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Antitumor Mechanisms of Immune Checkpoints PD-L1/PD-1 Blockade in Cancer Treatment

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ABSTRACT : *Programmed death-1 (PD-1) and its ligand (programmed death ligand 1, PD-L1) are negative regulators of immunity. They play a negative role in regulating immune response through interacting with immune cells, resulting in inhibited antitumor response. Tumor immunotherapy with PD-1 or PD-L1 antibody has been shown to be capable of prolonging survival of cancer patients and improving their life quality. Here we summarize the role of PD-L1/PD-1 in regulating immune response, antitumor mechanism and application of PD-L1/PD-1 blockade in cancer treatment.*

KEY WORDS: *PD-L1/PD-1, Immune checkpoints blockade, Antibody, Tumor immunotherapy*

I. INTRODUCTION

Previous researches demonstrate that tumor cells could evade host immune surveillance by several strategies, including down-regulation of cell surface major histocompatibility complex I molecules [1, 2]，secretion of immunosuppressive factors[3, 4], lack of T-cell costimulation [5, 6], and expression of death ligands or negative ligands[7, 8]. Programmed death-1 (PD-1) is a inducible receptor present on T cells and macrophages and plays a critical role in the negative regulation of immune responses[9]. Engagement of PD-1 by PD-L1 leads to the inhibition of TCR-mediated lymphocyte proliferation and cytokine secretion[10]. Immune checkpoint blockade could enhance anti-tumor immune response by blocking interaction between PD-L1 and PD-1 with antibody against PD-L1 or PD-1[11]. Immune checkpoint blockade in cancer therapy can induce tumor regression, prolong survival time and improve patients' life quality in lung cancer, melanoma and renal carcinoma, *etc* [12-18]. However, besides elicitation of antitumor immune response, immune checkpoint blockade is also associated with certain side-effects [12, 17, 18]. Therefore, it's still a challenge to enhance the antitumor immune response and at the same time reduce or eliminate side-effects during cancer immunotherapy.

Biological characteristics of PD-L1/PD-1 : PD-1, a member of the CD28 superfamily, is a 50-55 KDa type I transmembrane glycoprotein[19]. PD-1 is present on cell surface as a monomer, and the intracellular part of PD-1 contains an immunoreceptor tyrosine-based inhibitory motif (ITIM) and an immunoreceptor tyrosine-based switch motif (ITSM). Both motifs have a phosphorylated tyrosine when PD-1 is engaged, but only phosphorylation of tyrosine in the C-terminus of ITIM is a critical step for PD-1 function. Recruitment of tyrosine phosphatase SHP-1/2 after ITSM phosphorylation plays a negative role by dephosphorylating downstream effector molecules[20-22]. PD-1 is induced on many types of immune cells, including regulatory T cells (Tregs), activated CD4 and CD8 T cells, B cells, dendritic cells (DCs), mononuclear cells and myeloid cells[19, 23, 24].PD-L1 (also known as B7-H1) and PD-L2 (also known as B7-DC) are the PD-1 ligands[10, 25], which share 21–27% amino acid identity and a structural organization that consists of a signal sequence, IgV-like, IgC-like and transmembrane domains and a short cytoplasmic tail[25]. PD-L1 is selectively expressed on many tumors including lung, ovarian, melanoma, and renal tumors[26-28], and on cells within the tumor

microenvironment in response to inflammatory stimuli such as resting B cells, T cells，dendrtic cells[25, 28, 29]. Both preclinical and clinical trials have shown that the expression level of PD-L1 in malignant tumors like non-small cell lung cancer, gastric cancer and pancreatic cancer is significantly higher than that in adjacent or normal tissues[30-32]. PD-L2 is primarily expressed on myeloid dendritic cells (mDC) and monocytes in human heart, pancreas, lung and liver [25].

II. PD-L1/PD-1 REGULATION IN IMMUNE CELLS

T cells : Previous studies demonstrated that PD-1 up-regulation on spontaneous antigen-specific $CD8^+$ T cells occurs with T cell activation[33-35]. Blockade of PD-1/PD-L1 pathway augmented the frequencies of cytokine production, proliferation and total antigen-specific $CD8^+$T cell[33, 36], which suggests that PD-1 may be a regulator of antigen-specific $CD8^+$ T cells expansion[34, 35]. Blockade of the interaction between PD-1 and its ligands can promote the expansion of memory cells and $CD4^+$ T cells, and cytokine secretion[37], suggesting PD-1 may play a negative regulatory role in immune response of memory cells and activated $CD4^+$ T cells.

When co-cultured with allogeneic $CD4^+$ T cells, more $CD4^+CD25^+Foxp3^+$ Treg are induced by murine liver-derived DCs with high PD-L1 expression. However, PD-L1-deficient murine DCs fail to trigger $CD4^+CD25^+Foxp3^+$ Treg expansion[38] , which indicates that the effects of DCs on $CD4^+CD25^+Foxp3^+$ Treg induction and expansion are dependent on the PD-L1/PD-1 signaling pathway. It has been reported that TILs had increased PD-1 expression, and PD-1 on TILs can impair their immune function, including reducing cytokine production capability and impairing capacity to proliferate, by engaging PD-L1 in the tumor microenvironment[39, 40]. Blockade of PD-L1 or PD-1 can partially enhance T-cell function, tumor cell lysis, cytokine production and cell proliferation[40, 41]. Muenst *et al*.[42] found that PD-1 was positive in the TILs in 104 out of 660 breast cancer cases, and the expression level was associated with tumor size, grade, lymph node status and intrinsic subtypes of breast cancer.

DCs : PD-1 is expressed in activated DCs and can decrease the survival time of DCs and inhibit its ability of antigen presentation[24]. In wild type mice, LPS induces the expression level of PD-1 in DCs and apoptosis, while DCs from PD-1-deficient mice are resistant to apoptosis induced by LPS[24]. Moreover, PD-1 antibody can prolong the survival time of DCs during the process of maturation, suggesting that the PD-L1/PD-1 signaling pathway is involved in regulation of DC apoptosis[24].

Natural killer (NK) cells : Kit^+CD11b-NK cells express high PD-L1 and accumulate in lymphoid organs of cancer patients [43]. Adaptive transfer of Kit^+CD11b^- NK cells can promote tumor growth in pulmonary metastasis mouse models and significantly reduce dendritic and NK cell pools [43]. However, PD-1 is absent in normal NK cells but expressed on NK cells from multiple myeloma (MM) patients. Engagement of PD-1 with PD-L1 down-regulates NK cells against MM cells. CT-011, a novel antibody against PD-1, can enhance NK cell function against MM cells through affecting formation of immune complex and inducing cytoxicity in $PD\text{-}L1^+$ MM cells[44].

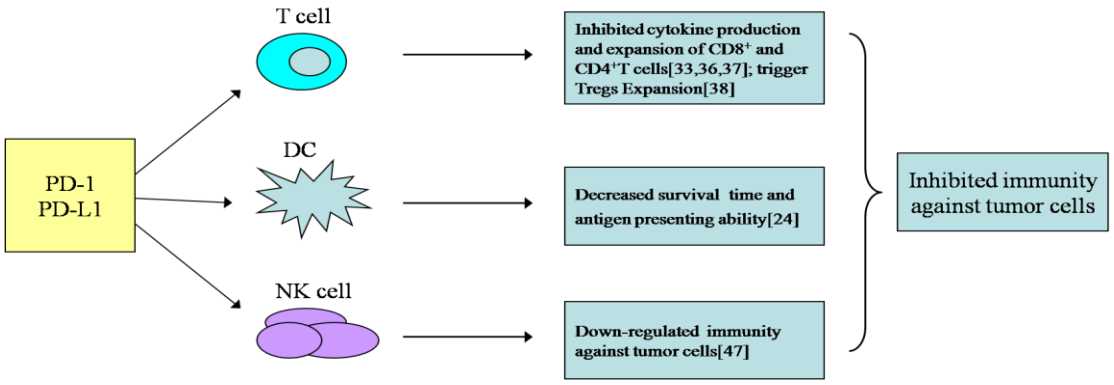

Figure 1. Effects of PD-L1/PD-1 on immune cells

III. ANTITUMOR MECHANISMS OF PD-L1/PD-1

PD-L1 is up-regulated and highly expressed in human tumor tissues due to the effects of inflammatory cytokines, such as IFN-γ, GM-CSF, IL-4 and LPS, *etc*. Through binding with PD-L1 or PD-L2, PD-1 inhibits cytokine production and the cytolytic activity of PD-1^+ tumor-infiltrating $CD4^+$ and $CD8^+$ T cells [17]. Both early preclinical and clinical trials of a fully human mAb against PD-1 have demonstrated clinical activity in patients with advanced melanoma and other cancers, associated with generally manageable side effects[45].Experiment in mice with advanced lymphoma showed that monocytic myeloid cells induced after adoptive transfer (AT) of tumor-specific $CD4^+$ T cells following cyclophosphamide treatment (CTX+CD4 AT) could mediate functional tolerization of antitumor $CD4^+$ effector cells through PD-L1/PD-1 pathway, resulting inhibited long-term tumor control and subsequent relapse. Blockade of PD-L1/PD-1 after CTX+CD4 AT therapy led to persistence of $CD4^+$ effector cells and durable antitumor effects[46].

By detecting PD-1 expression on $CD8^+$T cells from both healthy control and NSCLC patients' peripheral blood mononuclear cells, Zhang *et al.*[40] found that PD-1 expression on tumor infiltrating $CD8^+$ T cells was up-regulated, and the immune function, such as cytokine production capacity and ability to proliferate, of PD-$1^{high}CD8^+$ T cells was impaired. Blockade of PD-1/PD-L1 pathway partially restored cell proliferation and cytokine production, suggesting that PD-L1/PD-1 signaling is involved in $CD8^+$ T cell dysfunction. It has also been identified that low level of PD-1 was constitutively expressed on iNKT cells. Blockade of PD-L1/PD-1 pathway can not only prevent the induction of anergy in iNKT cells but also restore responsiveness of anergic iNKT cells, and production of IFN-γ, IL-4 and IL-2 by iNKT cells was also elevated[47]. Blockade of PD-L1 on myeloid dendritic cells (MDCs) could also enhance MDC-mediated T-cell activation and was accompanied by downregulation of T-cell IL-10 and upregulation of IL-2 and IFN-γ. T cells conditioned with the B7-H1-blockade MDCs had a more potent ability to inhibit tumor growth in mice model [48].

IV. CLINICAL APPLICATION OF PD-L1/PD-1 CHECKPOINT BLOCKADE THERAPY

Blockade of PD-L1/PD-1 has been widely applied in tumor clinical treatment. Expression level of PD-L1 in malignant tumor, such as HCC, melanoma, gastric cancer and pancreatic cancer, shows a negative correlation with tumor size and prognosis [42, 49, 50]. It has been shown that overall and progression-free survival rates for the high PD-L1 expression group were significantly lower than those for the low-expression group, demonstrating that PD-L1 expression in tumor cells is correlated inversely with the prognosis of patients with malignant melanoma and that PD-L1 expression is an independent prognostic factor for both overall and progression-free survival in these patients[50].

PD-L1/PD-1 blockades by specific monoclonal antibodies have been shown to reverse tumor-induced T cell exhaustion/dysfunction in patients with advanced melanoma [33], and potentiate or restore therapeutic anticancer immunity [51]. Blocking PD-L1 signaling allows longer persistence and enhanced infiltration of T cells into PD-L1-expressing tumor, indicating that this approach may be valuable as a means to enhance the therapeutic efficacy of combination immunotherapy against with melanoma[36]. PD-L1 expression was observed on more aggressive renal tumors[52], and PD-1 expression on tumor-infiltrating lymphocytes in Renal Cell Cancer (RCC) patients has proved to be associated with more advanced cancer and reduced overall survival[53]. Furthermore, high levels of soluble PD-L1 in the serum of RCC patients have been associated with larger tumors of advanced stages and grades and reduced survival. Anti-PD-1 antibodies has already shown promising studies in clinical trials including RCC patients, and the cumulative responses rates is 27% among patients with renal-cell cancer (9 of 33 patients)[18]. Increased OS of RCC patients treated with bevacizumab in combination with Interferon-α was observed in two phase III studies, which indicates maximal benefit for RCC patients is likely to be achieved when immunotherapy is combined with targeted agents [54-56].

Expression of B7-H1 and B7-DC were found in both the plasma and cytoplasm of cancer cells from surgically resected non small cell lung cancer (NSCLC) specimen [57, 58], but not in adjacent normal tissues[59]. However, conclusions derived from present data on the prevalence and prognostic role of PD-L1 expression in NSCLC are full of controversies. Some studies showed that PD-L1 was associated with histological types and overall survival, and might be a poor prognostic factor[59-61]. However, others indicates PD-L1 are of no independent prognostic value[58, 62, 63]. Clinical trials demonstrated that antibodies specific for PD-L1/PD-1 had promising antitumor efficacy in patients with NSCLC[17, 18]. Cumulative response rates were 18% among patients with non-small-cell lung cancer (14 of 76 patients), objective responses were observed across non–small-cell histologic types: in 6 of 18 patients (33%) with squamous tumors, 7 of 56 (12%) with non-squamous tumors, and 1 of 2 with tumors of unknown type [18]. Although PD-L1 positive tumors are expected to be more responsive to PD-1/PD-L1 inhibitors, particularly in tumors with high PD-L1 expression, responses in patients with PD-L1 negative tumors ranges from 3% to 20%[63]. Kim *et al.*[64] found that expression of PD-1 in soft tissue sarcoma (STS) cells is significantly associated with advanced clinic pathological parameters, including clinical stage, presence of distant metastasis, histological grade *etc.* It has been demonstrated that the infiltration of PD-1 positive lymphocytes and PD-L1 expression in STS cells are novel prognostic indicators for STS, and the expression levels of PD-L1 and PD-1 may provide new criteria for inclusion and exclusion of immune checkpoint PD-L1/PD-1 blockade therapy in STS clinical treatment.

V. CONCLUSION

Though immunotherapy targeting PD-L1/PD-1 has achieved great successes in many recent clinical trials, the underlying mechanisms regarding the antitumor effect of PD-L1/PD-1 signaling pathway remain to be explored. Both preclinical and clinical trials should focus on simplifying courses of treatment and reducing associated side-effects. Moreover, antineoplastic drugs should be reasonably applied to improve antitumor function of immune checkpoint blockade therapy. Altogether, treatment based on immune checkpoint PD-L1/PD-1 will definitely provide new strategies for cancer immunotherapy.

Competing interests : The authors declare that they have no competing interests.

AUTHORS' CONTRIBUTIONS

Xu Deng did the research work on PubMed and drafted the manuscript. Juan Liu and Yuan Wang revised the manuscript. Jingting Jiang and Changping Wu provided the conceptual design of the study, and edited final version of the manuscript. All authors have read and approved final manuscript.

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