Review

The Relationship Between the PD-1/PD-L1, Th17 and Treg Cells in Cancer Immunity

Running title: PD-1/PD-L1, Th17 and Treg Cells in Cancer Immunity

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ABSTRACT

Programmed cell death 1 (PD-1) and its ligand PD-L1 (programmed death 1 ligand 1) are important immune checkpoints, and their interaction negatively regulates effector T-cell activation and proliferation, as well as being an important pathway for tumor cells to evade immune surveillance. Blocking the binding of PD-1 to PD-L1 can relieve the inhibition of T cells by tumor cells or antigen-presenting cells, and restore their ability to recognize and kill tumor cells. However, PD-1/PD-L1 is complexly regulated and varies among tumors, occurring mainly at the genetic, transcriptional and post-transcriptional levels. In the last decade, immune checkpoints blocker has become an important part of the treatment for many malignant tumors, resulting in longer tumor remission. While achieving better efficacy, the blocking effect in solid malignancies is still deficient, which may be related to the complex tumor microenvironment. As important parts in the tumor microenvironment, Tregs and Th17 cells have been shown to be involved in tumor development. Currently, the complex relationship between the PD-1/PD-L1 pathway, Tregs and Th17 cells has not been fully elucidated. In this paper, we review the interaction between the PD-1/PD-L1 pathway, Tregs and Th17 cells, with the aim of providing new ideas for future tumor therapy.

INTRODUCTION

The rapid development of immunotherapy in recent years has brought significant development opportunities for tumor therapy. There are a wide variety of tumor immunological treatments, including vaccines, cytokines, antibody therapy, overt cellular immunotherapy, tumor lysis immunotherapy, immunomodulators, and immune checkpoint blockers, etc [1]. Among them, immune checkpoint inhibitors (ICIs) can enhance the anti-tumor immune response by regulating the activity of T cells, which has become a hot spot of research and one of the most promising strategies at present [2]. PD-1 and PD-L1 are important negative immunomodulatory factors [3]. PD-L1, which overexpressing on the surface of almost all tumor cells, can bind to PD-1 receptors on the surface of T cells and impair T cells function through intracellular signaling, causing immune escape and resistance to conventional resistance to radiotherapy [4]. The advent of ICIs with monoclonal antibodies (mAbs), particularly PD-1/PD-L1 blockers, has dramatically altered the therapeutic outlook for a wide range of advanced malignancies. Unlike chemotherapy and targeted therapies, ICIs set out to reprogram the tumor immune response and offer advantages in terms of long-term benefits for tumor patients after treatment. Although their side effects are considered manageable and well tolerated compared to radiotherapy or other targeted therapeutic agents, ICIs are still deficient in terms of clinical efficacy in blocking solid malignant tumors, with only 20% to 30% effective rates for monotherapy. Although immune checkpoint modulation has been extensively studied in the past decades, however, regulatory mechanisms controlling PD-1/PD-L1 expression remain incompletely understood. In addition to genetic mutations among different tumors, low PD-1/PD-L1 blocking response and drug resistance may also be related to the complexity of the tumor microenvironment (TME) [5]. Studies targeting immunotherapy resistance have been progressively carried out [6]. The interactions between the co-stimulatory molecules, PD-1 and PD-L1, are regulated in a wide range of immune cells. As key immunosuppressive regulators within TME, regulatory T cells (Tregs) critically influence tumor development and progression, with their abundance and functional activity modulating PD-1/PD-L1 inhibitor efficacy. The Treg/Th17 axis emerges as a pivotal regulator in both oncogenesis and autoimmune pathogenesis, wherein Th17 cells manifest context-dependent duality within tumor microenvironments (TME). Emerging evidence suggests intricate crosstalk between PD-1/PD-L1 signaling and this cellular axis, prompting systematic investigation. This review synthesizes current understanding of their immunomodulatory networks and delineates tripartite interactions shaping tumor immunity.

PD-1/PD-L1 pathway

PD-1, also known as CD279, is a 55 kDa-sized transmembrane protein containing 288 amino acids and is the transmembrane molecule of the immunoglobulin CD28 family. PD-1 was first isolated by the Ishida group in 1992 from mouse T-cell hybridomas experiencing programmed cell death [7]. Murine PD-1 (mPD-1) transcriptional activation correlates with apoptosis induction in T-cell hybridomas, while PD-1 engagement triggers both apoptotic pathways and cell cycle arrest mechanisms. PD-1 is involved in both adaptive and intrinsic immunity and is expressed in activated T cells, natural killer (NK) cells, B lymphocytes, macrophages, dendritic cells (DCs), and monocytes [8]. PD-1 recognizes two ligands, PD-L1 (CD274 or B7-H1) and PD-L2 (CD273 or B7-DC), which belong to the B7-CD28 protein family. PD-L1, a 33-kDa type I transmembrane glycoprotein (290 amino acids), features extracellular IgV/IgC domains critical for immune checkpoint functionality. PD-L1 exhibits constitutive expression across multiple immune lineages including T lymphocytes, B cells, regulatory T cells (Tregs), and antigen-presenting cells (APCs), while also demonstrating broad tissue distribution in non-hematopoietic compartments such as vascular endothelia, mesenchymal stromal populations, fibroblasts, and pancreatic islet cells. Notably, its physiological presence extends to

immune-privileged anatomical sites (e.g., ocular tissues, placental barrier, and testicular parenchyma), suggesting evolutionary conservation of immune checkpoint regulation in sanctuary microenvironments [9]. The expression of PD-L2 is mainly restricted by antigen-presenting cells (APCs). Tumor cells also express high levels of PD-L1, and the PD-L1/PD-1 signaling pathway has been suggested to contribute to tumor immune escape [10]. The intracellular domain of PD-1 contains two distinct tyrosine-based signaling motifs: an N-terminal immunoreceptor tyrosine inhibitory motif (ITIM) and a C-terminal immunoreceptor tyrosine-based switch motif (ITSM). Of these, the ITSM serves as the primary mediator of PD-1-mediated immunosuppression. Following PD-L1 engagement, ligand-induced ITSM phosphorylation triggers downstream signaling cascades that mediate immune inhibitory responses. The inhibitory mechanism of the PD-1/PD-L1 axis is different in T lymphocytes and B lymphocytes [10]. In T cells, upon PD-1/PD-L1 binding, the ITSM-mediated recruitment of SHP-1/2 phosphatases induces dephosphorylation of proximal T-cell receptor (TCR) signaling components (ZAP70 and CD3δ). This phosphatase-driven signal attenuation disrupts PI3K/AKT axis activation, resulting in the inhibition of Bcl-xl, the apoptosis-related factor, and cytokines by T lymphocytes. The PD-1/PD-L1 axis also inhibits T cell proliferation by blocking the Ras-ERK pathway [11]. In B cells, PD-1 inhibits activation and attenuates the immune response to antigens [11]. PD-1 activation initiates sequential phosphatase signaling through SHP-2 recruitment to its cytoplasmic ITSM domain. This signalosome assembly catalyzes the dephosphorylation of proximal BCR signaling mediators (Igα/β, SγK), ultimately driving cell apoptosis. Mechanistically, SγK inactivation propagates through ERK/PI3K/PLCγ2 axis disruption, triggering downstream calcium flux dysregulation and cell cycle arrest [12].

As a important regulator of T lymphocyte homeostasis, the PD-1/PD-L1 axis critically mediates immune tolerance while paradoxically contributing to autoimmune pathogenesis and chronic infection persistence. PD-1/PD-L1 interactions are referred to as "immune checkpoints" because its regulation of tumor antigen-specific T cell responses. Functioning synergistically cytotoxic T-lymphocyte-associated protein 4 (CTLA-4, CD152), they renforce T cell functional exhaustion by attenuating TCR activation thresholds and transcriptional repression of proinflammatory cytokines, thereby establishing immunosuppressive microenvironments conducive to tumor immune evasion.

The PD-1/PD-L1 pathway is involved in the regulation of central and peripheral immune tolerance by providing inhibitory signals through mechanisms such as blocking proliferation, inducing apoptosis, regulating T-cell differentiation, and immunosuppression. For example, peripheral CD4 tolerance is regulated by PD-1/PD-L1 pathway in a variety of ways, particularly in terms of lymphocyte stability and integrity. The dysregulated expression of PD-L1 in tumor cells correlates with immune evasion across various malignancies, highlighting the critical role of PD-L1 structural variations in oncogenic progression [13]. PD-L1 mediates apoptotic evasion in malignancies through dual resistance modalities: (1) Cell-intrinsic resistance programs driven by constitutive PD-L1 overexpression via oncogenic drivers (e.g., STAT3/MYC activation), and (2) Adaptive immune tolerance mechanisms facilitated by dynamic PD-L1 upregulation in response to IFN-γ/TNF-α signaling [14, 15]. Meanwhile, PD-L1 also expressed across myeloid (macrophages, dendritic cells, MDSCs) and lymphoid populations mediated by inflammatory cues, constituting a hallmark of adaptive immune resistance [16]. Paradoxically, It has been demonstrates context-dependent immunomodulation, where its TME-wide expression profile mechanistically links to enhanced tumor immunogenicity and favorable clinical outcomes.

Based on the pair of immune co-inhibitory molecules, inhibitors are often used to block the PD-1/PD-L1 signaling pathway and rescue the immune response. Currently, there are six monoclonal antibodies and three

monoclonal antibodies (Table 1). PD-1/PD-L1-targeting ICIs restore effector T cell populations, enhance their cytotoxic activity against chemotherapy-resistant tumors, reverse chronic infection-induced CD8+ T cell exhaustion, stimulate pro-inflammatory cytokine production, and reestablish sustained antitumor immunity [17,18]. Meanwhile, ICIs therapy has less toxic than standard chemotherapy, with the common side effect of immune-related adverse events (irAEs). irAEs are actually triggered by altered immune tolerance of the body after immune checkpoints have been blocked. Prolonged immune activation may induce autoimmune-like inflammatory adverse events through off-target tissue damage, with delayed autoimmune toxicity persisting post-treatment cessation. Given the expanding clinical use of anti-PD-1 antibodies, extended surveillance of ICI recipients remains imperative to monitor these chronic immunotoxicities.

Table 1. Approved PD-1/PD-L1 monoclonal antibody

Name	Target	Approval Date	Property	Indication
Nivolumab[85]	PD-1	December 2014(FDA)	IgG4, fully human	Non-small-cell lung cancer, Hodgkin' s lymphoma, colorectal cancer, etc.
Pembrolizumab[86]	PD-1	September 2014(FDA)	IgG4, humanized antibody	Advanced melanoma, breast cancer, bladder cancer, etc.
Cemiplimab[87]	PD-1	September 2018(FDA)	IgG4, humanized antibody	Metastatic cutaneous squamous-cell carcinoma
Toripalimab[88]	PD-1	December 2018(NMPA)	IgG4, humanized antibody	Advanced Chinese melanoma patients who had failed in systemic treatments
Sintilimab[89]	PD-1	December 2018(NMPA)	IgG4, fully human	Patients with relapsed or refractory classical Hodgkin lymphoma
Camrelizumab[90]	PD-1	May 2019(NMPA)	IgG4, humanized antibody	Patients with relapsed or refractory classical Hodgkin lymphoma
Atezolizumab[91]	PD-L1	May 2016(FDA)	IgG1, humanized antibody	Metastatic non-small cell lung cancer progressing after platinum-based chemotherapy, locally advanced or metastatic urothelial cancer that cannot be treated with chemotherapy and PD-L1-positive triple negative breast cancer
Avelumab[92]	PD-L1	March 2017(FDA)	IgG1, fully human	Metastatic merkel cell carcinoma, advanced renal cell carcinoma, and urothelial carcinoma, etc.
Durvalumab[93]	PD-L1	May 2017(FDA)	IgG1, fully human	Locally advanced or metastatic urothelial cancer and unresectable stage III non-small cell lung cancer

Important signaling pathways regulating PD-L1

High expression of PD-L1 is associated with poor prognosis in a variety of human cancers, including renal cell, breast, colorectal, gastric, non-small cell lung, papillary thyroid, and testicular cancers [19]. While the PD-1/PD-L1 axis can be regulated by a variety of signals. The review of the relevant pathways will provide ideas and therapeutic targets for antitumor immunotherapy (Figure 1).

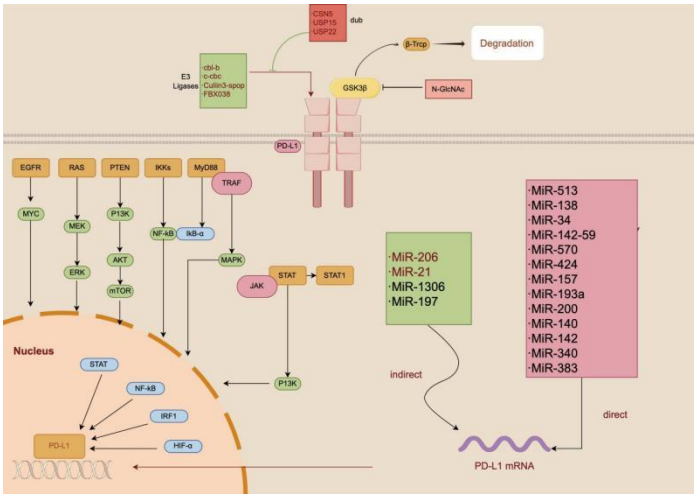

Figure 1. Schematic diagram of PD-L1 expression and its regulation.

PI3K/PTEN/Akt/mTOR pathway

The phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT) pathway is associated with cell proliferation and regulates a variety of processes related to cell proliferation and apoptosis, as well as influencing immune surveillance through the regulation of PD-L1 [20]. Mutations in PIK3CA (catalytic subunit of PI3K, alpha) or its negative regulator phosphatase and tensin homolog deleted on chromosome ten (PTEN) activate its regulation of immune responses, and the elevation of PD-L1 in glioblastomas is also mediated by PTEN deletion, which suggests the involvement of the PI3K pathway. Thereby, Tong et al. [20] showed that metastasis-associated colon cancer protein 1 (MACC1), cellular-mesenchymal epithelial converting factor (METF), and PD-L1 were also elevated in gastrocytomas, suggesting that the PI3K pathway is involved and thus contributes to the survival of the cancer cells. Mesenchymal epithelial transition factor (c-Met) and PD-L1 were significantly up-regulated in colon cancer tissues, and MACC1 regulated the expression of PD-L1 and tumor immunity through the c-Met/AKT/mTOR pathway. Inhibition of c-Met phosphorylation and its downstream cascade reactions, such as Akt phosphorylation and mammalian target of rapamycin (mTOR) phosphorylation, may provide new strategies for the treatment of various cancers. Inhibition of PI3K-related pathways can lead to downregulation of PD-L1 expression in different types of cancers, e.g., in renal cell carcinoma, inhibition of the HGF/c-Met pathway, the upstream of PI3K, can ultimately mediate the downregulation of PD-L1 expression [21]. Up-regulation of PD-L1 protein levels in tumor specimens from patients with glioblastoma multiforme is correlated with PTEN loss [22]. These regulatory mechanisms add new potential targets for immunotherapy.

Table 2. Promotional role of different pathways in immunotherapy of different tumors

Signaling Pathways	Therapeutic drugs	Type of Cancer	References
EGFR/GSK3β	Osimertinib	Non-small cell lung cancer	94
mTORC2/Akt/GSK3β	MTI-31	Non-small cell lung cancer	95
ATR	VE822	Breast cancer	96
PKCα/GSK3β/MITF	SA-49	Non-small cell lung cancer	97
NF-κB/CSN5	Curcumin	Triple-negative breast cancer, Colorectal cancer, Melanoma	98
AMPK	Metformin	Breast cancer, Lung cancer	99
EMT/β-catenin/STT3	Etoposide	Triple-negative breast cancer, Colorectal cancer	100
CMTM6	H1A	Breast cancer, Colorectal cancer	101
HIP1R	PD-LYSO	Colorectal cancer	102

RAS/RAF/MEK/MAPK-ERK pathway

The mitogen-activated protein kinase (MAPK) pathway serves as an important signaling hub that transduces extracellular stimuli into intracellular responses, orchestrating critical cellular processes including proliferation, differentiation, invasion, metastasis, and apoptosis. This phosphorylation-dependent activation system operates through three parallel cascades: c-Jun N-terminal kinase (JNK), p38MAPK, and extracellular signal-regulated kinase (ERK).Evidences have shown that PD-L1 can be regulated by ERK-MAPK pathway in different cancer. In human bronchial epithelial cell carcinogenesis, oncogene KRAS-driven PD-L1 expression is dependent on ERK, and KRAS mutation induces a significant increase in PD-L1 expression, while inhibition of ERK activation significantly reduces the increase in PD-L1 expression in KRAS-mutant cells [23]. Murine sarcoma viral oncogene homolog B1 (BRAF) inhibitor resistance resulted in increased PD-L1 expression in melanoma cells, which is mediated by c-Jun and signal transducer and activator of transcription 3 (STAT3). Meanwhile, the effect of STAT3 can be effectively reversed by mitogen-activated protein kinase (MEK) and the PI3K inhibitor and reduces PD-L1 expression [24,25]. In addition, activation of the RAS/MAPK pathway promotes triple-negative breast cancer immune evasion, and MEK inhibition upregulates MHC and PD-L1 expression on the cell surface, supporting clinical trials of MEK and PD-L1 combination targeting therapy [26]. Thus, combining these pathway factors is instructive both for understanding the mechanisms of tumor growth and for promoting precision immunotherapy.

EGFR pathway

The epidermal growth factor receptor (EGFR) is a transmembrane tyrosine kinase receptor and a member of the ErbB receptor family. Studies have shown aberrant expression of EGFR in many solid tumors [27]. The proliferation, angiogenesis, invasion, metastasis, and apoptosis of tumor cell are associated with EGFR. EGFR is usually mutated in non-small-cell lung cancer (NSCLC) [21]. High expression of PD-L1 is associated with EGFR mutations in NSCLC and is an independent negative prognostic factor for this disease [28]. PD-1 antibody blockade improves the survival of patients with EGFR-driven advanced NSCLC by enhancing effector T-cell function and decreasing the level of pro-tumor cytokines [29]. In another set of studies, Wang et al. [30] reported that EGFR activation induced Snail-dependent epithelial mesenchymal transition (EMT) and myc-dependent PD-L1 expression in human salivary adenoid cystic carcinoma.

In conclusion, the expression of PD-L1 in cancer cells is regulated by a variety of signaling pathways, including, PI3K/AKT, MAPK, and EGFR, etc., and the PD-L1 protein is degraded in the proteasome or lysosome through a variety of pathways, which improves the efficacy of cancer immunotherapy, and the advantages and disadvantages of different pathways for immunotherapy are summarized in Table 2.

Transcription factors regulate PD-L1 expression

Several transcription factors have been shown to regulate PD-L1 expression, including STAT, NF-κB, IRF1, and HIF-α. STAT3 drives tumor progression by dual mechanisms: (1) orchestrating cancer cell survival/proliferation while fostering immunosuppressive oncogenic niches in the tumor microenvironment, and (2) directly modulating PD-L1 expression across malignancies [28,31]. Xiao et al. [32] demonstrated that JAK-STAT pathway inhibition downregulates PD-L1 expression in bone marrow mesenchymal stem cells (MSCs), with IFNAR1 levels governing this immune checkpoint regulation in vitro. In addition, exogenous cellular stress, such as DNA double-strand breaks, can also lead to upregulation of PD-L1 in tumors, dependent on DNA double-strand break-activated STAT1 and STAT3 signaling[33]. NF-κB, a major transcription factor that promotes inflammatory responses and inhibits apoptosis, is activated in a variety of cancers and impairs effective anti-tumor immunity[34]. In the NF-κB family, p65 RelA/p50 is the most representative [35]. It has been shown that PD-L1 can be induced

constitutively by lymphocyte-driven IFN-γ, whereas IFN-γ-induced expression of PD-L1 is dependent on NF-κB. Meanwhile, the PI3K/AKT, STAT3 and c-Jun play a secondary role in IFN-γ-induced PD-L1 expression [36]. Therefore, transcription factor regulatory mechanisms play an important role in anti-PD1/PD-L1 therapy, and an in-depth study of their regulatory mechanisms is of great significance for tending to improve the effects of immunotherapy (Figure 1).

Non-coding RNAs regulate PD-L1 expression

Non-coding RNAs (ncRNAs) are not involved in protein coding, including microRNA (miRNA) and long non-coding RNA (lncRNA), etc., and have important roles in regulating gene expression as well as cell proliferation and apoptosis. MiRNAs can bind to the 3′-UTRs of mRNAs and the coding sequences to regulate gene expression and promote cleavage of mRNA transcripts, leading to their degradation or translational repression. Recent studies have shown that the certain miRNAs that increase PD-L1 expression in tumor cells is one of the major mechanisms of immune escape [37]. Pyzer et al. [38] demonstrated that MUC1 silencing downregulates PD-L1 protein expression in acute myeloid leukemia (AML) cells without altering mRNA levels, through miR-200c/miR-34a upregulation mediating post-transcriptional PD-L1 control. Circ-CPA4 orchestrates dual oncogenic effects in NSCLC by promoting tumor progression (growth, migration, stemness) and chemoresistance while suppressing CD8+ T cell activity within TME, mediated through the let-7 miRNA/PD-L1 axis [39]. Dong et al. [40] reported that miRNA-18a are key upstream regulators of PD-L1 and potential targets for cervical cancer therapy. In conclusion, several miRNAs have been identified to regulate PD-L1 expression by directly or indirectly manners. Direct regulation mainly affects the expression of PD-L1 mRNA by binding to it. The miRNAs that directly regulate PD-L1 expression include miRNA-513 [41], miRNA-34 [42], miRNA-570 [43], miRNA-152 [44], miRNA-200 [45], miRNA-138, miRNA-142-5p, miRNA-424, miRNA-193a, miRNA-133a and miRNA-140/142/340/383 [46]. Indirect regulators mainly refer to miRNAs that indirectly mediate PD-L1 expression by affecting regulatory factors including miR-20b, miR-21, miR-130b and miR-197 [46]. (Figure 1)

Regulation of PD-L1 post-translational modifications

Protein post-translational modifications (PTMs), such as ubiquitination, glycosylation, and phosphorylation, play important roles in the regulation of protein stability, translocation, and protein interactions [19]. PTMs of PD-L1 have become an important regulatory mechanism for tumor immunosuppression, and aberrant changes in PTMs directly affect PD-L1-mediated immune resistance [19]. Protein ubiquitination modifications can mediate substrate protein degradation through the proteasomal degradation pathway, and a variety of ubiquitin ligases (E3s) mediate the degradation of PD-L1, including β-TrCP [47], Cullin 3-SPOP [48], FBXO38 [49], Cbl-b and c-Cb1 [50], etc., whereas deubiquitinating enzymes such as CSN5 [51], USP15 [52], and USP22 [53] could stabilize the expression of PD-L1 protein from proteasomal degradation by deubiquitinating modifications of PD-L1. In addition, glycosylation modification of PD-L1 can also stabilize its protein expression, mainly N-linked glycosylation modification (N-GlcNAc). The half-life of fully glycosylated PD-L1 is approximately 12 h, whereas the half-life of non-glycosylated PD-L1 is only 4 h [19]. The immunosuppressive activity of PD-L1 is tightly regulated by ubiquitination and N-glycosylation. The study of Li et al [54]. revealed that the interaction of GSK3β with PD-L1 induced the degradation of β-TrCP via the proteasome pathway PD-L1, while glycosylation antagonizes GSK3β binding, linking the ubiquitination and glycosylation pathways to the tight regulation of PD-L1. Phosphorylation modifications, on the other hand, are involved in the regulation of PD-L1 stability mainly by modulating the above two modifications (Figure 1).

Tregs and Tumor Immune Evasion Tolerance

The discovery of Tregs by Gershon and Kondo in 1970 [55] laid the foundation for modern immuno-regulation studies. Sakaguchi's seminal identification of CD4+CD25+ Tregs

[56] established these cells as pivotal immunoregulatory players, driving sustained research focus over the past two decades. CD4+CD25+ Tregs cells are specifically characterized by fork-head winged-helix transcription factor (fork-headbox P3, Foxp3). Tregs are ontogenically classified into two subsets: thymus-derived natural Tregs (nTregs) exhibiting homeostatic quiescence, and peripherally induced Tregs (iTregs) [57]. nTregs require stimulus antigens for their expansion, and their inhibitory activity does not require TCR involvement. In contrast, originate from conventional CD4+ T cells (Tconv) both in vivo and in vitro, requiring coordinated signals from antigenic TCR engagement, costimulatory molecules, and cytokines (e.g., TGF-β1, IL-2) to drive their differentiation [58,59]. Tregs maintain immune equilibrium by suppressing effector T cell hyperactivation and preventing immunopathological damage, thereby serving as pivotal guardians of immune homeostasis and self-tolerance (Figure 2).

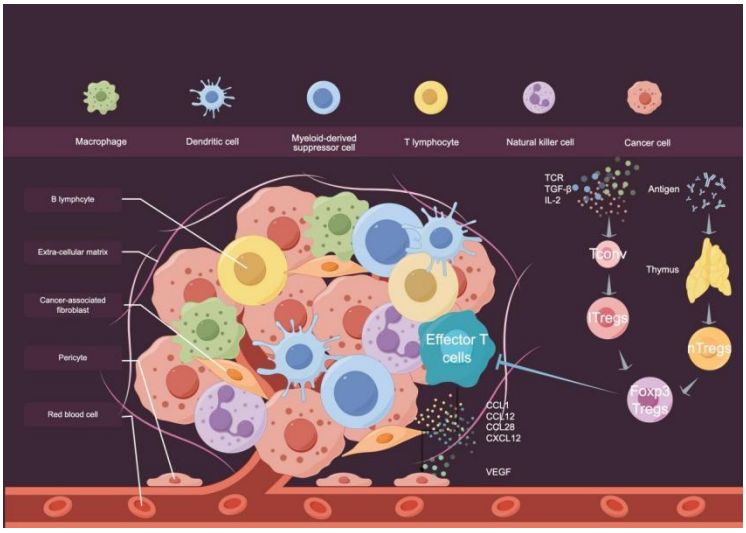

Figure 2. Schematic diagram of the Tregs production and immunosuppression.

The mechanism of Tregs immunosuppression has not been fully elucidated, and it is generally believed that CD4+CD25+Foxp3+Tregs downregulate the immune response through multiple pathways. These include cell contact-dependent inhibition, functional alterations, and immunosuppressive cytokine secretion, etc. Sakaguchi et al. [60] proposed that Treg-mediated suppression may either involve a core suppression mechanism complemented by auxiliary pathways, or alternatively, multiple mechanisms functioning in a coordinated manner. (Figure 2). Treg-mediated immunosuppression contributes to tumor progression through inhibition of antitumor immune responses. Furthermore, elevated Treg infiltration has been consistently observed in tumor tissues compared to adjacent non-tumor tissues [61,62]. As for their origination, Tregs in TME may be enriched by both peri-tumor and local Treg expansion [63]. Tumor-derived soluble mediators, including vascular endothelial growth factor (VEGF) and chemokines (CCL17/CCL22/CCL28/CXCL12), directly induce Treg expansion through paracrine signaling, attracting Tregs to the tumor bed [63]. Tumor-infiltrating Tregs are selectively depleted through an Fc-dependent mechanism, resulting in an increase in CD8+Teffs/Tregs at the tumor site and in peripheral blood65.Tumor-infiltrating CD4+ tissue-resident memory T cells (CD4+Th-TIL) demonstrate canonical tissue-resident memory characteristics [64], while Fcγ receptor-mediated Treg depletion enhances intratumoral CD8+ effector-to-Treg ratios yet elevates peripheral blood Treg populations through compensatory mechanisms [65]. Treg depletion in murine melanoma and colon carcinoma models augments tumor-specific T cell responses, suppresses tumor progression, and potentiates immunotherapy efficacy [66]. Conversely, elevated Treg infiltration correlates with adverse clinical outcomes, establishing Treg-mediated immunosuppression as a critical tumor immune evasion mechanism [67].

Role of Th17 cells in tumor immunity

Th17 cells, defined by their signature IL-17 production (the eponymous effector cytokine), undergo differentiation orchestrated by transcription factor retinoic acid receptor-related orphan receptor gamma-t (RORγt) and STAT3 activation, requiring specific cytokines [68]. A large number of studies have shown that IL-17 plays an important role in promoting tumor growth and invasion [69]. TME stromal components generate various chemokines that recruit Th17 cells through cytokine crosstalk [70]. While Th17 cells facilitate stromal infiltration of myeloid

populations (Macrophages/DCs) and lymphoid subsets (NK/memory T cells) by CCL2/CCL20, but these cells do not necessarily exert direct antitumor effects [71]. Meanwhile, Th17-derived chemokines drive coordinated CD8+ cytotoxic T lymphocyte recruitment and clonal expansion via paracrine activation circuits [71].

As shown above, Th17 cells promote both antitumor immunity and tumorigenesis [72, 73]. In terms of pro-tumorigenic activity, IL-17A exhibits dual oncogenic activity, driving tumor cell proliferation via autocrine/paracrine loops (produced by both Th17 cells and cancer cells) [72]. Mechanistically, it induces VEGF-mediated neovascularization and stimulates MMP-9-dependent metastatic cascades through tumor-stromal crosstalk [72, 73]. Conversely, emerging evidence indicates Th17 cells enhance antitumor immunity and patient survival. In B16 melanoma murine models, adoptive transfer of tumor-specific Th17 cells demonstrated potent CD8+ T cell activation, critical for antitumor efficacy, mediated through IL-17-driven inflammatory cascades [70]. Th17 polarization in pancreatic cancer murine models significantly attenuates tumor progression and extends survival [74]. While substantial evidence demonstrates Th17-driven facilitation of oncogenesis through invasion and neovascularization, emerging data confirm its paradoxical duality in coordinating antitumor immunity, a critical determinant of clinical survival outcomes across experimental and human studies. Cantini et al. reported a biphasic effect of Th17 cells using a mouse glioma model [75]. In summary, the Th17 response may be diverse, and it may play different roles for different targets. At present, the research data on the mechanism of Th17 cell production and regulation in tumors are still limited, and the experimental results are inevitably contradictory and need to be further investigated.

Association between PD-1/PD-L1 pathway, Tregs and Th17 cells in tumor immunity

PD-1/PD-L1 blockers can play a therapeutic role in targeting immune changes induced by the tumor

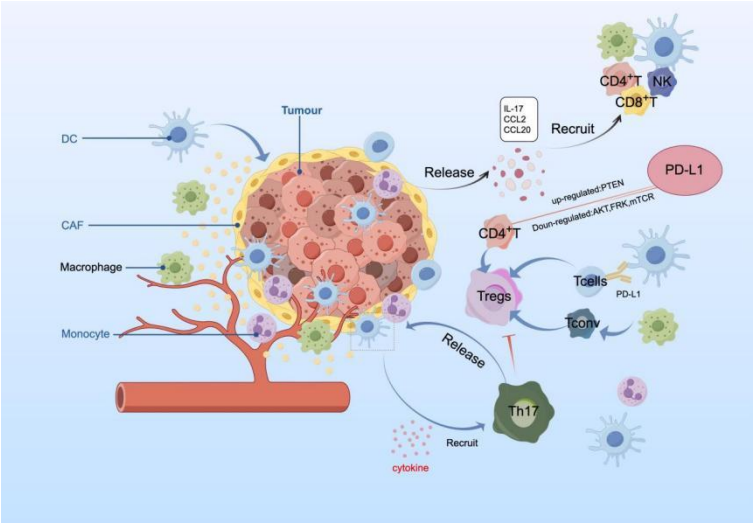

Figure 3. Schematic representation of the association between the PD-1/PD-L1 pathway, Tregs and Th17 cells in the tumor immune microenvironment.

microenvironment and help to restore tumor immunity (Figure 3). PD-1/PD-L1 blockade potentiates tumor-specific T cell cytotoxicity while suppressing IL-10-mediated immunosuppression, thereby amplifying pro-inflammatory cytokine networks and Teffs dominance over Tregs within tumors [76]. Notably, Tregs co-express PD-1/PD-L1, forming a self-reinforcing tolerance circuit through bidirectional checkpoint signaling [76]. PD-L1 can drives CD4+ T cell conversion to Tregs via PTEN upregulation and AKT/ERK2/mTOR axis inhibition. Interactions between PD-L1-expressing DCs and T lymphocytes can also promote Tregs development [77]. Tumor-associated macrophages (TAMs) promote the conversion of Tconv to Tregs, contributing to the accumulation of Tregs in tumors, and enhancing the expression of PD-1 on CD4+ T cells [78]. The lack of PD-L1 in APCs led to a decrease in the production of Tregs in CD4+ T lymphocytes. Francisco et al. [77] demonstrated that PD-L1 induces iTregs cell differentiation, maintenance, and functional activity through sustaining and upregulating Foxp3 expression in these regulatory T cells. Furthermore, stimulation of T lymphocytes with PD-L1-Ig significantly enhanced both Foxp3 expression levels and the immunosuppressive capacity of Treg populations [77]. This suggests that the PD-1/PD-L1 axis plays a key role in regulating the development and function of Tregs and that the PD-1 signaling pathway is also important for

maintaining Tregs suppression. Detection of peripheral blood Tregs/CD4+ T cells can be used to predict tumor immunotherapy efficacy and survival benefit [79-81].

Both Tregs and Th17 cells exhibit phenotypic plasticity. Notably, Th17 cells activated under specific conditions can downregulate IL-17 production while upregulating IFN-γ secretion in response to inflammatory cues, thereby acquiring Th1-like characteristics. These transitional cells, termed ex-Th17 cells, may contribute to autoimmune exacerbation and antitumor immune modulation through this functional reprogramming [82]. Notably, Treg populations demonstrate selective immunosuppressive capacity, effectively suppressing classical Th1 and Th17 cell proliferation while sparing ex-Th17 cell subsets [83]. Under cytokine stimulation, Tregs can undergo phenotypic reprogramming to reacquire Th17-like effector functions. Conversely, the reciprocal acquisition of Treg-like regulatory properties by Th17 cells remains poorly characterized. This reciprocal plasticity highlights novel therapeutic targets for modulating Th17-Treg dynamics in cancer immunotherapy. Emerging evidence indicates IL-17 signaling and Th17-derived cytokines critically influence both therapeutic outcomes and immune-related adverse events during checkpoint blockade therapy in oncology patients [84].

Meanwhile, irAEs frequently manifest alongside antitumor immunity, potentially mediated by IL-17-driven inflammatory pathways. Critical knowledge gaps persist regarding Th17 cell contributions to ICIs pharmacodynamics, particularly their dual roles in therapeutic efficacy. Current evidence suggests that achieving immune homeostasis represents a central challenge in immunotherapy. Therapeutic targeting of the Th17/Treg axis shows promise for simultaneously amplifying tumor-specific immunity while mitigating off-tissue damage through precision modulation of this cytokine-regulated equilibrium [84].

CONCLUSION

Among the many strategies for tumor therapy, the emergence of PD-1/PD-L ICIs has further clarified the importance of the PD-1 pathway in regulating the peripheral immune tolerance of the body. It is important to note that despite the clinical success of applying monoclonal antibodies to block PD-L1/PD-1-mediated immunosuppression in many tumors, blocking the PD-L1/PD-1 pathway is not sufficient to restore anti-tumor immunity in many cases due to a variety of factors, such as the presence of other immune checkpoints, that also promote tumor immune escape, and, as a result, a better understanding of PD-L1 regulation and its mechanisms will provide a basis for targeted therapy combined with immune checkpoint inhibitors, and provide a more effective and precise means to address tumor immune escape. Meanwhile, successful blockade of the PD-1 pathway is the key point of this immunotherapy, and the achievement of this blockade may be related to the enhancement of T cell immunity after releasing T cell inhibition, or it may be caused by interfering with the production or function of Tregs cells, and the specific mechanism is not clear. There is a complex correlation between the PD-1/PD-L1 pathway and the Tregs in the progression of the tumors and in the treatment, and the ratio and phenotype of Tregs have the potential to be biomarkers for predicting the therapeutic response of PD-1/PD-L1 antagonists. In addition, the Th17/Treg equilibrium plays a crucial role in preserving systemic immune homeostasis, suggesting that interventions targeting this axis could substantially influence clinical outcomes in oncology. While Th17 cells and associated cytokines exhibit dual roles in both tumor promotion and suppression, their precise mechanisms remain elusive. Furthermore, the temporal dynamics of Th17-mediated tumor immunity across distinct stages of carcinogenesis require systematic investigation. The functional duality of Th17 cells in tumor immunity warrants continued investigation across distinct phases of tumor progression. Advancements in immunotherapy research hold promise for elucidating Th17-mediated mechanisms, potentially refining immune-mediated cancer control strategies.

DECLARATIONS OF INTEREST

None.

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AUTHOR CONTRIBUTIONS

Rongxian Cao: Conceptualization; Project administration; Writing - original draft; and Writing - review & editing.

Hui Zang: Conceptualization; Project administration; Supervision; Writing - review & editing.

DATA AVAILABILITY STATEMENT

Not applicable

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