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REVIEW



# Research progress in the PD-1/PD-L1 pathway and IL-17A in lymphomas

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## Abstract

In recent years, the tumor microenvironment has become the focus of immunotherapy in patients with lymphoma, especially with increasing age. The programmed death 1 (PD-1) and programmed death 1 ligand (PD-L1) signaling pathway is an important mechanism of cancer immunomodulation, and abnormal activation in the tumor microenvironment shows that the PD-1/PD-L1 pathway may take part in the regulation of tumor immune escape. Interleukin-17A (IL-17A) is a pro-inflammatory cytokine that plays a crucial role in the lymphoma cancer microenvironment and has divided roles in both tumor growth and cancer elimination. Thus IL-17A is a potential target in cancer immunotherapy. Previous studies have shown that IL-17A up-regulates the expression of PD-L1 in cancers or in autoimmune diseases but whether there is an interaction or relationship between the PD-1/PD-L1 pathway and IL-17A in lymphoma has not yet been fully recognized. The aim of this review is to track the recent progress of the PD-1/PD-L1 pathway and IL-17A in lymphoma. A better understanding of the role of the PD-1/PDL1 pathway and IL-17A in the progression of lymphoma will help provide new therapeutic directions, especially in older patients.

**Keywords:** PD-1/PD-L1, IL-17A, lymphoma, tumor microenvironment, aging, immunotherapy

## Introduction

Lymphoma is a prevalent hematologic malignancy worldwide. In recent years, treatments for some types of lymphomas have been introduced, but relapsed or refractory lymphomas remain common and challenging. This situation has increased efforts to seek new treatments for lymphomas. One promising therapeutic target is programmed cell death protein 1 (PD-1), a receptor protein that is expressed by activated T cells, monocytes, macrophages, dendritic cells (DCs), natural killer (NK) cells, and B lymphocytes [1], and is especially overexpressed by tumor-specific T cells [2].

Normal antigen-presenting cells, macrophages, and dendritic cells express PD-1 ligands that combine with PD-1 receptors found on activated T cells. PD-1 is only expressed on the surface of activated T lymphocytes and not in resting T cells; therefore, it is a useful activation marker for T cells. Tumor cells overexpress programmed death 1 ligand (PD-L1), which then interacts with PD-1 ligands to activate the PD-1/PD-L1 signal pathway. This activation can suppress T cell function, thereby reducing the T cell to a dysfunctional state called exhaustion. This allows tumor immune escape and causes tumors to be highly refractory to conventional chemotherapy.

Previous studies have shown that the expression of PD-L1 predicts a worse outcome and is related to poor survival in patients with malignant lymphoma [3-6]. Cancer cells are capable of evading immune surveillance by the PD-1/PD-L1 signal pathway by 1) suppressing tumor-infiltrating lymphocyte activation and inducing cell apoptosis; 2) suppressing the production of cytotoxic T lymphocyte (CTL) granular enzyme and perforin; 3) inducing the secretion of inflammatory cytokines, such as IFN-γ, TNF-α, and IL-2, and enhancing the secretion of the immune inhibitory cytokine IL-10, 4) causing stagnation of the T cell cycle and accumulation of cells in the G0/G1 phase; and 5) promoting tumor cell epithelialization, tumor invasion, and metastasis [7]. The PD-1/PD-L1 signaling pathway now serves as a target for immunotherapy, and a broad range of anti-PD-1/PD-L1 antibodies that target its molecular mechanism is used as cancer cures.

Interleukin-17 (IL-17, also known as Interleukin-17A (IL-17A) and originally termed CTLA8) is produced by Th17 cells, γδT cells, NK cells, and CD8 T cells in the cancer

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microenvironment [8]. IL-17A is the prototypical member of the IL-17 family of pro-inflammatory cytokines and is the most extensively researched member of the IL-17 family [9, 10], as it plays a vital role in tissue inflammation and in the pathogenesis of many autoimmune diseases [11]. Despite extensive study in the field of inflammation, little is known regarding the presence and role of IL-17A in cancers. In the past decades, many studies have reported that IL-17A plays a dual role as both a tumor promotor and a tumor suppressor, and this duality may be related to the differences in the complex tumor microenvironment, tumor types, tumor development processes, tumor etiology, and tumor sensitivity to chemotherapeutic drugs.

In this context, IL-17A has also become one of the critical research hotspots in the field of lymphoma in recent years. IL-17A promotes tumor development in lymphoma and can even lead to drug resistance [12-14]. Past studies have reported that IL-17A enhances the expression of PD-L1 in many tumors and in autoimmune diseases [15, 16], but research on lymphoma is lacking. We have hypothesized that a relationship or interaction exists between the PD-1/PD-L1 signal pathway and IL-17A in lymphoma [17, 18]. The aim of the present review was therefore to provide a better understanding of the roles of PD-1/PDL1 and IL-17A in lymphoma to prompt new therapeutic ideas for the future treatment of this hematologic cancer.

## Expression and regulation of PD-1/PD-L1 in lymphoma

Zhang *et al*., using the TCGA and GTEx databases, found that all B7 family members, including B7-H5, were highly expressed in diffuse large B cell lymphoma (DLBCL), showing that the B7 family may play important roles in lymphoma immunization [19]. PD-L1 is not only expressed in DLBCL cancer cells but also in cancer-infiltrating non-malignant cells. Andorsky *et al*. showed that PD-L1 is highly expressed in Hodgkin lymphoma (HL) and anaplastic large cell lymphoma (ALCL), and many poor-prognosis DLBCLs originate from the activated B cell/non-germinal center B cell subtype and that PD-L1 suppresses the activity of tumor-associated T cells [20].

The mechanism of PD-1/PD-L1 expression is complex and is influenced by various factors. PD-1/PD-L1 expression plays vital roles in propagation, immigration, evasion, drug resistance, and immune evasion in lymphoma.

### Activation of the MEK/ERK, MAPK, and JAK/STAT pathways affects the expression of PD-1/PD-L1

In anaplastic lymphoma kinase (ALK)+ ALCL cells, the expression of PD-1 was inhibited by blocking the extracellular signal-regulated kinase (ERK) signal pathway and was upregulated by augmentation of ERK activity [21]. These responses suggested that PD-1 expression in ALCL is regulated by the ERK signal pathway [21]. The expression of PD-L1 can be enhanced by overexpression of the EBV-driven latent membrane proteins (LMP1 and LMP2) that activate the pro-proliferative nuclear factor (NF-κb)/mitogen-activated protein kinases (MAPK) signaling pathway [22]. The infiltrating macrophages associated with lymphoma are induced to express PD-L1 and PD-L2 by the IL-27/ signal transducer and activator of transcription 3 (STAT3) signal pathway [23]. Some chemotherapy drugs can upregulate PD-L1 expression in DLBCL cells in part through the promotion of the p-STAT3 pathway [24]. Song *et al*. have demonstrated that STAT3 activation confers high PD-L1 expression in natural killer/T cell lymphoma (NKTL) tumors and may enhance tumor immune evasion [25].

### Copy number alterations (CNAs) in chromosome 9p24.1 enhance PD-L1 expression

Chromosomal abnormalities (including chromosomal amplification, polysomy, gain, or translocation) of 9p24.1, which encodes the PD-L1 and PD-L2 proteins and Janus kinase 2, have been reported to lead to the overexpression of PD-L1 and PD-L2 [26]. Several previous studies have reported that the amplification of chromosome 9p24.1 enhances the abundance of both PD-L1 and its inducer, JAK2, in the related diseases of nodular sclerosing Hodgkin lymphoma and primary mediastinal large B cell lymphoma [27]. The JAK2 signal pathway also further strengthens PD-L1 expression in cell lines with 9p24.1 amplification [27]. As such, the CNAs of 9p24.1 in lymphomas provides a chance to examine the efficacy of immune checkpoint inhibitors targeting PD-1, as these inhibitors have shown effectiveness in the treatment of relapsed/refractory lymphomas [28].

### PD-L1 expression is induced by inflammatory factors (e.g., IFN-γ, IL-27, and IL-1α)

Duffield *et al*. demonstrated that, in addition to the known enhancement of PD-L1 expression by IFN-γ in DCs and monocytes, IL-27 and IL-1α can also increase the expression of PD-L1 in different immune cell subsets [29]. Chen *et al*. reported that PD-L1 expression could be induced in the tumor immune microenvironment by multiple cytokines, including IFN-γ , IL-1α, IL-10, IL-27, and IL-32γ, through different signaling mechanisms [29, 30].

## Application of PD-1/PD-L1 inhibitors in lymphoma treatment

In the past, the main treatment approaches for lymphomas, especially non-Hodgkin lymphomas, were surgery, radiotherapy, and chemotherapy. Today, a considerable proportion of lymphomas, particularly the aggressive forms, still progress/relapse after treatment. DLBCL is the most general type of non-Hodgkin lymphoma (NHL) in China, accounting for 30–40% of all cases, and it shows strong heterogeneity. The emergence of rituximab has resulted in satisfactory results when combined with chemotherapy, but 30–40% of all cases remain refractory/relapsed [31]. Deepening research on the tumor microenvironment and tumor immune regulation has given immunotherapy a significant role and is gradually finding wide use in lym-

phoma, especially in refractory/relapsed types. Immunotherapy, such as chimeric antigen receptor (CAR) T cell therapy and therapeutic blockade of immune checkpoints (especially the PD-1/PD-L1 checkpoint inhibitor), is a breakthrough in the therapy of malignant tumors [32, 33].

### Current PD-1/PD-L1 antibodies in lymphoma

To date, many types of anti-PD-1 or anti-PD-L1 antibodies have been produced (Table 1). The list from finished clinical trials targeting PD-1/PD-L1 in lymphoma includes anti-PD-1 antibodies (nivolumab [33, 34], pembrolizumab [35-37], geptanolimab [38], camrelizumab [39], tislelizumab [40], sintilimab [41]) and anti-PD-L1 antibodies (avelumab [42], atezolizumab [43], durvalumab [44].)

In classical Hodgkin lymphoma (cHL), NHL, and multiple myeloma, nivolumab is indicated as a breakthrough therapy for treating relapsed/refractory (R/R) patients [33, 45-47]. Nivolumab has also received approval for the treatment of relapsed or progressive cHL after autologous hematopoietic stem cell transplantation. The United States Food and Drug Administration recently approved a monoclonal anti-PD-1 antibody (pembrolizumab) for the treatment of adult and pediatric patients with refractory primary mediastinal large B cell lymphoma or those who have relapsed after treatment [35]. A monoclonal anti-PD-1 antibody (sintilimab) is also used to treat relapsed or refractory cHL and extranodal natural killer/T cell lymphoma (ENKTL) [44, 48].

### Combination of PD-1/PD-L1 antibodies and immunomodulatory drugs

In multiple solid cancer types, therapy that combines CTLA-4 and PD-1 blockers has shown remarkable clinical efficacy, and the discovery of the roles of CTLA-4 and PD-1 in cancer has stimulated concerted efforts to develop cancer immunotherapy treatments [49]. Clinical trials that test the combination of PD-(L)1 or CTLA-4 antibodies with molecular mediators of these pathways are becoming increasingly popular [50]. For example, Ma *et al*. have indicated that the combination of PD-1 and CTLA-4 can increase the effect of cord blood T cells on EBV-induced lymphoma growth in a humanized mouse model of cord blood, suggesting that PD-1/CTLA-4 blockade may be helpful for the treatment of EBV-induced diseases in hu-

**Table 1.** A summary of anti-PD-1 or anti-PD-L1 antibodies for lymphoma treatment.

| Target | Agent | Disease | Combination therapy | Phase study | Efficacy |
|---|---|---|---|---|---|
| PD-L1 | Durvalumab | High-risk DLBCL | R-CHOP | II | Effective |
| PD-L1 | Atezolizumab | RR-MCL/rr-MZL | Obinutuzumab or rituximab | II | Effective |
| | Atezolizumab | RR-FL | Obinutuzumab and bendamustine | Ib/II | Effective |
| | Atezolizumab | NHL/HL | - | I/II | Invalid |
| PD-L1 | Avelumab | RR-ENKTL | - | II | Effective |
| | Avelumab | RR-cHL | - | Ib | Effective |
| | Avelumab | RR-DLBCL | Rituximab/ bendamustine and rituximab | Ib | Effective |
| PD-1 | Nivolumab | RR-FL, RR-cHL | - | I/II | Effective |
| | Nivolumab | RR-DLBCL | - | II | Low overall |
| | Nivolumab | RR-HL, RR-PMBCL | Brentuximab vedotin | I/II | Effective |
| | Nivolumab | RR-DLBCL, RR-FL | Ibrutinib | I/II | Effective |
| PD-1 | Pembrolizumab | RR-PMBCL, RR-HL/ cHL | - | Ib/II/III | Effective |
| | Pembrolizumab | RR-FL | Rituximab | II | Effective |
| | Pembrolizumab | RR-cHL | Gemcitabine, vinorelbine, and liposomal doxorubicin | II | Effective |
| | Pembrolizumab | RR-cHL | Brentuximab vedotin | III | Effective |
| PD-1 | Geptanolimab | RR-PTCL | - | II | Effective |
| PD-1 | Camrelizumab | R/R cHL | - | II | Effective |
| | Camrelizumab | R/R cHL/HL | Decitabine | II | Effective |
| | Camrelizumab | RR-PMBCL | GVD chemotherapy | II | Effective |
| PD-1 | Tislelizumab | R/R cHL | - | II | Effective |
| PD-1 | Sintilimab | R/R ENKTL, R/R cHL | - | II | Effective |

**Note:** MCL/MZL, mantle cell or marginal zone lymphoma; ENKTL, extranodal NK/T cell lymphoma; cHL, classical Hodgkin lymphoma; PMBCL, primary mmediastinal large B cell Lymphoma; NHL, non-Hodgkin lymphoma; PTCL, peripheral T cell lymphoma; GVD, gemcitabine, vinorelbine, and pegylated liposomal doxorubicin; RR, relapsed/refractory; DLBCL, diffuse large B cell lymphoma; FL, follicular lymphoma; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone.

mans. In addition, some evidence supports a greater clinical benefit for the combined use of CTLA-4 antibodies and PD-1 antibodies than for either antibody type alone [51]. Many other clinical trials and pre-clinical tumor model experiments are also ongoing to assess the effect of other combinations of checkpoint proteins and anti-PD-1/PD-L1 antibodies. This approach has expanded from CTLA-4 and PD-1 to include Tim-3, Lag-3, and most recently, TIGIT PD-1/TIM-3, PD-1/LAG-3, and PD-1/TIGIT) [52-57].

### Combination of PD-1/PD-L1 antibodies and chemotherapeutic drugs

Chemotherapy is one of the main tumor treatment methods. It kills tumor cells by inducing DNA damage, cell cycle arrest, and eventually cell apoptosis. The antitumor action of chemotherapeutic drugs is affected by the immune status of patients, which provides ideas for the development of combination regimens using a PD-1/PD-L1 blockade with existing chemotherapeutics. One study has demonstrated an important synergistic effect of a PD-1 inhibitor and various chemotherapeutic drugs, such as cisplatin, cytarabine, etoposide, oxaliplatin, and carboplatin, in the treatment of DLBCL. One interesting finding was that no difference was observed in cytotoxicity between the groups with or without the PD-L1 inhibitor [58]. Smith *et al*. have reported overall and complete response rates of 90% and 77% in DLBCL patients given a combination treatment with the PD-1 antibody pembrolizumab and R-CHOP therapy (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone). Their results showed that the combination of PD-L1 inhibitor and R-CHOP did not increase severe toxicity, nor did it impede the safe delivery of 6 cycles of chemotherapy while providing high efficacy [59]. Wei *et al*. have shown that a combination of PD-1/PD-L1 inhibitors increased the antitumor immune response in DLBCL and that patients given the combined treatment had longer survival than those given the chemotherapy drug or the PD-1/PD-L1 inhibitor alone [24].

### Combination of PD-1/PD-L1 antibodies and radiotherapy

The development and success of checkpoint blockades in the clinical setting have increased interest in the combination of radiotherapy and PD-1/PD-L1 blockade, and some pre-clinical evidence highlights the synergistic potential of this combination [60, 61]. For example, regimens containing asparaginase/pegaspargase, when combined with radiotherapy, are very effective and are regarded as the foundation of localized NKTL treatments. A retrospective study identified the combination of an anti-PD-1 antibody with anlotinib and pegaspargase as a promising regimen "sandwich" with radiotherapy for treating localized NTKL, as it was less toxic and had better tolerance [62]. One ongoing phase I/II trial (NCT01976585) investigating local radiotherapy in combination with the local application of immunostimulatory agents in patients with indolent lymphoma is providing further support for the combination of radiotherapy and PD-1 / PD-L1 blockade [63].

### Combination of PD-1/PD-L1 antibodies and CAR-T therapy

CAR-T therapy is a type of gene therapy that uses a T cell receptor (TCR) or CAR to engineer T cells. Therefore, it can specifically recognize tumor antigens and kill tumor cells [64]. China leads globally in the total number of CAR-T cell therapies, with two CD19-targeted CAR-T cell therapies recently approved [65, 66]. These CAR-T therapies have shown great success and unprecedented results in the treatment of refractory/relapsed lymphoma, leukemia, and myeloma [67]. However, some patients show no response to CAR-T cell therapy and even relapse after the therapy. Therefore, studies are now reporting that the application of reduced-dose PD-1 blockade therapy combined with CAR-T cell therapy can enhance the antitumor effect in pre-clinical models and clinical trials, indicating that this might represent a promising treatment option for relapsed/refractory lymphomas [68-70].

## Role of IL-17A in tumors

Th17 cells and IL-17A play a significant part in tumor progression. Recent studies have confirmed that IL-17A promotes tumor growth during early tumorigenesis, whereas IL-17A suppresses tumor growth in established tumors by enhancing antitumor immunity [71]. In lymphomas, most studies have demonstrated that IL-17A promotes tumor growth; therefore, inhibition of IL-17A production may represent an important strategy for enhancing the sensitivity and therapeutic benefits of chemotherapy [14, 72]. However, Xin *et al*. have described adoptive immunotherapy using Th17 cells in DLBCL tumor–bearing mice and have verified that IL-17 has an antitumor effect in lymphoma [73]. At present, therefore, the role of IL-17A in cancer remains controversial.

### Tumor-promoting functions of IL-17A

IL-17A promotes cancer by directly stimulating tumor cells or by indirectly inducing an immunosuppressive tumor microenvironment. IL-17A could promote angiogenesis through the VEGF pathway and the CXCR-2-dependent pathway to promote tumor growth [74, 75]. Okuyama *et al*. found that treatment with an antagonistic IL-17A antibody in mice inhibited tumor development by elevating IFN-γ production, indicating that IL-17A exerts its antitumor activity by influencing IFN-γ production [76]. Chang *et al*. also showed that the IL-17A produced by Th17 cells in a K-ras (G12D) mouse lung cancer model could induce tumor growth by recruiting myeloid suppressor cells [77]. Some studies have revealed that IL-17A's effects on the nuclear factor NF-κB and p38 MAPK signaling pathways can stimulate tumor growth [78, 79]. IL-17A can increase tumor cell invasion and metastasis, while also supporting the survival of tumor cells in faraway organs by directly upregulating ERK signaling [80]. IL-17A can enhance tumor growth by inducing IL-6 expression because IL-6 activates the oncogenic transcription factor STAT3 and upregulates pro-survival and pro-

angiogenic genes in tumors [81].

**Tumor-suppressing functions of IL-17A**

Kryczek *et al*. have shown increases in tumor growth and metastasis in IL-17–deficient mice and related the increases to decreases in tumor-specific interferon-gamma (+) T cells and interferon-gamma (+) natural killer cells in the tumors. These findings confirmed that IL-17A may have a protective role in cancer immunity and that it can restrain tumor growth and metastasis by IFN-c producing NK and T cells [82]. The results of Martin-Orozco indicate that Th17 cells and IL-17A play a protective role by inhibiting tumors and hindering tumor development through the activation of tumor-specific CD8 (+) T cells [83]. Benchetrit *et al*. have shown that IL-17A inhibited the growth rate of lymphoma J558L and mastocytoma P815 tumors, suggesting that the antitumor activity of IL-17 is host-dependent and involves T lymphocytes [84]. Another study revealed that IL-17A accelerated DC recruitment into tumor tissues, thereby leading to CTL expansion—a crucial event for the antitumor effect [83].

## Conclusion

Some cancer patients have shown remarkable antitumor responses to therapies that block the PD-L1/PD-1 signal pathway; however, the tumor responses after PD-1/PD-L1 immunotherapy are limited, and some patients were completely unresponsive. Therefore, new checkpoint inhibitors are needed for combined use with PD-L1/PD-1 inhibitors to increase the response rate in tumors, especially in lymphoma. The better understanding of PD-1/PD-L1 and IL-17A provided by this review draws attention to possible interactions occurring in the tumor microenvironment that may aid in finding novel and promising immunotherapeutic targets for curing lymphoma. However, further in vitro and in vivo research is needed to develop and implement novel ways to combat tumors.

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