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REVIEW ARTICLE

Research progression of PD-1/PD-L1 in non-small cell lung cancer

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Abstract

Lung cancer is the leading cause of cancer-related mortality worldwide. Despite great progress in the development of target agents, most people who do not harbor a mutation do not benefit from these agents. Immunotherapy, which stimulates the body's immune system to improve the anti-tumor immunity effect, is a new therapeutic method for non-small cell lung cancer (NSCLC). Programmed cell death 1 (PD-1) and its ligand (PD-L1) belong to the CD28/B7 immunoglobulin super-family and are co-stimulatory molecules that show negative regulation effects. Combined with its ligand, PD-1 can modulate the tumor micro-environment, enabling tumor cells to escape host immune surveillance and elimination and play a key role in the clinical significance of NSCLC. An increasing number of clinical trials have suggested that immune checkpoint inhibitors, including anti-PD-1 and anti-PD-L1 monoclonal antibodies, are beneficial and safe for NSCLC. Here, we review the brief history of PD-L1 as a biomarker, mechanism of action, and critical role of PD-1/PD-L1 in the treatment of NSCLC as well as the current research status and future directions.

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With the deterioration of human living environment, the incidence of cancer worldwide is increasing each year, and lung cancer has become one of the most common malignant tumors; its incidence and mortality rate rank first among all malignant tumors [1–2]. This is also true in China, where the annual mortality of lung cancer is approximately 456 people per million people [3], replacing liver cancer as the leading cause of cancer death. In recent years, the morbidity and mortality of lung cancer have steadily increased, seriously threatening the life and health of humans [4]. For non-small-cell lung cancer (NSCLC), accounting for 80%–85% of primary lung cancers, approximately 75% of patients are diagnosed in the middle and late stages. The average survival periods for these stages are 12.9 months and 3 years, while the 5-year survival rates 19% and 11%, respectively [5]. Current treatment methods for NSCLC mainly include surgery, chemotherapy, radiotherapy, and molecular targeted therapy. Surgical treatment remains the only curative treatment, but many patients with NSCLC cannot undergo surgery. In recent years, studies of cancer immunotherapy have increased after molecular targeted therapy was developed. Programmed cell death-1 (PD-1) and its ligand programmed cell death-ligand 1 (PD-L1) have been examined as targets of immune therapeutic drugs in clinical trials and showed good efficacy and tolerance [6], showing potential for treating many patients with advanced lung cancer.

PD-1/PD-L1 expression as a bio-marker in early studies

In 1992, the Japanese scholar Ishida [7] discovered PD-1 in a T cell hybridoma 2B4.11 of mouse apoptosis. Because this molecule could inactivate T cells, Ishida named the protein "programmed death 1". PD-1 is an immunoglobulin B7-CD28 family member composed of an extracellular region, hydrophobic transmembrane region, and intracellular segment. The intracellular segment contains an immunoreceptor tyrosine-based inhibitory motif and immunoreceptor tyrosine-based switch motif (ITSM). However, subsequent studies did not confirm the direct relationship between PD-1 and

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programmed cell death. Many years later, researchers deleted PD-1 to observe the effect on autoimmune disease, which began to clarify the function of PD-1 [8]. Freeman [9] confirmed the binding of a novel B7 molecule with PD-1, which inhibited the proliferation of T cells and production of cytokines. This molecule was named PD-L1, and the activation of ITSM is closely related to the response activity of effector T cells. PD-1 can be expressed on activated CD4+ T cells, CD8+ T cells, B cells, natural killer T cells, monocytes, and dendritic cells. Francisco [10] showed that PD-1 is also expressed in regulatory T cells (Treg) and can promote the proliferation of Treg cells to inhibit the immune response.

PD-1/PD-L1 expression in tumor cells

PD-L1 is highly expressed in many malignant tumors, including NSCLC [11–12], melanoma [13], renal cell carcinoma [14], prostate cancer [15], breast cancer [16], and glioma [17]. Studies [18–19] have shown that PD-L1 is also expressed in tumor-infiltrating dendritic cells, tumor-infiltrating lymphocytes, and tumor-infiltrating macrophages. The expression of PD-L1 may occur through two mechanisms [20]. Oncogene tumor control, also known as the innate resistance of tumor cells, occurs through PI3K-AKT, EGFR, ALK/STAT3, and other signaling pathways to induce tumor cell expression of PD-L1. The expression of PD-L1 is continuous and independent of the inflammation reaction in the tumor microenvironment [21–23]. Tumor immunity is driven by the microenvironment of T cells, also known as adaptive immune resistance, while PD-L1 expression is induced by inflammatory signals produced by the anti-tumor immune response, a non-persistent process that can prevent the body from infection-induced and immune-mediated tissue damage [24]. In addition, Spranger [25] showed that in melanoma models, the up-regulation of PD-L1 was closely related to CD8 T cells and did not depend on oncogene signaling. These studies indicate which patients may benefit from immune checkpoint blockade, the future studies are needed to clarify the role of these two mechanisms in different tumors. Notably, Butte [26] showed that PD-L1, in addition to binding PD-1, binds CD-80 (B7-1) to activate T cell surface binding, and then CD-80 transfers a negative regulation signal as a receptor rather than as a ligand.

PD-1/PD-L immune regulation

Mechanism of PD-1/PD-L on cellular immune regulation

PD-1 has two ligands, PD-L1 and PD-L2. PD-1 is located on the surface of activated T lymphocytes and can specifically recognize PD-L on antigen-presenting cells to activate the PD-1/PD-L1 pathway. This enables ITSM of the cytoplasmic region C of PD-1 to recruit and activate protein tyrosine phosphatase SHP-1 or SHP-2, thereby inhibiting the phosphorylation of ZAP-70 and preventing its binding to CD3ε, which can decrease the Ras-MAPK pathway, PCK pathway, and calcium-calmodulin pathway and result in decreased expression of activator protein-1, nuclear factor of activated T-cells, and nuclear factor-κB transcription factors. Thus, the proliferation, differentiation, and secretion of cytokines of T cells is inhibited. In addition, it can inhibit the proliferation of T cells by reducing the expression of the anti-apoptosis gene B-cell lymphoma-extra large and reduce T cell function by reducing the expression of GATA-3, Tbet, Eomes, and other transcription factors [27]. The PD-1/PD-L signaling pathway can also inhibit the phosphorylation of PI3K and serine/threonine kinases mediated by CD28, as well as weaken activation of the TCR/CD28 signal to immune cells [28]. Therefore, one of the main functions of the PD-1/PD-L signaling pathway is to inhibit the expression of transcription factors, thus inhibiting the activation of lymphocytes. These studies confirm that PD-1/PD-L signaling negatively regulates T cell immunity.

Mechanism of PD-1/PD-L on hum-oral immune regulation

Nishimura [29] found that the PD-1/PD-L signaling pathway not only participates in cellular immune regulation, but also regulates plasma cell production of antibodies. B cells can be activated by the direct identification of antigen peptides of antigen-presenting cells or by a combination of Tfh and co-stimulatory molecules. A previous study showed that high expression of PD-1 in Tfh cells and PD-L1 and PD-L2 in the germinal center of B cells resulted in upregulation [30] and that PD-1 had an inhibitory effect on cell immunity. These results indicate that the PD-1/PD-L signaling pathway affects the activation of B cells by inhibiting Tfh cells to reduce antibody generation. Additionally, this pathway can directly inhibit the phosphorylation of Igβ, Sy K, PLCγ2, and ERKI/2 by recruiting SHP-2 to inhibit the activation of B cells and secretion of cytokines [31]. Therefore, it is thought that PD-1 plays an important role not only in cellular immunity, but also in humoral immunity.

PD-1/PD-L1 closely related to immune evasion of lung cancer

Gene mutations that have been detected in NSCLC include those in EGFR, KRAS, and ALK, among others. Patients with KRAS mutations exhibit higher expression of PD-1 compared to those with wild-type KRAS. Additionally, the expression of PD-L1 protein is higher in patients with EGFR mutations and ALK gene

rearrangement [32]. Patients with expression of PD-1 and PD-L1 also have different clinical manifestations. Patients expressing PD-1 are typically smokers, male, and have adenocarcinoma, which is consistent with the clinical characteristics of patients with KRAS gene mutations. Those expressing PD-L1 are typically non-smoking, female, and have adenocarcinoma, which agrees with the clinical features of patients with EGFR mutations [33]. The EGFR signaling pathway, by inducing PD-L1 expression, can help tumors escape the body's anti-tumor immune response, and EGFR-TKIs can block the PD-1 signaling pathway, reduce the expression of PD-L1, and improve the overall survival rate of patients [34]. In patients with EGFR mutations and high expression of PD-L1, the sensitivity of gefitinib and erlotinib are increased, which may be because EGFR inhibitors down-regulate the expression of PD-L1 [33]. Lin [35] found that in lung adenocarcinoma patients with EGFR mutation, more than 50% showed abnormal expression of PD-L1. Among 56 patients with EGFR mutations who underwent EGFR-TKI treatment (positive rates of PD-L1 and PD-1 were 53.6% and 32.1%), PD-L1-positive patients showed a better disease control rate, longer progression-free survival, and better overall survival, suggesting that PD-L1 is a useful biomarker for EGFR-TKI.

Over-expression of the PD-L1 gene can lead to NSCLC immune escape, and recently numerous clinical studies have demonstrated that inhibiting the PD-L1 or PD-1 gene can be used in the treatment of NSCLC [36]. Blocking both PD-1 and PD-L1 can result in a good response rate for NSCLC [37]. Therefore, in the future, immune monitoring inhibitors are likely to become an important aspect of conventional treatment of NSCLC.

Potential of PD-1/PD-L1 as a target molecule in clinical therapy

Targeted immunotherapy for blocking PD-1/PD-L1 was widely evaluated in the oncology field in 2013. In NSCLC, most studies of immunotherapy involved allogeneic tumor vaccine, autologous cell therapy, and T-cell modulators [38]; multiple II or III phase clinical trials have also been conducted [39]. In 2006, the US FDA approved a humanized anti-human PD-1 monoclonal antibody for clinical treatment studies of cancer and infectious diseases. Following the listing of anti-CTLA4 antibody, anti-PD-1 antibody entered clinical trials in October 2011 to evaluate drug safety, adverse drug reactions, and survival benefit, among other factors.

Brahmer [40] reported a dose escalation phase I clinical trial (NCT00730639) of 127 patients undergoing re-treatment for NSCLC. Twelve cycles of anti-PD-1 antibody (Nivolumab) (1–10 mg/kg, 1–2 weeks) were administered to explore the safety and efficacy of anti-Nivolumab treatment of lung squamous cell carcinoma and NSCLC. The study showed that anti-PD-1 antibody had good safety and that the overall survival of re-treated patients with advanced NSCLC was significantly improved. Gettinger [41] reported another randomized phase III clinical trial (NCT01673867) of 574 patients with first-line treatment failure NSCLC. Following 1:1 random grouping, one group was treated with anti-PD-1 antibody (3 mg/kg, 1–12 weeks), while the other group received docetaxel until disease progression or the patient could no longer tolerate the toxic side effects to compare the overall survival of these two second-line treatment options. The study showed that overall survival was longer with nivolumab than with docetaxel. The median overall survival was 12.2 months (95% confidence interval [CI], 9.7–15.0) among 292 patients in the nivolumab group and 9.4 months (95% CI, 8.1–10.7) among 290 patients in the docetaxel group (hazard ratio for death, 0.73; 96% CI, 0.59–0.89; $P = 0.002$). At 1 year, the overall survival rate was 51% (95% CI, 45–56) with nivolumab versus 39% (95% CI, 33–45) with docetaxel. With additional follow-up, the overall survival rate at 18 months was 39% (95% CI, 34–45) with nivolumab versus 23% (95% CI, 19–28) with docetaxel. These results indicate that among patients with advanced NSCLC that had progressed during or after platinum-based chemotherapy, overall survival was longer with nivolumab than with docetaxel. Clinical trials of anti-PD-L1 antibodies for treating NSCLC are mostly in the phase I/II/III to evaluate the best dose and adverse reactions [42]. Spigel [43] reported a multicenter, dose escalation phase I clinical trial (NCT01375842) of 53 patients with locally advanced/metastatic NSCLC (who had undergone surgery or radiotherapy) given different doses of anti-PD-1 drugs (1, 3, 10, or 20 mg/kg, 1–3 weeks) for 1 year to study the clinical activity, safety, and bio-markers of anti-PD-L1 antibody (MPDL3280A) for NSCLC. The study showed that the median duration of treatment was 106 days (range 1–324 days), objective response rate was 24%, and progression-free survival at 24 weeks was 48%. The curative effect of MPDL3280A was correlated with PD-L1 expression. The adverse reaction rate of 3/4 was 34% (including pericardial transfer, dehydration, breathing the difficulty, fatigue, diarrhea, and pneumonia). In addition, MPDL3280A treatment of partial NSCLC patients showed delayed efficacy [44].

As additional studies are conducted, the role of PD-1/PD-L in immune regulation and the study, prevention, diagnosis, and treatment of various types of clinical diseases will be clarified [45]. Anti-PD-L1 antibody testing will reveal which population will benefit from treatment, biomarkers, and the presence of a synergistic anti-tumor effect between immune drugs [46]. As a negative synergistic stimulation signal, PD-1/PD-L plays an important role in the immune response regardless of breadth or depth,

as well as plays a critical role in immune tolerance and immune injury. PD-1/PD-L is a promising target molecule for tumor immunotherapy.

Summary and outlook

Immune drug therapy as a new treatment regimen for NSCLC (in addition to chemotherapy, radiotherapy, and molecular targeted therapy, etc.) can improve the response rate, reduce side effects, has economic advantages, and be used as an outpatient drug. Combination chemotherapy based on such drugs or single drug treatment is not only suitable for elderly patients with poor organ function and poor physical fitness who refuse chemotherapy, but also can be used as a palliative treatment [47]. Additional studies are needed to verify the feasibility of PD-1/PD-L1 as biomarkers and validate the clinical value of combination PD-1/PD-L1 inhibitors and other therapies, as well as to develop "PD-1/PD-L1 testing guidelines" to determine which population is suitable for tumor immunotherapy, optimize the immune therapy, and avoid the damage caused by immune toxicity to patients. When the immune drug is used, the length of treatment, use alone or in combination, groups that will show the greatest benefit, drug resistance mechanisms, and how to overcome drug resistance require further evaluation.

Conflicts of interest

The authors indicated no potential conflicts of interest.

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