

Problems and prospects of PD-1/PD-L1 inhibitors

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Abstract. The current gold standard for monotherapy or combination therapy for patients with advanced cancer is programmed death ligand 1 (PD-L1) and receptor 1 (PD-1) inhibitors, which are typical immune checkpoint inhibitors (ICI). Rarely do therapeutic responses of cancer treatment have the breadth, depth, and tenacity that drugs based on PD-1 do. The distinctions in effectiveness and toxicity of PD-1/PD-L1 inhibitors have drawn much interest since a number of solid tumors were authorized for treatment with PD-1/PD-L1 inhibitors. However, the drug resistance and prediction of PD-1 inhibitory therapy has troubled the patients when it comes to selecting the most suitable treatment scheme. Plus, the mAbs are not perfect drugs for some inevitable defects in physical and chemical properties. Exploring the structure of PD-1/PD-L1 inhibitors has to be done more. It goes without saying that focused attention should be given to the improved PD-1/PD-L1 inhibitors' structural design and enhancing ways of medication efficacy in order to improve PD-1-based immunotherapy for cancer treatment. For instance, the pharmaceutical industry anticipates that combining PD-1 inhibitors with other medicines to improve response rates would be a future research focus. Appropriate clinical biomarkers should be developed to refine the PD-1 inhibitor response population. As a result, here the basic structure and mechanisms of PD-1/PD-L1 inhibitors were concluded. The shortcomings and prospects of inhibiting PD-1 treatment are also covered.

Keywords: PD-1, PD-L1, Immunotherapy.

1. Introduction

Immunotherapy is the process of artificially enhancing or suppressing people's immune system for the purpose of diminishing or increasing its immunological state in order to treat disease [1]. Immunotherapies can be used to treat various diseases, and the most common ones in clinical practice are tumor immunotherapy. In contrast to earlier surgery, chemotherapy, radiation, and targeted therapy, immunotherapy targets the body's immune system rather than tumor cells and tissues. Long duration of action, modest efficacy, and versatility of tumors that it can treat are the hallmarks of immunotherapy for cancer [1]. PD-1 inhibitory therapy is one of the most prominent immunotherapy therapeutic modalities.

The co-inhibitory transmembrane protein known as "programmed cell death 1 protein" (PD-1) is extensively expressed on activated T lymphocytes, B lymphocytes, and other immune cells. One of PD-1's ligands, PD-L1, is able to send inhibitory signals that control the balance of T cell activation and promote immunological tolerance. Combining PD-1 and PD-L1 causes T cells undergoing programmed death and permits tumor cells to escape the immune system. PD-L1 antibodies and PD-1 antibodies are two types of drugs targeting at PD-1. By specifically targeting PD-1 on the surface of immune cells, PD-1 antibodies can prevent the growth of malignant tumor cells, tumor-infiltrating lymphocytes, while PD-L1 antibodies have the capability to inhibit tumor growth by precisely targeting PD-L1 on the surface of tumor cells. The application of PD-1/PD-L1 inhibitors in the chemotherapy of cancer has significant research value.

However, not all patients can benefit from PD-1/PD-L1-based immunotherapy, despite their promise as a cancer treatment. Therefore, there has been a lot of interest in figuring out how to make PD-1 inhibitory therapy more effective. Therefore, to avoid the possibility that some patients may fail to respond to such drugs, biomarkers are being sought to more accurately predict the target population and effectiveness of PD-1 suppressive therapy [1].

This article describes the PD-1 pathway mechanism and the structure of PD-1-based monoclonal antibody agents. And PD-1/PD-L1 inhibitors' developmental problems and remedies were also discussed.

2. PD-1/PD-L1 inhibitors' structural basis

2.1. PD-1 antibodies and PD-L1 antibodies' structural similarities

Monoclonal antibodies of the IgG family, which have two light chains and two heavy chains, mainly make up PD-1/PD-L1 monoclonal antibodies. The variable region, or top half of the antibody, binds to the antigen and controls the drug's effectiveness. For example, pembrolizumab is more active than nivolumab because the binding rate of the upper half is different [2]. The lower half of the antibody is related to the half-life in the body and is the main scavenging fragment in the body. All antibodies were divided into four types according to different glycosylation levels. The bulk of PD-1 inhibitors are composed of IgG4 antibodies, and IgG1 antibodies are main components of PD-L1 inhibitors.

PD-1 antibody is directed against the antigen on the T cells. To stop immune cells that are coupled to antibodies from killing T cells, IgG4 monoclonal antibody is mainly used. IgG4 antibody has no ADCC and CDC effects, and its great disadvantage is that it is unstable, and subsequent processing and modification must be carried out. Moreover, IgG4 is not prone to produce anti-antibody, so the dosage of PD-1 antibody is much lower than that of PD-L1 antibody in clinical trials.

The IgG1 antibody, which binds to the antigen on the tumor's surface and functions as a signal conduction blocker, is the anti-PD-L1 antibody. The lower portion of the antibody, which has been glycosylated, will bind to NK cells or macrophages, start ADCC and CDC, and destroy the tumor cells. Therefore, the action intensity of ADCC was positively correlated with the efficacy of the antibody. But only Avelumab kept ADCC and CDC effects. Atezolizumab and Durvalumab modified segment FcγR to remove ADCC and CDC in order to decrease the synthesis of anti-antibody, whereas Avelumab did not. The IgG4 antibody of PD-L1 was created on the isotype framework, and Pembrolizumab will undergo S228P modification by transplanting the variable region sequence of strong-affinity anti-human PD-1 antibody of mouse to human IgG4 carrying stable S228P Fc-mutation [2]. It has been demonstrated that this mutation stabilizes interchain disulfide bond formation and prevents Fab exchange. It eliminates the toxicity and unpredictable therapeutic efficacy of immunotherapy brought on by IgG4 instability.

2.2. PD-1 antibodies and PD-L1 antibodies' structural distinctions

The amino acid sequence near the N terminus of the antibody molecule is highly variable. The formed domain is called the variable region (V region). The difference of antibody is partially determined by the difference of variable region. In the variable region, there are three regions with highly variable amino acid composition and sequence, which are called hypervariable regions. This region forms a spatial conformation complementary to the epitope, also known as the complementarity determining region (CDR). The variable region is the main structure for antibody to recognize and specifically bind antigen, in which CDR plays a decisive role.

Different PD-1 inhibitors have different complementary determinant regions for PD-1 binding. The overlap between Pembrolizumab binding region and PD-L1 binding site is larger than that of Nivolumab, and there is almost no overlapping PD-1 binding site between Nivolumab and Pembrolizumab [2]. Sindilizumab, whose binding epitope is distinct from that of Pembrolizumab and Nivolumab, can interfere with the overlap between the PD-L1 and PD-L2 binding sites, inhibiting the PD-1 combination of both proteins [3]. Differences in the CDR region also affect the binding site of the antibody. In contrast to Pembrolizumab, which mostly binds to the adaptable PD-1's C'D loop, Nivolumab binds to residues in the FG loop, the BC loop of the IgV domain, and the N-terminal loop [2].

IgG's binding force with FcRn can change as a result of minute changes in the CDR region of the molecule. The role of the IgG domain is regulating the interaction of FcRn and IgG. This was investigated utilizing surface plasmon resonance in an in vitro research to assess the sustained binding capacity of IgG to FcRn (SPR). It was discovered that altering just one amino acid residue might boost FcRn's affinities by around 80 times [4].

The difference of CDR region will lead to the difference of affinity between antibody drugs and FcRn, which is mainly reflected in drug clearance and drug distribution. In terms of drug clearance, the affinity constant and dissociation constant of PD-1 antibody and FcRn are related to the half-life of the drug. The FcRn-mediated cycling pathway is the non-specific clearance of IgG antibodies in vivo. Most IgG circulates in the blood through the FcRn-mediated recycling pathway, while IgG without FcRn is degraded. The IgG molecules with higher binding capacity to FcRn had longer half-life. Immunoglobulin G (IgG) molecule protection against lysosomal degradation is possible through the FcRn repair route. IgG enters catabolic cells by liquid phase endocytosis to form endosomal bodies including FcRn. When endosomes become more acidic, FcRn's affinity for IgG rises, enabling IgG to bind to the protein through certain binding sites in the Fc domain. Once bound, the FcRn-IgG complex will return to the cell surface, and when physiological pH is reached, bound IgG molecules will be released. Atezolizumab, Avelumab, and Durvalumab have half-lives of 27, 6, and 17 days, respectively [2]. In terms of drug distribution, FcRn-mediated endocytosis is one of the main ways in which IgG antibodies are distributed in vivo. To assess the biodistribution of pembrolizumab in healthy cynomolgus monkeys, the drug was combined with TFP-N-sucDf and then radiolabeled with ^{89}Zr [5]. ^{89}Zr -N-sucDf-pembrolizumab demonstrated preferential uptake in lymph nodes, spleens, tonsils, and other lymphoid tissues in the animals given just tracer.

Even if the CDR region is the same, there may still be differences between antibody drugs. In addition to differences in physicochemical properties, possible differences in post-translational modifications, such as heterogeneous glycosylation of C terminus and N terminus should also be considered.

3. The mechanism of PD-1/PD-L1 inhibitors

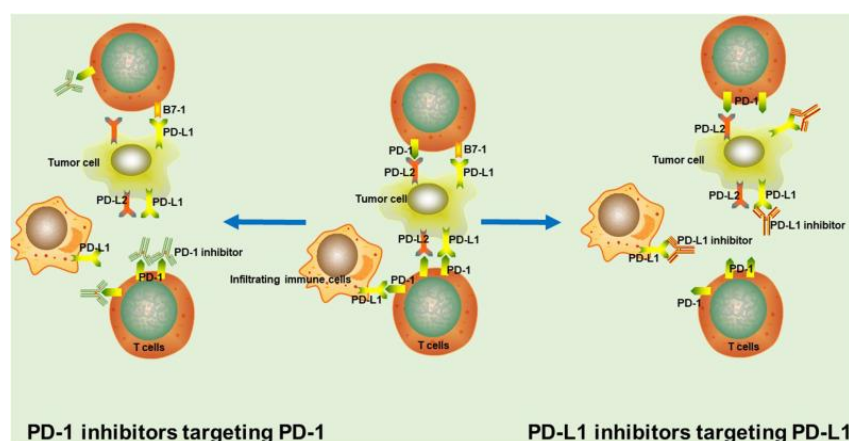


Figure. 1 PD-1/PD-L1 inhibitors' function [2].

Many human tumor tissues have PD-L1 protein expression that has been identified. Combination of PD-L1 and PD-1 prohibits T cells from activating, which causes T cells to die. This procedure is crucial in the negative control of immune response.

When the body comes into touch with foreign infections or antigen invasion, antigen-presenting cells like macrophages and dendritic cells typically capture the antigen. They then process the antigen to create an epitope that can be recognized by T cells, bind with MHC molecules, and present the antigen outside the cell for recognition by T cells. T cells bind to MHC molecules of APCs through TCR. Moreover, B7.1(CD80) or B7.2(CD86) on the surface of early T cells attach to the costimulatory signal CD28 receptor. T cells become effector T cells after activation upon receiving a

favorable regulatory signal, which starts the immunological response. The binding of PD-L1 and PD-1 can prevent T cells from becoming activated, leading to T lymphocytes death. When there is persistent antigen stimulation, in order to avoid excessive response, effector T cells up-regulates PD-1 expression on the surface. The combining of PD-1 and PD-L1 on the surface of APCs cells transmits negative regulatory signals to T cells. Thereby, T cell death or decreased T cell proliferation occurs [6].

Activation of PD-1 and PD-L1 binding is the mechanism by which malignancies circumvent host tumor antigen-specific T cell immunity [7]. The PD-1 pathway is continuously activated in the tumor microenvironment as a result of the tumor microenvironment inducing the PD-1 proteins overexpressing in infiltrating T cells [8]. And PD-1 ligands, PD-L1 and PD-L2, are up-regulated by tumor cells. This promotes immune tolerance and ultimately prevents autoimmunity. In order to free T cells from their tired state, inhibitors of PD-1/PD-L1 can stop the pathways for negative regulatory signals.

Through the patient's own immune system being triggered, PD-1/PD-L1 inhibitors can thereby fighting cancer. Monoclonal antibody therapy based on the PD-1/PD-L1 pathway prevent T lymphocytes from being inhibited by tumor cells. Moreover, it improves the immune system's capacity to identify and eliminate foreign tumor cells. The camouflage of tumor cells will be decisively recognized by immune cells. As a result, T cells can restore the ability to kill cancer cells, so as to alleviate the disease.

PD-1 drugs block both ligands, in contrast to PD-L1 inhibitors, which primarily inhibit the PD-1/PD-L1 pathway and hardly impact the PD-1/PD-L2 pathway. Furthermore, by inhibiting the co-inhibitory effect of B7.1 and PD-L1, PD-L1 inhibitors, unlike PD-1 inhibitors, totally boost T cell activity and cytokine production.

4. Current drawbacks of PD-1-based therapy

4.1. Drug resistance

PD-1/PD-L1 monoclonal antibody agents have enormous potential, but because to the issue of drug resistance, not all patients can benefit from this pharmacological-based approach. There are two kinds of drug resistance. One is called the primary (innate) resistance, indicating that the patients lack of positive effect after the first therapy; the other is called the secondary (acquired) resistance, indicating that patients' response to therapy is objective at first but ultimately develops into progressive diseases over time. The effectiveness of PD-1 blocking therapy currently shows to be influenced by several variables, including tumor immunogenicity, T-cell exclusion, exosomes.

Recent findings showing that individuals sensitive to PD-1 therapy contained more nonsynonymous single nucleotide mutations. Plus, higher HLA Class I and Class II New epitope loads than nonresponders were detected. The status of immunogenic tumor antigens and the effectiveness of T lymphocytes targeting malignancies could be inferred from this. T cell exclusion will upregulate many other immunosuppressive factors, while PD-1/PD-L antibody can only reverse part of the inhibitory effects, much more immunosuppressive proteins will still work, leading to poor therapeutic response. For instance, the analysis of the mice model of colorectal cancer showed that inhibitors such as LAG-3 were up-regulated, leading to resistance to PD-1 inhibitory drugs. As demonstrated by recent investigations, PD-L1 can be found in isolated exosomes in the plasma of individuals who have different types of cancer. Inhibiting T cell-mediated immunity and promoting the growth of several tumor types are the effects of TEX-bound PD-L1.

4.2. Biomarkers of PD-1-based therapy

The greatest barrier to PD-1-based therapies' practical implementation is their subpar response rate in some individuals. So it is essential for patients to determine if they are qualified to receive such medication by choosing biomarkers. Because the effectiveness of PD-1 suppressive medication can be accurately and delicately forecast by biomarkers.

For instance, the therapeutic effects of such drugs are correlated with biomarkers representing the immune microenvironment and the internal properties of tumor cells. PD-L1 expression, tumor mutational burden (TMB), and microsatellite instability (MSI) are examples. According to research, positive correlations exist between PD-L1 expression and the potency of PD-1/PD-L1 monoclonal antibody treatments [9]. Additionally, there are several FDA-approved studies that look at PD-L1 expression in IHC for auxiliary diagnosis. Neoantigens, which are hypothesized to help the immune system recognize cancers and enhance antitumor T lymphocytes' proliferation, are abundant in tumor cells with elevated TMB expression. As a result, TMB partially implies the PD-1 suppressive therapeutic response. MSI reflects DNA replication errors caused by mismatch repair gene defects, which is approved for Pembrolizumab efficacy prediction of mismatch repair gene defects and highly unstable microsatellite solid tumor by FDA in 2017 for the first time [10]. Besides, gut microbiota and circulating biomarkers were also found to be valuable predictors. Therefore, the establishment of multiple biomarkers would provide patients with more appropriate treatment.

5. Strategies to design better PD-1/PD-L1 inhibitors

5.1. Bispecific antibody design

Artificial antibodies with two distinct antigen-binding sites that may engage with both targets and T cells to induce a variety of immunological responses are referred to as dual antibody medicines. Bisspecificity antibodies, which add a particular antigen binding site in comparison to monoclonal antibodies, have a substantial therapeutic benefit due to their high specificity, powerful targeting, high interest, excellent stability, lower dose requirements, and reduced toxicity and adverse effects. Since bispecificity antibodies, unlike monoclonal antibodies, have distinct biological properties such as eliciting a directed immune response by attaching to several epitopes, the pipeline for their development has grown in recent years.

Confirmed by a study, PD-1 and CTLA-4 dual antibody treatment, which uses the medication MEDI5752 as an example, is considerably safer and more efficacious than mAb therapy [11]. The DuetMab platform was used to create MEDI5752, which uses amino acid mutations in the heavy chain of the Hole to eliminate the hole chain's ability to bind to protein, a Knob-Into0Hole to prevent heavy chain mismatches, a modified disulfide bond to avoid heavy and light chain mismatches, and a modified disulfide bond to prevent heavy and light chain mismatches. Besides, MEDI5752, L234F, L235E, and P331S mutations were employed to remove ADCC and other antibody-related effects. The PD-1/CTLA-4 dual specific antibody MEDI5752 may readily bind to CTLA-4-activated PD-1 and bind to PD-1 and CTLA-4 targets on the same cell. The antibody's capacity to bind to CTLA-4 is dramatically improved as the ratio of PD-1 to CTLA-4 rises. This is mostly caused by the double specific antibody's two targets' synergistic binding impact. Immune-related adverse events (irAEs) were decreased as a result of the antibody's binding to PD-1+/CTLA-4+ double-expressing T cells. Additionally, unlike previous PD-1 MAbs, MEDI5752 can block PD-1 targets by inducing CTLA-4-dependent PD-1 endocytosis and degradation. Studies on animal models revealed that following injection, MEDI5752 was mostly accumulated in tumors, and that this aggregation was largely reliant on the binding of antibody to PD-1.

IBI319 is a PD-L1/4-1BB dual-antibody designed by Cinda Bioengineering [12]. The Fab targeting PD-1 is derived from Sintilimab, an antibody already marketed by Cinda, and the heavy chain is mutated M54S to eliminate the heterogeneity caused by methionine oxidation. The anti-4-1BB component was made of a 4-1BB mab and modified with M101A and G106A in the heavy chain's CDR region to stop methionine oxidation and decrease antibodies' affinity. In addition, the Fc terminus of the antibody was mutated with L234A, L235A, and N297Q to eliminate the binding of the antibody to FC γ r, thereby eliminating the ADCC and other effects of the antibody, while preserving the binding ability of the antibody to FcR. In animal studies, IBI319 demonstrated a dose-dependent therapeutic effect and was superior to the combination of two MAbs. In terms of toxicity, no associated hepatocellular toxicity was detected in the IBI319 treatment group, while some toxicity

was observed in both CD137 mab treatment groups, suggesting that IBI319 treatment is safer than CD137 mab. By contrast with the first-generation immunotherapeutic drugs, the second-generation immunotherapeutic drugs can achieve superior effect in immunotherapy and reduce the occurrence of adverse reactions.

Dual antibody therapies are an improved form of monoclonal antibody drugs and have emerged as one of the key immunotherapy drug development areas. At this point, dual antibody medication research and development is highly valued by Chinese and international pharmaceutical companies, and a growing variety of pharmaceuticals are being created and used in clinical trials. The global market for dual antibody medications is anticipated to continue expanding quickly as these drugs are approved and listed one after the other. It is anticipated that this will in the future give people with linked conditions more hope.

5.2. Small molecules design

With shorter half-lives and greater flexibility in timing and dose adjustment, small molecule PD-L1/PD-1 inhibitors have distinct advantages over therapeutic antibodies. These advantages help to reduce immune-related adverse events and increase the benefit-hazard ratio. Additionally, oral delivery is more practical for use as monotherapy and in conjunction with other targeted medications. It should be noted that these substances frequently promote tissue permeability and may improve anticancer activity. Small molecule medications, on the other hand, don't have this issue, and they also have benefits including minimal immunogenicity, good patient compliance, affordability, and ease of storage. Consequently, the creation of PD-1 small molecule inhibitors has emerged as a popular research area. PPI has been labeled as an untreatable target as it is much more challenging to develop small molecule medications that can directly inhibit the interaction of two proteins than it is to do so for more conventional therapeutic targets. The following causes account for the majority of it.

First of all, when two proteins, whether they are the same or different, come into touch, a protein interaction takes place at the interface of that particular location. The interaction interface typically has a surface area of 1500 to 3000 Å², which is greater than the receptor-ligand contact region (300 to 1000 Å²) and has a high degree of hydrophobicity. Furthermore, PPI interfaces frequently lack pockets or grooves and are flat, which makes it harder for planned small molecule to attach. Also, the amino acid residues implicated in PPI are either continuous or discontinuous in their protein structures respectively, leading to high-affinity protein binding. Small molecule drugs find it challenging to inhibit such high-affinity interactions. Additionally, PPI-targeting pharmaceuticals require a greater molecular mass (> 500 Da) than conventional small molecule medications (200–500 Da).

Even when the standard approaches to PPI inhibitor creation are ineffective, suitable solutions can still be developed. PPI inhibitors have been subjected to high-throughput screening (HTS), one of the most popular techniques for discovering novel drugs. Finding molecular fragments out of fragment libraries is the goal of fragment-based drug discovery (FBDD). Because PPI contact regions often consist of discontinuous hot-spots, which may be utilized to detect and confirm PPI budding drug fragments by X-ray crystallography and other techniques, FBDD is a superior strategy for designing PPI inhibitors than high-throughput screening. After that, fragment joining, fragment optimization, and fragment self-assembly were used to create the final PPI seedling compound. Additionally, there have been two design methodologies for PPI modulators based on the structure design since hot-spots can offer crucial structural information and serve as the foundation for the logical design of PPI inhibitors. The first one is based on hot-spot structures, and fresh designs or biological isostructures can provide new small molecule inhibitors. The structures of the other are mimicked by the second design, a peptide-like one, mostly by computational methods and phage display. Plus, software-assisted virtual screening may also be used to screen chemicals.

An alternative to antibody therapy may be INCB086550, which shares some biological characteristics with the PD-L1/PD-1 monoclonal antibody [13]. In vitro, INCB086550 causes PD-L1 dimerization and internalization, stimulates the generation of stimulus-dependent cytokines in

primary human immune cells, and selectively inhibits the PD-L1/PD-1 interaction. By preventing the PD-L1/PD-1 pathway, INCB086550 stimulated T cell activation in CD34⁺ humanized mice and slowed tumor growth in vivo. PD-L1/PD-1 inhibition in peripheral blood cells, along with immune activation and cancer progression suppression, were confirmed by early clinical data from patients (NCT03762447). Though small-molecule immune checkpoint inhibitors have been reported before, this is the first time complete preclinical data and early clinical data have been made public for a pharmacogenic small-molecule inhibitor capable of preventing the interaction between PD-1/PD-L1. It is encouraging to witness that preliminary clinical activity of INCB086550 supports its future investigation in patients and resembles the preclinical performance of currently licensed PD-L1 antibodies. Small molecule PD-L1 inhibitors are therefore anticipated to be a crucial and efficient substitute for reestablishing antitumor immunity in cancer victims.

5.3. Combination therapy enhances tumor recognition

For patients with low immunogenicity of TMB and MSI stable antigen presentation disorder, antigen recognition can be alleviated by combined chemotherapy, oncolytic virus, tumor vaccine, etc. When initiating tumor death, chemotherapy can induce the release of tumor antigen, give damage-related signals, and change DC into immune-stimulated APC to activate CD8⁺T cells. Decitabine, for instance, can improve afterwards antigen recognition in esophageal cancer by up-regulating MAGE-A3 expression. Oncolytic viral therapy, like autoimmunity, can lead to tumor antigens releasing, which improves the activation and release of T cells and reduces drug resistance of PD-1/PD-L1inhibitors. Clinical studies of melanoma patients have shown that when PD-1 inhibitory therapy is combined with a peptide vaccine, can improve the overall survival rate through improving T cell activation.

5.4. Bacteria transplantation

Many studies have pointed out that immunotherapy combined with high-dose broad-spectrum antibiotics will reduce the treatment efficiency due to intestinal flora imbalance. Ten patients with resistant metastatic melanoma participated in a clinical study, in which the toxicity and viability of fecal microbiota transplantation (FMT) and the PD-1/PD-L1 monoclonal antibodies' reinstatement are thoroughly evaluated [14]. This investigation's results were encouraging, and in the intestinal lamina propria and microenvironment of the tumor, it was discovered that FMT therapy was linked to favourable alterations in the infiltration of immune cells and gene expression patterns. It showed that intestinal flora transplantation can relieve the drug resistance of PD-1.

Better methods of medication delivery are also being searched for due to the issue that PD-1 immunotherapy barely works for a small fraction of the population. The microbial drug delivery system exemplified by *Escherichia coli* differs from the conventional abiotic drug delivery system in that it preferentially colonizes the tumor system, as well as a microorganism. In a recent study, bacteria were used as drug carriers in PD-1 treatment strategies. Nissle1917, a harmless strain of *E. coli*, was transformed by genetic engineering to synthesize PD-1 antibody and CTLA-4 antibody in vivo [15]. The results showed that after a single local injection into the tumor, the bacteria could function in the tumor of mice for at least two weeks. And the bacteria are mainly enriched in tumor sites without affecting normal tissues. Compared with traditional antibody therapy, the therapeutic effect of this therapy is also significantly better.

6. Conclusion

The pattern of cancer treatment has radically changed and obtained great success thanks to cancer immunotherapy over the past ten years. At present, a variety of immunosuppressive drugs have been marketed. Among these, the PD-1/PD-L1 antibody medication, a powerful and all-encompassing anti-tumor agent, is crucial in the field of treating tumors. Nevertheless, PD-1-based therapies are not applicable to all tumor patients. Unsolved issues include how to combat drug resistance and discover

biomarkers that can precisely forecast the success of PD-1 suppressive therapies. Moreover, there are also problems of the PD-1/PD-L1 inhibitors molecular design. Antibodies' immunogenicity is also a very important factor, as we all know. Since antibodies are biological macromolecules, they frequently cause a cytokine storm when they enter the human body, triggering a powerful immunological response, a range of clinical side effects, and in some extreme circumstances, even death. To circumvent such problems, it is currently unknown whether small molecule PD-1 and PD-L1 inhibitors can be made. Plus, ways to improve the efficacy of drugs strategically also deserves more consideration. In a nutshell, after considering their therapeutic potential and underlying defects, there is no denying that PD-1 suppressive therapy shows promise in cancer immunotherapy. Current studies on PD-1 suppressive therapy is continuously investigating methods for better structural design and drug resistance evasion. It is hoped that in the follow-up drug structure design, the concept of "Quality by Design" will be further optimized and the PD-1 inhibition therapy will be further developed into a more safe, reliable and effective immunotherapy strategy.

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