Immune Checkpoint Inhibitors Current Advances and Future Perspective

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Abstract. Immune therapy has become the fourth method to treat tumors after the traditional methods including radiotherapy, chemotherapy and surgery. Immune therapies use humans' innate immune system to fight against tumors. Nowadays there are many immune therapies used in clinic, including immune checkpoint inhibitors, cancer vaccines, cytokine therapies, and so on. One of the most mature and widely used immune therapies is immune checkpoint inhibitors (ICIs). Because tumor surface have some proteins that can bind to the receptors on the immune cells, once they are bound the function of the immune system will be inhibited and so tumors can live in human bodies and not be killed by the immune system. Immune checkpoint inhibitor is a method that uses different proteins to block the receptors on the immune cells and the ligands on the tumor cells. In that way, the immune cells will be activated, and kill the tumors. It is worth mentioning that immune checkpoint inhibitors CTLA-4 and PD-1 have made some process in clinical. This article will review some immune checkpoints, make detailed introductions about immune checkpoints CTLA-4, PD-1, and PD-L1 and their recent advances and some immune checkpoints under investigation.

Keywords: Immune checkpoint, immune therapy, CTLA-4, PD-1, PD-L1.

1. Introduction

Tumor immune therapy uses use human innate immune system to kill tumors and protect human bodies. Immune therapies developed rapidly these years since 1984. Tumor immune therapy is divided into two different types due to its function. Active immunotherapy like tumor vaccines imports immunogenic substances into a human body to stimulate the body to produce a specific immune response to kill tumors. Passive immunotherapy like antibody treatment and cytokine therapies uses immune response products including antibodies, immune effector cells and some immune peptides imported into the patient's bodies to active their innate immune system to kill the tumors. In antibody treatment, immune checkpoint inhibitor is the most concerned therapy. Immune checkpoints is a wide range of molecules of the immune system, which is used to prevent immune cells like T cells and NK cells from killing the original cells. However, tumor cells have developed to over-express these molecules to inhibit the innate immune system and escape from the immune system to grow into tumors. Immune checkpoint inhibitors are to activate the inhibited immune system by using special molecules to block the receptors and antigens. And once the immune system is activated the tumor cells can be recognized and killed. CTLA-4, PD-1, and PD-L1 are the immune checkpoints that have been used and studied the most. Drugs using these immune checkpoints have been approved by FDA in the past few years and get progress in clinical trials. However, although immune checkpoint inhibitors developed rapidly, many immune checkpoints are under investigate, like TIM-3, and LAG-3 the exact mechanisms are unknown. Despite of the immune checkpoint inhibitor is more safe and -lasting, it still has many disadvantages like side effects which might kill the original cells when using the immune checkpoint inhibitors. Current studies have found that the use of immune checkpoint inhibitors in different type of cancers like liver cancer, lung cancer and esophageal caners, etc. do have a better curative effects compared with other treatments. The most wildly used immune checkpoint inhibitor PD-1 and PD-L1 have been proved that they are effective in many cancers like liver cancer and lung cancer. Pembrolizumab and nivolumab (drugs using

immune checkpoint PD-1) was proved that they can treat liver cancer and esophageal cancer without serious side effects[1,2]. However, although immune checkpoint inhibitors show a promising future it still have adverse events during treatments. Scientists have found the use of immune checkpoint inhibitor would damage patients' body more or less. The use of ipilimumab and nivolumab would cause kidney damage and the kidney damage occurred more frequently in patients who use combination ipilimumab and nivolumab. And in the published cases of using ipilimumab and nivolumab combination therapy to treat patients with melanoma all the patients have biopsy-proven granulomatous or diffuse acute interstitial nephritis[3]. And the adverse effects of immune checkpoint CTLA-4 currently include a slight rash on the skin after use, abdominal pain, diarrhea, side effects in the digestive system in addition to abdominal pain and diarrhea and even ileitis. Some patients will also have diabetes or thyroid dysfunction and so on after use. The circumstances may vary depending on the user's physical factors[4].

2. CTLA-4

T cells have a transmembrane receptor called CTLA-4. CTLA-4 acts as a switch by binding to a receptor on the surface of the antigen cell, thereby terminating the immune response. CTLA-4 inhibitors also inhibit the CTLA-4 molecule, causing T cells to multiply rapidly and then attack tumor cells. CTLA-4 transmits inhibitory signals to T cells, thereby inhibiting T cell activation. At the same time, CD28, which is homologous to CTLA-4, transmits stimulatory signals and activates T cells to inhibit the binding of CTLA- 4 and B7, which can enhance the effect of immunotherapy. In our bodies, B7 recognizes and binds to CTLA-4, which reduces the immune response of T cells. Therefore, the tumor cells pass through the immune checkpoint, which is called immune escape. CTLA-4 mab severs the binding of CTLA-4 to B7 by binding to CTLA-4. It cuts the connection like a knife. The binding of CTLA-4 monoclonal antibody to CTLA-4 also promotes the binding of CD28 and B7, which activates T cells and thus enhances immune recognition and killing. The immunosuppression of CTLA-4 and PD-1 is very different from that of PD-L1. CTLA-4 checkpoint inhibitors enhance the immune function, making immune cells more aggressive. It is for this reason that it has greater side effects. Ipilimumab was given the go-ahead by the American Food and Drug Administration (FDA) on March 25, 2011. Since then, this immune checkpoint inhibitor has been officially used to treat cancer. The principle of this drug is very simple, it blocks the binding of CTLA-4 to the B7 molecular ligand, so as to ensure the proliferation and activation of T cells, and further achieve anti-tumor effects. Ipilimumab has shown promising results in clinical trials, with significant clinical improvements compared to controls. But the strange thing is that when ipilimumab is used clinically, it often has side effects such as headache, itching, and rash. Ipilimumab can also cause immune diseases in the digestive system, nervous system, skin and even liver and hormone-producing glands. New cancer therapy options are being developed as a result of improvements in our understanding of the immune system's regulatory mechanisms. As of now, clinical data offers proof-of-concept that inhibiting harmful immune regulatory pathways can result in measurable tumor responses. The very long duration of objective tumor regression following the use of monoclonal antibodies that inhibit CTLA4 in patients with advanced melanoma is the most promising finding. A better understanding of the mechanisms of toxicity and response will make it possible to more precisely characterize the study population and provide adjuvant drugs to control toxicity or response [5]. Although the application of CTLA-4 inhibitors has been extensive, it is not only recognized by many countries including China and the United States, but also widely used in clinical treatment. However, CTLA-4 is not only resistant but also has some side effects such as the body may produce some reactions after use. But as the first operational immune checkpoint inhibitor, it will always be a milestone in the history of human cancer.

3. PD-1

In 2014, PD-1 monoclonal antibody Opdivo Nivolumab, also known as O drug, was successfully marketed. Thus began a new era of tumor immunotherapy. Since then, PD-1 inhibitors have been recognized and purchased by more and more people around the world. Its sales are also rising rapidly. An essential immunosuppressive molecule is PD-1. T cells are under the control of the PD-1 protein that is expressed on their surface. Normal cells express the PD-L1 protein and bind to the PD-1 protein to make the T cells "quiet down." However, some tumor cells also gradually learn how to express PD-L1, which allows T cells to put the brakes on the fight against tumor cells. T-cells lose their ability to attack tumor cells. The T cells now treat the tumor cells as they would any other cell, losing their aggression against them. PD-1 monoclonal antibody is one such miracle drug, which can prevent the PD-L1 protein expressed by tumor cells from binding to T cells so that T cells can kill tumor cells. At present, PD-1 monoclonal antibody has a significant effect on lung cancer, melanoma and other cancers. PD-1 monoclonal antibody is also still being studied, and PD-1 monoclonal antibody may have therapeutic effects on more cancers in the future. PD-1 monoclonal antibody also has some resistance like most immune checkpoint inhibitors, which may be a common disease of immune checkpoint inhibitors. “In recent years, nivolumab therapy has achieved notable success. In addition, a large proportion of acquired resistance occurs after the initial response, which suggests the need to understand resistance on a mechanistic basis. Primary or acquired resistance to some antibodies may occur in tumor therapy[6]. At present, PD-1 is still under study, although some related drugs have been developed, but due to the own reasons of PD-1 inhibitors, such as resistance, this type of drug is still under study. As with many immune checkpoint inhibitors, it would be a great advance in the future if we could overcome the two major problems of resistance and side effects.

4. PD-L1

PD-1 is an essential immunological checkpoint that communicates inhibitory information to T cells to fend against autoimmune reactions. To circumvent immune responses, cancers manufacture more of the PD-1 ligand (PD-L1). PD-L1 blocking drugs may have an amazing, long-lasting effect on patients with a range of malignancies. Numerous studies have demonstrated that IFNs, which encourage T lymphocyte cross-priming by dendritic cells (DCs), are crucial for limiting tumor growth. However, in the tumor microenvironment (TME), type I IFN expression is constrained or diminished. In fact, type I synthesis and innate sensing may be inhibited by the TME's increased DNA and antigen degradation as well as some tumor cells' lack of cGAS-STING pathway signaling. IFNs are among the greatest effective viruses at triggering the production of PD-L1, which inhibits the resulting T-cell attack on the tumor by creating a negative feedback loop. We combine anti-PD-L1 antibodies with IFN to target the PD-L1 and IFN-receptor in order to overcome the aforementioned constraints. IFN is thought to target tumor tissues more precisely.IFN-anti-PD-L1 therapy improves antigen cross-presentation while overcoming the immune suppression brought on by PD-L1.

In certain circumstances, anti-PD-L1 medication has been effective. The outcomes of a phase II/III randomized, open label, clinical trial evaluating the success rate of pembrolizumab and docetaxel in the management of patients with advanced non-small-cell cancers of the pulmonary tract show that: the drug known as group demonstrated a modest but substantial reduction in overall survival, but no such enhanced performance was seen in progression-free survival. Pembrolizumab, however, when evaluated just in the patient the fraction in which PD-L1 had been found in at least 50% of cells in the tumor, it significantly increased the amount of progression-free survival and length of life benefit, highlighting the growing significance of careful cohort selection in clinical trials. Numerous medications are anti-PD-L1. For the past 20 years, oncogenic proteins that are preferentially changed or overexpressed in cancer cells have been the target of therapeutic medications meant to treat cancer. Examples include specific oncogenic pathways or targets in malignant cells that are attempted to be blocked by targeted drugs (such as trastuzumab or imatinib). The group worked with developed the

small chemical inhibitor SI-2. Every one of the members of the same group of coactivators that combined that cause cancer have high levels in a variety of cancer subtypes of tissue.[7]

Anti-PD-L1 provides benefits, however there are also drawbacks. It has been suggested that the production of immune-suppressive signals by T cells is what makes PD-1/PD-L1 blocking medications effective. It has been assumed that a sufficient number of tumor-infiltrating lymphocytes (TILs) is related to a greater response to PD-1/PD-L1 blocking medicine.To (re-)activate tumor-specific T cells, however, PD-1/PD-L1 blocking treatment alone would not be adequate, especially in the presence of substantial cellular infiltration. In these situations, other unfavorable co-inhibitors might be required to be slowed down or stimulatory signals may require additional enhancement in order to trigger T-cell (re-)activation.[8]

5. TIM-3

Immune cells like T cells laid out Tim-3 more frequently. macrophages, and others. Tim-3 synthesis in various tissues of organisms is yet unclear. Separate proteins were taken out of the organs of the kidney, liver, spleen, and the lung tissues. Tim-3 expression was extremely noticeable in the kidney, according to a Western blot analysis, demonstrating that different organs expressed Tim-3 in various ways. New prospects for the treatment of cancer have been made possible by recent developments in immunotherapy. For example, it has been indicated that multiple immunosuppressive mechanisms in nasopharyngeal carcinoma include interleukin-10, growth factors, Fas-ligand, Foxp3+ regulatory T cells and Galectin-9, and that the Galectin-9/Tim-3 axis is a specific mechanism of reduced immunity in nasopharyngeal carcinoma [9].

Additionally, this immunotherapeutic medication with axis targeting is currently accessible. For those with recurrent NPC, immunotherapy that targets NPC-specific immunosuppression may offer new hope. Clinicians must decide whether immunotherapy can be used as a salvage treatment option. They investigated this question by comparing immunological changes around tumors in patients with primary and recurrent nasopharyngeal cancer. The study's objectives are to assess the immunologic changes brought on by chemotherapy and radiation treatment for initial NPC and to determine the potential therapeutic impact of immune-modulating drugs for individuals who would eventually develop periodic NPC. [9]

6. LAG3

LAG3 is a member of the immunoglobulin superfamily [10], an immune checkpoint that is generally expressed in activated T cells, NK cells, B cells, and DC cellular roles. LAG3 binds MHC class II, Gal-3, α-syn, and LSECtin [10]. Several previous studies found that LAG3 was upregulated in CD+ T cells [11]. LAG3 may be the third advanced IC to be investigated in clinical follow-up after CTLA-4 and PD-1, and is promising mainly in blocking the melanoma and other cancer actions of LAG3, especially in combination with other IC blockades [10]. Previous research found that in PD-1/LAG-3 double knockout mice model the transplanted tumors are rejected, while the mice model with PD-1 single knocked experience delayed tumor growth[11].The Eftilagimod alpha, is the initial first-in-class LAG3 modulator, which could active APCs by binding MHC class II, stimulate the proliferation of DCs, enhance Treg immunosuppression to CD8+ T cells. In clinic trails, the Eftilagimod alopha has made some progress, and the other trails are still studying. It started clinical trials in 2013 as the first anti-LAG-3 antibody to be produced commercially[12]. However, in spite of LAG3 has huge potential in immunetherapies, LAG3 was only discovered in 1990, and many of its mechanisms are under investigation.

7. Conclusion

Immune checkpoint inhibitors are to use immune checkpoints to activate the inhibited T cells and immune system to produce toxicity factors and kill tumor cells. Compared with traditional therapies,

immune checkpoint inhibitor has longer treatment effect and are less harmful in a clinic. Up to now, many tumor drugs that depend on immune checkpoints have been developed and approved by the FDA. The most widely used ICI are CTLA-4, PD-1 and PD-L1. Anti-tumor drugs using these immune checkpoints are still developing, and studies about other immune checkpoints under investigation like TIM-3, LAG-3 are still going. In clinic, the main problem is the side effects and low efficiency of immune checkpoint inhibitors. So, reducing drug toxicity to human body is important. Finding or creating special antibodies to block the receptors and antigens is promising. Apart from the single use of immune checkpoints, drugs that combine different immune checkpoints are worth developing. In short, immune checkpoint inhibitor provides a new treatment for tumor patients and is promising.

Authors Contribution

All the authors contributed equally and their names were listed in alphabetical order.

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