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PD-1/PD-L1 Signaling Pathway and Tumor Immune Escape

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Abstract

PD-1 and its ligands PD-L1 and PD-L2 are widely expressed on the surface of a variety of cells and are a group of costimulatory molecules related to negative immune regulation. The activation of the PD-1/PD-L1 signaling pathway is beneficial for tumors to escape from immune surveillance, but the specific tumor immune escape mechanism is not yet clear. As far as the efficacy of anti-PD-1 and anti-PD-L1 antibodies is concerned, more in-depth research on tumor immune escape mechanisms is still needed. The article summarizes these findings to provide ideas for antitumor immunotherapy.

Keywords

Programmed Death 1, Programmed Death Ligand 1, Neoplasms, Immunotherapy

1. Introduction

At present, research on PD-1/PD-L1 signaling pathway has become a hot spot in the field of tumor immunity. In the past ten years, anti-PD-1/PD-L1 signaling pathway antibodies have achieved certain results in the treatment of Hodgkin's lymphoma, cervical cancer, bladder cancer, malignant melanoma, breast cancer, etc. [1] [2]. However, many tumors do not respond to or have low response rates to clinically approved PD-1 and PD-L1 inhibitors, indicating that more in-depth research on the PD-1/PD-L1 signaling pathway in tumors is needed [3]. In addition, the current situation of cancer in my country is still severe. According to statistics, in 2018, there were 870,000 new cancer cases in China, and the mortality rate reached 57.3%. There is a long way to go for tumor-related research. The article focuses on the molecular structure and expression of PD-1 and its ligands, PD-1/PD-L1 intracellular signal transduction, PD-1/PD-L1 and tumor immune

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escape and the anti-PD-1/PD-L1 antibody therapy is reviewed to provide ideas for anti-tumor immunotherapy.

2. Molecular Structure and Expression of PD-1 and Its Ligand

2.1. PD-1 Molecular Structure and Expression

PD-1 (programmed cell death protein 1), or CD279, is a type I transmembrane protein with a relative molecular mass of 50,000 to 55,000, which belongs to the CD28 member of the immunoglobulin superfamily. The molecule was first obtained from apoptotic T-cell hybridoma 24B.11 in mice in 1992, because it is involved in cell apoptosis, it was named "programmed death receptor-1" [4]. PD-1 is composed of two parts, the extracellular region and the cytoplasmic region. The extracellular region is composed of an IgC domain; there are 2 tyrosine residues at the end of the intracellular region, of which the C-terminal tyrosine residue constitutes an immunoreceptor tyrosine conversion motif (immunoreceptor tyrosine-based switch motif, ITSM), the N-terminal tyrosine residue constitutes an immunoreceptor tyrosine inhibition motif (Immunoreceptor tyrosine-based inhibitory motif, ITIM).

PD-1 is mainly expressed on the surface of T cells during thymus development. PD-1 has low expression on immature CD4-CD8-double negative T cells, activated NK cells, monocytes and Langerhans cells. Mature resting T cells basically do not express PD-1. Under the stimulation of antigen receptor signals and cytokine signals, PD-1 can be induced to express in peripheral CD^{4+} and CD^{8+} T cells, B cells, NKT cells, monocytes and activated DC subsets [5]. In addition, estrogen can stimulate the expression of PD-1 on T cells and APCs. IL-2, IL-7, IL-15 and IL-21 can also induce the expression of PD-1 on T cells.

2.2. Molecular Structure and Expression of PD-L1 and PD-L2

PD-L1 (Programmed cell death 1 ligand 1, B7-H1, CD274) and PD-L2 (Programmed cell death 1 ligand 2, B7-DC, CD273) belong to type I transmembrane proteins, which are composed of IgV and IgC-like domains, signal sequences, transmembrane domains and intracellular domains. PD-L1 and PD-L2 are two ligands of PD-1 and belong to the B7 family. PD-L1 is widely expressed in hematopoietic and non-hematopoietic cells, constitutively expressed on B cells, T cells, DC, and macrophages; in non-hematopoietic cells such as pancreatic islet cells, vascular endothelial cells, fibroblastic reticulum cells, neurons, astrocytes and some immune-exempt sites, such as placental trophoblast, optic neurons and retinal pigment epithelial cells are also expressed on the surface [6]. The expression level of PD-L2 is low and the range is limited, which is limited to activated DC, macrophages, mast cells derived from bone marrow and some peritoneal B1 cells. The expression of PD-L1 and PD-L2 depends on the stimulation of cytokines, such as IFN-γ, IL-1 and IL-2 can induce the expression of PD-L1 in B cells, T cells and vascular endothelial cells; IL-2, IL-7 and IL-15 could induce T cells to up regulate PD-L1 expression; IL-4 and GM-CSF could stimulate DC to express PD-L2.

3. PD-1/PD-L1 Intracellular Signal Transduction

The mechanism of PD-1/PD-L signal pathway antagonizing TCR (T cell receptor) signal transduction has always been a research hotspot. Studies have shown [7] that PD-1/PD-L1 intracellular signal transduction is mainly based on the PI3K-AKT and JAK-STAT signal pathways.

3.1. PI3K-AKT Signal Pathway

Induction experiments show that the tyrosine residues in ITSM (immunoreceptor tyrosine-based switch motif), play a key role in the inhibition of T cell activity by PD-1 [7]. After TCR was cross-linked with MHC (major histocompatibility complex) class I or class II antigens, tyrosine residues were phosphorylated, and phosphatases SHP-1 and SHP-2 could bind to ITSM sequence of cytoplasmic tail of PD-1. This leads to the direct dephosphorylation of the proximal signaling molecules physically related downstream of the TCR complex. The activation of PD-1 can enhance the activity of protein phosphatase and tensin homologs (protein phosphatase and tensin homolog, PTEN). PTEN is a cell phosphatase, which can further inhibit the activity of PI3K, and simultaneously activate Foxp3 to promote the differentiation of T cells into Treg; block the PI3K-AKT signaling pathway and reduce the response of T cells to TCR stimulation signals, leading to the inhibition of T cell proliferation, Cell damage, protein synthesis is blocked, and IL-2 release is reduced, thereby promoting tumor immune escape.

3.2. JAK-STAT Signal Pathway

JAK-STAT is a signal transduction pathway that is stimulated by cytokines. There are a variety of proteins involved in the interaction, which can regulate the body's immune function and cell proliferation, differentiation, and apoptosis [8]. The transmission process of the JAK-STAT signaling pathway is relatively simple, consisting of tyrosine kinase-related receptors, JAK and STAT. STAT is divided into 7 kinds of proteins: STAT1, STAT2, STAT3, STAT4, STAT5, STAT6, STAT7, and they are localized in the cytoplasm and activated after stimulation to form dimers and transmit signals to the nucleus. Many growth factors and cytokines transmit signals through the JAK-STAT signaling pathway, including IL-2-7, GM-CSF, PDGF, EGF, IFN, etc. In addition, JAK-STAT signal can cause immunosuppression and participate in the regulation of inflammation, obesity, stem cell maintenance and microenvironment formation before tumor metastasis. STAT (signal transducer and activator of transcription) can be used as a transcription inducer to influence gene expression through epigenetic modification, induce epithelial to mesenchymal transition (EMT), form a microenvironment that promotes tumor growth and promote tumor stem cell self-renewal and differentiation. In addition, STAT3 and STAT5 are closely related to tumor development. Studies have shown [8] [9] that continuous and crescendoing activation of STAT3 is the initiating factor for tumorigenesis; STAT5 plays a key role in the function and development of Treg and activated STAT5 is closely related to tumor immune escape.

4. PD-1/PD-L1 and Tumor Immune Escape

4.1. PD-1/PD-L1 Inhibit Anti-Tumor Immune Response

EMT is a transdifferentiation process in which tumor cells show different levels of mesenchymal phenotypes. It is a strategy for tumor cell infiltration and metastasis and changing the immunogenicity of antigens. It is of great significance for tumor cells to escape immune surveillance. Chen *et al.* [10] proved that tumor cells regulate PD-1/PD-L1 signaling pathway through the EMT axis, causing CD^{8+}T cell dysfunction and Foxp3+Treg transformation, and promoting tumor immune escape. The study of Raimondi *et al.* [11] also confirmed that MT in patients with non-small cell lung cancer can activate the PD-1/PD-L1 signaling pathway and promote tumor cells to escape immune killing. The latest study by Pichler *et al.* [12] showed that the PD-1/PD-L1 signaling pathway can promote renal cell carcinoma with sarcomatoid differentiation. Sarcoma-like differentiation is a highly aggressive form of renal cell carcinoma, which originates from EMT. The preliminary results of clinical trials that block the PD-1/PD-L1 signaling pathway in patients with sarcomatoid renal cell carcinoma showed that the objective remission rate and complete remission rate were 62% and 18%, respectively. Therefore, blocking the PD-1/PD-L1 signaling pathway may be a promising idea for the treatment of MT in patients with renal cell carcinoma. In addition, Pramod *et al.* [13] pointed out that cancer stem cells can actively participate in the overexpression of PD-L1 induced by ET through histone modification, activate the PD-1/PD-L1 pathway, and promote tumor immune escape.

Treg is the main immune negative regulatory cell. There are currently two recognized regulatory mechanisms: Treg's negative regulation of CD^{4+} and CD^{8+}T cells, and the surface of Treg PD-L1 inhibits the anti-tumor activity of PD-1 + CD^{8+}T cells [14]. This process is a two-way antagonistic process. Treg secretes cytokines such as TGF-β and IL-10 to inhibit the body's anti-tumor immune response [14]; and the PD-1 on the surface of lymphocytes promotes and amplifies the secretion of TGF-β. Therefore, in TME, continuously high expression of PD-1 can not only promote the generation of Treg, but also continue to inhibit the anti-tumor effect of effector T cells. Studies have shown that blocking the PD-1/PD-L1 signaling pathway can enhance the cytolytic activity of tumor-specific T cells, inhibit the production of IL-10, and help improve the body's anti-tumor effect [15].

In the process of tumor occurrence and development, 17.8% of tumors are related to chronic infection. With the progression of tumors and the continued existence of tumor antigens, CTL (Cytotoxic T lymphocyte) gradually loses its proliferation, cytokine secretion and cytotoxic effects, and eventually turns into depleted CTL [16]. It was found that PD-1 was highly expressed on the surface of depleted CTLs, and blocking PD-1/PD-L1 signaling pathway could restore the proliferation, cytokine secretion and cytotoxicity of CTLs. The PD-1/PD-L1 signaling pathway can induce the transformation of CTL to depleted CTL, inhibit

the body's anti-tumor immunity, and promote tumor development.

Tumor microenvironment (TME) can not only affect the function of T cells, but also affect the differentiation of B cells. When monocytes or macrophages combine with PD-1 high Breg to activate the PD-1/PD-L1 signaling pathway, it can induce PD-1 high Breg to secrete IL-10. IL-10 acts as an immunosuppressive cytokine that regulates CTL activation and induces effector T cell dysfunction.

4.2. PD-1 Related Tumor Exosomes and Tumor Immune Escape

Normal human blood has 2 quadrillion exosomes circulating all the time [17], and tumor patients' blood contains about 4 quadrillion exosomes [18]. Exosomes are a type of extracellular vesicles commonly secreted by cells, with a diameter between 40 and 150 nm, with a lipid bilayer, containing DNA, RNA, and protein and other components [19]. Early hypotheses support that exosomes may act as cellular "garbage bags" to eliminate redundant and/or non-functional cellular components. Studies have shown [20] that exosomes can promote tumor development and are related to the body's anti-PD-1 antibody-related reactions. Chen *et al.* [21] found that the exosomes released by metastatic melanoma cells carry PD-L1 on the surface. Electron microscopic observation and ELISA test confirmed that the PD-L1 carried by the exosomes is similar to the PD-L1 on the tumor cell surface of melanoma patients. The same structure can also bind to T cells. Through reverse protein array technology and Western blotting analysis, it was found that the level of PD-L1 carried by exons in patients with metastatic melanoma was significantly higher than that in patients with primary melanoma. The level of PD-L1 was positively correlated with IFN-γ level and tumor size. Circulating exosomes spread from tumor tissue to all parts of the body, bind to PD-1 on the surface of peripheral immune cells, and inhibit the anti-tumor immune response. In vitro, incubating these exosomes with activated CD^{8+} T cells can induce T cell dysfunction. In addition, Capello *et al.* [22] found that exosomes in pancreatic adenocarcinoma tissues contain B cell targets and can play a decoy effect against complement-mediated cytotoxicity. This is because humoral immune response will be triggered in the process of tumor development, and autoantibodies against tumor associated antigens will be produced. The surface of pancreatic cancer exosomes will express a large number of specific antigens against these antibodies. These circulating antibodies will combine with exosomes, weaken the complement mediated cytotoxicity against tumor cells, and induce tumor immune escape.

5. Anti-PD-1/PD-L1 Antibody Therapy

Anti-PD-1/PD-L1 antibody therapy is currently the first-line therapy for a variety of solid tumors and hematologic tumors. At present, the most widely used blocking antibody drug targeting immunosuppressive receptors is anti-PD-1/PD-L1 antibody. The antibodies against PD-1/PD-L1 targets currently in clinical use are as follows (**Table 1**) [23].

Table 1. Anti-PD-1/PD-L1 antibodies that have been used in clinical treatment and their indications [23].

Drug name	Target	Type of antibody	Indications
Nivolumab	PD-1	IgG4	Metastatic melanoma, adjuvant treatment of melanoma, metastatic non-small cell lung cancer, classical Hodgkin's lymphoma, renal cell carcinoma, head and neck squamous cell carcinoma, hepatocellular carcinoma, urethral cancer, bladder cancer, mismatch repair defect colon cancer
Pembrolizumab	PD-1	IgG4	Highly microsatellite unstable tumors, melanoma, non-small cell lung cancer, classic Hodgkin's lymphoma, head and neck squamous cell carcinoma, urethral cancer, gastric cancer
Atezolizumab	PD-L1	IgG1	Advanced bladder cancer, metastatic non-small cell lung cancer, locally advanced or metastatic urethral cancer
Durvalumab	PD-L1	IgG1	Locally advanced or metastatic urethral cancer
Avelumab	PD-L1	IgG1	Locally advanced or metastatic urethral cancer, metastatic Merkel cell carcinoma in adolescents and adults

Anti-PD-1/PD-L1 antibody therapy provides a durable clinical response and improves overall survival. However, only patients with certain tumor types responded to immune checkpoint therapy. In addition, significant challenges remain, including how to address drug resistance and reduce the incidence of immune-related adverse events [24]. In the future, Immune checkpoint therapy will expand to all areas of oncology and actively develop combination treatment regimens with surgery, radiotherapy, chemotherapy, targeted therapy and other immunotherapy inhibitors. The future of immune checkpoint therapy is promising, with opportunities to further improve outcomes for cancer patients.

6. Summary

The PD-1/PD-L1 signaling pathway plays a fundamental role in tumor immunity, and tumor cells change or defect the expression of cell-related molecules involved in immune monitoring through this, so that they can escape the host immune response. Blocking the PD-1/PD-L1 signaling pathway to treat different tumors has fully demonstrated its target potential. In order to fully understand the complex mechanisms that occur in these pathological states, further research is necessary. Anti-PD-1/PD-L1 antibody therapy is playing an increasingly important role in the field of tumor therapy, and encouraging results have been achieved in trials for the treatment of various malignant tumors. In the future, we can improve the efficacy of tumor immunotherapy and reduce adverse reac-

tions by finding new targets and combination therapy. However, there are still some controversies in immunotherapy, such as the blindness, experience and limitations of some therapeutic methods. I believe that with the deepening of research, the tumor immune escape mechanism will become clearer, and anti-tumor immunotherapy programs will be more effective, precise and individualized, benefiting more cancer patients.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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