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Research Progress on the Role of the PD-1/PD-L1 Pathway in Immune Thrombocytopenia

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Abstract

The widespread use of immune checkpoint inhibitors (ICIs), particularly Programmed cell death protein 1/programmed death ligand 1(PD-1/PD-L1) inhibitors, has significantly improved the survival prognosis of patients with various malignancies but has also brought about unique immune-related adverse events (irAEs). Among these, ICI-related immune thrombocytopenia (ITP), a rare but potentially life-threatening hematologic adverse event, is gaining increasing clinical attention. This article systematically reviews the pathogenic mechanisms of ITP associated with PD-1/PD-L1 inhibitors and explores the potential role of the PD-1/PD-L1 pathway in the pathogenesis of primary ITP. A deep understanding of the bidirectional relationship between the PD-1/PD-L1 pathway and ITP is of great significance for optimizing the safety management of tumor immunotherapy and exploring novel therapeutic strategies for ITP.

Keywords

PD-1 Inhibitor, PD-L1 Inhibitor, Immune Thrombocytopenia, Immune-Related Adverse Events, Immune Tolerance

1. Introduction

PD-1 and PD-L1 are key negative costimulatory molecules that maintain immune homeostasis and peripheral tolerance. The physiological function of the PD-1/PD-L1 signaling pathway is to limit T cell overactivation and prevent autoimmune responses. Tumor cells achieve immune escape by overexpressing PD-L1, which binds to PD-1 on the surface of effector T cells, inducing T cell exhaustion. PD-1/PD-L1

inhibitors, developed based on this mechanism, reactivate anti-tumor immunity by blocking this pathway and have become the standard treatment for various malignancies.

However, the therapeutic window of immune checkpoint inhibitors is accompanied by a unique spectrum of toxicities—irAEs. These adverse events can affect multiple organ systems, with common ones including dermatitis, colitis, hepatitis, and pneumonia. Hematologic irAEs are relatively rare, but when they occur, they are often severe and even life-threatening. ICI-related ITP is one of the most representative types.

Notably, the PD-1/PD-L1 pathway is not only involved in the occurrence of drug-related ITP but also plays a potential role in the pathogenesis of primary ITP. Recent studies have found abnormal PD-1/PD-L1 expression in patients with primary ITP, and enhancing this pathway's signaling may represent a new therapeutic strategy. This bidirectional relationship suggests that the PD-1/PD-L1 pathway may play an important role in maintaining platelet immune homeostasis.

This article will systematically review the association between the PD-1/PD-L1 pathway and ITP from two dimensions—drug-related ITP and primary ITP—to provide a reference for clinical practice and future research.

2. PD-1/PD-L1 Inhibitor-Associated Immune Thrombocytopenia

2.1. Epidemiological Characteristics

Although the incidence of ITP associated with PD-1/PD-L1 inhibitors is lower than that of other common irAEs, large-scale real-world data analyses have confirmed a significant safety signal. A retrospective pharmacovigilance study of the US FDA Adverse Event Reporting System (FAERS), analyzing data up to September 2022, identified 329 ICI-related ITP reports, including 160 for nivolumab, 125 for pembrolizumab, 27 for atezolizumab, and 17 for durvalumab. Reporting odds ratio (ROR) analysis showed that pembrolizumab (ROR 12.6), avelumab (ROR 10.32), nivolumab (ROR 9.76), and durvalumab (ROR 7.91) all had significant disproportionate reporting signals, indicating a statistical association between these drugs and ITP occurrence [1]. Another study based on VigiBase, the World Health Organization's individual case safety report pharmacovigilance database, found that from 2010 to 2018, ITP accounted for 40% (68/168) of ICI-related hematologic complications [2].

The incidence of ITP in the general population is 2 to 5 per 100,000 persons [3], while the incidence of ICI-related ITP is approximately 0.25% (214/86,467) based on the largest multicenter cohort study across 29 US hospitals [4]. Regarding mortality, the case fatality rate of ICI-related ITP is approximately 11% - 31%, highlighting its clinical severity [1] [2] [5] [6]. The median time to onset of ICI-related ITP is 68 days (range 4 - 875 days) after the first dose. Notably, ITP can occur early in treatment or be delayed until several months after treatment completion,

an atypical temporal distribution that complicates clinical recognition [1].

2.2. Pathogenesis

The exact mechanism by which PD-1/PD-L1 inhibitors cause ITP is not fully elucidated, but current evidence supports the involvement of multiple immune-mediated mechanisms.

Disruption of peripheral immune tolerance. The PD-1 and PD-L1 are considered to be the major immune checkpoint molecules. The interaction of PD-1 and PD-L1 negatively regulates adaptive immune response mainly by inhibiting the activity of effector T cells while enhancing the function of immunosuppressive regulatory T cells (Tregs), largely contributing to the maintenance of immune homeostasis that prevents dysregulated immunity and harmful immune responses [7]. ITP patients exhibit an abnormality in the PD-1/PD-L negative costimulatory pathway, characterized by increased expression of the receptor (PD-1) on T cells and decreased expression of the ligand (PD-L1) on dendritic cells (DCs). In vitro experiments showed that PD-L1 promoted T cell apoptosis and inhibited their activation and proliferation. This imbalance may disrupt peripheral immune tolerance and contribute to the pathogenesis of ITP [8].

Involvement of humoral immune mechanisms. PD-1 is expressed not only on T cells but also on B cells. In a case of nivolumab-related ITP reported by Kanameishi *et al.*, upregulation of PD-1 expression on the surface of B cells was observed, suggesting that B cells may also participate in this process [9]. Notably, ICI-related ITP is often accompanied by positivity for platelet-associated IgG (PAIgG). In a case of nivolumab-related ITP reported by Jotatsu *et al.*, PAIgG-mediated platelet destruction was detected, indicating the involvement of humoral immunity in disease occurrence [10]. However, evidence for humoral immune mechanisms is currently derived primarily from case reports, and their role in ICI-related ITP requires further confirmation.

Impaired megakaryocyte differentiation. The PD-1/PD-L1 pathway may affect not only peripheral platelet destruction but also thrombopoiesis by megakaryocytes in the bone marrow. This study conducted the first prospective longitudinal investigation by collecting peripheral blood mononuclear cell samples from a patient before and after two episodes of ITP induced by PD-1 inhibitor therapy (the initial occurrence and a recurrence triggered by rechallenge), and performing transcriptomic sequencing analysis, thereby obtaining time-matched data for mechanistic analysis. The findings demonstrate that ICI-induced ITP involves a dual pathogenic mechanism combining immune-mediated platelet destruction and intrinsic megakaryopoietic impairment, providing a novel conceptual framework for understanding this immunotherapy complication. [11]. It has been reported that myelosuppression, in combination with peripheral platelet destruction, may represent the underlying pathological basis of ICI-related ITP [12].

Furthermore, genetic susceptibility may play a role. Certain single nucleotide

polymorphisms in the PD-1 and CTLA-4 genes may increase an individual's risk of developing ITP, although research in this area is still in its early stages [13].

3. Role of the PD-1/PD-L1 Pathway in Primary ITP

3.1. Abnormal PD-1/PD-L1 Expression in Patients with Primary ITP

Primary ITP is an acquired autoimmune disorder characterized by increased platelet destruction and decreased platelet production. In recent years, accumulating evidence suggests that functional defects in the PD-1/PD-L1 pathway contribute to the pathogenesis of ITP.

A study by Zhong *et al.* found that the expression levels of PD-1 and PD-L1 in the peripheral blood of patients with chronic ITP were significantly lower than those in healthy controls. This low expression was observed not only on CD4+ T cells but also on CD8+ T cells. More importantly, PD-1 expression levels were negatively correlated with disease activity, suggesting that downregulation of the PD-1/PD-L1 pathway may be associated with disease progression in ITP [14].

Further research by Han *et al.* elucidated the molecular mechanism underlying PD-1 downregulation. They found aberrant hypermethylation of the PD-1 gene promoter region in CD8+ T cells from ITP patients. DNA methylation is an important epigenetic modification, and promoter hypermethylation typically leads to transcriptional silencing. Therefore, PD-1 promoter hypermethylation may be the molecular basis for reduced PD-1 expression in ITP patients [15].

3.2. PD-1/PD-L1 Pathway and Cytotoxic T Cell-Mediated Platelet Destruction

Cytotoxic T lymphocytes (CTLs) play a significant role in platelet destruction in ITP. Olsson *et al.* first reported the existence of CTL responses against autologous platelets in ITP patients. Subsequent studies confirmed that CTLs from ITP patients can directly lyse autologous platelets in vitro [16].

The PD-1/PD-L1 signaling plays a critical role in regulating CTL function. Binding of PD-1 to PD-L1 recruits Src homology region 2-containing protein tyrosine phosphatase 2 (SHP2), inhibiting the Phosphoinositide 3-kinase/protein kinase B (PI3K/Akt) signaling pathway downstream of the T cell receptor (TCR), thereby reducing T cell proliferation and effector function [17]. In ITP patients, due to downregulated PD-1 expression, this negative regulatory mechanism is weakened, leading to CTL hyperactivation. In vitro experiments by Han *et al.* showed that activating the PD-1 pathway with a PD-L1-Fc fusion protein significantly inhibited CTL-mediated platelet destruction in ITP patients. This finding directly confirms the potential value of enhancing PD-1 signaling for controlling ITP [15].

3.3. Effects of PD-1/PD-L1 Pathway Abnormalities on Other Immune Cells and Megakaryocytes

Regarding regulatory T cells (Tregs), the dysfunction of the PD-1/PD-L1 signaling

pathway may be caused by sPD-1, whose level is correlated with the severity of ITP. Restoration of the Th1/Th2 and Treg/Th17 imbalance in ITP patients can be achieved by activating the PD-1/PD-L1 pathway with sPD-L1. In contrast, blockade of this pathway using anti-PD-1 may aggravate the disease through increased interferon-gamma (IFN-γ) production [18].

Regarding B cells, studies have found that PD-1 shapes optimal B cell memory and antibody-mediated immunity through both B cell-intrinsic and -extrinsic mechanisms, suggesting that B cell dysregulation is a potential cause of infectious and autoimmune complications following anti-PD-1/PD-L1 immunotherapy [19].

Regarding megakaryocytes, it has been reported that both megakaryocytes and platelets can express PD-L1, suggesting that PD-1/PD-L1 pathway dysfunction may directly act on megakaryocytes or platelets and contribute to the pathogenesis of ITP [20] [21].

4. Clinical Management of ICI-Related ITP

According to the NCCN Clinical Practice Guidelines in Oncology: Management of Immunotherapy-Related Toxicities (Version 1.2026), the clinical management of suspected PD-1/PD-L1 inhibitor-related ICI-related ITP emphasizes differential diagnosis by excluding causes such as bone marrow metastasis, Disseminated Intravascular Coagulation (DIC), and Heparin-Induced Thrombocytopenia (HIT), combined with grade-specific management based on platelet count and bleeding risk. First-line therapy is centered on corticosteroids: for grade 1 toxicity (platelets 75 - 100 $\times 10^9$/L), ICIs may be continued with close monitoring; for grade 2 (50 - 75 $\times 10^9$/L), ICIs should be withheld and prednisone 0.5 - 1 mg/kg/day initiated; for grade 3 (25 - 50 $\times 10^9$/L), ICIs should be withheld or permanently discontinued, and prednisone 1 - 2 mg/kg/day or methylprednisolone administered; for grade 4 (<25 $\times 10^9$/L), ICIs are typically permanently discontinued, and in addition to high-dose corticosteroids, Intravenous Immunoglobulin, Thrombopoietin Receptor Agonists, or platelet transfusions may be considered. Regarding treatment modifications: ICIs should be withheld when toxicity reaches grade 2 or higher or when no improvement is seen within 48 - 72 hours of corticosteroid therapy. Rechallenge with ICIs may only be cautiously considered after toxicity resolves to grade ≤ 1 and in the absence of severe bleeding, with the recognition that patients who experience early-onset toxicity have a higher risk of recurrence. For steroid-refractory cases, second-line immunosuppressive therapies such as mycophenolate mofetil, rituximab, or infliximab may be considered. These strategies require individualization to balance antitumor efficacy against bleeding risk [22].

5. Therapeutic Potential of Enhancing PD-1/PD-L1 Signaling

Based on the above findings, enhancing PD-1/PD-L1 signaling represents a potential direction for further exploration in ITP treatment. Decitabine, a DNA me-

thyltransferase inhibitor, can restore gene expression through demethylation. The study by Han *et al.* showed that low-dose decitabine reversed the hypermethylation status of the PD-1 promoter in CD8+ T cells from ITP patients, restored PD-1 expression, and reduced CTL cytotoxicity against platelets. This effect was counteracted by a PD-1 blocking antibody, suggesting that its action may involve activation of the PD-1 pathway. Mechanistically, the phosphorylation levels of PI3K and AKT in CD8+ T cells were significantly reduced after decitabine treatment, indicating successful activation of PD-1-mediated negative signaling. Furthermore, decitabine has an independent effect of promoting megakaryocyte maturation and platelet production [14]. Therefore, the potential therapeutic effect of decitabine in ITP may involve dual mechanisms: on one hand, restoring PD-1-mediated negative immune signaling through epigenetic regulation, and on the other hand, directly promoting megakaryocyte maturation and platelet production.

Preliminary clinical studies have explored the efficacy of this strategy. Based on available clinical research data, low-dose decitabine has shown certain efficacy and manageable safety in the treatment of ITP that is refractory or relapsed after corticosteroid therapy [23] [24]. However, current evidence supporting the use of decitabine in ITP remains preliminary. The exact mechanisms, optimal patient population, and long-term safety of decitabine in ITP require further validation through larger prospective studies. Nevertheless, these findings offer a new perspective for ITP treatment-restoring immune checkpoint function through epigenetic regulation rather than relying solely on global immunosuppression, an approach that warrants further investigation.

6. Conclusion and Outlook

A complex bidirectional relationship exists between the PD-1/PD-L1 pathway and immune thrombocytopenia. On the one hand, PD-1/PD-L1 inhibitors can induce rare but potentially fatal ITP by breaking immune tolerance, requiring clinicians to maintain vigilance for hematologic adverse events when applying these effective anti-tumor drugs. On the other hand, patients with primary ITP exhibit functional defects in the PD-1/PD-L1 pathway, and enhancing this pathway's signaling may represent a novel therapeutic strategy for ITP.

Currently, several challenges remain in the field of ICI-related ITP. Its exact incidence may be underestimated, partly because platelet monitoring was not routine in past clinical trials. In-depth research on pathogenesis is needed, particularly regarding the interaction network among T cells, B cells, and megakaryocytes. Regarding treatment, more prospective studies are required to optimize management algorithms, clarify the timing of second-line therapy, and determine drug sequencing. For primary ITP, strategies based on epigenetic regulation to restore PD-1 expression warrant further clinical validation.

As the indications for immune checkpoint inhibitors expand and new generations of immunotherapies emerge, the spectrum of hematologic adverse events

will continue to evolve. A deep understanding of the role of the PD-1/PD-L1 pathway in platelet immune homeostasis will not only help improve the safety of tumor immunotherapy but may also lead to breakthroughs in the treatment of autoimmune hematologic diseases.

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Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

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