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Emerging immune checkpoint and its combination therapy in cancer treatment

Xiaozheng Yue

Faculty of Biological Sciences, University of Leeds, Leeds, LS2 9JT, UK

3409230439@qq.com

Abstract. In recent decades, cancer immunotherapy has become a cornerstone of cancer treatment, standing alongside traditional methods such as surgery, chemotherapy and radiation therapy. This article provides a comprehensive exploration of cancer immunotherapy, with a particular focus on the critical role of immune checkpoints in cancer treatment. It covers classic immune checkpoints such as CTLA-4 and PD-1, as well as emerging checkpoints such as TIGIT, TIM-3, LAG-3, VISTA, and IDO-1, elucidating their mechanisms and ongoing clinical trials. In addition, the promising areas of combination therapy involving immune checkpoint inhibitors (ICIs) are investigated. In this study, the combined action and synergistic effect of different ICIs such as CTLA-4 and PD-1 were investigated. In addition, it examines how ICIs can be strategically paired with other treatment strategies, including EGFR TKIs, anti-VEGF /VEGFR therapies, radiotherapy, and mRNA-based vaccines. These combinations are designed to enhance anti-tumor responses and overcome drug resistance. In conclusion, this article provides a comprehensive overview of cancer immunotherapy, highlighting its critical role in modern oncology. It points to the richness and complexity of immune checkpoints, highlighting their importance, challenges, and the development of combination therapies aimed at harnessing the potential of the immune system to fight cancer.

Keywords: immune checkpoint, combination therapies, cancer immunotherapy.

1. Introduction

With the deepening understanding of tumor biology and human immune mechanism in recent decades, Cancer immunotherapy has become one of the seven pillars of cancer treatment alongside surgery, cytotoxic chemotherapy, targeted therapy, radiotherapy, hormonal therapy and cell therapy [1]. Moreover, according to Science, one of the top ten annual scientific breakthroughs in 2013 was cancer immunotherapy [2]. By conducting immune surveillance of tumor cells, immune checkpoints can reinvigorate anti-tumor T cell activity and dynamically regulate the anti-cancer immune response. And since the development and clinical use of immune-checkpoint inhibitors (ICIs) targeting CTLA4, PD-1, and PD-L1won the 2018 Nobel Prize for Medicine and Physiology [3], immune checkpoints has become the most promising anti-tumor method towards melanoma, non-small cell lung cancer (NSCLC), bladder cancer, renal cell carcinoma, and breast cancer. CTLA4 antibody Ipilimumab and PD-1 antibody pembrolizumab have achieved FDA approval for multiple cancer types, significantly improving survival rates[4]. Ongoing research explores combination therapies, biomarkers, and resistance mechanisms to expand their effectiveness and applications in cancer treatment. However,

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due to the unpredictability and complexity involved with immunotherapy, adverse reactions and unsuccessful therapies are still possible.

At present, the questions that need further study include: i) the degree of expression and interaction of immune checkpoints themselves; ii) resistance, tumor-specific/patient-specific selection, and relevant combination therapies. In this review, we will provide a brief overview of classic immune checkpoints, with a focus on emerging immune checkpoints and how can the therapeutic effect of immune checkpoint be enhanced by the combination of other molecules/therapeutics.

Although there are many treatments that eliminate tumors by external forces such as surgery, radiation, and chemotherapy, the body's own immune system is still a powerful weapon for controlling and destroying tumor cells, distinguishing tumor cells from normal cells by recognizing tumor-specific antigens. When the TCR recognizes the antigen, the relevant signaling pathway is activated, and the T cells achieve selective destruction of cancer cells under the co-regulation of the co-stimulatory signal and the inhibitory signal (i.e. the immune checkpoint).Immune checkpoints can be a double-edged sword(see Figure 1). After T cells perform their immune function, immune checkpoints act as negative immunologic regulators to suppress T cell function to prevent autoimmunity. However, the surface of tumor cells has evolved immune checkpoint ligands, so that immune checkpoint molecules become the tools of immune evasion of tumor cells. Therefore, we are actively researching and developing inhibitors and antagonists to block immune checkpoints and thus activate endogenous and specific anti-tumor immune responses. Among them, CTLA-4 and PD-1 channels have become the most classic and most representative two. At the same time, TIGIT, TIM-3, LAG-3 and other emerging checkpoints are also worthy of our attention.

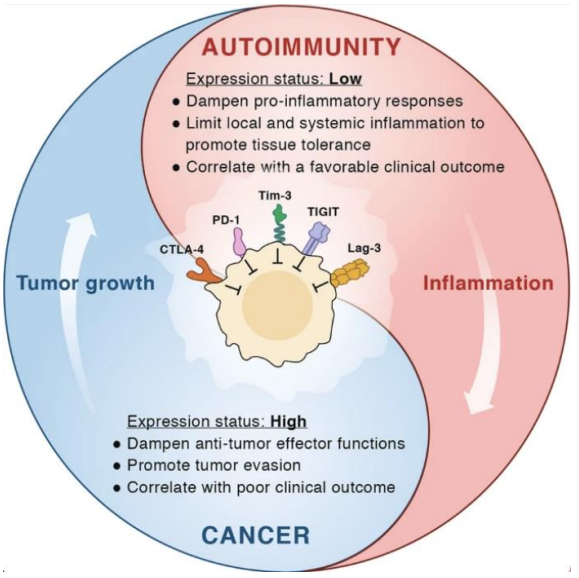

Figure 1. The role of immune checkpoints in cancer and autoimmunity.

Cancer uses immune checkpoint to evade immune surveillance and inhibit effector T cell function. On the other hand, immune checkpoints can maintain tissue tolerance and avoid autoimmune diseases [5].

2. Classic immune checkpoint

2.1. CTLA-4

CTLA-4(Cytotoxic T lymphocyte Antigen 4) is an obligate protein receptor only on the surface of T cells. CTLA-4 competes with another co-stimulatory protein, CD28, to bind the B7 molecule on antigen-presenting cells (apc) (i.e. sharing ligands CD80 and CD86) [6]. When CD28 binds to B7, T cells are activated. When CTLA-4 binds more strongly to the B7 molecule than CD28, it sends a

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inhibitory signal to T cells, blocking T cell immunity. Some tumor cells can use CTLA-4 to evade the immune system. By overexpressing the CTLA-4 ligand, tumors can suppress the activation of tumor-specific T cells, allowing them to grow and evade immune surveillance. Immune checkpoint inhibitors targeting CTLA-4 have been shown to block the inhibitory signal of CTLA-4, allowing T cells to remain activated and attack cancer cells more effectively. As the first clinical immune checkpoint inhibitor, the humanized CTLA-4 antibody ipilimumab has been shown to extend the survival rate of patients with metastatic melanoma by 10 years [7].

2.2. PD-1

Different from the early regulatory immune response of CTLA-4T cell activation, PD-1 is more widely expressed in immune cells, and its binding with the ligand PD-L1/PD-L2 can inhibit the activity of efficent T cells in peripheral tissues. PD-1 is highly expressed in tumor cells of human tumors to evade immune surveillance. By blocking the binding of PD-1 and its ligand, T cells can be rescued from exhaustion and the specific anti-tumor cell immune response can be restored. Despite clinical success and U.S. Food and Drug Administration approval for PD-1 inhibitors, most patients receiving monotherapy with PD-1 inhibitors experience only a brief response or no response at all, and there are issues related to drug resistance [8,9].

3. Novel immune checkpoint

3.1. TIGIT

T cell immunoglobulin and ITIM domain (TIGIT) are mainly expressed on the surface of T cells and NK cells, and are also negative regulators of cytotoxic lymphocytes. As a member of the PVR-like proteins family, an important emerging cancer immunotherapy target, TIGIT has three ligands: CD155, CD112, and CD113 and has the highest affinity for CD155. The main mechanisms of action are as follows: i) tolerogenic dendritic cells are produced when TIGIT binds with CD155, which are manifested as reduced antigen presenting capacity, reduced expression of co-stimulant molecules, and reduced secretion of proinflammatory cytokines; ii) compete for ligands with DNAM-1 cofactors that can activate lymphocytes (See Figure 2 for the rest). Clinical trials on TIGIT inhibitors have never stopped, including Tiragolumab, Etigilimab and others. More than 50 clinical trials have been registered with ClinicalTrials.gov, and although most of the recent studies have failed [10], we cannot deny that NSCLC is a good target. And the potential of combination therapy of TIGIT with PD-1 etc. in cancer treatment [11].

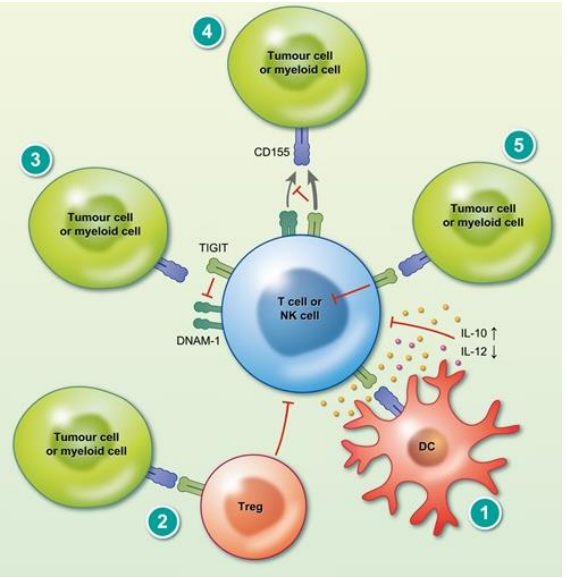

Figure 2. Five action mechanism of TIGIT.

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TIGIT-CD155 binding: tolerance (reduced activity) of CD155-secreting dendritic cells; 2) Overexpression of TIGIT results in high inhibition of Tregs; 3) Disrupt the dimerization of DNAM-1 and inhibite DNAM-1 binding to CD155 ligand; 4)TIGIT has a higher binding affinity for CD155 and competes with DNAM-1 to bind the CD155 ligand; 5) TIGIT's cytoplasmic tail allows it to send inhibitory signals to T cells and NK cells directly[12].

3.2. TIM-3

As a member of the TIM family, T-cell immunoglobulin and mucin domain 3 (TIM-3) can be expressed on effector T cells, dendritic cells, NK cells and monocytes.TIM-3 mainly binds to four ligands: Gal-9, HMGB1, PtdSer, and Ceacam-1. Binding with Gal-9 induced the influx of calcium ions, and binding with PtdSer formed the surface marker of apoptosis, both of which led to the apoptosis of T cells. Binding with Ceacam-1 negatively regulates the immune response while regulating the antiviral response. Binding to HMGB1 is associated with innate immune activation [13,14]. The high expression of TIM-3 in solid tumors such as hepatocellular carcinoma and colon cancer resulted in significant T cell exhausted. Studies have shown that blocking signaling pathways such as TIM-3/Gal-9 can significantly enhance T cell immune efficacy [15,16]. TIM-3 antagonists such as Sym023 have also entered clinical studies [14].

3.3. LAG-3

lymphocyte activation gene 3 (LAG-3), a member of the type I transmembrane protein family, is mainly found in activated T cells, B cells, plasma cells and NK cells. The main mechanism of action of LAG-3 is as follows: due to its special structure similar to the helper receptor of CD4, LAG-3 is more easily bound to the Class II major histocompatibility complex (MHC-II) than CD4, thus preventing the activation of CD4+T cells and negatively regulating the immune efficacy of T cells. Today's research focuses on anti-LAG-3 blocking monoclonal antibodies, such as BMS-986016 (Relatlimab) and IMP321 (Eftilagimod Alpha), which are already in clinical studies. Relatlimab is already approved for melanoma treatment. Relatlimab has also been found in recent studies to be useful in treating NSCLC or stomach cancer [13].However, with further research, LAG-3 may have non-MHC-II ligands that are still not understood, such as LSECtin, a C-type lectin that is mainly expressed in the liver. LAG-3 has also been shown to have multipathway inhibitory effects on other immune cells, including CD8+T cells, but the details of the mechanism have also not been elucidated [17].

3.4. VISTA

V-set immunoglobulin domain suppressor of T cell activation (VISTA) is widely expressed on most bone marrow and lymphocytes, and belongs to the B7 family with PD-1 and CTLA-4. The ligands of VISTA have not yet been fully identified, and potential ligands currently include PSGL-1 (which binds to VISTA only at acidic PH such as the tumor microenvironment), VSIG3 (or IgSF11), etc [18]. The mechanism of how VISTA interacts with immune cells is not fully understood, but it is certain that VISTA can maintain a quiescent state of T cells and bone marrow cells, and inhibit some TLR signaling and the production of pro-inflammatory cytokines in bone marrow cells[19]. The high expression of VISTA in tumors such as colon cancer demonstrates the clinical potential of VISTA blocking therapy. VISTA antagonist monoclonal antibodies: VSTB112, P1-068767 (BMS-767), and SG7 are three important ones. They have all been shown to have the effect of blocking VISTA from binding to possible ligands and enhancing T-cell immune function [20].

3.5. IDO-1

Indoleamine 2,3-dioxygenase 1 (IDO-1) is an immunosuppressive enzyme that can be expressed in macrophages, neoplastic cells and placenta. The consumption of tryptophan and the conversion into kynurenine could lead to the occurrence of immunomodulatory effects, induce the apoptosis of T cells, inhibit the replication and immune function of T cells. Specifically, IDO-1 induces stress responses such as impaired T cell effectors by stimulating GCN2 kinase, a sensor with low tryptophan content, in T cells

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through catabolism of tryptophan; Meanwhile, kynurenine, as a metabolite, reduces the survival rate of CD4+T cells and promotes the differentiation of regulatory T cells [21]. Epacadostat, an inhibitor of the IDO-1-inhibiting enzyme, has entered phase III clinical trials. In clinical phase I and Phase II treatment, Epacadostat has demonstrated a good ability to reduce tryptophan metabolism in advanced melanoma. However, Phase III clinical trials showed a decrease in the effectiveness of the treatment. However, in other clinical studies, IDO-1 has been very effective in the treatment of urothelial carcinoma [14].

4. Combination therapy of immune checkpoints

Research on immune checkpoint combination therapy has been extensive. Immune checkpoint inhibitors can be combined not only with each other, but also with other functional molecules and other therapeutic approaches. At the same time, since PD-1 is one of the most popular and well-studied immune checkpoints, many emerging immune checkpoints will consider the combination of their antagonists and anti-PD-1 antagonists

4.1. Immune checkpoint inhibitor + immune checkpoint inhibitor

4.1.1. CTLA-4+PD-1. Since both anti-PD-1 and anti-CTLA-4 treatments alone only have the desired effect in a small percentage of patients, and the problem of drug resistance is inevitable, CTLA-4 plus PD-1 blockers have become the focus of attention. Reversing T cell depletion can be accomplished by combining the two distinct regulatory mechanisms: Through Treg cells, CTLA-4 controls T cell activation in lymph nodes and tissues and suppresses DC activity; PD-1 prevents effector T cell and NK cell activation in peripheral tissues. Currently, Nivolumab + Ipilimumab has made significant strides in the clinical treatment of non-small cell lung cancer and advanced melanoma [22,23].

4.1.2. TIGIT+PD-1. Tiragolumab, an anti-Tigit antagonist, and Atezolizumab, a PD-1 antagonist, have been shown to be beneficial in the treatment of lung cancer. However, the clinical treatment effect of small cell carcinoma and non-small cell carcinoma is not good, and serious adverse reactions may occur [14]. They also form a synergistic effect by blocking different immune checkpoint pathways to restore immune function.

4.1.3. TIM-3+PD-1. The TIM-3 inhibitor mAb has been used with a variety of immune checkpoint inhibitors. For instance, Phase I and Phase II trials involving advanced solid tumors have begun using the mAb Sabatolimab from TIM-3 and spartalizumab from PD-1 [24]. Patients with advanced solid tumors were successfully assessed in Phase I clinical studies using sabatolimab in conjunction with PDR001 [14].

4.1.4. LAG-3+PD-1. The anti-LAG-3 mAb Relatlimab has shown great potential in combination with the anti-PD-1 mAb Nivolumab, and is already approved for melanoma treatment [14]. In summary, this is just an overview of some of the combinations that have been studied, but it is already clear that the specificity of the cancer, as well as the influence of many other factors, such as the state of the immune response, the influence of the tumor microenvironment, and subtle differences in the expression and control of different checkpoints, are factors that affect the effectiveness of the combination therapy between immune checkpoints. When searching for the appropriate immune checkpoint combination, we can identify the specific biomarkers of patients with the help of whole exome sequencing, immunohistochemical analysis and peripheral blood immunophenotype, and then select according to the specific immune mechanism of patients [22].

4.2. Immune checkpoint inhibitor + other approaches

4.2.1. Immune checkpoints + functional molecules. The combination of ICIs(immune checkpoint inhibitors) and EGFR TKIs (tyrosine kinase inhibitors) offers promise for the treatment of EGFR mutant

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NSCLC. ICIs offer long-lasting anti-tumor effects with lower response rates, while EGFR TKIs produce rapid immune responses that frequently have short lifetimes. Although newer studies reveal reduced response rates in EGFR mutant tumors, it is likely because of their lower mutation burden and an immunosuppressive microenvironment that these tumors have lower response rates. EGFR mutations correlate with PD-L1 expression in NSCLC, suggesting potential susceptibility to anti-PD-1 therapy.

Immune checkpoint inhibitors (ICIs) may also be used in conjunction with anti-VEGF/VEGFR therapy to treat cancer, particularly renal cell carcinoma (RCC). Angiogenesis, which prevents the establishment of new blood vessels in tumors, is inhibited by treatments like bevacizumab, sunitinib, and acitinib, which simultaneously reduce the number of immune-suppressive cells and encourage T cell infiltration into the tumor microenvironment. Preclinical research has demonstrated that combining inhibitors of the PD-1 and VEGF pathways can improve t cell invasion[25].

Additionally, PD-1/PD-L1 inhibitors (like nivozumab or pembrolizumab) and anti-VEGF kinase inhibitors (like sunitinib or pazopanib) have been demonstrated to have positive anti-tumor effects in clinical investigations of RCC. Patients with untreated RCC have demonstrated efficacy and safety with the VEGFR inhibitor Axitinib when combined with the PD-L1 inhibitor Avelumab. In patients with advanced RCC who had not received treatment, similar outcomes were seen with acitinib and pembrolizumab [26].

4.3. Immune checkpoints + other therapeutic methods

4.3.1. Immune checkpoints +radiotherapy. In the post-radiotherapy immunotumor microenvironment (TME), memory-activating CD4+ T cells and activating mast cells have been linked to increased overall survival in a number of malignancies. Local radiation in conjunction with CTLA-4 suppression promotes the survival of patients with resistant metastatic cancer by increasing the ratio of CD8+ T cells to TREGs and improving the functionality of various intra-tumor T cells. This in vitro impact is increased by PD-1 inhibition when combined with radiation therapy, especially in some hematological tumors, where radiation therapy induces a systemic anti-tumor response that causes the reversal of non-radiation damage. Clinical studies have demonstrated that after concurrent chemoradiotherapy, consolidation therapy with anti-PD-L1 monoclonal antibody (durvalumab) prolongs progression-free survival in non-small cell lung cancer [27].

4.4. Immune checkpoints +mRNA-based

Innate immune sensors are activated by self-replicating RNA structures in the cytoplasm when mRNA-based vaccinations that encode neoantigens are given to patients. This results in an effective immune response. These highly tailored immunizations have the capacity to deliver many antigens at once. It was initially used on melanoma patients to significantly increase T cell infiltration and decrease metastatic occurrences. Cancer vaccines and immune checkpoint inhibitors (ICIs) are combined to treat T cell depletion. Preclinical studies show that DNA-based vaccines with CTLA-4 and PD-1 double blocks, which totally eliminate tumors in mouse models, boost CD8+ T cell infiltration. Clinical trials against solid tumors are evaluating the efficacy of mRNA cancer vaccines in combination with anti-PD-1, anti-PD-L1, or anti-PD-L1 plus anti-CTLA-4 monoclonal antibodies [28].

5. Conclusion

In short, cancer immunotherapy has completely changed the outlook of cancer treatment and become a powerful weapon against various malignant tumors. Immune checkpoints, both classical and emerging, play a crucial role in regulating the immune response in the tumor microenvironment. Understanding its mechanism and exploring new targets are important steps to advance cancer immunotherapy. Combination therapy has emerged as a promising way to enhance the efficacy of immune checkpoint inhibitors. Pairing different ICIs, such as CTLA-4 and PD-1, has shown synergistic effects, offering hope for improved patient outcomes. In addition, the strategic integration of ici with other therapeutic modalities, including targeted therapy, anti-angiogenic drugs, radiation therapy, and MRNa-based

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vaccines, offers a multifaceted approach to enhancing anti-tumor immunity. While significant progress has been made, challenges such as resistance mechanisms and patient-specific responses remain. Future research will undoubtedly uncover new checkpoints and improve combination strategies to overcome these barriers and extend the benefits of immunotherapy to a wider range of cancer patients.

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