Review

# Progress in CTLA-4-related immunotherapy for tumors

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**Abstract**

CTLA-4 (Cytotoxic T Lymphocyte Antigen-4) is an immune checkpoint molecule that can inhibit T cell activation and enhance Regulatery T cell function, thereby reducing the body's immune capacity. In cancer treatment, Ipilimumab, a monoclonal antibody targeting CTLA-4, can effectively inhibit the function of CTLA-4, thereby enhancing the activity and killing ability of T cells. Ipilimumab can also be used in combination with PD-1 and PD-L1 inhibitors for better efficacy. Currently, the FDA has approved Ipilimumab for the treatment of diseases such as melanoma, lung cancer, and colorectal cancer. Although this immunotherapy has shown good efficacy, the side effects and safety issues of the treatment need to be highly considered, and further exploration is still needed. Therefore, considering the safety of CTLA-4 therapy, the future direction of immunotherapy mainly involves combining it with other immune checkpoint inhibitors to improve efficacy and reduce side effects.



**Keyword**

tumor; mechanism;CTLA-4, PD-1, Ipilimumab, melanoma, non-small cell lung cancer, renal cell carcinoma, colorectal cancer, immune-related adverse events, novel immune checkpoint

## 1. Background of Immunotherapy

### 1.1 Overview of CTLA-4 molecule

CTLA-4, also known as cytotoxic T lymphocyte antigen-4, is a member of the immunoglobulin superfamily of adhesion molecules. It is an important co -inhibitory molecule that provides an immune inhibitory signal to T cells.

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CTLA-4 is mainly expressed on activated T cells after they have produced their effector functions. Upon binding to its ligands CD80 and CD86, CTLA-4 transmits inhibitory signals into the cell, resulting in a reduction in T cell activity and termination of T cell activation, thereby inhibiting the immune response. CTLA-4 is well recognized as a key immune checkpoint[1], and studying its function has led to new progress in the treatment of autoimmune diseases and cancer.

Due to its ability to decrease T cell activity during T cell activation, the CTLA-4 molecule can be used to reduce the immune response in the body. In the treatment of autoimmune diseases, the CTLA-4 molecule is undoubtedly a key pathway and one of the crucial checkpoints for immune checkpoint blockade[2]. In the treatment of autoimmune diseases, a key strategy for the CTLA-4 molecule is to promote its expression, thereby allowing it to bind to the CD80 and CD86 ligands on APCs, reduce the proliferative and differentiating activity of T cells, and thus decrease the immune damage to the body.

## 1.2 Immune escape mechanism of cancer

The immune escape mechanism of tumors is very complex, closely related to the tumor cells themselves, the microenvironment of tumor growth, and the host immune system.

### 1.2.1 Tumor cell factors

Firstly, the lack of tumor-specific antigens in tumor cells themselves, and the similarity in structure between the tumor-expressed antigens and normal proteins, weaken the immune recognition and killing ability of the body, and the body cannot produce effective anti-tumor immune responses. At the same time, tumor cells reduce or lose the expression of tumor antigens through antigen modulation, thereby evading recognition and killing by the immune system.

Secondly, the expression level of MHC I molecules on tumor cells themselves is very low, usually cannot reach the number of normal cells, and sometimes even absent, so CTL cannot kill tumor cells.

Thirdly, the co-stimulatory signals of tumor cells are abnormal. Most tumor cells have reduced or missing tumor antigens, and although a small number of tumor cells can express tumor antigens, their surface CD80 and CD86 molecules are lacking, or even high expression of PD-L1 and other co-inhibitory molecules, which enables

tumor cells to achieve immune escape. This series of abnormal co-stimulatory signals leads to the failure of T cell activation to proceed smoothly, and cannot produce effective immune response to tumor cells.

Fourthly, tumor cells can express or secrete certain immunomolecules that inhibit the body's anti-tumor immune function. Immune molecules such as epidermal growth factor, IL-10, and IL-33 can all play an immunosuppressive role in the body's response to tumors. Tumor cells can even express FasL to induce tumor-specific T cell apoptosis.

Fifthly, tumor cells induce the activation and proliferation of Tregs. Tumor cells can actively induce the body to produce Tregs, which can express T cell inhibitory molecules such as LAG-3, GITR, CTLA-4, and PD-1, as well as locally deplete IL-2 and secrete IL-10 and TGF-β[4], thereby allowing tumors to evade the body's immune system attack.

Finally, tumor cells have a certain anti-apoptotic effect, which can be achieved by the expression of anti-apoptotic proteins such as Bcl-2 or by the downregulation or mutation of proapoptotic proteins such as BAX.[5] They also have low expression or do not express apoptosis-inducing molecules such as Fas, thereby escaping CTL-induced apoptotic mechanisms.

### 1.2.2Tumor microenvironmental factors

The main mechanism by which the body forms tumors is that the tumor microenvironment can promote the growth of tumor cells, while also protecting tumor cells from recognition and killing by the body's immune system. The tumor microenvironment is a complex composition, which includes substances that promote tumor cell proliferation and differentiation, as well as components that inhibit the body's immune response, such as Tregs and immune inhibitory factors. The combined action of these substances creates a local microenvironment that is conducive to tumor growth, thus achieving the goal of promoting immune suppression and tolerance to tumor-associated antigens[6].

### 1.2.3 Host immune function factors

The strength of the host's own immune system cannot be ignored. When the host is suffering from certain diseases such as HIV or long-term use of certain immunosuppressive drugs, the immune system of the body itself will decrease, which will also lead to the recognition and killing of tumor cells by the body's immune system. In addition, tumor cells can also affect the microenvironment. Certain substances expressed by tumor

cells that inhibit the immune function of the body can also cause a decrease in the immune function of the body in turn.

## 2. Function and mechanism of CTLA-4

The molecular mechanism of CTLA-4 involves a competitive inhibitory action. CTLA-4 has a higher affinity for CD80 and CD86 than CD28, which effectively reduces T cell activation.[7] In cancer treatment, after T cells recognize and proliferate in response to tumor cell antigens presented by APCs, they roam the body in search of cancer cells. Eventually, immune negative regulation is triggered through the T cell receptor (TCR) to shut down the anti-tumor T cell response.[8] Therefore, the main strategy of cancer treatment based on the action of CTLA-4 is to block the binding of CTLA-4 with CD80/CD86, to avoid the generation of immune negative regulation.

The main mechanism of action of CTLA -4 is that it can be promoted by other substances or interact with some other substances. For example, indoleamine 2,3-dioxygenase (IDO), an enzyme produced by myeloid-derived suppressor cells (MDSCs), dendritic cells (DCs), and macrophages in the tumor microenvironment, can deplete tryptophan and inhibit T cell proliferation through tryptophan catabolites (such as L-kynurenine), promoting the differentiation and activation of Tregs and CTLA-4 expression. [9] CTLA-4 can also bind to protein phosphatase 2A (PP2A), which controls DNA damage response by regulating ataxia-telangiectasia mutated (ATM) autophosphorylation/activation levels, inducing cell apoptosis. [10] In cells, CTLA-4 is mainly located in the cytoplasm of resting T cells, while the level of CTLA-4 on the cell membrane is higher during T cell activation [1], thus CTLA-4 in the cytoplasm can interact with PP2A to activate ATM, amplify DNA damage response, and induce apoptosis. [11] In addition, during TCR activation, CTLA-4 is upregulated by the Src homology 2 domain-containing protein tyrosine phosphatase-2 (SHP-2) pathway, which contains inhibitory PI3K downstream signals, resulting in acute immune negative regulation of T cells. [12]

In addition to inhibiting T cell activation, CTLA-4 also maintains and controls the function of Tregs, which reduce the body's immune response. CTLA-4 in Treg cells can interact with protein kinase C-η (PKC-η) and recruit GIT2, PIX, and PAK2 to form a complex that depletes APC CD80/86[7]. This reduces the binding of CD80/CD86 on APCs to co-stimulatory molecules on T cells, thereby blocking co-stimulatory signals

and reducing T cell activation. Therefore, the interaction between CTLA-4 and PKC-η is crucial for the inhibitory function of Treg cells[13], and a decrease in CTLA-4 expression or function can lead to the development of autoimmune diseases[14].

## 3.Clinical application of CTLA-4

### 3.1 Ipilimumab

Monoclonal antibody against CTLA-4

Ipilimumab is a human immunoglobulin G1 (IgG1) monoclonal antibody that acts as an inhibitor of the CTLA-4 immune checkpoint. It binds to CTLA-4 to inhibit CTLA-4 binding to CD80/CD86 and is the first drug to improve overall survival in patients with advanced melanoma [15,16]. Ipilimumab acts indirectly on the immune system by blocking T cell activation inhibition and reducing Treg immunosuppressive activity to enhance anti-tumor immunity. [17,18] Ipilimumab has been used in the treatment of melanoma in clinical trials, and can be used together with nivolumab in the treatment of advanced melanoma, advanced renal cell carcinoma, non-small cell lung cancer and other cancers, and good experimental results have been achieved [19-21]. Therefore, Immunocheckpoint inhibitors can be a reasonable and effective treatment for cancer patients. [22]

### 3.2 Combination therapy

combination of Ipilimumab and anti-PD-1 drugs

Programmed cell death Protein 1 (PD-1) is a transmembrane protein that plays a critical role in suppressing immune response and promoting autoimmune tolerance by initiating antigen-specific T cell apoptosis and inhibiting Treg apoptosis. [23]PD-1 combines with its ligand to play a role, namely programmed cell death ligand 1 (PD-L1). The signal generated by PD-1 will prevent the phosphorylation of key TCR signaling intermediates [24], activate downstream signaling pathways and inhibit T cell secretion of cytokines [25], thus preventing T cell activation and inducing T cell apoptosis. In the tumor microenvironment, the expression of PD-L1 on tumor cells and antigen-presenting cells is abnormally high, so PD-1/PD-L1 is closely related to tumor immune escape [25], and tumor cells can escape immune killing by binding their own overexpression of PD-L1 to PD-1 expressed on antigen-stimulated T cells [26]

Since CTLA-4 and PD-1/PD-L1 are key immune checkpoints that play a key role in immune regulation, current studies have shown that blocking CTLA-4 and PD-1/PD-L1 pathways also plays a great

role in cancer treatment. The important idea is to prevent their binding with their own ligands. Thus, T cells can play a role in strengthening the cell killing mechanism of the body's immune system against tumors. Therefore, CTLA -4 and PD-1/PD-L1 are target molecules for the development of therapeutic antibodies [27].

At present, immune checkpoint blocking targeting the inhibitory immune receptors CTLA-4 and PD-1/PD-L1 has become an effective method for cancer treatment [28]. Immunocheckpoint inhibitor anti-ctLA-4 antibody Ipilimumab is mainly used in the treatment of melanoma patients [12]. PD -L1 immune checkpoint inhibitors PD-1 antibodies pembrolizumab and nivolumab are more commonly implicated in colorectal cancer (CRC), melanoma, renal cell carcinoma (RCC), bladder cancer (BC), NSCLC, head and neck cancer, and other cancer types under clinical investigation [29]. In addition, six drugs that target PD-1 and one drug that targets CTLA-4 have been approved for the treatment of different types of cancer, and these immune checkpoint inhibitors have made a huge impact on the clinical treatment of cancer. Survival of cancer patients has been greatly prolonged with monotherapy, but more than 50% of patients do not respond to treatment, and long-term effects of the drug have been observed in only a small percentage of patients. [30, 31]

Mouse models have shown tumory-associated high endothelial varices (TA-HEV) to be the primary site of lymphoid entry into the tumor, while analysis of tumor biopsies in 93 patients with metastatic melanoma showed that TA-HEVs demonstrated better response and survival after anti-PD-1 / anti-ctLA-4 combination therapy. [32] In clinical practice, clinical trials of nivozumab and ipilimumab combined with ICI mab have also shown excellent efficacy for patients with melanoma or renal cell carcinoma [33]. The use of monoclonal antibodies prevents the inhibition of T cell activation and induces the release of effector cytokines and cytotoxic particles to activate T cells targeting tumor cells [34]. The combination of CTLA-4 and PD-1/PD-L1 antibodies not only activates, but also effectively enhances the immune response, including against tumor cells, by synergistically blocking Treg-mediated immunosuppression. [35] Immune checkpoint blocking targeting CTLA-4\PD-1/PD-L1 is currently the most promising systematic therapy, which can be used to treat or even cure many types of cancer, not just melanoma patients [36].

### 3.3 Practical experience in combination therapy

Treating with Ipilimumab alone has some limitations, [37]Primary and secondary resistance to single agent checkpoint blockade is an emerging problem. [37]Primary and secondary resistance to single agent checkpoint blockade is an emerging problem in daily clinical routine. However, recent studies suggest that a combination of two immune checkpoint inhibitors may prevent primary resistance [38]. nivolumab and pembrolizumab are commonly used clinically in combination with Ipilimumab, and the objective response rate (ORR) for this treatment is significantly higher than that for single antipd-1 [39]. At present, combined drugs have been used to treat melanoma, renal cell carcinoma, non-small cell lung cancer and other cancers [40].

## 4.Treatment of different types of cancer

### 4.1 Cutaneous melanoma

For cutaneous melanoma, most patients are diagnosed at an early stage, and surgical treatment is usually the preferred treatment [41]. But still, about 10 percent of melanoma patients are diagnosed with advanced melanoma, where the cancer often has metastasized and cannot be treated with surgery. [42] Thus, the use of immune checkpoint inhibitors became a revolutionary event. Early on, ipilimumab, a CTLA-4 inhibitor, was approved by the FDA for the treatment of metastatic melanoma [43], but this drug needs to be modified as patients develop resistance to the drug. Nivolumab and ipilimumab immunocheckpoint inhibitors have been approved for the treatment of advanced melanoma and have shown promising results. [44]Pembrolizumab also improved progression-free survival and overall survival (OS) relative to ipilimumab. [45]. However, at present, these immune checkpoint inhibitors have some adverse effects, need to be highly careful in clinical use.



### 4.2 Non-small cell lung cancer

Lung cancer can be divided into two categories according to the main histomorphologic characteristics, prognostic and therapeutic significance: small cell carcinoma (SCLC) and non-small cell carcinoma (NSCLC), among which non-small cell carcinoma is more common. [46] Most patients with non-small cell lung cancer need systemic treatment, and these patients usually have disease recurrence after surgery, and some patients are even inoperable. [47] For resectable NSCLC, there has

been no new progress in treatment except surgical treatment in the past period of time, and the recurrence rate and mortality after surgery will continue to increase with the progression of disease stage. Therefore, the emergence of immunoadjuvant therapy has become a therapeutic means to improve the survival rate of patients with NSCLC. [48] At present, the first-line treatment for advanced NSCLC is nivolumab plus ipilimumab. This method has a longer overall survival than chemotherapy, and the data taken are very satisfactory. [49] And a chemotherapy-free combination of nivolumab and ipilimumab showed a sustained long-term response in patients with advanced NSCLC and tumors with PD-L1 expression greater than or equal to 1% or less at a four-year follow-up. [50] However, it is worth noting that the occurrence of immune-related adverse events still needs to be paid attention to, and more biomarkers should be used to conduct trials to further study the combination of nivolumab and ipilimumab. [51]



### 4.3 Renal cell carcinoma

Renal cell carcinoma (RCC) is a malignant tumor that is the seventh most common cancer in men and the ninth most common cancer in women. [52]The most common is the clear cell type (70 -- 90%), followed by papillary (10 -- 15%) and chromophobe RCCs (3 -- 5%)[53]. Therefore, the treatment of clear cell renal cell carcinoma (ccRCC) is the focus. Medical treatment of RCCS has been transitioning from non-specific immunotherapy with cytokines to targeted therapy of vascular endothelial growth factor (VEGF) and now to new immunotherapy drugs. [54] Clear cell RCC (ccRCC), frequently harbors characteristic second-hit loss-of-function mutations in VHL on a background of loss of chromosome 3p, where VHL resides, the mutation causes the mutant cells to secrete more VEGF. And because CCRCCS are highly permeated by immune cells, VEGF tyrosinase inhibitors (TKIs), immune checkpoint blockers (ICBs), and combinations of these drugs are now widely used to treat the disease. [55] Currently, the most effective approved immunotherapy is nivolumab plus ipilimumab in previously untreated and advanced stages of prior treatment

### 4.4 Colorectal cancer

Colorectal cancer (CRC) is the third most common cancer diagnosed globally and the second leading cause of cancer-related death [61]. CRC patients can be divided into three groups: microsatellite instabilities - high (MSI-H), microsatellite instabilities - low (MSI-L) and microsatellite stability (MSS). At

present, nivolumab plus ipilimumab can be used in most dMMR/MSI-H mCRC patients. This treatment has a better response than nivolumab alone [62,63]. However, for the majority of pMMR/MSI-L, the application of immunotherapy has not shown a good therapeutic effect, or even efficacy. [64] Currently, immunotherapy is being explored in combination with other therapies, such as ICIs in combination with radiotherapy, ICIs in combination with small molecule TKIs (such as MEK inhibitors and anti-angiogenesis agents), and ICIs in combination with bispectic antibodies. Clinical use of these combination therapies still requires further studies on safety and efficacy. [65]



## 5. Side effects and safety issues

Although these immune checkpoint inhibitors (ICIs) have achieved good clinical results, they have certain side effects. In addition to certain drug resistance, they may also cause irAEs. The combination of these ICIs may lead to immune system activation and promote the release of inflammatory cytokines by T cells. Such as interferon gamma and tumor necrosis factor, which may lead to excessive extra-tumor inflammation and autoimmunity [66-68]. irAEs caused by ICIs are most common in the skin, gastrointestinal tract, liver and endocrine system, and often cause pyitis, rash, diarrhea, fatigue, nausea, elevated transaminase or colitis [69,70], and may also cause diabetes, myocarditis and other diseases, but these diseases are relatively uncommon [71]. ICI may also be neurotoxic and cause a range of neurological complications, such as encephalitis, aseptic meningitis, multiple sclerosis, myasthenia gravis and peripheral neuropathy. [72]

According to the General Terminology Standards for Adverse Events (CTCAE), immune-related adverse events are classified into five levels of toxicity: asymptomatic/mild (level 1), moderate (level 2), severe (level 3), life-threatening (level 4), and fatal (level 5) [73]. However, a recent study showed that different immune checkpoint inhibitors have different safety profiles, and anti-PD-1 drugs generally show a more favorable safety profile compared to anti-CTLA-4 drugs. [74] In untreated melanoma, 27.3% of patients treated with anti-ctLA-4 developed Grade 3 or 4 irAE, while 16.3% of patients treated with anti-PD-1 developed grade 3 or 4 irAE. Combined treatment with anti-ctLA-4 and anti-PD-1 resulted in a significant increase in the incidence and severity of irAEs, with 55% of patients exhibiting high-grade irAEs[75]. In addition, CTLA-4 inhibitor mainly acts on lymphatic organs, while PD-1

inhibitor is believed to mainly act on tumor microenvironment, resulting in different IRAes. The former mainly causes pituitaritis and colitis, while the latter mainly causes nephritis, pneumonia, thyroiditis, etc. [76,77]

## 6. Prospect of the future

At present, most patients develop resistance after using anti-PD-1mab and anti-ctla-4mab, resulting in unsatisfactory long-term efficacy. [78] Therefore, finding new immune checkpoints that trigger monoclonal antibodies against them is a new task, Lymphocyte activating gene -3 (LAG-3), T-cell immunoglobulin and the mucin domain containing omega-3 (TIM-3), T-cell immunoglobulin and ITIM domain (TIGIT), T-cell-activated V-domain Ig inhibitor (VISTA), B7 homologous 3 protein (B7-H3), and B and T-cell lymphocyte attenuator (BTLA) ) have been shown to be promising new therapeutic targets with potential clinical applications. [79] For some specific diseases, such as advanced liver cancer and colorectal cancer, the combination therapy of ICI with other ICI, TKI, anti-VEGF and other drugs should also be actively explored. [80] In addition, attention should be paid to whether CTLA-4 and other molecules are affected by other factors in cancer treatment. For example, studies have shown that intestinal microflora can affect the blocking of CTLA-4 [81], and studies have also shown that short-chain fatty acids (SCFA) can limit and block the anti-tumor effect of CTLA-4 on the body [82]. These factors need to be further studied in the course of treatment.

## 7.Conclusion

Existing studies have shown that CTLA-4 is an important target for cancer therapy. Use of CTLA-4 immunosuppressant alone is not very satisfactory, and there are some side effects. Therefore, combination therapy has become a new direction of immunotherapy development, such as the study of new immune checkpoints LAG-3, TIGIT, VISTA, B7-H3 and BTLA. In the future, further research is still needed on how to combine drugs to better improve efficacy and reduce side effects, so as to achieve better tumor treatment.



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