Review Article

The role of the programmed cell death protein-1/programmed death-ligand 1 pathway, regulatory T cells and T helper 17 cells in tumor immunity: a narrative review

Lanfang Zhang^, Mingjuan Zhang, Jinxiu Xu, Shan Li, Yu Chen, Wenjing Wang, Juntian Yang, Shengyun Li, Meiling Gu

Department of Chemotherapy Unit 2, Weihai Municipal Hospital, Cheeloo College of Medicine, Shandong University, Weihai, China

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Correspondence to: Lanfang Zhang, PhD. Department of Chemotherapy Unit 2, Weihai Municipal Hospital, 248 Tongyi Road, Weihai 264200, China. Email: zlfxueye@163.com.

Abstract: Tumor immunotherapy, especially that involving programmed cell death protein-1 (PD-1)/programmed death-ligand 1 (PD-L1) immunosuppressive checkpoint inhibitors, has become an important part of tumor treatment strategy in the past decade. Blocking PD-1/PD-L1 signaling pathway can reduce the inhibitory effect of PD-1 pathway on T cells, promote the anti-tumor activity of activated T cells, and prolong the remission period of tumor. While PD-1/PD-L1 immunotherapy is effective in the treatment of solid malignant tumors, it also has shortcomings, due to the complexity of the tumor microenvironment (TME). Regulatory T cells (Tregs) and T helper 17 (Th17) cells play an important role in the TME and are closely related to the occurrence and development of tumors. Tregs can inhibit the anti-tumor immune effect, while Th17 cells play a dual role in tumor immunity, which not only promotes tumorigenesis but also promotes anti-tumor immunity. In the occurrence and development of tumor, PD-1/PD-L1 pathway, Tregs and Th17 cells are interrelated. However, the complicated relationship between the PD-1/PD-L1 pathway, Tregs, and Th17 cells has not been fully clarified. Here, we summarize the immunoregulation mechanisms and discuss the crosstalk between the PD-1/PD-L1 pathway, Tregs, and Th17 cells, with the aim of providing novel insights for future cancer treatment.

Keywords: Tumor; programmed cell death protein-1 (PD-1)/programmed death-ligand 1 (PD-L1); T helper 17 cells (Th17 cells); regulatory T cells (Tregs)

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Introduction

The emergence of immune checkpoint inhibitor (ICI)-targeted immunotherapy has greatly and successfully changed the treatment landscape for several advanced malignant tumors. The mechanism of immunocheckpoint blockers is different from chemotherapy and targeted therapy. The mechanism of ICI is targeted at tumor immune response, which can prolong the remission period after treatment. Programmed cell death protein-1 (PD-1)/programmed death-ligand 1 (PD-L1) blocker is the most widely used ICI in clinical practice. It breaks the immune tolerance of the body to tumor by blocking the PD-1/PD-L1 pathway and effectively enhances the anti-tumor

^ ORCID: 0000-0003-3159-9004.

immunity.

The interaction between PD-1 and PD-L1 plays a role in the regulation of both regulatory T cells (Tregs) and T helper 17 (Th17) cells. As an important type of suppressive immune cell in the TME, Tregs have crucial involvement in the occurrence and development of tumors. The number and function of Tregs and Th17 cells influence the blocking effect of PD-1/PD-L1 inhibitors and are vital to tumor development. Meanwhile, Th17 cells in TME play a dual role in tumor development. The roles of the PD-1/PD-L1 pathway, Tregs, and Th17 cells in tumor occurrence and development are intertwined; however, this complex relationship has yet to be fully explored. Herein, we summarize the immunoregulation mechanisms of the PD-1 pathway, Tregs, and Th17 cells, and examine the crosstalk between the three in tumor progression. We present the following article in accordance with the Narrative Review reporting checklist (available at http://dx.doi.org/10.21037/atm-20-6719).

The PD-1/PD-L1 pathway and tumor immune escape

PD-1, which belongs to the immunoglobulin superfamily, is a 288 amino-acid membrane protein and an important immunosuppressive molecule. PD-1 was originally cloned from the apoptotic mouse T cell hybridoma 2B4.11 (1). It's binding leads to cell cycle blockade but not cell death. PD-1 is expressed on multiple immunocytes, including activated T cells, B cells, natural killer cells (NKs), monocytes, and dendritic cells (DCs) (2,3). The expression of PD-1 on the surface of activated T cells occurs during the initial activation phase.

PD-1 recognizes two ligands, PD-L1 and programmed death-ligand 2(PD-L2, B7-DC or CD273). PD-L1 is expressed by a wide range of cells, including T cells, B cells, Tregs, antigen-presenting cells (APCs), vascular endothelial cells, mesenchymal stem cells, reticular fibroblasts, and islet cells. PD-L1 has also been detected in immune privilege sites such as the eyes, placenta, and testes (4). Moreover, PD-L1 is highly expressed on tumor cells. Compared with PD-L1, the expression range of PD-L2 was narrower, mainly in macrophages and dendritic cells. The PD-L1/PD-1 signaling pathway has been identified as a contributor to tumor immune escape (5,6). The C and N-terminal amino acid residues of the intracellular domain of PD-1 have two independent phosphorylation sites: the immunoreceptor tyrosine-based inhibitory motif (ITIM) and the immunoreceptor tyrosine-based switch motif (ITSM) (7). ITSM plays an important role in the immunosuppression of PD-1. The combination of PD-1 and PD-L1 can phosphorylate ITSM and activate intracellular pathways, which ultimately plays an immunosuppressive role. The inhibition mechanism of PD-1 / PD-L1 pathway on T and B lymphocytes is different (6). When PD-1 binds to PD-L1 in T cells, SHP-1/2 molecules are recruited into the C-terminal ITSM to dephosphorylate TCR activation signaling and inhibit the downstream PI3K/AKT pathway, thereby reducing the expression of apoptosis-related genes and inhibiting the cytokine secretion by T lymphocytes (8). Further, the PD-1/PD-L1 pathway can influence the Ras-ERK pathway to inhibit T-cell proliferation (9). In B cells, PD-1 also shows an inhibitory effect. PD-1 can inhibit the B cell activation and weaken the immune response of B lymphocytes to antigens. Following PD-1 activation, SHP-2 molecules are recruited to the C-terminal of PD-1 to dephosphorylate BCR signaling molecules, such as Igα/β or SγK, therefore desphosphorylating ERK, PI3K, and PLCγ2, leading to acute Ca2+ disorder and the stagnation of B-cell growth (10,11).

The binding of PD-1 to its ligands triggers inhibitory signals involved in the regulation of central and peripheral tolerance through the inhibition of T-cell proliferation, cytokine synthesis, and cytotoxic activity (12). PD-1/PD-L1 pathway regulates and maintains the tolerance of peripheral CD4 + T cells through a variety of ways, such as maintaining the stability and integrity of lymphocytes. Increasing evidence from animal models and clinical data shows that PD-1 plays an important role in limiting anti-tumor T cell responses. After the expression of the PD-L1 gene, tumorigenesis and invasiveness are also be enhanced in vivo. In many cancers, the abnormal expression of PD-L1 in tumor cells is related to immune escape, which indicates that the structural differences of PD-L1 are crucial to the development of tumors (13). PD-L1 may participate in cancer cell apoptosis through two mechanisms: congenital resistance and adaptive resistance. Overexpression of PD-L1, promoted by oncogenic and constitutive activation signals, can trigger innate (tumor cell innate) resistance (14-18). PD-L1 is not only expressed in tumors, but is also expressed in immune cells (macrophages, DC, myeloid suppressor cells, and lymphocytes) of the TME through inflammatory signaling, which is considered as adaptive resistance (19,20). Previous studies have shown that the expression of PD-L1 is related to an enhanced anti-tumor immune response, which is associated with improved

prognosis in tumor patients.

PD-1/PD-L ICI therapy can restore the number of effector T cells (Teffs), promote their cytotoxic immune response against chemotherapy-resistant tumors, restore the activity of CD8+ T cells depleted in chronic viral infection (21), promote the synthesis of pro-inflammatory cytokines, and restore sustained immunity to tumors (22-25). ICI therapy can enhance the body's natural defense against tumors by promoting a T-cell-specific immune response. ICI therapy has lower toxicity than standard chemotherapy, but it can also result in immune-related adverse events (irAEs). After blocking the immune checkpoint, the immune tolerance will change and induce iraes. In long-term immune activation, the misdirected stimulation of the immune system toward a normal tissue can lead to autoimmune-like or inflammatory side effects. Even after anti-PD-1 antibody treatment is stopped, delayed autoimmune toxicity can even occur as time passes. Therefore, in view of the rapid increase in the number of patients receiving treatment with anti-PD-1 agents, long-term follow-up is necessary in order to observe the possible delayed adverse reactions after treatment. There is no unified standard for the upper limit of the duratio16n of ICI use except for the occurrence of disease progression, intolerance or death of patients, and the optimal treatment time of ICI is still an outstanding issue.

Tregs and suppression of antitumor immunity

In 1970, Gershon and Kondo discovered a suppressor T cell population that could down-regulate the immune response (26). Owing to the observations of Sakaguchi's group (27), CD4+CD25+ Treg cells have been one of the most important research focuses in the field of immunology in the last 20 years. The transcription factor fork-head box P3 (Foxp3) is specifically expressed in CD4+CD25+Treg cells. Based on the developmental process, Tregs have been categorized into two major groups: natural Tregs (nTregs) and inducible Tregs (iTregs) (28). nTregs are generated in the thymus and are mitotically quiescent in basal conditions (29). The expansion of nTregs requires antigen stimulation, while TCR engagement is unnecessary in the inhibitory activity of nTregs (30). In contrast, iTregs develop from conventional CD4+ T (Tconv) cells in the periphery and can be generated in vitro. Antigenic TCR stimulation, costimulatory molecules, and cytokines, such as transforming growth factor-beta 1 (TGF-β1) and Interleukin-2 (IL-2), promote the development of iTreg cells (31-33). Tregs inhibit T-cell immunity and avoid the damage caused by T cell overactivation. Therefore, Tregs plays an important role in maintaining immune homeostasis and self-tolerance (34).

FoxP3+Tregs were reported to significantly inhibit the activation, proliferation and/or effector functions of other CD4+ ,CD8+ T cells, NK-like cells, NK T cells, B cells and DCs (35). The immunosuppressive mechanism of Tregs is not fully understood. CD4+CD25+Foxp3+Tregs are generally believed to down-regulate immune responses in multiple ways. This includes cell contact-dependent suppression, functional modification (36,37) and the secretion of immunosuppressive cytokines (38). Sakaguchi *et al.* suggested that each type of Treg may have a common core inhibition mechanism or several other complementary mechanisms (39). Another possibility is that multiple inhibition mechanisms coordinate and cooperate with each other. Therefore, the dysfunction of certain pathways may not be enough to seriously affect immunosuppression. There is increasing evidence to suggest that the immunosuppressive functions of Tregs promote tumor progression by inhibiting anti-tumor immunity (40). The infiltration rate of Tregs in tumor tissues has been found to be higher than that in adjacent tissues (41-43). The enrichment of Tregs in tumor tissues can be achieved by recruitment of Tregs around the tumor and local expansion of Tregs themselves (44). Some soluble molecules in the tumor immunosuppressive microenvironment can also promote Treg expansion (44,45). Tregs are attracted to the tumor bed by vascular endothelial growth factor (VEGF) or chemokines (such as CCL17, CCL22, CCL28, and CXCL12) secreted by tumor cells or immune cells (44,46). Tumor-infiltrating Tregs were reported to be selectively depleted through Fc-dependent mechanisms involving Fcγ-receptor-expressing macrophages within the TME, resulting in an increase in the ratio of CD8+ Teffs/Tregs at tumor sites and Tregs in peripheral blood (47,48). In mouse models of melanoma and colon cancer, a reduction in Tregs can increase the response of anti-tumor T cells and reduce tumor growth (49,50). Treg depletion can improve anti-tumor immunity and enhance the curative effect of tumor treatment. Moreover, a high proportion of Tregs is associated with poor prognosis, suggesting that Treg-mediated T-cell suppression is an important mechanism for tumor cells to escape the immune response (51-53).

Role of Th17 cells in cancer progression

Th17 cells are a subset of T cells that produce IL-17 which is the most important effector produced by Th17 cells and is also the source of Th17 nomenclature. Their differentiation process is controlled by the transcription factors orphan nuclear receptor gamma t (RORγt) and signal transducer and activator of signal transducer and activator of transcription 3 (STAT3) and requires exposure to various cytokines (54,55). A number of studies have demonstrated the important role played by IL-17 in the promotion of tumor growth and invasion (56-61). Tumor-associated cells and fibroblasts secrete a large number of cytokines, and the pro-inflammatory cytokine-rich environment can recruit Th17 cells to the TME (62). Th17 cells in the TME can promote the influx of monocytes/macrophages, DCs, NKs, memory CD4+ and CD8+ T cells through the secretion of the chemokines CCL2 and CCL20 (63,64); however, these cells may not have a direct anti-tumor effect. Moreover, Th17 cells not only recruit CD8+ cytotoxic T cells, but also promote their activation and expansion (63,64).

It is clear that Th17 cells play a multiple role in tumor immunogenicity, promoting both anti-tumor immunity and tumorigenesis (63,65-70). IL-17A has been found to promote tumor cell growth and proliferation. IL-17A can be produced by both Th17 cells and tumor cells (67). IL-17A promotes angiogenesis by stimulating tumor cells to produce VEGF and promotes tumor invasion and metastasis through matrix metalloproteinase-9 produced by tumor and other cells (67-70). Several recent reports have suggested that Th17 responses may have a therapeutic benefit in improving anti-tumor immunity and survival. In a B16 mouse model of melanoma, adoptive T-cell therapy with tumor-specific Th17 cells prompted strong activation of tumor-specific CD8+ T cells (which are required for an anti-tumor effect), indicating that Th17-driven inflammation can play a key role in anti-tumor immunity (71). The induction of Th17 responses in mouse pancreatic cancer models has also been shown to delay tumor growth and improve survival (63). Based on experimental evidence, there is little doubt that Th17 responses can drive tumor progression, invasion, and angiogenesis. On the other hand, it is also obvious from experimental models and clinical studies that Th17 responses can support strong anti-tumor immunity and benefit patient survival. Cantini *et al.*, also using a mouse glioma model, reported a biphasic role of Th17 cells (67). Th17 reactions may be heterogeneous, and different effector functions may produce different results. Currently, the regulation mechanism of Th17 cells in tumors is still limited, and the experimental results are inevitably contradictory; consequently, further study is needed.

Crosstalk between PD-1/PD-L1, Tregs, and Th17 cells in tumors

PD-1/PD-L1 blockers can target the immune changes caused by the TME and recover tumor immunity. PD-1/PD-L1 inhibitors have a variety of functions, such as enhancing the cytolytic activity of tumor specific T cells, reducing the production of IL-10, promoting the synthesis of pro-inflammatory cytokines, promoting the existence of TEFs, and reducing the number and inhibitory function of Tregs in tumor site (24,25,72,73). Francisco *et al.* showed that PD-L1 could convert naive CD4+ T cells to Tregs through the simultaneous upregulation of gene of phosphate and tension homology deleted on chromosome ten (PTEN) and downregulation of AKT, ERK2, and Mtor (74). Tregs express PD-1 and PD-L1, which plays a role in the regulation of T cell tolerance (75). Although the PD-1/PD-L1 signaling pathway has been found in Foxp3+ Tregs, the role of PD-1/PD-L1 in regulating Treg function and activity has not been fully elucidated (76). The interaction between PD-L1-expressing DCs and T lymphocytes promotes Treg development (77). Francisco *et al.* reported that PD-L1 induced the differentiation, maintenance, and function of iTreg cells by sustaining and increasing their expression of Foxp3 (74). In the presence of PD-L1-Ig, Foxp3 expression and inhibitory Treg function were found to be increased following the activation of T lymphocytes (74). Furthermore, PD-1/PD-L1 binding was shown to reduce T cell production, cytokine release, and survival. These results suggest that the host environment and PD-1 signaling may play an important role in the regulation of Treg development and function. Raimondi *et al.* observed that the regulated compartmentalization of PD-1 discriminates CD4+CD25+ resting Tregs from activated T cells (78). The PD-1 signaling pathway is also important for maintaining Treg inhibition. Compared with PD-1^{hi}CD4+ Tregs, PD-1^{low}CD4+ Tregs showed a higher ability to induce B-cell apoptosis and to inhibit CD4+ helper T cells (Th) (79).

Both Tregs and Th17 cells are thought to have potential plasticity. When Th17 cells are activated under certain conditions, they may lose the ability to secrete IL-17 and obtain the ability to secrete IFN-γ in the role

of pro-inflammatory signal. In doing so, they will gain characteristics similar to those of Th1 cells, also known as ex-th17 cells, which may play a role in enhancing autoimmunity and anti-tumor immunity (80). Interestingly, Tregs can inhibit the proliferation of classical Th1 and Th17 cells, but not that of ex-Th17 cells (81). Under the influence of cytokine, Tregs are able to reacquire Th17-like characteristics. Conversely, the transition to Th17 cells acquiring Treg-like characteristics has not been well described. Tumor-infiltrating cells that produce IL-17 and are Foxp3-, transdifferentiate into IL-17A^{neg}Foxp3+ cells, termed "ex-Th17 Tregs" (81). Tumor-associated conversion between Th17 and Treg cells provides insights for targeting the dynamic change of Th17-Treg cells in cancer immunotherapy.

Recent studies have shown that IL-17 and Th17 cells may play an important role in the efficacy and toxicity of checkpoint-blocking therapy in cancer patients (82). The anti-tumor response is mostly related to autoimmune toxicity, which may be related to the level of IL-17. The role of Th17 cells in checkpoint-blocking therapy has not been fully elucidated. The ultimate goal of immunotherapy is to decouple toxicity from persistent anti-tumor immunity. In future, the Treg/Th17 axis may be effectively regulated to enhance tumor immune function and reduce adverse immune reactions in healthy tissues.

Conclusions

The emergence of PD-1 blockers as cancer treatment strategies highlights the importance of understanding the role of PD-1 in the regulation of peripheral tolerance. It has been unclear whether most of the success of PD-1 blockers is attributable to the elimination of inhibitory effects of T cells, thereby enhancing the immunity of T cells, or to interference with the generation or function of Treg cells, which undermines the potential mechanisms of tumor immune escape. The PD-1 pathway and Tregs have a complex association in the progression and treatment of tumors. The proportion and phenotype of Tregs may serve as biomarkers for predicting the clinical efficacy of PD-1/PD-L1 antagonists. Additionally, the balance between Th17 cells and Tregs is essential for maintaining immune balance in vivo. Treatment of the Treg/Th17 axis may have a profound impact on the survival of cancer patients. Th17 cells and related cytokines not only promote tumor occurrence, but also inhibit tumor growth. Although the related mechanism has not been determined, the exploration of Th17 cells in tumor immunity at different stages of tumor development is still of research value. Future research in the field of immunotherapy may provide new insights into tumor regression, further improving our ability to use the immune system in the fight against cancer.

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Footnote

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