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REVIEW

Regulatory Mechanisms of Co-Inhibitory Receptors in Tuberculosis Immunity: Implications for Therapeutic Targets

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Abstract: Tuberculosis (TB) is a chronic infectious disease caused by *Mycobacterium tuberculosis* (*Mtb*). Despite significant advancements in anti-tuberculosis treatment strategies in recent years, TB remains a major infectious disease threat worldwide. Chronic *Mtb* infection drives T cell exhaustion—characterized by upregulated co-inhibitory receptors—which correlates with TB chronicity, treatment failure, and relapse. Immune checkpoint inhibitors (ICIs) targeting co-inhibitory receptors have achieved groundbreaking progress in the treatment of various malignancies. However, their application in the field of tuberculosis remains controversial. This study provides a comprehensive analysis of TB disease assessment and treatment from the perspective of T cell exhaustion. We investigate the correlation between co-inhibitory receptor expression levels and both disease activity and progression. Furthermore, we analyze the dual impact of targeting these receptors on anti-TB immunity: While blockade of co-inhibitory receptors in T cell exhaustion states restores anti-tuberculosis immunity, excessive inhibition—particularly in hyperimmune conditions—induces detrimental hyperinflammation, exacerbating tissue damage and disrupting immune homeostasis, ultimately worsening clinical outcomes. To address this duality, we emphasize the necessity of personalized immunotherapy strategies based on individual immune profiling, alongside developing novel co-inhibitory receptor blockers and immune modulatory vaccines. This review presents a novel perspective on the application of targeting co-inhibitory receptors in tuberculosis treatment, which will advance the development and application of immunotherapy.

Keywords: tuberculosis, co-inhibitory receptors, T cell exhaustion, therapeutic targets

Backgrounds

Tuberculosis (TB) is a chronic infectious disease caused by *Mycobacterium tuberculosis* (*Mtb*). According to the World Health Organization (WHO)'s 2024 Global Tuberculosis Report, an estimated 10.8 million new TB cases occurred globally in 2023, including approximately 740,000 in China, resulting in over 1.25 million deaths worldwide.[1] Although drug therapy is the principal clinical intervention for TB control, the emergence of drug resistance and immune escape mechanisms poses significant challenges to the elimination of this disease. Long-term chronic tuberculosis infection causes the patient's immune cells to be continuously stimulated by TB-specific antigens, ultimately leading to T cell exhaustion, functional impairment, and local immune suppression, which is regarded as a key mechanism that leads to the impairment of the T-cell response against pathogens.[2] T cell exhaustion is mechanistically linked to progressive depletion of key effector cytokines (including IL-2, IFN-γ, and TNF-α), diminished T-cell proliferative capacity, and ultimately, failure to control persistent *Mtb* infection.[3,4] Studies demonstrate that exhausted T cells exhibit sustained

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upregulation of multiple co-inhibitory receptors. This overexpression represents a critical immune evasion mechanism employed by *Mtb*.[5]

Multiple co-inhibitory receptors collectively orchestrate immune regulation. Among these, the CTLA-4 and PD-1 pathways represent the most extensively studied and clinically validated therapeutic targets.[6,7] Recent advances in cancer immunotherapy have elucidated the pivotal role of immune checkpoint molecules.[8] However, the emergence of immune-related adverse events associated with these treatments is driving research expansion beyond classical PD-1 and CTLA-4 to encompass emerging co-inhibitory receptors,[9] such as T-cell Immunoglobulin and Mucin-Domain Containing-3 (TIM-3), Lymphocyte-Activation Gene 3 (LAG-3), and B and T Lymphocyte Attenuator (BTLA),[10] as shown in Figure 1. Among common co-inhibitory receptors, PD-1, CTLA-4, BTLA, and TIGIT belong to the CD28 family, while others such as TIM-3, LAG-3, and CD244 are members of other subfamilies within the immunoglobulin superfamily (IgSF).[11] In fact, within the normal physiological mechanism, co-inhibitory receptors represent a molecular family expressed on immune cell surfaces that suppress immune cell activation through diverse mechanisms.[12] These molecules are essential for maintaining peripheral tolerance and preventing excessive immune responses that may cause immunopathological damage.[13] However, their persistent upregulation can compromise effective immunity.[11]

The connection between T cell exhaustion, co-inhibitory receptor expression, and progression of disease highlights these pathways as promising therapeutic targets. Blockade of these receptors represents a potential immunotherapeutic strategy to reinvigorate anti-TB immunity and improve infection control. Immune checkpoint inhibitors (ICIs), pharmacological agents targeting co-inhibitory receptors, are extensively applied in cancer immunotherapy and have shown promising preliminary results in chronic viral infections and autoimmune diseases.[12,14] Nevertheless, therapeutic strategies targeting co-inhibitory receptors remain untapped in tuberculosis management. This clinical gap is partly attributed to the risk of TB reactivation following ICI administration, paradoxically contradicting the conventional wisdom that enhanced *Mtb*-specific T-cell immunity should improve pathogen containment.[15]

This review synthesizes current research on co-inhibitory receptors in tuberculosis, elucidating dynamic correlations between receptor expression levels and disease activity and progression. It further deciphers the dual regulatory effects of targeting these receptors on anti-tuberculosis immunity through cellular and animal models. Confronting challenges in TB immunotherapy, we emphasize the necessity of personalized immunotherapy strategies based on individual immune profiling, alongside developing novel co-inhibitory receptor blockers or vaccines. These findings will provide valuable insights into the field of tuberculosis immunology and point towards new directions for achieving the WHO goal of eliminating tuberculosis by 2035.

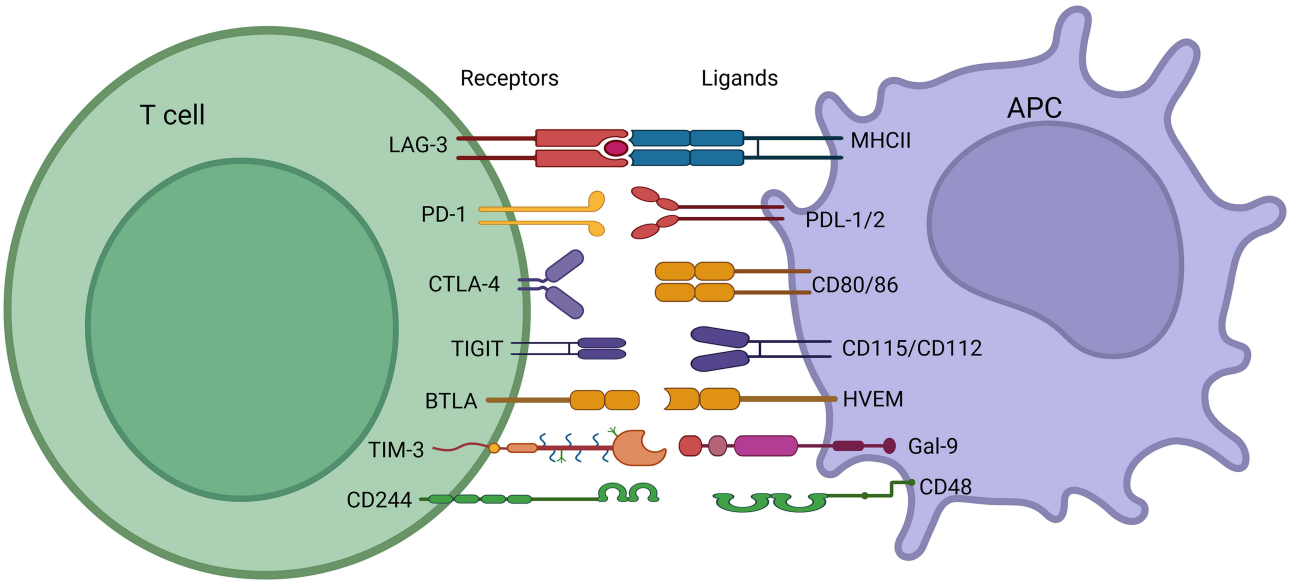

Figure 1 Schematic representation of the interaction between co-inhibitory receptors and their ligand.

The Relationship Between the Expression Levels of Co-Inhibitory Receptors and Disease Activity and Prognosis of Tuberculosis

PD-1/PD-L1

PD-1 (CD279), a member of the Immunoglobulin Superfamily (IgSF), is predominantly expressed on the surface of T cells.[16] Its ligands, Programmed Cell Death Ligand 1 (PD-L1) and Programmed Cell Death Ligand 2 (PD-L2), are primarily expressed on the surfaces of antigen-presenting cells (APCs) and tumor cells.[17] PD-1 binds predominantly to its ligands, PD-L1/2, in peripheral tissues, inhibiting T cell activation.[18] Studies have demonstrated that blocking the PD-1/PD-L1 axis enhances immune control of infectious diseases.[19]

Studies have shown that in patients with active TB or latent tuberculosis infection (LTBI), the expression of PD-1 is significantly elevated on the surface of circulating monocytes,[20] macrophages,[21,22] natural killer (NK) cells,[23,24] neutrophils,[25] and mucosal-associated invariant T (MAIT) cells.[26,27] In the adaptive immune system, increased PD-1 expression has also been observed in B cells,[20] CD4+ T cells,[28,29] CD8+ T cells,[20,30] and NKT cells[31] in the peripheral blood, as well as in lung tissues[22,32] of active TB or LTBI patients. Furthermore, increased PD-1 expression has been detected in local body fluids, such as pleural effusion[33] and bronchoalveolar lavage fluid.[34] The upregulation of PD-1 expression at different stages of TB infection, across various anatomical sites, and in different immune cell types suggests that PD-1 plays a significant role in TB's immune response and pathological processes.

High PD-1 1 expression levels are typically linked to impaired immune function, which can negatively impact treatment outcomes in TB patients[35–38] and promote progression to more severe forms of the disease,[39,40] leading to poor prognosis. For example, McCaffrey et al demonstrated that elevated PD-1 levels could predict the progression of LTBI to active tuberculosis.[37] Studies have also shown a strong correlation between high PD-1 levels and Mtb load,[35,36] although the causal relationship between them remains unclear. Day et al found that smear-positive TB patients, compared to smear-negative patients, exhibited significantly more than double PD-1 expression on CD4+ T cells, suggesting that active *Mtb* antigen stimulation may drive PD-1 expression.[23] Moreover, a decrease in PD-1 expression levels indicates clinical improvement of TB patients. Several studies prospectively recruited treatment-naïve patients with active TB and conducted follow-up with PD-1/PD-L1 testing during anti-TB therapy. The results demonstrate that successful TB treatment reduces PD-1/PD-L1 expression levels in the peripheral blood of these patients.[36,37,41–43] These findings suggest that PD-1 could be a promising biomarker for monitoring TB treatment efficacy.

Other Co-Inhibitory Receptors

In addition to PD-1, CTLA-4, LAG-3, TIM-3, BTLA, CD244, and TIGIT are also co-inhibitory receptors that regulate the strength and tolerance of immune cells. While sharing the overarching function of immune suppression, these receptors exhibit distinct expression profiles, mechanisms of action, and specific impacts on anti-tuberculosis immunity.

CTLA-4 is mainly expressed in T cells in lymphoid tissues. It competes with the co-stimulatory molecule CD28 by binding to CD80 and CD86, thereby suppressing T cell activation.[44,45] LAG-3 is expressed on activated CD4+ and CD8+ T cells, NK cells, and regulatory T cells (Tregs).[46] LAG-3 binds with higher affinity to MHC II molecules, transmitting inhibitory signals that suppress T cell activation and proliferation.[10,47,48] It also enhances its immunosuppressive effects in synergy with other inhibitory molecules, such as PD-1 and TIGIT.[47,49–52] TIM-3 is widely expressed in innate and adaptive immune cells.[53,54] TIM-3 binds to several ligands, such as Galectin-9, Phosphatidylserine (PtdSer), Carcinoembryonic Antigen-Related Cell Adhesion Molecule 1 (CEACAM1), and High Mobility Group Box 1 (HMGB1),[55] regulating T cell exhaustion and tolerance.[56] BTLA (CD272) and CD244 (2B4), members of the IgS superfamily, bind to their ligands Herpesvirus Entry Mediator(HVEM) and CD48 to inhibit T cell function.[57,58] TIGIT, a recent member of the CD28 superfamily, is specifically expressed in NK and effector T cells.[59,60] It inhibits immune responses by competing for binding with CD155 and CD112[61] or directly binding to CD226.[62] The interactions between co-inhibitory receptors and their ligands are shown in Figure 1.

Several studies have demonstrated that the expression levels of TIM-3, CTLA-4,[63–65] BTLA,[66–71] LAG-3,[72] and CD244[73,74] were significantly elevated in TB patients, as well as in Mtb antigen-stimulated CD4+ T cells,[3] CD8+ T cells,[75,76] NK cells,[77] and MAIT cells.[78] Upregulation of LAG-3 and TIM-3 expression has also been observed in non-

human primates, particularly macaques infected with *Mtb*.[79,80] Similar to PD-1/PD-L1, the expression levels of TIM-3,[76,81,82] CTLA-4,[65] BTLA,[67] and CD244[83] significantly decreased after effective anti-tuberculosis treatment. Further research has shown a positive correlation between the expression of TIM-3,[84] LAG-3,[80] BTLA[71] and bacterial load.[84] Their expression levels also correlated with the severity of tuberculosis in patients.[76,85,86] Studies have also found that higher BTLA expression is associated with cavitary lesions in pulmonary tuberculosis.[71] This suggests that, besides PD-1, the expression levels of other co-inhibitors of disease severity and prognosis are also high.[72] Moreover, their expression levels change during different stages of tuberculosis treatment, making them potential biomarkers for assessing immune function and disease progression.[72,83]

In summary, changes in the expression of these common inhibitory receptors can serve as potential biomarkers for assessing immune function and evaluating TB's progression, severity, and therapeutic efficacy.

The Role of Targeting Co-Inhibitory Receptors in Tuberculosis

Appropriately Blocking Overexpressed Co-Inhibitory Receptors to Restore the Anti-Tuberculosis Immune Response

PD-1/PD-L1

Innate immune cells play a crucial role in anti-tuberculosis immunity before activating the adaptive immune response. Studies indicated that inhibiting PD-1/PD-L1 enhanced innate immune cells' functions such as proliferation, apoptosis, and cytokine secretion, thereby improving the clearance of *Mtb*.[22,24,26,36,87] Within the adaptive immune response, the coordinated regulation of effector T cell proliferation, adhesion, and apoptosis is essential for efficient *Mtb* recognition and elimination. Sada-Ovalle et al found through in vitro experimental models that blocking of Tim-3 and PD-1 decreased the colony-forming units(CFU).[88] Studies also indicated that inhibiting the PD-1/PD-L1 pathway significantly reduced the proliferation and apoptosis of *Mtb*-specific T cells in the blood and local fluids.[22,89] Furthermore, studies indicated that PD-1 overexpression reduced the production of key cytokines and blocking the PD-1/PD-L1 pathway can significantly enhance the functions of adaptive immune cells (especially CD4+ and CD8+ subsets) in tuberculosis patients, particularly the secretion of cytokines (IFN-γ, TNF-α, IL-6).[20,22,23,34,88–91] What's more, inhibiting PD-1 on CD8+ T cells enhanced their cytotoxicity against *Mtb*-infected macrophages, thereby aiding in the control of *Mtb* infection.[32]

In mouse models, Sun et al demonstrated that PD-L1 monoclonal antibodies promote apoptosis of *Mtb*-infected macrophages. Crucially, combination therapy with isoniazid plus PD-L1 monoclonal antibody significantly reduced TB recurrence rates compared to isoniazid monotherapy.[92] Additionally, Kamboj et al's study similarly demonstrated that anti-PD-1 treatment in mice, following anti-tuberculosis chemotherapy, significantly reduced bacterial load in the lungs and spleen.[93] Sakai S's study also demonstrated that bacterial numbers in the spleen of PD-1-deficient mice were significantly reduced compared with wild-type mice at 6 and 12 weeks after BCG infection.[94]

Preclinical evidence demonstrates that PD-1/PD-L1 blockade restores anti-tuberculosis immunity and reduces relapse rates (Table 1). Building on its clinically validated role in cancer and chronic infections, targeting this pathway holds significant potential for TB management.[95] However, to translate this potential into feasible clinical applications, extensive and in-depth research is still required to address critical issues such as efficacy, safety, optimal application strategies, and integration with existing anti-tuberculosis regimens.

Other Co-Inhibitory Receptors

Apart from PD-1, other co-inhibitory receptors, including LAG-3, TIM-3, CTLA-4, BTLA, and CD244, also contribute significantly to suppressing anti-tuberculosis immunity. However, the research on other co-inhibitory receptors in tuberculosis is relatively scarce. For instance, upregulation of LAG-3,[72,86] CTLA-4, and CD244[73,74] is associated with defects in CD8+ T cell function, while increased expression of TIM-3, CTLA-4, BTLA, and CD244 is linked to reduced secretion of cytokines, including IL-12 and IFN-γ.[63,66,67,74,76] A study has found that CTLA-4 blockade reverses Treg-mediated suppression of anti-TB Th1 responses, enhances T-cell proliferation, and restores the ability to restrict intracellular BCG and *Mtb* growth in macrophages.[96] Additionally, Jayaraman et al demonstrated that genetic knockout or blockade of TIM-3 in mice infected with *Mtb* significantly reduced bacterial load in the lungs and spleen.[3] Targeting

Table 1 The Role of Targeted Co-Inhibitory Receptors in Tuberculosis

References	Sample	Blocking Method	Co-Inhibitory Receptor Types	Blocking Effect
Alvarez IB et al[24]	PBMCs	anti-PD-1 or anti-PD-Ls mAbs	PD-1	Augmentation of NK cell lytic degranulation and IFN-γ production
Jiang J et al[26]	PBMCs	anti-PD-1 mAbs	PD-1	Elevation of MAIT cell IFN-γ production
Singh A et al[36]	PBMCs	anti-PD-1 mAbs	PD-1	Protection of NKT cells from apoptosis and enhancement of NKT cell lytic degranulation
Singh A et al[20]	PBMCs	anti-PD-L1/L2 mAbs	PD-L1	Enhancement of *Mtb*-specific IFN-γ and IL-2 production by CD3+ T cells
Shen L et al[22]	PBMCs	anti-PD-1 or anti-PD-Ls mAbs	PD-1	Enhancement of CD4+ T-cell proliferation and macrophage phagocytic/killing activity
Day CL et al[23]	PBMCs	anti-PD-L1 mAbs	PD-1	Enhancement of PPD-induced IFN-γ production
Singh A et al[34]	PBMCs	anti-PD-1/PD-L1 mAbs	PD-1	Augmentation of *Mtb*-specific IFN-γ, TNF-α, and IL-2 production by CD3+ T cells
Suarez GV et al[32]	PEMC and PBMCs	anti-PD-Ls mAbs	PD-1	Enhancement of antigen-specific CD8+ T cell cytotoxicity against IFN-γ-activated macrophages and *Mtb*-specific CD8+ T cell-mediated killing of CD14+ cells
Qu P et al[87]	BMDMs	anti-PD-1 or anti-PD-Ls mAbs	PD-1	Impairment of mycobactericidal activity and enhancement of IL-6 production in macrophages
Sada-Ovalle et al[88]	PBMCs	anti-PD-L1 and anti-TIM-3 mAbs	PD-1/TIM-3	Reduction in CFU and restoration of T cell polyfunctional cytokine production (IL-6, IFN-γ, TNF-α)
Li J et al[89]	PFMCs	anti-PD-L1 mAbs	PD-L1	Increase in IFN-γ-producing T cell frequency
Jurado JO et al[90]	PBMC and PFMC	anti-PD-L1/2 mAbs	PD-L1/2	Enhancement of pathogen-specific CD8+ T cell degranulation and IFN-γ+ lymphocyte frequency
Tezera LB et al[91]	PBMCs	spartalizumab	PD-1	Dose-dependent augmentation of *Mtb* growth and elevation of TNF-α secretion
Li J et al[89]	PFMCs	anti-PD-1 mAbs	PD-1/PD-L1	Increase in IFN-γ+ T cell frequency
Sun M et al[92]	C57BL/6 mice	anti-PD-L1 mAbs	PD-L1	Significant reduction in bacterial load, alleviation of pathological lesions, and decreased recurrence
Kamboj D et al[93]	BALB/cmice/ PBMCs	anti-PD-1 mAbs	PD-1	Restoration of protective polyfunctional T cells (PFTs) promoting bacterial clearance and reduction in FoxP3+ Treg cell frequency with associated IL-10+/TGF-β+ Treg cell populations
Shao L et al[96]	Treg	CTLA-4 blockade	CTLA-4	Induced reversal of Treg-mediated suppression of Th1 response and abrogation of Treg-driven inhibition of TB antigen-specific T cell proliferation, with restoration of T Cell-dependent intracellular Mycobacterial control
Das G et al[80]	Macaque lung CD4+ T-cells	LAG-3 siRNA	LAG-3	Enhancement of *Mtb* killing efficacy in co-culture systems with concurrent upregulation of IFN-γ expression
Chen J et al[86]	PBMCs	sLAG-3	LAG-3	Upregulation of IFN-γ and granzyme B expression in CD8+ T cells
Yang B et al[73]	PBMCs	Anti-CD244 mAb	CD244	Signaling-mediated enhancement of IFN-γ and TNF-α production
Wang X et al[76]	PBMCs	anti-Tim-3 mAb	Tim-3	Significant increase in IFN-γ production
Jayaraman P et al[3]	C57BL/6 mice	anti-TIM3 mAb/TIM3$^{-/-}$ mice	TIM-3	TIM3 blockade-mediated multi-organ (lung/spleen) CFU reduction and delayed mortality in *Mtb*-infected C3HeB/FeJ mice
Sada-Ovalle et al[97]	PBMCs	anti-Tim3 mAb	TIM-3	Contribution to intracellular bacterial replication control in human macrophages
Wang Y et al[74]	SCID mice	LV-lncRNA	CD244	lncRNA-CD244–depressed CD8$^+$ T cells can more potently control in vivo *Mtb* infection than lncRNA-CD244–expressed CD8$^+$ T cells in SCID mice
Qu P et al[87]	Mice on C57BL/6 background	*Pdl1*$^{\Delta M\Phi}$ mice/anti-PD-L1 or anti-PD-1	PD-1	Treatment with anti-PD-L1 or anti-PD-1 benefited protection against M.tb infection in WT mice, while Pdl1$^{\Delta M\Phi}$ mice exhibited the increased susceptibility to M.tb infection
Sakai S et al[94]	C57BL/6 mice	PD-1$^{-/-}$ mice	PD-1	Bacterial numbers in the spleen of PD-1-deficient mice were significantly reduced compared with wild-type mice at 6 and 12 weeks after BCG infection
Fortune SM et al[98]	C57BL/6 mice	PD-1 KO mice	PD-1	Adoptive transfer of PD-1 KO CD4 T cells led to early mortality of the reconstituted mice

(*Continued*)

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Table 1 (Continued).

References	Sample	Blocking Method	Co-Inhibitory Receptor Types	Blocking Effect
Khader S et al[99]	C57BL/6 and PD-1 deficient mice	PD-1 deficient mice	PD-1	*M.tb* antigen-specific T cell proliferation was dramatically reduced in PD-1 deficient animals compared with wild-type littermates
Barber DL et al[100]	C57BL/6	PD-1 KO mice	PD-1	PD-1 deficiency in CD4 T cells is sufficient to trigger increased susceptibility to *Mtb*
Lázár-Molnár E et al[101]	C57BL/6 mice	PD-1–deficient mice	PD-1	The lungs of the PD-1-/- mice showed uncontrolled bacterial proliferation and focal necrotic areas and showed dramatically reduced survival compared with wild-type mice
Sakai S et al[102]	TCRα KO mice	PD-1 KO mice	PD-1	The parenchymal effector CD4 T cells derived from PD-1 KO mice accelerated the mortality of the TCRα KO mice infected with *Mtb*
Kauffman KD et al[103]	Non-human primates	anti-PD-1 mAb	PD-1	PD-1 blockade increased bacterial loads in pulmonary granulomas but did not result in disseminated infection

Abbreviations: PFMCs, pleural fluid mononuclear cells; PBMCs, Peripheral Blood Mononuclear Cells.

TIM-3 enhanced the mice's resistance to *Mtb* infection and improved their survival rate.[3,15] Das et al found that silencing LAG-3 signaling enhanced killing of *Mtb* and increased IFN-γ expression.[80] Chen et al found that blocking LAG-3 increased the expression of IFN-γ and granzyme B on CD8+T cells.[86] Blockade of CD244 signaling enhances the production of IFN-γ and TNF-α.[73] Additionally, CD244-depleted CD8+ T cells exhibit a stronger ability to control in vivo *Mtb* infection compared to CD244-expressing CD8+ T cells in mice.[74] For specific references, see Table 1.

Blockade of Co-Inhibitory Receptors Attenuates Suppression on Effector Cell Functions by Tregs

Tregs are essential for maintaining immune tolerance and preventing autoimmune diseases. However, excessive activation of Tregs may result in heightened immune suppression, contributing to the development of TB.[104] Research indicated that co-inhibitory receptors suppressed effector T cell function directly and modulated immune responses by promoting the development and activity of Tregs and myeloid-derived suppressor cells (MDSCs).[96,105] Several studies have shown increased expression of PD-1/PD-L1 on Tregs in TB patients,[106–109] along with higher levels of CTLA-4[96] and TIGIT, which decreased following anti-tuberculosis treatment.[96] The increased expression of co-inhibitory receptors on Tregs promoted their expansion[104] and enhanced their suppression of effector cell functions.[96] In contrast, inhibiting co-inhibitory receptors effectively suppressed Treg proliferation.[93,96,110,111]

These studies suggest that co-inhibitory receptors mediate immune suppression by directly inhibiting effector T cell function and promoting the proliferation of immune suppressive cells, further inhibiting effector T cells. Therefore, blocking co-inhibitory receptors may restore the anti-tuberculosis immune response of effector T cells (Table 1 and Figure 2), although their effectiveness requires further validation in prospective clinical trials.

Excessive Blocking of Co-Inhibitory Receptors Can Lead to Excessive Inflammation and Undermine the Balance of Anti-Tuberculosis Immunity

It is generally understood that inhibiting the excessive expression of co-inhibitory receptors on immune cells tends to enhance anti-tuberculosis immunity. However, under certain conditions, blocking co-inhibitory receptors may lead to excessive inflammation in the body, thereby exacerbating the deterioration of the disease.[112] Several studies in mouse models have shown that genetic knockout of PD-1 increases susceptibility to *Mtb* and elevates mortality rates. For example, research by Barber et al demonstrated that PD-1 knockout mice were more susceptible to *Mtb* infection.[87,100] Andknockdown of PD-1 in mice results in a significant reduction in antigen-specific T cell proliferation, uncontrolled bacterial growth in the lungs, and the formation of focal necrotic areas, ultimately leading to decreased survival rates in these mice.[98,99,101] A study on non-human primates found that administering anti-PD-1 antibody therapy to rhesus macaques two weeks after infection increased pro-inflammatory cytokines and the number and functionality of specific CD8+ T cells. However, the treated group showed higher *Mtb* load and disease severity than controls.[103] Moreover,

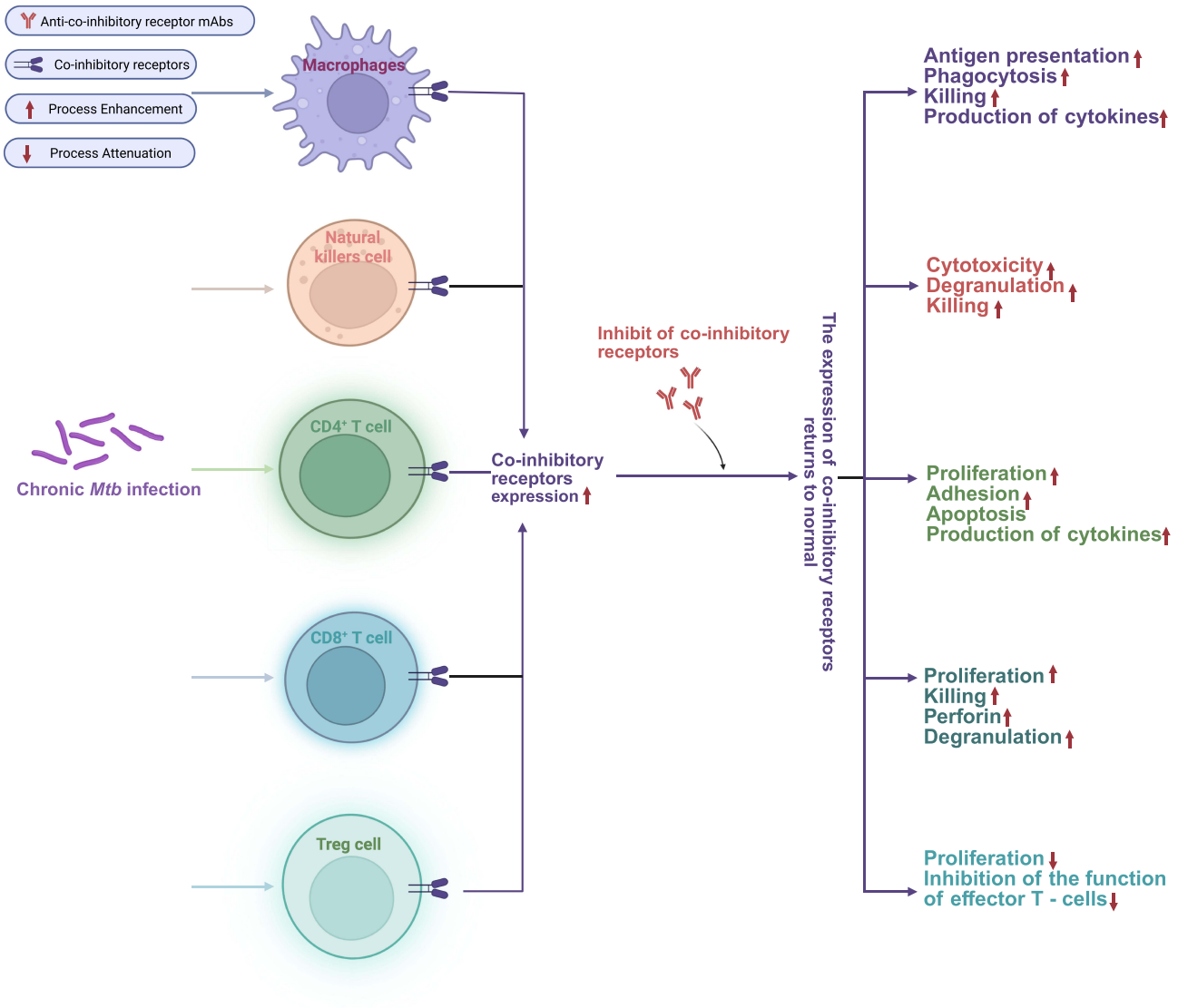

Figure 2 Restoration of immune function through co-inhibitory receptor blockade. In tuberculosis infection, high expression of co-inhibitory receptors on immune cells impairs immune responses. Blocking these receptors restores protective T cell activity, reduces Treg-mediated immune suppression, and enhances anti-tuberculosis immunity. *Mtb: Mycobacterium tuberculosis*; red upward and downward arrows indicate enhancement and weakening of the process, respectively.

Ogishi et al reported a case of a child with genetic PD-1 deficiency who developed abdominal tuberculosis.[113] Although the child was successfully treated for the infection, they later died from excessive systemic autoimmune inflammation.

In terms of the mechanism, studies have demonstrated that inhibiting PD-1 signaling accelerates *Mtb* growth by promoting excessive TNF-α secretion. And excessive TNF-α is responsible for accelerated *Mtb* growth, thereby leading to *Mtb* reactivation.[91] Sakai et al found that increasing the producing capacity of IFN-γ of CD4 T cells by approximately two-fold exacerbates lung infection and leads to the early death of the host, despite enhancing control in the spleen.[102] This suggests that the body requires PD-1 inhibition to prevent excessive production of IFN-γ, which could otherwise lead to harmful outcomes and host mortality. In fact, there exists an intrinsic negative feedback mechanism exists to prevent excessive IFN-γ production in vivo, thereby avoiding lethal immune-mediated pathology. For example, *Mtb* induced IFN-γ production and upregulates PD-1 expression in immune cells.[33,105,114] In turn, PD-1 inhibited the production of cytokines like IFN-γ and TNF-α by Th1 cells, forming a regulatory feedback loop.[90]

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These findings highlight the importance of balancing cytokine secretion in TB to optimize the host immune response. Insufficient cytokine production can result in an inadequate anti-TB response, while excessive production may cause harmful inflammation. Therefore, moderate cytokine levels are necessary for effective *Mtb* infection control (Figure 3).

Why Does Targeting Co-Inhibitory Receptors Yield Contradictory Results in TB Animal Studies?

In tuberculosis animal models, the research results on blocking or knocking down the PD-1/PD-L1 pathway show contradictions, which may be closely related to multiple mechanistic differences. We propose the following hypotheses:

Firstly, differences in the intensity and mode of blockade may be an important factor. For example, one study found that anti-PD-L1 or anti-PD-1 treatments provided protection against *Mtb* infection in wild-type mice, while PD-L1-deficient mice exhibited increased susceptibility.[87] This might be due to the selective anti-PD-L1 antibody achieving partial signal blockade in mice, moderately reversing T-cell exhaustion, and thereby enhancing anti-tuberculosis immunity. In contrast, PD-L1 gene-deficient mice completely lost negative feedback regulation, leading to excessive T-cell activation and cytokine storms, which caused lung tissue necrosis and uncontrolled infection.

Secondly, we discusses the contradictory findings from mouse experiments, where blocking PD-1/PD-L1 in mice disrupts anti-tuberculosis immunity, while blocking TIM-3 and CD244 results in enhanced anti-tuberculosis immunity, which warrants further discussion. It is important to note that there are numerous co-inhibitory receptors, which raises an important question: why do so many pathways seem to perform similar functions? Anderson et al have proposed a model in which CTLA-4 and PD-1 represent the first tier of co-inhibitory receptors, primarily responsible for maintaining self-tolerance and limiting T cell clonal expansion in lymphoid organs, while Lag-3, Tim-3, and TIGIT represent second-tier co-inhibitory molecules that play unique and specific roles in modulating immune responses, particularly at sites of tissue inflammation.[10] This distinction suggests that CTLA-4 and PD-1 receptors dominate in maintaining self-tolerance,[12] and targeting CTLA-4/PD-1 in individuals with infectious diseases may interfere with the core mechanisms that preserve self-tolerance, thereby more easily disrupting systemic immune balance and triggering excessive inflammatory responses. In contrast, targeting secondary molecules such as TIM-3/CD244, which act specifically within the peripheral inflammatory microenvironment, theoretically reduces the risk of systemic immune dysregulation (Figure 4). However, research on co-inhibitory molecules beyond PD-1 and CTLA-4 remains relatively limited, and given that immune homeostasis regulation is a complex biological process, the specific mechanisms remain to be further explored.

Lastly, the host's immune baseline state may also be a critical factor. Hosts with impaired immune function may benefit more from ICIs, while hosts with already healthy or strong immune states might experience an overactive immune response due to ICIs, leading to disease exacerbation.

All in all, the immune system has evolved to effectively defend against infections and restore tissue homeostasis.[115,116] The expression of co-inhibitory receptors serves as a natural physiological balancing mechanism designed to fine-tune organ-specific inflammatory responses and mitigate T cell-mediated tissue damage. Co-inhibitory receptors act as brakes in the immune system, preventing excessive T cell activation and reducing the risks of immune pathology and autoimmunity.[117] These receptors are essential to prevent T cell-driven exacerbation of infections. Therefore, either the overexpression or the absence of co-inhibitory receptors is detrimental to the host's immune response against *Mtb*. to control tuberculosis infection, the immune system must precisely balance immune cell activation and pathogen suppression to prevent excessive inflammation and tissue damage,[118] ultimately achieving effective infection control while protecting the host's health.

The Paradox of TB Reactivation Following ICI

Multiple studies have shown that cancer patients treated with ICIs have an increased risk of developing tuberculosis.[119,120] However, there are also studies indicating that there is no correlation between the use of ICI and the incidence of tuberculosis. The incidence of pulmonary tuberculosis during the use of ICI was very low, and the use of ICI and the occurrence of tuberculosis might be coincidental.[121–124] The association between ICI and tuberculosis development may be influenced by various confounding factors. For example, cancer itself can lead to immune system

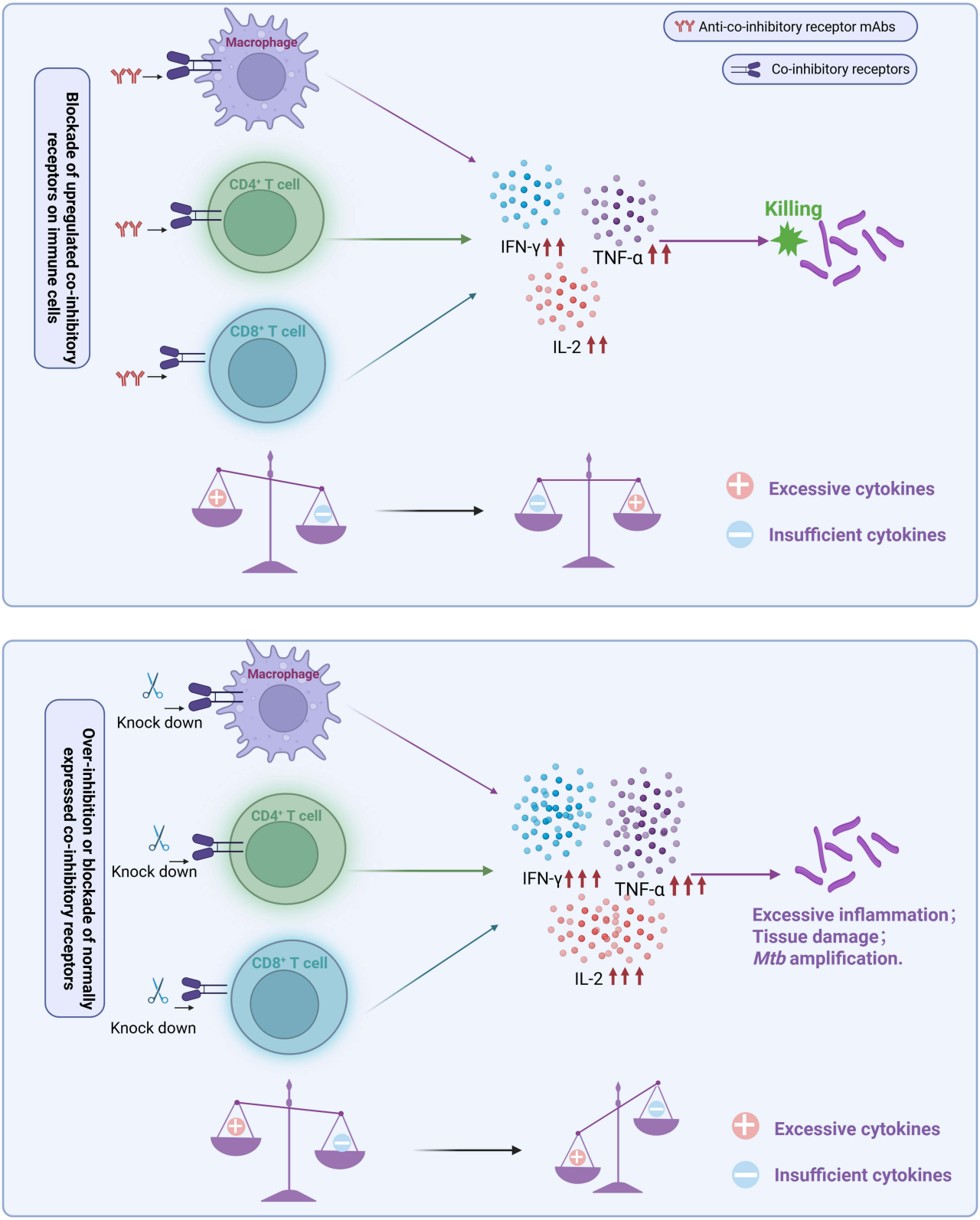

Figure 3 Hypothesis on the Impact of Targeting Co-inhibitory Receptors on Anti-Tuberculosis Activity in Individuals with Different Immune States. In T cell exhausted individuals, blocking the overexpression of co-inhibitory receptors restores cytokine production, thereby enhancing control of *Mtb*. However, excessive blockade of co-inhibitory receptors leads to an overproduction of cytokines, resulting in heightened inflammation and increased *Mtb* proliferation. The red upward arrow indicates an increase in cytokine secretion.

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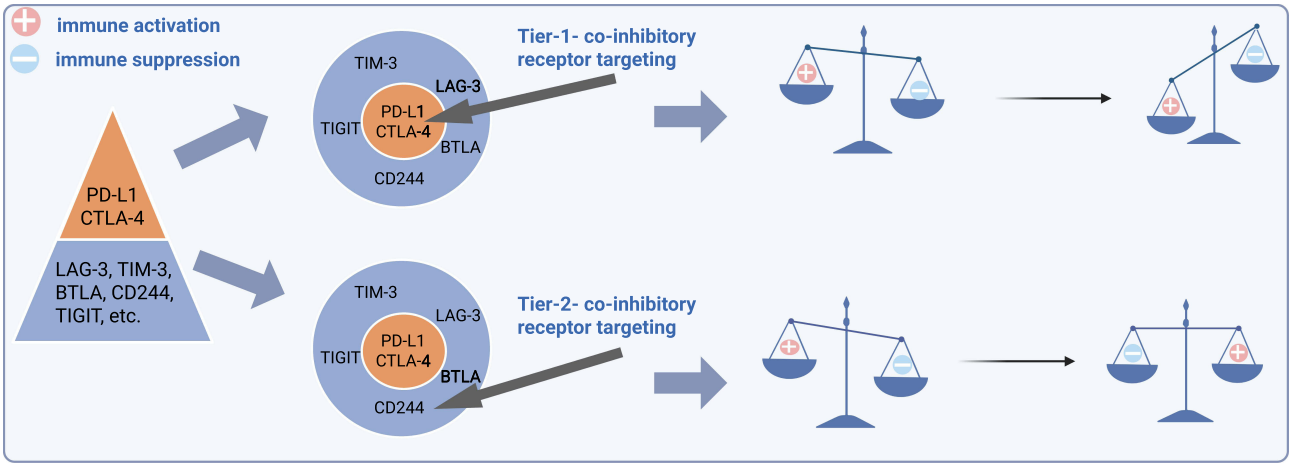

Figure 4 Role of co-inhibitory receptors in different tuberculosis infection stages. In immune exhaustion-type TB, co-inhibitory receptor antagonists restore immune responses and improve clinical outcomes. In contrast, in hyper-inflammatory TB, receptor blockade exacerbates inflammation and may worsen disease progression.

suppression, or patients may be receiving other immunosuppressive treatments such as chemotherapy or glucocorticoids.[122] Therefore, the occurrence of tuberculosis infection in cancer patients after receiving ICI treatment may be related to pre-existing risk factors rather than being directly attributable to ICI therapy itself. It is important to emphasize that although both cancer and infectious diseases exhibit upregulation of co-inhibitory receptors, the mechanisms of action of these diseases differ. Moreover, the dosages used in cancer treatment may not be suitable for enhancing immunity against tuberculosis. Therefore, the risk of tuberculosis reactivation observed during cancer treatment should not lead to a complete dismissal of the value of co-inhibitory receptor blockers in the field of infectious diseases. Targeted therapy of co-inhibitory receptors still holds significant potential in the treatment of tuberculosis. However, this argument requires further research and validation.

The Prospects of Targeted Co-Inhibitory Receptors in TB

Personalized Immunotherapy Tailored to Individual Immune Statuses

Targeting co-inhibitory receptors holds great promise in the treatment of tuberculosis. However, it also presents significant challenges. There are complex interactions among the host, the pathogen, and the environment, which affect the pathogenesis, clinical manifestations, and treatment response of tuberculosis. Consequently, TB is not a uniform pathology but a heterogeneous disease characterized by distinct immune and molecular pathophysiological mechanisms. In recent years, advancements in bioinformatics have enabled the integration of large-scale epidemiological and multi-omics datasets, providing new insights into the diverse phenotypes of TB.

Recent studies have performed cluster analyses on publicly available gene expression data, identifying two distinct TB phenotypes. Phenotype A exhibited high expression of genes associated with inflammation and immunity, while metabolic and proliferative activity was reduced. In contrast, Phenotype B displayed active metabolic and proliferative pathways.[125] DiNardo et al further proposed three non-mutually exclusive TB phenotypes: one characterized by defects in IL-12-IFN-γ signaling, another by excessive inflammation, and the third by immune exhaustion.[126] These distinct phenotypes guide the future selection of co-inhibitory receptor-based therapies. The existence of different phenotypes indicates that their specificity should be considered in treatment strategies to achieve personalized medicine.

As mentioned, mouse models have reported conflicting results on the protective and harmful effects of blocking co-inhibitory receptors. These findings highlight the crucial role of an individual's immune status in shaping the therapeutic response. Specifically, it suggests that TB patients with impaired immune function may benefit more from co-inhibitory receptors blockade. In contrast, those with a healthy immune status may be at greater risk of exacerbating the infection. Building on these findings, we propose that blocking co-inhibitory receptors in TB patients with immune exhaustion phenotypes could enhance the immune response, thereby improving the clearance of *Mtb*. Conversely, the same treatment

could trigger an overactive immune response for patients with an excessive inflammation phenotype, potentially impairing infection control and leading to a poor prognosis of the disease (Figure 5). In clinical practice, significantly elevated levels of inflammatory markers in patients, such as ultra-high concentrations of interferon-γ, TNF-α, and IL-6, often indicate an excessive immune activation state. In such cases, blocking co-inhibitory receptors may exacerbate the inflammatory cascade, leading to an increased risk of tissue damage. In contrast, if the patient is in the late stage of chronic tuberculosis infection with low inflammatory characteristics (eg, persistently low levels of key cytokines), it may suggest an immune dysfunction driven by T cell exhaustion. In this context, targeting co-inhibitory pathways could potentially restore the anti-tuberculosis immune response. With advancements in detection technologies, it is anticipated that in the future, an economical and convenient dynamic monitoring system for co-inhibitory molecules will be established, providing a basis for precise immune intervention.

As research on co-inhibitory receptors in TB advances, the potential for personalized treatment continues to grow. Co-inhibitory receptors may serve as novel therapeutic targets for TB. We recommend selecting appropriate patients for co-inhibitory receptor blockers based on tuberculosis type and immune status. Additionally, the expression levels of relevant co-inhibitory receptors should be closely monitored, allowing for prompt medication discontinuation once normal levels are restored. Some studies have shown that co-inhibitory receptor expression changes as tuberculosis infection progresses.[72] Future research should focus on regulating co-inhibitory receptor activity at different stages of infection to optimize therapeutic outcomes.

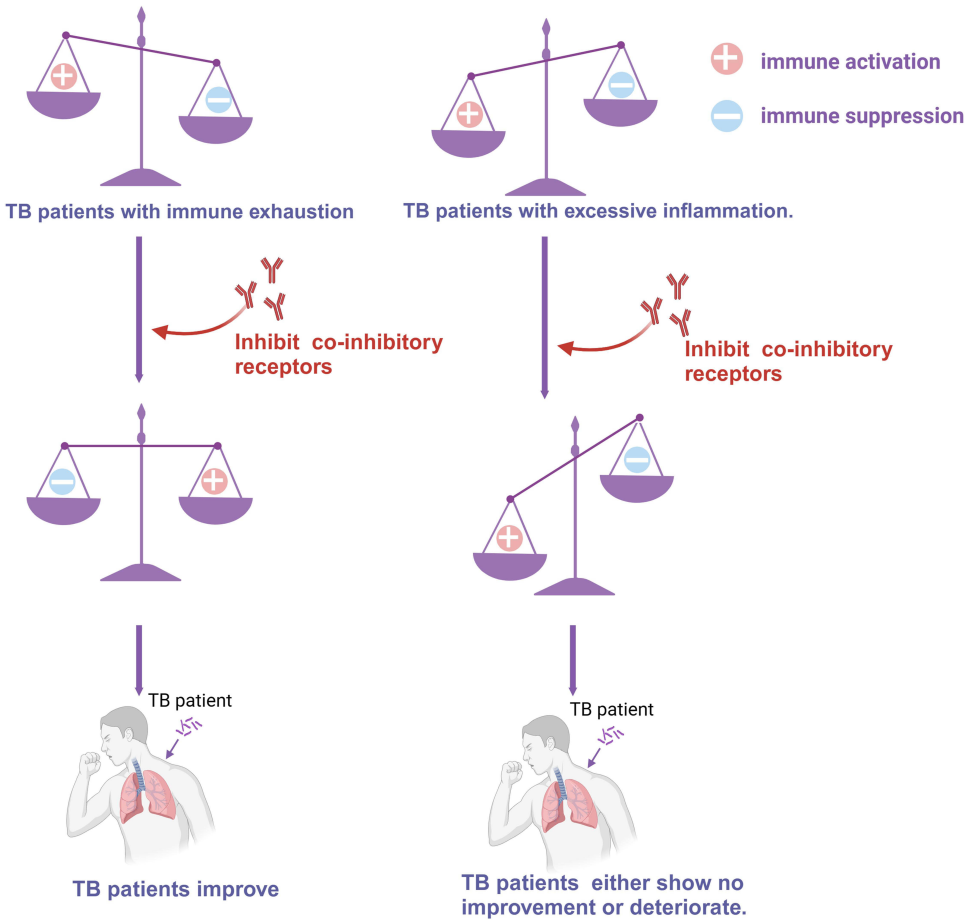

Figure 5 Hierarchical Model of Co-inhibitory Receptors and the Hypothesis of Therapeutic Effects of Tiered Targeting. Targeting primary co-inhibitory receptors (eg, PD-1/CTLA-4) may disrupt core mechanisms maintaining self-tolerance, potentially triggering excessive immune activation. In contrast, secondary co-inhibitory receptors (eg, TIM-3, LAG-3, BTLA-4) can be targeted with reduced impact on immune homeostasis, thereby reversing T-cell exhaustion.

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The Potential of Targeting Secondary Co-Inhibitory Receptors in Immunotherapy

In current immunotherapy research, CTLA-4 and PD-1 receptors have been extensively studied and serve as targets for immune modulation in various diseases, especially showing significant efficacy in cancer immunotherapy. However, the application of these receptors in cancer treatment has been associated with the emergence of immune-related adverse events (irAEs), prompting the academic community to explore alternative co-inhibitory receptor targets.

The hierarchical model of co-inhibitory receptors (primary: CTLA-4/PD-1; secondary: LAG-3/TIM-3/TIGIT) suggests that secondary receptors (eg, TIM-3, LAG-3, TIGIT) primarily regulate immune responses within inflammatory tissue microenvironments, rather than systemic tolerance.[10] Theoretically, blocking these receptors is less likely to disrupt the homeostasis of lymphoid tissues, thereby minimizing the risk of autoimmune sequelae and pathological over-inflammatory responses, unlike targeting CTLA-4 and PD-1, which can affect systemic immune homeostasis (Figure 4). At the same time, these receptors may finely regulate immune responses at local lesions (eg, granulomas), making them ideal targets for localized immune modulation without triggering systemic immune activation.

Therefore, in addition to continuing to explore the immune regulatory roles of CTLA-4 and PD-1, future research should focus more on the potential roles of secondary-level co-inhibitory molecules (such as LAG-3, TIM-3, and TIGIT) in tuberculosis immunity. However, related research is still in its early stages, and the clinical feasibility and safety of targeting these receptors need to be thoroughly evaluated through rigorous preclinical and translational studies.

Immune Modulatory Vaccines for Tuberculosis: Learning from Cancer Treatment

Although ICIs have made significant progress in cancer treatment, some patients still experience severe adverse reactions, which has promoted the search for equally effective therapies with less toxicity. Vaccination is an economically effective intervention measure to enhance the host's immunity against tuberculosis. However, the only widely used tuberculosis vaccine, Bacillus Calmette-Guérin (BCG), has an unsatisfactory protective effect on adults, and the new candidate vaccines under clinical development have not yet surpassed the protective advantages of BCG.[127,128] This highlights the urgent need for a strategic approach to the next generation of tuberculosis vaccines. T cells that recognize the epitopes derived from immunosuppressive proteins expressed by immunosuppressive cells are defined as anti-regulatory T cells (anti-Tregs).[129] Multiple immunogenic epitopes of immunosuppressive proteins (such as indoleamine 2,3-dioxygenase (IDO) and PD-L1) have been identified and characterized.[130,131] Since anti-regulatory T cells can directly respond to regulatory immune cells by inhibiting their inhibitory function and promoting a more pro-inflammatory microenvironment, they seem to be important for immune homeostasis.[132,133]

The research conducted by Grauslund et al indicates that by activating regulatory T cells that target PD-L1-derived epitopes through peptide vaccines, it is possible to effectively restore the immune homeostasis of patients through immune regulation in the tumor microenvironment and promotion of tumor-specific T cell responses.[134,135] A clinical trial demonstrated that the immunomodulatory vaccine IO102/IO103, which targets IDO and PD-L1, precisely eliminates IDO+/PD-L1+ cells that mediate immune suppression by activating specific T cells, successfully reversing the tumor microenvironment from an immunosuppressive state to an immunosupportive state.[136] When used in combination with nivolumab, this vaccine showed promising results in improving the response rate and median progression-free survival in melanoma patients.

Compared to traditional ICIs, vaccine-induced, antigen-specific T cells can precisely target the sources of immune suppression, effectively avoiding the risk of systemic immune overactivation. This strategy also demonstrates unique potential in the treatment of tuberculosis. Therefore, we believe that immune-modulatory vaccines with fewer side effects and lower regulatory levels, compared to traditional ICIs, hold promising potential in the treatment of tuberculosis.

Conclusions

Targeting co-inhibitory receptors demonstrates significant therapeutic potential for reversing T-cell exhaustion, restoring effector function, and enhancing pathogen clearance in chronic *Mtb* infection. However, excessive inhibition of these pathways, especially PD-1/PD-L1, may lead to immune hyperactivation, exacerbating inflammation and tissue damage, highlighting the critical importance of maintaining equilibrium between immunodeficiency and excessive immune

responses. Therefore, precision host-directed therapies that modulate co-inhibitory pathways according to individual immune status are essential. Future research priorities should focus on: (1) Personalized immunotherapy based on individual immune status achieves maximized therapeutic efficacy while effectively controlling risks; (2) Advancing the development of novel co-inhibitory receptor blockers; (3) Designing immune-modulatory vaccines targeting co-inhibitory receptors.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no conflict of interest.

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