Proceedings of the 2nd International Conference on Biological Engineering and Medical Science (ICBioMed 2022), Part I
DOI: 10.54254/2753-8818/3/20220242

The Mechanism of Action of Anti-CTLA4 and Advantages, Limitations and Development in Cancer Treatment

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Abstract. At present, with the frequent occurrence of cancer, especially malignant cancer, more and more scholars begin to pay attention to the treatment method, treatment effect, prognosis, and side effects of cancer. Anti-CTLA-4 immunosuppressive agents have become another pillar of the treatment of related cancers with high efficacy, low toxicity, and good prognosis. Research on Anti-CTLA-4 has never stopped. This article focuses on Anti-CTLA-4, summarizes the related mechanism, clinical treatment, and toxic side effects of CTLA-4, and hopes to provide a new research direction for researchers.

Keywords: ICIs, CTLA-4, ipilimumab, side effects

1. Introduction

According to the cancer deaths in the United States by A Cancer Journal for Clinicians in 2022, the total number of new cases, deaths, incidence trends, and survival rates of various cancers in the United States are summarized, and it is estimated that there will be about 2.37 million new cancers and 640,000 cancer deaths in the United States by 2022. The analysis of the data shows that malignant tumor is a major disease threatening human life and social development, especially for patients with advanced cancer. Most patients with advanced tumors have lost the opportunity for surgery, become resistant to chemical therapy, are unable to tolerate further chemoradiotherapy, and have a poor prognosis. But in recent years, tumor immunotherapy, which activates the body's immune system to kill tumor cells, has achieved great success and solved this problem well. It has become another effective therapy for comprehensive tumor treatment after surgery, chemotherapy, and radiotherapy. Anti-ctla-4 immunotherapy is one of the important components. The treatment has excellent outcomes and prognosis for cancers such as melanoma. However, after many studies, few papers have been found to provide a comprehensive overview of immunotherapy against CTLA-4. It is hoped that this article can provide some people who have just come into contact with the treatment of Immune checkpoint inhibitors with some understanding and research direction of Immune checkpoint inhibitors.

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2. Mechanism of CTLA-4 action

There are many mechanisms of action of CTLA-4, but the most important one that can be used as an immunosuppressant is the neighboring competition mechanism. The following will introduce the various action mechanisms of CTLA-4 by focusing on the neighboring competition mechanism.

2.1. Proximity competition mechanism

Although CTLA-4 is infrequently produced on the surface of T-cells during the early stages of T-cell activation, its high affinity for B7 makes it more competitive than CD28. APC expresses a small number of B7 molecules. CTLA-4 competitively preempts the binding of B7 to prevent CD28 from binding to B7, preventing CD28 from conducting costimulatory signals and preventing the initiation of T-cell activation cascades. When APC expresses a high level of B7, CD28 binds to more B7, and the two bind to deliver a costimulatory signal that activates T-cells along with other signals. Highly activated T-cells express large amounts of CTLA-4. At this point, CTLA-4 can bind with B7 to send out a powerful inhibitory signal and halt the development and activation of T-cells.

2.2. Mediate cell apoptosis

By forcing activated T-cells to undergo apoptosis, CTLA-4 inhibition may be accomplished. The number of the effector cells produced by activated T - cell diminishes when they undergo apoptosis, which in turn limits the release of cytokines and, eventually, suppresses the immune system.

2.3. Control cell cycle development by inhibiting IL-2 secretion

The inhibition of CTLA-4 was not entirely due to T-cell apoptosis. By reducing IL-2 release and blocking IL-2R gene expression, it can prevent cell proliferation. In addition, CTLA-4 can also control the development of the cell cycle and make the cell cycle stop in G0/G1 phase and not develop to the S phase.

2.4. Remote signal mode

In the late stage of T-cell activation, due to the interaction between TCR and CD28, many intermediates of the T-cell activation cascade are generated in T-cells. These products are dephosphorylated before the cascade can continue. At the same time, T-cells' surfaces were highly expressed with CTLA-4. The intracellular YVKM sequence of CTLA-4 is phosphorylated at Tyr201 as a result of CTLA-4 interacting with B7. Phosphorylated Tyr201 binds to PTP-1D and prevents SHC and ZAP-70 from binding to PTP-1D. This prevents dephosphorylation of SHC and ZAP-70 and the phosphoinositol pathway required for T-cell activation and activation of the Ras signaling pathway.

2.5. CTLA-4 and TGF-β

TGF-β is secreted by Th3 cells. TGF-β has the ability to reduce T-cell reactivity, block T-cell activation, and stop T-cell growth. CTLA-4 can promote T-cell to produce TGF-β. Like CTLA-4, TGF-β1 gene-deficient mice can develop lymphocyte hyperplasia disorder, organ failure, etc. In vitro experiments, CTLA-4 inhibited only 38% of T-cell reactivity in TGF-β gene-deficient mice and 95% of T-cell reactivity in normal control mice [1]. It can be seen from this study that TGF-β is involved in at least part of the negative regulatory effect mediated by CTLA-4.

3. Anti-ctla-4 drugs and indications

The Anti-CTLA-4 drugs currently in clinical use are Ipilimumab and Tremelimumab. Clinical use methods include single-drug therapy and combination therapy. The following sections will focus on clinical therapies and introduce the anti-CTLA-4 drug Ipilimumab and some indications suitable for the use of combination therapy.

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3.1. Single drug therapy

At present, Ipilimumab is the most commonly used Anti-CTLA-4 drug in the clinic. The recombinant human IgG1 immunoglobulin monoclonal antibody is named Ipilimumab. CTLA-4 is binded by ipilimumab. A factor that inhibits the T-cell activation pathway is called CTLA-4. Ipilimumab inhibits CTLA-4 and promotes T-cell proliferation and activation. Ipilimumab, for instance, may unintentionally facilitate a T-cell autoimmune reaction against a tumor in cases of melanoma.

3.2. Combination therapy

Although monotherapy has a good clinical effect, its effective rate is only 10% ~ 20%. The therapeutic combination of Anti-CTLA-4 with Anti-PD-1 medications is the most popular. Different expression patterns of CTLA-4 and PD-1 and their corresponding ligands. This leads them to play different complementary roles in the immune response, allowing them to produce synergistic effects in combination therapy. Nivolumab is a commonly used drug against PD-1. In an analysis of data from the Phase III experiment of advanced cancer patients, compared to 46 percent for nivolumab and 30 percent for ipilimumab alone, the combining of nivolumab and ipilimumab showed a longer-lasting survival rate of 53 percent after 4 years of follow-up.

3.3. Indications

In clinical therapy, it is crucial to select the best course of action based on the patient's physical state and the kind of cancer present.

3.3.1. Metastatic colorectal cancer. Post-treatment progression of microsatellite high instability or mismatch repair defects while dealing with colorectal cancer that has spread.

3.3.2. Malignant tumor of the renal tubular epithelium. Moderate or low-risk treatment for renal tubular epithelial cancer that was untreated before.

3.3.3. Melanoma with brain metastases. To treat metastatic melanoma and at least one measurable, unirradiated BMS with no neurological symptoms.

4. Side effects

Although Immune checkpoint inhibitors have a higher cure rate and better prognosis than other therapies in the treatment of cancer, it still has some toxic and side effects.

4.1. Immune-associated pneumonia

Immunotherapy inhibitor-associated pneumonia can be fatal, although being rare among immune-related adverse events. Numerous clinical investigations have reported that immune-associated pneumonia frequency is less than 5% with monotherapy and greater than 5% with combination therapy. The prevalence of pneumonia linked with anti-CTLA-4 therapy is lower than that of anti-PD-1 therapy, in contrast to the majority of immune-related adverse outcomes. Different tumor types have a different incidence of immune-associated pneumonia and compared to melanoma, NSCLC occurs more frequently in all grade levels and grade 3+ pneumonia.

4.2. Hepatotoxicity

Immune checkpoint-associated hepatitis is rare, with an overall incidence of 5% to 10%. However, the two-drug combination therapy significantly increased the incidence of hepatitis compared with monotherapy. According to Callahan [2] et al., the prevalence of grade 3-4 hepatitis increased by as much as 59% when Nivolumab and Ipilimumab were used together. ICI-associated hepatitis is a serious adverse reaction that should be detected and treated early.

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4.3. Renal toxicity

Relatively speaking, Immunity-Related Negative Renal system events are quite infrequent. However, for Ipilimumab, there are only a few reports of renal-related adverse reactions caused by Ipilimumab, whose manifestations are similar to anti-PD-1 mab, mainly including nephritis, renal failure, and lupus nephritis [3-4].

4.4. Endocrine system toxicity

Most Immune-Related Adverse Events of the endocrine system occurred about 15 weeks after treatment [5]. Compared with other Immune-Related Adverse Events, Adverse reactions to the endocrine system are very special and often irreversible [6]. Thyroid, pituitary, and adrenal glands are frequently affected endocrine organs [7].

4.5. Dermal toxicity

Among the adverse reactions caused by intracerebellar pathogenicity index therapy, skin-related adverse reactions are the most common, and the incidence of Anti-CTLA-4 and Anti-PD-1 antibodies are more common, with corresponding incidences of 43–45 and 34% [8-10]. The most common clinical manifestations are rash, pruritus, and vitiligo.

5. A vision for the future

Future studies should concentrate on adverse events, drug resistance, and efficient predictive biomarkers in light of the present state of research and clinical effectiveness of anti-CTLA-4.

5.1. Negative immune-related effects

Immune checkpoint inhibitor therapy has increased patient survival and slowed the course of numerous diseases, although side effects can sometimes occur. In studies using Ipilimumab, only 10%–26% of patients experienced immune-related side effects, although at least 80% of people had adverse events of varying severity throughout therapy [11].

5.2. Drug resistance

Only a small percentage of immunotherapy patients saw long-lasting improvements in their condition, despite the fact that immune checkpoint inhibitor medication enhanced outcomes for individuals with many cancer types. At present, researchers need to understand the biological basis of this phenomenon more deeply, so as to realize the individualized and precise implementation of immunotherapy for immune checkpoint inhibitors patients. This requires multiple aspects of research to find the biological reasons for immune checkpoint inhibitors' resistance.

5.3. Predictive biomarker

Although Immune checkpoint inhibitors have achieved excellent results in cancer treatment, not all patients who receive treatment benefit from them. In the treatment of Immune checkpoint inhibitors, there are patients who blindly use drugs, and the effective rate of Immune checkpoint inhibitors treatment for them is only 20%. Therefore, it is very important to select appropriate biomarkers and select patients with the best therapeutic effect.

6. Conclusion

This article focuses on anti-CTLA-4 and summarizes the related mechanism, clinical treatment, and toxic side effects of CTLA-4. Starting from the main mechanism of action of CTLA-4, the near competition mechanism is mainly present in cancer. In the treatment of immunosuppressive agents, monotherapy and combination therapy are the most commonly used. Although there are still some side effects in the process of treatment, such as liver failure, severe skin reactions, and lung problems, there is still no denying the good effect of immunosuppressive therapy in cancer treatment. It is hoped that future studies will address the toxic side effects and drug resistance of anti-CTLA-4

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immunosuppressive agents and find effective predictive biomarkers. In summary, anti-CTLA4 immunosuppressive agents have made outstanding contributions to the treatment of cancer.

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