal antibodies, and therapies for chronic infections can be used to identify novel targets and infections in farm animals.

PD-1, PD-L1, and CTLA-4 are potential targets to restore the function of exhausted T cells. Numerous studies using antibodies and peptide molecules to disrupt the PD-1 signaling cascade and cancer patient research studies support these results (Tao et al. 2020; Cao et al. 2023). Additionally, bovine checkpoint blockade studies have shown increased IFN-γ production in BLV-infected cattle. Based on the literature, the results contribute to research to develop new treatments for other types of infections in cattle. In addition, these results contribute to research in immunology, virology, bacteriology, and biotechnology aimed at elucidating the mechanisms of infectious diseases that cause immunosuppression.

Author Contributions

All authors contributed directly to the conception and design of the study, revision of the manuscript, and approval of the submitted version.

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