Mechanism and Clinical Application of PD-1/PD-L1 Inhibitors in Immunotherapy

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Abstract. Tumor immunotherapy is currently a hot research topic in the field of oncology, and is an efficacious mode of tumor treatment. Programmed cell death receptor PD-1 (PD-1) is an important immunosuppressive molecule, which is mainly expressed in activated T and B cells. PD-1/PD-L1 inhibitors can block the binding of PD-1 to PD-L1, block the negative regulatory signals, and restore the activity of T cells, thus enhancing the immune response.

Keywords: PD-1/PD-L1. Tumor immunotherapy, immunosuppressive molecules.

1. Introduction

Malignant Tumor seriously harmed human health, caused nearly 10 million deaths in 2020[1]. There are many clinical treatments toward it currently, including biomarker testing, chemotherapy, hormone therapy, hypothermia, immunotherapy, photodynamic therapy, radiation therapy, stem cell transplant and targeted therapy. In recent years, immunotherapy became a heated topic among the cancer research field, and the developments in this area was selected as the 2013 Breakthrough of the Year by Science [3]. Among the three major therapies, which are PD1/PD-L1 (programmed death protein 1/programmed cell death ligand 1) inhibitors, CTLA-4 (Cytotoxic T-lymphocyte–associated antigen 4) inhibitors and CAR-T (Chimeric antigen receptor T cell) adoptive cell therapies, PD1/PD-L1 and CTLA-4 are more intensively studied [4]. Tasuku Honjo, also a Nobel Prize winner in 2018 for his discovery of cancer therapy by inhibition of negative immune regulation [5], first identified PD-1 as an inducible gene in 1992 and contributed to the establishment immunotherapy of cancer in an PD-1 inhibitor approach [6]. This article provides a review of PD-1/PD-L1 target based tumor immunotherapy.

2. Mechanism of PD-1/PD-L1 and their inhibitors

The function of PD-1/PD-L1 pathways was mainly studies on T cells, which is to inhibit T cell function in order to the regulate the magnitude of inflammation and protect he normal tissues from being damaged. PD-L1, as a transmembrane protein, binds with PD-1 and conduct inhibitory signals toward the proliferation of CTLs (cytotoxic T cell), leading to the immune tolerance, a phenomenon where the immune system loses the control to mount an inflammatory response, and prevent the emergence of autoimmune disease [7]. However, the physiology role of PD-1 and PD-L1 provided prominent mechanisms for tumor cell to avoid immunosurveillance, as their binding with each other inhibits the cytotoxicity of CTLs and exert immunosuppression [8].

There are mainly ways to construct PD-1/PD-L1 inhibitors, which are antibodies, peptides, small molecular inhibitors in different targets and forms, genetical engineering approaches and several new concept inhibitors including bispecific antibodies and targeted carriers using nanomaterials.

2.1 Antibodies

Antibody inhibitors are the major form of first-generation drugs available in clinical trials used for inhibiting PD-1 signaling pathway. As the pioneer in the cancer immunotherapy, antibody inhibitors are highly successful for its high specificity and affinity against antigens. Antibodies targets either PD-1 or PD-L1, preventing them from forming complex and activate PD-1, which effectively restore the body's immune response to tumor cells. Antibodies can also be clinically applied along with

chemotherapy and radiation therapy in order to increase the overall patient survival rate, but whether combined therapies toxicity level is safe for patients stills needs further systematical evaluations [4].

2.2 Peptides

In spite of antibodies, many peptides are capable to disrupt the protein-protein interaction between PD-1 and PD-L1. The peptide inhibitors are considered as potential alternatives and supplements for monoclonal antibody as it overcomes the its disadvantage of poor oral bioavailability, high cost, poor tissue and tumor penetration and long half-life [8].

2.3 Small molecule inhibitors

Small molecule inhibitors mainly focused on interfering the PD-L1-related interactions. There are three main functions of small molecule inhibitors: inhibiting PD-L1/PD-1 interaction through BMS-8 and BMS-202 which are able to dissociate PD-1/PD-L1 complex [9], inhibiting PD-1/SHP2 interaction by phosphorylating Y248 in the cytoplasmic domain of hPD-1 with MB (lene blue), an FDA-approved chemical for treating methemoglobinemia [10], and triggering the autophagic degradation of PD-L1 and destabilizing PD-L1 by small molecules [8].

2.4 Genetic engineering approaches

2.4.1 RNAi technology

RNAi technology utilizes siRNA (small interfering RNA) to trigger RNAi silencing of PD-L1 genes. Compared to the traditional cancer immunotherapy approaches, RNAi technology is a therapy with no T-cell-dependent which greatly increased the inhibition proficiency. However, their therapeutic use has faced numerous challenges involving safety and potency [11].

2.4.2 CRISPR/Cas technology

Clustered regularly interspaced short palindromic repeats/CRISPR associated nucleases (CRISPR/Cas) system was developed for efficient genome manipulation with advantages of a highly efficient mutation rate and simple-to-design target-specific RNA molecules [12].
Now, two CRISPR/Cas system was applied for cancer immunotherapy, which are CRISPR/Cas9 system and CRISPR/Cas13a system. With the help of CRISPR/Cas9 system, the task of anti-tumor immunity can be achieved by knocking out PD- L1 gene from tumor cells, like knocking off β-catenin from lung cancer cells and HPV16 E6/E7 cancer protein and PD-1 to enhance the killing effect on cervical cancer cells. Compared to CRISPR/Cas9 system, CRISPR/Cas13a system is able to trigger procedural death of cancer cells by enhancing the activity of RNA enzyme with crRNA (CRISPR RNA) [4].

2.5 New concept PD-1/PD-L1 inhibitors

Bispecific antibody is a newly emerged form of ICI (immune checkpoint inhibitor) with co-targeting PD-1 and PD-L1, PD-1 and co-stimulatory molecules, PD-1 and immune checkpoint, PD-L1 and LAG-3, oncogenic receptor tyrosine kinase and PD-L1, and other molecules [13]. Nanomaterial carriers are also applied in cancer immunotherapy in recent years. The aggregation of nanomaterials and porous carriers can deliver the siRNA to tumor cells, which can better perform the tumor cell killing effect [14].

3. The current application of PD-1/PD-L1 inhibitors

PD-1/PD-L1 blockade has demonstrated important activity acrosd many different tumor types clinically, including bladder cancer, breast cancer, colorectal cancer, diffuse large B cell lymphoma, follicular lymphoma, gastric cancer, head and neck squamous cell carcinoma, Hodgkin's lymphoma, melanoma, ovarian cancer, non–small cell lung cancer, pancreatic cancer, renal cell carcinoma, prostate cancer, sarcoma, small cell lung cancer, and uterine cancer [15].
Among all the different forms of PD-1/PD-L1 inhibitors, antibodies are most widely applied for clinical use currently. Until July 2020, there have been more than 2,000 clinical trials of anti-PD-1 antibodies and over 1,000 clinical trials of anti-PD-L1 antibodies [16].
Until March 2022, there are ten approved Anti-PD-1 monoclonal antibodies and five approved Anti-PD-L1 monoclonal antibodies by either FDA (Food and Drug Administration) or NMPA (National Medical Products Administration) (Table 1) [13].

Table 1 List of Anti-PD-1 and Anti-PD-L1 monoclonal antibodies [13]

Generic Name	Target	Approval Date	Certification Body
Nivolumab	PD-1	2014-12-22 2015-03-04 2019-08-23	FDA NMPA
Cemiplimab	PD-1	2018-09-28	FDA
Pembrolizumab	PD-1	2014-09-04 2018-07-20	FDA NMPA
Dostarlimab	PD-1	2021-04-22 2021-08-17	FDA
Zimberelimab injection	PD-1	2021-08-25	NMPA
Penpulimab injection	PD-1	2021-08-03	NMPA
Toripalimab injection	PD-1	2018-12-17 2019-10-09 2020-10-14	NMPA
Tislelizumab injection	PD-1	2019-12-26	NMPA
Camrelizumab for Injection	PD-1	2019-05-29	NMPA
Sintilimab injection	PD-1	2018-12-24	NMPA
Atezolizumab	PD-L1	2016-05-18 2016-10-18 2020-02-11	FDA NMPA
Durvalumab	PD-L1	2017-05-01 2019-12-06	FDA NMPA
Avelumab	PD-L1	2017-03-23 2017-05-09	FDA
Sugemalimab	PD-L1	2021-12-20	NMPA
Envafolimab	PD-L1	2021-11-24	NMPA

4. Conclusion

To sum up, the immune checkpoint inhibitors targeting PD-1/PD-L1 is at a fast developing stage, with increasing amount of approved antibodies and new-emerging advanced technologies. With a high potential of application in cancer immunotherapy, PD-1/PD-L1 inhibitors are still facing problems and challenges to be widely clinically applied. PD-1/PD-L1 inhibitors have significant individual differences, and its high cost limited its scope of application. In the future, there is a need to develop more reliable and sensitive assays for tumor diagnosis, efficacy observation, prognosis assessment, etc., to provide the best treatment strategy for clinical patients and improve the practical application in the clinic.

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