

Research progress of PD-1/PD-L1 and IL-17A on Lymphomas

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Abstract

In recent years, tumor microenvironment has become the focus of immunotherapy point in lymphoma. Programmed death 1 (PD-1) and programmed death 1 ligand (PD-L1) signaling pathway is one of important mechanism of cancer immunomodulatory, and its abnormal activation in tumor microenvironment shows that PD-1/PD-L1 pathway may take part in the regulation of tumor immune escape. IL-17A is a pro-inflammatory cytokine which plays a crucial role in lymphoma cancer microenvironment and it act divided roles in both tumor growth and cancer elimination, so IL-17A has also become a hot topic in cancer immunotherapy. In previous study, papers have reported that IL-17A up-regulated the expression of PD-L1 in cancers or in autoimmune diseases while fewer research in lymphoma. We guess that whether there is an interaction or relationship between PD-1/PD-L1 pathway and IL-17A in lymphoma. Therefore, we aimed to review the progress of PD-1/PD-L1 pathway and IL-17A on lymphomas in this paper. We hope the better understanding of PD-1/PDL1 pathway and IL-17A can bring us an inspiration to find novel lymphomas therapeutic directions in future.

Key words: PD-1/PD-L1, IL-17A, Lymphoma, tumor microenvironment, immune

Introduction

Lymphoma is one of hematological malignancy which is prevalent in world. In recent years, some types of lymphomas have become treatable, while relapsed or refractory lymphomas remain ordinary and challenging, which push us to seek new treatments for lymphomas. PD-1 is expressed on the activated T cells, monocytes, dendritic cells (DCs), natural killer (NK) and B lymphocytes, macrophages[1], especially, over-expressed on the tumor-specific T cells. it is highly expressed on tumor-specific T cells[2]. Normal antigen-presenting cells, macrophages, and dendritic cells express PD-1 ligands that combine with PD-1 receptors on the activated T cells. As PD-1 is just expressed on the surface of activated T lymphocytes, instead of resting T cells, therefore, it can be used as an activation marker on T cells. When tumor cells over-express PD-L1, PD-1 interacts with PD-1 ligands, then the activation of PD-1/PD-L1 signal pathway can suppresses T-cell function, reducing the T-cell to a dysfunctional state called exhaustion, leading to tumor immune escape and being highly refractory to conventional chemotherapy.

In some previous studies, it has reported that the expression of PD-L1 predicts a worse outcome and is related to poor survival rate in malignant lymphoma patients[3-6].

Cancer cells capable of evading immune-surveillance via PD-1/PD-L1 signaling pathway: by 1) suppressing TIL activation and inducing cells apoptosis, 2) suppressing the production of CTL granular enzyme and perforin 3) inducing the secretion of inflammatory cytokines, such as IFN- γ , TNF- α , IL-2 and enhancing the secretion of the immune inhibitory cytokine IL-10, 4) stagnating the T cell cycle, leading to accumulation of cells in G0/G1 phase 5) promoting tumor cell epithelial materialization, tumor infiltration and metastasis [7]. Based on the molecular mechanisms of the PD-1/PD-L1 signaling pathway, as a target for immunotherapy, an amount of anti-PD-1/PD-L1 antibodies are applied for curing cancers.

Interleukin-17 (IL-17; also known as IL-17A, originally termed CTLA8) is produced by Th17 cells, T cells, Natural Killer (NK) cells, and CD8 T cells in the cancer microenvironment [8]. IL-17 is the prototypical member of the IL-17 family of pro-inflammatory cytokines and it is the most widely studied member in the IL-17 family [9, 10], which plays a vital role in tissue inflammation and the pathogenesis of many autoimmune diseases [11]. Despite IL-17A is widely studied in inflammation field, but too little is known about their presence and role in cancers. In the past decades, many studies reported that IL-17A plays a dual role of tumor-promoting and tumor-suppressing in tumors, which may be related to complex tumor microenvironment, different tumor types, tumor development process, tumor etiology and tumor sensitivity to chemotherapeutic drugs. In this context, in recent years, IL-17A has also become one of the critical research hotspots in the field of lymphoma. While in lots of studies, IL-17A has been proved to promote tumor development in lymphoma, even leading to drug resistance [12-14]. In past study, it has reported that IL-17A could enhance the expression of PD-L1 in many tumors or in autoimmune diseases [15, 16], while little research in lymphoma. We guess that whether there is a relationship or interaction between PD-1/PD-L1 signal pathway and IL-17A in lymphoma [17, 18].

Therefore, we hope to provide a better understanding of PD-1/PDL1 and IL-17, which may provide novel therapeutic directions for the treatment of lymphomas.

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

Using the TCGA and GTEx databases, the study of Wei Zhang found that all B7 family members were highly expressed in diffuse large B cell lymphoma (DLBCL), beside B7-H5, showing that B7 family may play important roles in lymphoma immunization [19]. PD-L1 is not only expressed in DLBCL cancer cells, also in cancer-infiltrating non-malignant cells. The study of David J. Andorsky show that PD-L1 is highly expressed in HL, ALCL and many poor prognosis DLBCLs originate from the ABC/non-GCB subtype, and it suppress the activity of Tumor-Associated T Cells [20]. The mechanism of PD-1/PD-L1 expression is complex. Various factors appear to influence the expressing of PD-1/PD-L1. And PD-1/PD-L1 expression played vital roles in propagation, immigration, evasion, drug-resistance and immune evasion of lymphoma.

1.1 The activation of MEK / ERK、MAPK、JAK/STAT pathway: In anaplastic lymphoma kinase (ALK)+ anaplastic large cell lymphoma (ALCL) cells, the study found that the expression of PD-1 was inhibited by blocking the extracellular signal-regulated kinase (ERK) signal pathway and was upregulated by the augmentation of ERK activity, suggesting that the expression of PD-1 is regulated by ERK signal pathway in ALCL [21]. EBV-driven overexpression of latent membrane proteins [LMP1 and LMP2] activates the pro-proliferation NF-Kb/MAPK signal pathway and leads to high PD-L1 expression [22]. And in infiltrating macrophages of lymphoma, it has been proved that the expression of PD-L1 and PD-L2 are induced by the IL-27/STAT3 signal pathway [23]. In another study, it shows that some chemotherapy drugs can upregulate PD-L1 expression in DLBCL cells partially through promoting the p-STAT3 [24]. And in NKTL tumors, Tammy Linlin Song demonstrated that STAT3 activation confers high PD-L1 expression, which may enhance tumor immune evasion [25].

1.2 The copy number alterations (CNAs) in chromosome 9p24.1: The chromosomal abnormalities (including chromosomal amplification, polysomy, gain, or translocation)

of 9p24.1, encoding 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 structural amplification of chromosome 9p24.1 increases the abundance of both PD-1 ligands and their induction, JAK2, in the related diseases of nodular sclerosing Hodgkin lymphoma and primary mediastinal large B-cell lymphoma[27]. In addition, JAK2 signal pathway further augmented PD-1 ligand expression in cell lines with 9p24.1 amplification[52]. As such, the CNAs of 9p24.1 in lymphomas provides chance for examining the efficacy of immune checkpoint inhibitors targeting PD-1, which show to be effective in the treatment of relapsed/refractory lymphomas[29].

1.3 Induced by inflammatory factors such as IFN- γ , IL-27 and IL-1a: In the study of Amy S. Duffield, the results suggested that beyond the known role of IFN- γ in promoting PD-L1 expression on DCs and monocytes, IL-27 and IL-1a can also increase the expression of PD-L1 on different immune cell subsets[30].

2. Application of PD-1/PD-L1 inhibitor in lymphoma

In past, Lymphomas, especially non-Hodgkin lymphomas, the main approaches for treatment were surgery, radiotherapy and chemotherapy, while still there are a considerable proportion of lymphomas are progress/relapse after treatment, especially in aggressive lymphomas. DLBCL is the most general type of NHL in China, with strong heterogeneity. With the emergence of rituximab, we have achieved satisfactory results after the treatment of rituximab combined with chemotherapy, while there are still 30-40 % are refractory/relapsed. With the deepening research on tumor microenvironment and tumor immune regulation, immunotherapy has played a significant role and gradually been widely used in lymphoma, especially in refractory/relapsed lymphoma.

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 therapy of malignant tumor[31, 32].

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

To date, many types of anti-PD-1 or anti-PD-L1 antibodies have been produced. The below is the finished clinical trials targeting on PD-1/PD-L1 in lymphoma: anti-PD-1 antibodies (Nivolumab[32, 33], Pembrolizumab[34-36], Geptanolimab[37], Camrelizumab[38], Tislelizumab[39], Sintilimab[40]) and anti-PD-L1 antibodies: (Avelumab[41], Atezolizumab[42], Durvalumab[43].)

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[44-47]. And Nivolumab has received approval for the treatment of relapsed or progressive classical Hodgkin lymphoma 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[34]. A monoclonal anti-PD-1 antibody (sintilimab) is also used for the treatment of relapsed or refractory classical Hodgkin lymphoma (cHL) and extranodal natural killer (NK)/T-cell lymphoma (ENKTL) [48, 49].

2.2 PD-1/PD-L1 antibodies combination with immunomodulatory drugs

In multiple solid cancer types, the therapy of combining CTLA-4 and PD-1 blockers has shown remarkable clinical efficacies, and the discovery of CTLA-4 and PD-1 has made great effort to the development of cancer immunotherapy[50]. Many clinical trials testing the combination of PD-(L)1 or CTLA-4 blockade with molecular mediators of these pathways are becoming more and more popular and have been proved to improve clinical treatment efficacy and response of cancer [51]. For example, the results of Shi-Dong Ma's study indicated that the combination of PD-1 and CTLA-4 can increase the effect of cord blood T cells to control the outgrowth of EBV-induced lymphomas in the cord-blood humanized mouse model, suggesting that PD-1/CTLA-4 blockade might be helpful for treating certain EBV-induced diseases in humans. What's more, there is also evidence shows that the combined use of CTLA-4 antibodies and PD-1 antibodies shows greater clinical benefit than either antibody types alone [52]. There are additional clinical trials and pre-clinical tumor model experiments also being conducted to evaluate the effect of other checkpoint proteins combined with anti-PD-1/PD-L1 antibodies. It 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, PD-1/TIGIT) [53-58].

2.3 PD-1/PD-L1 antibodies combination with chemotherapeutic drugs

Chemotherapy is one of the main methods for cancer treatment, the way of killing tumor cells is by inducing DNA damage, cell cycle arrest and ultimately apoptosis. The antitumor effect of chemotherapeutic drugs is affected by the immune status of patients, which provides us ideas for the development of combination regimens using PD-1/PD-L1 blockade with established chemotherapeutics. One study demonstrated an important synergistic effect of PD-1 inhibitor and chemotherapeutic drugs like cisplatin, cytarabine, etoposide, oxaliplatin, and carboplatin in Diffuse large B-cell lymphoma (DLBCL). And there was no difference in cytotoxicity between the groups with and without PD-L1 inhibitor[59]. Besides, Stephen D Smith et al 'study evaluated that the overall and complete response rate was 90% and 77% in untreated DLBCL patients who treated with PD-1 anti-body pembrolizumab and R-CHOP therapy (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone). And the results show that PD-L1 inhibitor and R-CHOP does not increase severe toxicity, nor impede the safe delivery of 6 cycles of chemotherapy and have high efficacy[60]. In the study of Ting Wei et al, they show that the combination with PD-1/PD-L1 inhibitor can increase the antitumor immune response in DLBCL, which shows more longer survival rate compared with the single chemotherapy drug or single PD-1/PD-L1 inhibitor[24].

2.4 PD-1/PD-L1 antibodies combination with radiotherapy

With the clinical success of checkpoint blockade, combining radiotherapy with PD-1 / PD-L1 blockade is regarded as special interest, and pre-clinical evidence highlights the synergistic potential of this combination[61, 62]. For example, sparginase/pegaspargase containing regimens combined with radiotherapy are very effective and it is considered to be the cornerstone of localized Natural killer/T-cell lymphoma (NKTCL) treatment. A retrospective study indicates that the combination of anti-PD-1 antibody with anlotinib and pegaspargase is a promising regimen "sandwich" with radiotherapy for treating localized NTKL, which is less toxicity and better tolerance[63]. What's more, one ongoing phase I/II trial (NCT01976585) investigating

local radiotherapy in combination with local application of immunostimulatory agents in patients with indolent lymphoma further support the combination of radiotherapy and PD-1 / PD-L1 blockade[64].

10 PD-1/PD-L1 antibodies combination with Car-T therapy

Car-T therapy is one type of gene therapy in which researchers use TCR or chimeric antigen receptor (CAR) to engineer T cells, therefore, it can specifically recognize tumor antigens and kill tumor cells[65]. China leads the total number of CAR-T cell therapies in the world, with two CD19-targeted CAR-T cell therapies recently approved [66, 67]. We get great success and unprecedented results in Car-T therapy in refractory/relapsed lymphoma, leukemia and myeloma[68]. while some of patients does not respond to CAR T cell therapy or relapses after CAR T cell therapy. Therefore, studies have reported that the application of reduced-dose PD-1 blockade therapy combined with CAR-T cell therapy has been applied to enhance anti-tumor effect in preclinical models and clinical trials, which being a promising treatment option for relapsed/refractory lymphomas[69-71].

3.Role of IL-17A in tumor

Th17 cells and interleukin (IL)-17A play a significant role in the progression of tumor. Recent studies have shown that IL-17A promotes tumor growth during early tumorigenesis, whereas in established tumors, IL-17A suppresses tumor growth by enhancing antitumor immunity[72]. In lymphomas, the most parts of studies show that IL-17A plays a role in promoting tumor growth, so the inhibition of producing IL-17A may be an important strategy to enhance the sensitivity and therapeutic benefit of chemotherapy[73, 74]. While in another study, Xin X et. set up an adoptive immunotherapy of Th17 cells on DLBCL tumor bearing mice, proving that IL-17 play an antitumor effect on lymphoma[75]. Therefore, the role of IL-17A in cancer remains controversial.

3.1 Tumor-promoting functions of IL-17A

IL-17A plays a tumor-promoting effects role by directly stimulating tumor cells or by indirectly inducing an immunosuppressive tumor microenvironment.

IL-17A could promote angiogenesis through the VEGF pathway and CXCR-2-dependent pathway to promote tumor growth[76] [77]. In Hiromi Okuyama et. study, they find treatment with an antagonistic IL-17A antibody in mice can inhibits tumor development through elevating IFN- γ production [9] indicates IL-17A play an antitumor activity through influencing IFN- γ production[78]. The work by Chang showed that the production of IL-17A by Th17 cells in the mice lung cancer model K-ras (G12D) was enough to induce the growth of tumor through the recruitment of myeloid suppressor cells[79]. Some studies revealed that IL-17A affect the nuclear factor (NF)- κ B and p38 mitogen-activated protein kinases (MAPK) signaling pathway can stimulate tumor growth[80, 81]. IL-17A increases tumor cell invasion and endothelial cell migration, and supports the survival of tumor cells at distant organs by directly up-regulating ERK signaling[82]. IL-17A can promote tumor growth by inducing IL-6, because the IL-6 activate oncogenic transcription factor signal transducer and activator of transcription 3 (STAT3), and up-regulate pro-survival and pro-angiogenic genes in tumors[83].

3.2Tumor-suppressing functions of IL-17A

The study of Ilona Kryczek show that the growth and metastasis of tumor were increased in the IL-17-deficient mice, which is related to the decreased of tumor specific interferon-

gamma(+) T cells and interferon-gamma(+) natural killer cells in the tumors, showing that IL-17A may play a protective role in cancer immunity, and it can restrain tumor growth and metastasis by IFN- γ producing NK and T cells[84]. The results of Martin-Orozco indicate that Th17 cells and IL-17A play a protective role through inhibiting tumors and hindering tumor development by activation of tumor-specific CD8(+) T cells[85]. In the study of Fabrice Benchetrit, their results show that IL-17A inhibited the growth rate of lymphoma J558L and mastocytoma P815, suggesting that the anti-tumor activity of IL-17 is a host-dependent mechanism involving T lymphocytes[86]. Another study revealed that IL-17A accelerated dendritic cell (DC) recruitment into the tumor tissues, thus leading CTL expansion, which is crucial for the antitumor effect[87].

Conclusion

In some cancer, lots of patients have got remarkable anti-tumor effects by blocking the PD-L1/PD-1 signal pathway, however, the response rates against tumors after PD-1/PD-L1 immunotherapy were limited and even some of them were completely unresponsive. Therefore, we should find another new checkpoint inhibitors to combination with PD-L1/PD-1 inhibitors for raising up its response rate in tumor, especially in lymphoma. With a better understanding about the PD-1/PD-L1 and IL-17A in our review, we speculate that they maybe have an interaction in tumor microenvironment, which may help us to find a novel and promising immunotherapeutic target in curing lymphoma. However, this guess needs further in vitro and in vivo research, so that we can develop and implement novel ways to combat tumors.

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