**Review**

**Research Progress in the PD-1/PD-L1 Pathway and IL-17A in Lymphomas**

Li Yanga, Xin Xua, \*

*a Department of Geriatrics, Guangzhou First People’s Hospital, Guangzhou, Guangdong Province, 51000, China.*

\* Correspondence author: Xin Xu

Mailing address: Department of Geriatrics, Guangzhou First People’s Hospital, Guangzhou, Guangdong Province, 51000, China.

Email: eyxuxin@scut.edu.cn

**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 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 (TIL) 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 IL-17A and originally termed CTLA8) is produced by Th17 cells, γδT cells, natural killer (NK) cells, and CD8 T cells in the cancer 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.

1. **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 HL and ALCL, and many poor-prognosis DLBCLs originate from the ABC/non-GCB 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.

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

In anaplastic lymphoma kinase (ALK)+ anaplastic large cell lymphoma (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/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](https://pubmed.ncbi.nlm.nih.gov/?term=Song+TL&cauthor_id=30054295) *et al*. have demonstrated that STAT3 activation confers high PD-L1 expression in NKTL tumors and may enhance tumor immune evasion [25].

* 1. **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].

* 1. **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].

**2. 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 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 lymphoma, 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].

* 1. **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), non-Hodgkin lymphoma (NHL), and multiple myeloma (MM), 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 (HSCT). The FDA 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 (NK)/T cell lymphoma (ENKTL) [44, 48].

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

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Target | Agent | Disease | Combinationtherapy | Phasestudy | 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 response |
| PD-1 | NivolumabNivolumabPembrolizumabPembrolizumab | rr-HL,rr-PMBCLrr-DLBCL,rr-FLrr-PMBCL, rr-HL/cHLrr-FL | brentuximab vedotinibrutinib-Rituximab | I/III/IIIb/II/IIIII | effectiveeffectiveeffectiveeffective |
|  | 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; PTCL, Peripheral T cell lymphoma; GVD, gemcitabine, vinorelbine, and pegylated liposomal doxorubicin; rr, relapsed/refractory; DLBCL, diffuse large B cell lymphoma; FL, follicular lymphoma

* 1. **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 humans. 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].

**2.3 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 diffuse large B cell lymphoma (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].

**2.4 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 Natural killer/T cell lymphoma (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].

**2.5 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 chimeric antigen receptor (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].

**3. Role of IL-17A in tumors**

Th17 cells and interleukin (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.

**3.1 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 mitogen-activated protein kinase (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 signal transducer and activator of transcription 3 (STAT3) and upregulates pro-survival and pro-angiogenic genes in tumors [81].

**3.2 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 dendritic cell (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.

**Declarations**

**Authors’ contributions:** The article is written by Li Yang, and Xin Xu provides guidance on article.

**Availability of data and materials:** Not applicable.

**Financial support and sponsorship:** None.

**Conflicts of interest:** Xin Xu is a member of the Editorial Board of *Aging Pathobiology and Therapeutics*. All authors declare no conflicts of interest and were not involved in the journal’s review or decisions related to this manuscript.

**Ethical approval and consent to participate:** Not applicable.

1. Keir ME, Butte MJ, Freeman GJ, & Sharpe AH. PD-1 and its ligands in tolerance and immunity. *Annu Rev Immunol,* 2008*,* 26: 677-704. <https://doi.org/10.1146/annurev.immunol.26.021607.090331>

2. Ahmadzadeh M, Johnson LA, Heemskerk B, Wunderlich JR, Dudley ME, White DE*, et al.* Tumor antigen-specific CD8 T cells infiltrating the tumor express high levels of PD-1 and are functionally impaired. *Blood,* 2009*,* 114(8): 1537-1544. <https://doi.org/10.1182/blood-2008-12-195792>

3. Kiyasu J, Miyoshi H, Hirata A, Arakawa F, Ichikawa A, Niino D*, et al.* Expression of programmed cell death ligand 1 is associated with poor overall survival in patients with diffuse large B-cell lymphoma. *Blood,* 2015*,* 126(19): 2193-2201. <https://doi.org/10.1182/blood-2015-02-629600>

4. Miyoshi H, Kiyasu J, Kato T, Yoshida N, Shimono J, Yokoyama S*, et al.* PD-L1 expression on neoplastic or stromal cells is respectively a poor or good prognostic factor for adult T-cell leukemia/lymphoma. *Blood,* 2016*,* 128(10): 1374-1381. <https://doi.org/10.1182/blood-2016-02-698936>

5. Ishikawa E, Nakamura M, Shimada K, Tanaka T, Satou A, Kohno K*, et al.* Prognostic impact of PD-L1 expression in primary gastric and intestinal diffuse large B-cell lymphoma. *J Gastroenterol,* 2020*,* 55(1): 39-50. <https://doi.org/10.1007/s00535-019-01616-3>

6. Ruan J, Ouyang M, Zhang W, Luo Y, & Zhou D. The effect of PD-1 expression on tumor-associated macrophage in T cell lymphoma. *Clin Transl Oncol,* 2021*,* 23(6): 1134-1141. <https://doi.org/10.1007/s12094-020-02499-0>

7. Jiang Y, Chen M, Nie H, & Yuan Y. PD-1 and PD-L1 in cancer immunotherapy: clinical implications and future considerations. *Hum Vaccin Immunother,* 2019*,* 15(5): 1111-1122. <https://doi.org/10.1080/21645515.2019.1571892>

8. Iwakura Y, Ishigame H, Saijo S, & Nakae S. Functional specialization of interleukin-17 family members. *Immunity,* 2011*,* 34(2): 149-162. <https://doi.org/10.1016/j.immuni.2011.02.012>

9. Chung SH, Ye XQ, & Iwakura Y. Interleukin-17 family members in health and disease. *Int Immunol,* 2021*,* 33(12): 723-729. <https://doi.org/10.1093/intimm/dxab075>

10. McGeachy MJ, Cua DJ, & Gaffen SL. The IL-17 Family of Cytokines in Health and Disease. *Immunity,* 2019*,* 50(4): 892-906. <https://doi.org/10.1016/j.immuni.2019.03.021>

11. Ruiz de Morales JMG, Puig L, Daudén E, Cañete JD, Pablos JL, Martín AO*, et al.* Critical role of interleukin (IL)-17 in inflammatory and immune disorders: An updated review of the evidence focusing in controversies. *Autoimmun Rev,* 2020*,* 19(1): 102429. <https://doi.org/10.1016/j.autrev.2019.102429>

12. Zhong W, Zhu Z, Xu X, Zhang H, Xiong H, Li Q*, et al.* Human bone marrow-derived mesenchymal stem cells promote the growth and drug-resistance of diffuse large B-cell lymphoma by secreting IL-6 and elevating IL-17A levels. *J Exp Clin Cancer Res,* 2019*,* 38(1): 73. <https://doi.org/10.1186/s13046-019-1081-7>

13. Zhong W, Li Q. Rituximab or irradiation promotes IL-17 secretion and thereby induces resistance to rituximab or irradiation. *Cell Mol Immunol,* 2017*,* 14(12): 1020-1022. <https://doi.org/10.1038/cmi.2017.124>

14. Zhong W, Xu X, Zhu Z, Yang L, Du H, Xia Z*, et al.* Increased interleukin-17A levels promote rituximab resistance by suppressing p53 expression and predict an unfavorable prognosis in patients with diffuse large B cell lymphoma. *Int J Oncol,* 2018*,* 52(5): 1528-1538. <https://doi.org/10.3892/ijo.2018.4299>

15. Ma YF, Chen C, Li D, Liu M, Lv ZW, Ji Y*, et al.* Targeting of interleukin (IL)-17A inhibits PDL1 expression in tumor cells and induces anticancer immunity in an estrogen receptor-negative murine model of breast cancer. *Oncotarget,* 2017*,* 8(5): 7614-7624. <https://doi.org/10.18632/oncotarget.13819>

16. Shuai C, Yang X, Pan H, & Han W. Estrogen Receptor Downregulates Expression of PD-1/PD-L1 and Infiltration of CD8(+) T Cells by Inhibiting IL-17 Signaling Transduction in Breast Cancer. *Front Oncol,* 2020*,* 10: 582863. <https://doi.org/10.3389/fonc.2020.582863>

17. Stein S, Henze L, Poch T, Carambia A, Krech T, Preti M*, et al.* IL-17A/F enable cholangiocytes to restrict T cell-driven experimental cholangitis by upregulating PD-L1 expression. *J Hepatol,* 2021*,* 74(4): 919-930. <https://doi.org/10.1016/j.jhep.2020.10.035>

18. Wang X, Yang L, Huang F, Zhang Q, Liu S, Ma L*, et al.* Inflammatory cytokines IL-17 and TNF-α up-regulate PD-L1 expression in human prostate and colon cancer cells. *Immunol Lett,* 2017*,* 184: 7-14. <https://doi.org/10.1016/j.imlet.2017.02.006>

19. Zhang W, Qiu Y, Xie X, Fu Y, Wang L, & Cai Z. B7 Family Members in Lymphoma: Promising Novel Targets for Tumor Immunotherapy? *Front Oncol,* 2021*,* 11: 647526. <https://doi.org/10.3389/fonc.2021.647526>

20. Andorsky DJ, Yamada RE, Said J, Pinkus GS, Betting DJ, & Timmerman JM. Programmed death ligand 1 is expressed by non-hodgkin lymphomas and inhibits the activity of tumor-associated T cells. *Clin Cancer Res,* 2011*,* 17(13): 4232-4244. <https://doi.org/10.1158/1078-0432.Ccr-10-2660>

21. Yamamoto R, Nishikori M, Tashima M, Sakai T, Ichinohe T, Takaori-Kondo A*, et al.* B7-H1 expression is regulated by MEK/ERK signaling pathway in anaplastic large cell lymphoma and Hodgkin lymphoma. *Cancer Sci,* 2009*,* 100(11): 2093-2100. <https://doi.org/10.1111/j.1349-7006.2009.01302.x>

22. Lv K, Li X, Yu H, Chen X, Zhang M, & Wu X. Selection of new immunotherapy targets for NK/T cell lymphoma. *Am J Transl Res,* 2020*,* 12(11): 7034-7047. <https://doi.org/10.1186/s13287-020-01909-y>

23. Horlad H, Ma C, Yano H, Pan C, Ohnishi K, Fujiwara Y*, et al.* An IL-27/Stat3 axis induces expression of programmed cell death 1 ligands (PD-L1/2) on infiltrating macrophages in lymphoma. *Cancer Sci,* 2016*,* 107(11): 1696-1704. <https://doi.org/10.1111/cas.13065>

24. Wei T, Li M, Zhu Z, Xiong H, Shen H, Zhang H*, et al.* Vincristine upregulates PD-L1 and increases the efficacy of PD-L1 blockade therapy in diffuse large B-cell lymphoma. *J Cancer Res Clin Oncol,* 2021*,* 147(3): 691-701. <https://doi.org/10.1007/s00432-020-03446-w>

25. Song TL, Nairismägi ML, Laurensia Y, Lim JQ, Tan J, Li ZM*, et al.* Oncogenic activation of the STAT3 pathway drives PD-L1 expression in natural killer/T-cell lymphoma. *Blood,* 2018*,* 132(11): 1146-1158. <https://doi.org/10.1182/blood-2018-01-829424>

26. Jelinek T, Mihalyova J, Kascak M, Duras J, & Hajek R. PD-1/PD-L1 inhibitors in haematological malignancies: update 2017. *Immunology,* 2017*,* 152(3): 357-371. <https://doi.org/10.1111/imm.12788>

27. Green MR, Monti S, Rodig SJ, Juszczynski P, Currie T, O'Donnell E*, et al.* Integrative analysis reveals selective 9p24.1 amplification, increased PD-1 ligand expression, and further induction via JAK2 in nodular sclerosing Hodgkin lymphoma and primary mediastinal large B-cell lymphoma. *Blood,* 2010*,* 116(17): 3268-3277. <https://doi.org/10.1182/blood-2010-05-282780>

28. Wang Y, Wenzl K, Manske MK, Asmann YW, Sarangi V, Greipp PT*, et al.* Amplification of 9p24.1 in diffuse large B-cell lymphoma identifies a unique subset of cases that resemble primary mediastinal large B-cell lymphoma. *Blood Cancer J,* 2019*,* 9(9): 73. <https://doi.org/10.1038/s41408-019-0233-5>

29. Duffield AS, Ascierto ML, Anders RA, Taube JM, Meeker AK, Chen S*, et al.* Th17 immune microenvironment in Epstein-Barr virus-negative Hodgkin lymphoma: implications for immunotherapy. *Blood Adv,* 2017*,* 1(17): 1324-1334. <https://doi.org/10.1182/bloodadvances.2017007260>

30. Chen S, Crabill GA, Pritchard TS, McMiller TL, Wei P, Pardoll DM*, et al.* Mechanisms regulating PD-L1 expression on tumor and immune cells. *J Immunother Cancer,* 2019*,* 7(1): 305. <https://doi.org/10.1186/s40425-019-0770-2>

31. Ardeshna KM, Kakouros N, Qian W, Powell MG, Saini N, D'Sa S*, et al.* Conventional second-line salvage chemotherapy regimens are not warranted in patients with malignant lymphomas who have progressive disease after first-line salvage therapy regimens. *Br J Haematol,* 2005*,* 130(3): 363-372. <https://doi.org/10.1111/j.1365-2141.2005.05603.x>

32. Nagasaki J, Togashi Y, Sugawara T, Itami M, Yamauchi N, Yuda J*, et al.* The critical role of CD4+ T cells in PD-1 blockade against MHC-II-expressing tumors such as classic Hodgkin lymphoma. *Blood Adv,* 2020*,* 4(17): 4069-4082. <https://doi.org/10.1182/bloodadvances.2020002098>

33. Ansell SM, Lesokhin AM, Borrello I, Halwani A, Scott EC, Gutierrez M*, et al.* PD-1 blockade with nivolumab in relapsed or refractory Hodgkin's lymphoma. *N Engl J Med,* 2015*,* 372(4): 311-319. <https://doi.org/10.1056/NEJMoa1411087>

34. Younes A, Santoro A, Shipp M, Zinzani PL, Timmerman JM, Ansell S*, et al.* Nivolumab for classical Hodgkin's lymphoma after failure of both autologous stem-cell transplantation and brentuximab vedotin: a multicentre, multicohort, single-arm phase 2 trial. *Lancet Oncol,* 2016*,* 17(9): 1283-1294. [https://doi.org/10.1016/s1470-2045(16)30167-x](https://doi.org/10.1016/s1470-2045%2816%2930167-x)

35. Armand P, Rodig S, Melnichenko V, Thieblemont C, Bouabdallah K, Tumyan G*, et al.* Pembrolizumab in Relapsed or Refractory Primary Mediastinal Large B-Cell Lymphoma. *J Clin Oncol,* 2019*,* 37(34): 3291-3299. <https://doi.org/10.1200/jco.19.01389>

36. Ding W, LaPlant BR, Call TG, Parikh SA, Leis JF, He R*, et al.* Pembrolizumab in patients with CLL and Richter transformation or with relapsed CLL. *Blood,* 2017*,* 129(26): 3419-3427. <https://doi.org/10.1182/blood-2017-02-765685>

37. Chen R, Zinzani PL, Lee HJ, Armand P, Johnson NA, Brice P*, et al.* Pembrolizumab in relapsed or refractory Hodgkin lymphoma: 2-year follow-up of KEYNOTE-087. *Blood,* 2019*,* 134(14): 1144-1153. <https://doi.org/10.1182/blood.2019000324>

38. Shi Y, Wu J, Wang Z, Zhang L, Wang Z, Zhang M*, et al.* Efficacy and safety of geptanolimab (GB226) for relapsed or refractory peripheral T cell lymphoma: an open-label phase 2 study (Gxplore-002). *J Hematol Oncol,* 2021*,* 14(1): 12. <https://doi.org/10.1186/s13045-021-01033-1>

39. Song Y, Wu J, Chen X, Lin T, Cao J, Liu Y*, et al.* A Single-Arm, Multicenter, Phase II Study of Camrelizumab in Relapsed or Refractory Classical Hodgkin Lymphoma. *Clin Cancer Res,* 2019*,* 25(24): 7363-7369. <https://doi.org/10.1158/1078-0432.Ccr-19-1680>

40. Chen J, Zhang H, Zhu L, Zhao Y, Ding Y, & Yuan Y. Tislelizumab for the treatment of classical Hodgkin's lymphoma. *Drugs Today (Barc),* 2020*,* 56(12): 781-785. <https://doi.org/10.1358/dot.2020.56.12.3233362>

41. Tao R, Fan L, Song Y, Hu Y, Zhang W, Wang Y*, et al.* Sintilimab for relapsed/refractory extranodal NK/T cell lymphoma: a multicenter, single-arm, phase 2 trial (ORIENT-4). *Signal Transduct Target Ther,* 2021*,* 6(1): 365. <https://doi.org/10.1038/s41392-021-00768-0>

42. Kim SJ, Lim JQ, Laurensia Y, Cho J, Yoon SE, Lee JY*, et al.* Avelumab for the treatment of relapsed or refractory extranodal NK/T-cell lymphoma: an open-label phase 2 study. *Blood,* 2020*,* 136(24): 2754-2763. <https://doi.org/10.1182/blood.2020007247>

43. Geoerger B, Zwaan CM, Marshall LV, Michon J, Bourdeaut F, Casanova M*, et al.* Atezolizumab for children and young adults with previously treated solid tumours, non-Hodgkin lymphoma, and Hodgkin lymphoma (iMATRIX): a multicentre phase 1-2 study. *Lancet Oncol,* 2020*,* 21(1): 134-144. [https://doi.org/10.1016/s1470-2045(19)30693-x](https://doi.org/10.1016/s1470-2045%2819%2930693-x)

44. Armand P, Shipp MA, Ribrag V, Michot JM, Zinzani PL, Kuruvilla J*, et al.* Programmed Death-1 Blockade With Pembrolizumab in Patients With Classical Hodgkin Lymphoma After Brentuximab Vedotin Failure. *J Clin Oncol,* 2016*,* 34(31): 3733-3739. <https://doi.org/10.1200/jco.2016.67.3467>

45. Xu-Monette ZY, Zhou J, & Young KH. PD-1 expression and clinical PD-1 blockade in B-cell lymphomas. *Blood,* 2018*,* 131(1): 68-83. <https://doi.org/10.1182/blood-2017-07-740993>

46. Xie W, Medeiros LJ, Li S, Yin CC, Khoury JD, & Xu J. PD-1/PD-L1 Pathway and Its Blockade in Patients with Classic Hodgkin Lymphoma and Non-Hodgkin Large-Cell Lymphomas. *Curr Hematol Malig Rep,* 2020*,* 15(4): 372-381. <https://doi.org/10.1007/s11899-020-00589-y>

47. Goodman A, Patel SP, & Kurzrock R. PD-1-PD-L1 immune-checkpoint blockade in B-cell lymphomas. *Nat Rev Clin Oncol,* 2017*,* 14(4): 203-220. <https://doi.org/10.1038/nrclinonc.2016.168>

48. Chen R, Zinzani PL, Fanale MA, Armand P, Johnson NA, Brice P*, et al.* Phase II Study of the Efficacy and Safety of Pembrolizumab for Relapsed/Refractory Classic Hodgkin Lymphoma. *J Clin Oncol,* 2017*,* 35(19): 2125-2132. <https://doi.org/10.1200/jco.2016.72.1316>

49. Chen L, Han X. Anti-PD-1/PD-L1 therapy of human cancer: past, present, and future. *J Clin Invest,* 2015*,* 125(9): 3384-3391. <https://doi.org/10.1172/jci80011>

50. Haanen JB, Robert C. Immune checkpoint inhibitors. *Immuno-Oncology,* 2015*,* 42: 55-66. <https://doi.org/10.1159/000437178>

51. Larkin J, Chiarion-Sileni V, Gonzalez R, Grob JJ, Cowey CL, Lao CD*, et al.* Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma. *N Engl J Med,* 2015*,* 373(1): 23-34. <https://doi.org/10.1056/NEJMoa1504030>

52. Tobin JWD, Bednarska K, Campbell A, & Keane C. PD-1 and LAG-3 Checkpoint Blockade: Potential Avenues for Therapy in B-Cell Lymphoma. *Cells,* 2021*,* 10(5): 1152. <https://doi.org/10.3390/cells10051152>

53. Chen BJ, Dashnamoorthy R, Galera P, Makarenko V, Chang H, Ghosh S*, et al.* The immune checkpoint molecules PD-1, PD-L1, TIM-3 and LAG-3 in diffuse large B-cell lymphoma. *Oncotarget,* 2019*,* 10(21): 2030-2040. <https://doi.org/10.18632/oncotarget.26771>

54. Lee YH, Lee HJ, Kim HC, Lee Y, Nam SK, Hupperetz C*, et al.* PD-1 and TIGIT downregulation distinctly affect the effector and early memory phenotypes of CD19-targeting CAR T cells. *Mol Ther,* 2022*,* 30(2): 579-592. <https://doi.org/10.1016/j.ymthe.2021.10.004>

55. Tan J, Yu Z, Huang J, Chen Y, Huang S, Yao D*, et al.* Increased PD-1+Tim-3+ exhausted T cells in bone marrow may influence the clinical outcome of patients with AML. *Biomark Res,* 2020*,* 8: 6. <https://doi.org/10.1186/s40364-020-0185-8>

56. Ge Z, Peppelenbosch MP, Sprengers D, & Kwekkeboom J. TIGIT, the Next Step Towards Successful Combination Immune Checkpoint Therapy in Cancer. *Front Immunol,* 2021*,* 12: 699895. <https://doi.org/10.3389/fimmu.2021.699895>

57. Josefsson SE, Beiske K, Blaker YN, Førsund MS, Holte H, Østenstad B*, et al.* TIGIT and PD-1 Mark Intratumoral T Cells with Reduced Effector Function in B-cell Non-Hodgkin Lymphoma. *Cancer Immunol Res,* 2019*,* 7(3): 355-362. <https://doi.org/10.1158/2326-6066.Cir-18-0351>

58. Zhang R, Lyu C, Lu W, Pu Y, Jiang Y, & Deng Q. Synergistic effect of programmed death-1 inhibitor and programmed death-1 ligand-1 inhibitor combined with chemotherapeutic drugs on DLBCL cell lines in vitro and in vivo. *Am J Cancer Res,* 2020*,* 10(9): 2800-2812.

59. Smith SD, Till BG, Shadman MS, Lynch RC, Cowan AJ, Wu QV*, et al.* Pembrolizumab with R-CHOP in previously untreated diffuse large B-cell lymphoma: potential for biomarker driven therapy. *Br J Haematol,* 2020*,* 189(6): 1119-1126. <https://doi.org/10.1111/bjh.16494>

60. Zhuang H. Abscopal effect of stereotactic radiotherapy combined with anti-PD-1/PD-L1 immunotherapy: Mechanisms, clinical efficacy, and issues. *Cancer Commun (Lond),* 2020*,* 40(12): 649-654. <https://doi.org/10.1002/cac2.12111>

61. Park SS, Dong H, Liu X, Harrington SM, Krco CJ, Grams MP*, et al.* PD-1 Restrains Radiotherapy-Induced Abscopal Effect. *Cancer Immunol Res,* 2015*,* 3(6): 610-619. <https://doi.org/10.1158/2326-6066.Cir-14-0138>

62. Sun P, Wang Y, Yang H, Chen C, Nie M, Sun XQ*, et al.* Combination of Anti-PD-1 Antibody, Anlotinib and Pegaspargase "Sandwich" With Radiotherapy in Localized Natural Killer/T Cell Lymphoma. *Front Immunol,* 2022*,* 13: 766200. <https://doi.org/10.3389/fimmu.2022.766200>

63. Hammerich L, Marron TU, Upadhyay R, Svensson-Arvelund J, Dhainaut M, Hussein S*, et al.* Systemic clinical tumor regressions and potentiation of PD1 blockade with in situ vaccination. *Nat Med,* 2019*,* 25(5): 814-824. <https://doi.org/10.1038/s41591-019-0410-x>

64. Porter DL, Levine BL, Kalos M, Bagg A, & June CH. Chimeric antigen receptor-modified T cells in chronic lymphoid leukemia. *N Engl J Med,* 2011*,* 365(8): 725-733. <https://doi.org/10.1056/NEJMoa1103849>

65. First-Ever CAR T-cell Therapy Approved in U.S. *Cancer Discov,* 2017*,* 7(10): Of1. <https://doi.org/10.1158/2159-8290.Cd-nb2017-126>

66. Golubovskaya V. CAR-T Cell Therapy: From the Bench to the Bedside. *Cancers (Basel),* 2017*,* 9(11): 150. <https://doi.org/10.3390/cancers9110150>

67. Tang J, Shalabi A, & Hubbard-Lucey VM. Comprehensive analysis of the clinical immuno-oncology landscape. *Ann Oncol,* 2018*,* 29(1): 84-91. <https://doi.org/10.1093/annonc/mdx755>

68. Zhang R, Deng Q, Jiang YY, Zhu HB, Wang J, & Zhao MF. Effect and changes in PD‑1 expression of CD19 CAR‑T cells from T cells highly expressing PD‑1 combined with reduced‑dose PD‑1 inhibitor. *Oncol Rep,* 2019*,* 41(6): 3455-3463. <https://doi.org/10.3892/or.2019.7096>

69. Song W, Zhang M. Use of CAR-T cell therapy, PD-1 blockade, and their combination for the treatment of hematological malignancies. *Clin Immunol,* 2020*,* 214: 108382. <https://doi.org/10.1016/j.clim.2020.108382>

70. Wang J, Deng Q, Jiang YY, Zhang R, Zhu HB, Meng JX*, et al.* CAR-T 19 combined with reduced-dose PD-1 blockade therapy for treatment of refractory follicular lymphoma: A case report. *Oncol Lett,* 2019*,* 18(5): 4415-4420. <https://doi.org/10.3892/ol.2019.10783>

71. Vitiello GA, Miller G. Targeting the interleukin-17 immune axis for cancer immunotherapy. *J Exp Med,* 2020*,* 217(1): e20190456. <https://doi.org/10.1084/jem.20190456>

72. Guo HZ, Niu LT, Qiang WT, Chen J, Wang J, Yang H*, et al.* Leukemic IL-17RB signaling regulates leukemic survival and chemoresistance. *Faseb j,* 2019*,* 33(8): 9565-9576. <https://doi.org/10.1096/fj.201900099R>

73. XU X, LI Q, Zhu G, DU F, & Zhao Z. Th17 cells adoptive immunotherapy impacts tumor growth of diffuse large B-cell lymphoma-bearing mice. *Journal of Leukemia & Lymphoma,* 2015: 722-725.

74. Numasaki M, Watanabe M, Suzuki T, Takahashi H, Nakamura A, McAllister F*, et al.* IL-17 enhances the net angiogenic activity and in vivo growth of human non-small cell lung cancer in SCID mice through promoting CXCR-2-dependent angiogenesis. *J Immunol,* 2005*,* 175(9): 6177-6189. <https://doi.org/10.4049/jimmunol.175.9.6177>

75. Nicola S, Ridolfi I, Rolla G, Filosso P, Giobbe R, Boita M*, et al.* IL-17 Promotes Nitric Oxide Production in Non-Small-Cell Lung Cancer. *J Clin Med,* 2021*,* 10(19): 4572 <https://doi.org/10.3390/jcm10194572>

76. Okuyama H, Tominaga A, Fukuoka S, Taguchi T, Kusumoto Y, & Ono S. Spirulina lipopolysaccharides inhibit tumor growth in a Toll-like receptor 4-dependent manner by altering the cytokine milieu from interleukin-17/interleukin-23 to interferon-γ. *Oncol Rep,* 2017*,* 37(2): 684-694. <https://doi.org/10.3892/or.2017.5346>

77. Chang SH, Mirabolfathinejad SG, Katta H, Cumpian AM, Gong L, Caetano MS*, et al.* T helper 17 cells play a critical pathogenic role in lung cancer. *Proc Natl Acad Sci U S A,* 2014*,* 111(15): 5664-5669. <https://doi.org/10.1073/pnas.1319051111>

78. Xiang T, Long H, He L, Han X, Lin K, Liang Z*, et al.* Interleukin-17 produced by tumor microenvironment promotes self-renewal of CD133+ cancer stem-like cells in ovarian cancer. *Oncogene,* 2015*,* 34(2): 165-176. <https://doi.org/10.1038/onc.2013.537>

79. Cochaud S, Giustiniani J, Thomas C, Laprevotte E, Garbar C, Savoye AM*, et al.* IL-17A is produced by breast cancer TILs and promotes chemoresistance and proliferation through ERK1/2. *Sci Rep,* 2013*,* 3: 3456. <https://doi.org/10.1038/srep03456>

80. Wu HH, Hwang-Verslues WW, Lee WH, Huang CK, Wei PC, Chen CL*, et al.* Targeting IL-17B-IL-17RB signaling with an anti-IL-17RB antibody blocks pancreatic cancer metastasis by silencing multiple chemokines. *J Exp Med,* 2015*,* 212(3): 333-349. <https://doi.org/10.1084/jem.20141702>

81. Tartour E, Fossiez F, Joyeux I, Galinha A, Gey A, Claret E*, et al.* Interleukin 17, a T-cell-derived cytokine, promotes tumorigenicity of human cervical tumors in nude mice. *Cancer Res,* 1999*,* 59(15): 3698-3704.

82. Kryczek I, Wei S, Szeliga W, Vatan L, & Zou W. Endogenous IL-17 contributes to reduced tumor growth and metastasis. *Blood,* 2009*,* 114(2): 357-359. <https://doi.org/10.1182/blood-2008-09-177360>

83. Martin-Orozco N, Muranski P, Chung Y, Yang XO, Yamazaki T, Lu S*, et al.* T helper 17 cells promote cytotoxic T cell activation in tumor immunity. *Immunity,* 2009*,* 31(5): 787-798. <https://doi.org/10.1016/j.immuni.2009.09.014>

84. Benchetrit F, Ciree A, Vives V, Warnier G, Gey A, Sautès-Fridman C*, et al.* Interleukin-17 inhibits tumor cell growth by means of a T-cell-dependent mechanism. *Blood,* 2002*,* 99(6): 2114-2121. <https://doi.org/10.1182/blood.v99.6.2114>