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Immune Checkpoint Inhibitors: Review, Challenge and Future Prospect

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Abstract. As known, Immune checkpoint inhibitors (ICIs) are an emerging pillar of immunotherapy, which significantly reduce toxicity compared to traditional therapies. By blocking immune checkpoint-related signaling pathways, ICIs relieve T-cell suppression and activate anti-tumor immune responses. Nowadays, ICIs have achieved desirable effects in a wide range of advanced cancers, and many new blocking targets have entered clinical trials. However, the clinical application of ICIs continues to face dual challenges: therapeutic resistance and immune-related adverse events (irAEs), which persist as significant obstacles to their broader clinical implementation. Current research focuses on biomarker screening, and optimization of combination therapy strategies, aiming to achieve precision immunotherapy. Investigating the mechanisms underlying drug resistance and the pathogenesis of irAEs could provide critical insights for optimizing clinical dosing regimens and improving therapeutic outcomes. This review integrates the targets, and clinical applications, and focuses on challenges and directions for the development of ICIs.

Keywords: ICIs; PD-1/PD-L1; CTLA-4; resistance; irAEs.

1. Introduction

Cancer is a group of diseases characterized by abnormal cells growing and spreading unchecked in the body, which is extensively recognized as a major factor threatening global public health. The proto-onco genes and tumor suppressor genes occur in mutations containing deletion mutations, point mutations, chromosomal translocations, and other mutations caused by multi-reasoned mechanisms, which lead to the development of tumors.

According to American cancer statistics, in 2024, the country witnessed approximately 2,001,140 new cancer cases and 611,720 cancer-related deaths in the current year [1]. Although there are many traditional cancer therapies like primary site surgery, chemotherapy, and radiation therapy, their strict limitations and fierce adverse effects remain an inevitable challenge. For instance, when the tumor leaves its initiative tissue, starting the process of distant metastasis, the method of surgery may be unlikely to be effective. Radiation therapy, which uses ionizing radiation to damage DNA, can cause strong systemic toxicity and severe organ-specific damage. Utilizing specific cytotoxic medicine including alkylating agents, alkaloids, and antimetabolites to kill and inhibit tumor cells is Chemotherapy. These two methods can effectively interfere with and inhibit the metabolism of tumor cells but also yield harm to autologous cells. The resistance can sharpen their curative effects, either.

Because of the high specificity, durable response, and reduced side effects, novel immune therapies have become a major focus of current research. Among those, immune checkpoint inhibitors (ICIs) exhibit transformative potential and have been given great expectations. The management of many cancers has been revolutionized by ICIs, particularly anti-CTLA-40 and anti-PD-1 antibodies. Drugs targeting these two pathways have received regulatory approval: Lpilimubab, Pembrolizumab, et al. Recently, the appearance of VISTA, CD39, CD73, lAG-3, and corresponding targeted drugs reprinted that novel immune checkpoints have become a hot area for ICIs [2].

As the name indicates, ICIs are related to multiple immune cell mechanisms to manifest their ability to counter the tumor. Thymus-dependent lymphocyte cell (T cells) is an indispensable component of anti-tumor immune. The activation of T cells requires the following two conditions: the first one is

that T cell receptor (TCR) must bind to the antigen peptide presented by the major histocompatibility complex (MHC) on the antigen-presenting cell (APC); secondly, The co-stimulatory receptor CD28 on the T cell must engage with B7 ligand present on the APC. Both signals are vital in the activation of T cells, and the latter are the so-called immune checkpoints.

Inhibitory checkpoint molecules constitute a class of surface-expressed receptors on T cells. When T cells activate and proliferate, these molecules are upregulated to negatively adjust T cell activity, thereby preventing the overactivation of immune responses and maintaining immune homeostasis.

According to the widely accepted '3E' model, which describes how the host immune system eliminates premalignant cell precursors and controls microscopic tumors through dynamic equilibrium until tumor cells acquire genetic or epigenetic alterations that enable them to achieve their immune escape. The third 'E' is the word 'Escape', which means that tumor cells have already developed the ability to evade immune recognition and clearance. On this basis, Claudia Galassi et al. have put forward the '3C' model [3]. The second 'C' represents the word 'Coercion'. Tumor cells that fail to camouflage and are successfully recognized by the immune system can evade immunity by inhibiting the activity of immune effector cells through some kinds of pathways. The mechanism includes changes in immune regulatory ligands.

One important transmembrane protein found on the surface of T cells is called programmed cell death protein-1 (PD-1), which is a member of the CD28 superfamily. It functions by negatively regulating immune responses. Programmed cell death protein ligand 1 (PD-L1) and programmed cell death protein ligand 2 (PD-L2) are ligands of PD-1. Multiple tumor cells express PD-L1 and use PD-1/PD-L1 signal to inhibit T-cell activation and down-regulate the immune response, thereby enabling the third 'E' incident.

To deal with the immune evasion of cunning tumor cells, immune checkpoint inhibitors come into view, becoming one of the most potential and promising immune medicines. They selectively target key regulatory molecules such as PD-1, its ligand PD-L1, and other molecules (e.g. cytotoxic T-lymphocyte-associated protein 4 (CTLA-4)), these therapies rebuild antitumor immunity and disrupt tumor immune evasion mechanisms, thereby restoring effective immune surveillance against malignancies.

This review aims to describe the current research on immune checkpoint inhibitors and to illustrate the possible solutions to these existing deficiencies.

2. The Relevant Mechanism

2.1. CTLA-4

CTLA-4 is a transmembrane protein, constitude with extracellular domain, transmembrane domain, and intracellular domain. As an inhibitory checkpoint expressed on T cells, CTLA-4 plays a critical role in the negative regulation of T cell activation.

As an indispensable part of the activation process of T cells, APC (e.g. Dendritic Cells, Macrophages, B cells), express two ligands belonging to the B7 class of molecules: CD80 and CD86. Upon encountering an antigen, APCs present it to naive T cells to trigger activated T cell-mediated immune effector functions [4].

CTLA-4 exhibits a high affinity for CD80 and CD86. Both of them are the natural ligands of CD28. The combination between CD28 and CD80 provides a co-stimulatory signal, which is essential for T cell activation. However, the existence of CTLA-4 can block the interaction between CD28 and B7, thereby inhibiting the activation signals of T cells. CTLA-4 exists as a dimer, and its extracellular domains form homodimers through disulfide bonds, it is confirmed that CTLA-4 interacts with both ligands with higher affinity and avidity than CD28 [5].

2.2. PD-1/PD-L1

PD-1 is a membrane receptor protein found mainly on the surface of immune cells, belonging to the CD28/CTLA-4 superfamily. The outer cytoplasmic region of PD-1 contains several sites, such as Y248, Y223, and Y201, which are phosphorylated to modify the immunomodulatory function of PD-1. It also contains an N-terminal immunoglobulin variable region (IgV) and a C-terminal immunoglobulin-like region (IgC) for binding to its ligand.

By attaching to its two ligands mentioned above, PD-1 suppresses the human immune response. In normal organisms, PD-1 binds to its two ligands of co-inhibitory molecules, inhibiting T cells signal transduction, maintaining immune system homeostasis, and avoiding autoimmune disorders. But when the occurrence of tumor invasion happens, this signal creates possible opportunities for immune evasion. The precise mechanism is that PD-L1, and PD-L2 expressed on the surface of solid tumors bind to PD-1 on the surface of T cells. Triggers for PD-L1/PD-1 binding SHP2 phosphatase recruitment and PD-1 phosphorylation, then PD-1-associated SHP2 dephosphorylates CD28 and TCR signaling elements, thus preventing T cell activation.

PD-1/PD-L1 signal directly inhibits effector T-cell function through inhibition of the TCR signaling pathway, and long-term PD-1 signal leads to high expression of depletion markers in T-cells, thereby inducing T-cell depletion. Additionally, PD-1/PD-L1 signal strengthens the immune-suppressive role of regulatory T-cells (Tregs), which release cytokines like IL-10 and TGF-β and directly prevent CD8+ cytotoxic T-cells (CTLs) and Th1 cells from activating, proliferating, and dying. Tregs can also further weaken the immune response by secreting chemokines such as CCL22 and recruiting more Tregs, M2-type macrophages, etc. to form an immunosuppressive network.

The immune checkpoint inhibitors mentioned above block the combination of PD-1 and PD-L1, which has shown promising results in cancers.

2.3. Novel Target Sites

Lymphocyte Activation Gene-3 (LAG-3) recognizes conformationally stable complexes of peptides and MHCII In addition, α-synuclein fibrils and LAG-3 ligands such as liver sinusoidal endothelial cell lectin (LSECtin) were also identified. LAG-3 suppresses the activation of CD4+ T cells when they are stimulated by a homologous peptide that forms a complex with MHCII [6].

The intracellular region of LAG-3 consists of approximately 60 amino acid residues, including the FSAL sequence, KIEELE sequence, and 10–15 tandem repeats of glutamate (EX-repeat). The possible mechanism is that the combination of LAG-3 and its ligands could FSAL to interact with downstream signaling molecules to give out inhibitory signals to prevent T-cell activation.

V-domain Ig Suppressor of T cell Activation (VISTA) is a type I transmembrane protein and is one of the emerging immune checkpoints. It is expressed multiple myeloid and regulatory T cells, acting as a negative immune checkpoint molecule to inhibit T-cell-mediated immune response. VISTA demonstrates unique therapeutic advantages over PD-1/CTLA-4 inhibitors, particularly in some low mutational burden tumors.

3. Representative Drugs and Clinical Applications

As a representative anti-PD-1 drug, Pembrolizumab gains striking success in a series of clinical trials. For instance, pembrolizumab significantly prolongs both median overall survival (OS) and progression-free survival (PFS) compared with chemotherapy in patients with non-small cell lung cancer (NSCLC) with high PD-L1 expression (≥50%). Additionally, the five-year survival rates for pembrolizumab and chemotherapy were 31.9% and 16.3%. (NCT02142738 [7]). A clinical trial included no pre-treatment Triple-negative breast cancer (TNBC) patients shows that PFS was considerably longer with chemotherapy plus pembrolizumab than with chemotherapy alone in patients with PD-L1 expressing tumors and a Combined Positive Score (CPS) ≥10, but there was almost no difference in PFS for individuals with low CPS (NCT02819518 [8]). In another clinical

trial comparing the efficacy of pembrolizumab with chemotherapy in Advanced gastric and gastroesophageal junction cancers, patients in the CPS ≥1 group demonstrated a median overall survival (OS) of 10.6 months. This figure was slightly lower than the chemotherapy (Placebo plus cisplatin) group (11.1 months), but non-inferiority was demonstrated in the study assessment [9]. In advanced Hepatocellular carcinoma (HCC), the PFS of using pembrolizumab was 4.5 months, accompanied by a moderate objective remission rate (NCT02658019 [10]). However, the efficacy was poor compared to first-line drugs (tyrosinase inhibitors, TKIs).

As shown above, pembrolizumab has quite good safety, and the frequency of grade 3 or higher adverse events was markedly reduced compared to chemotherapy. Ongoing clinical trials are aimed at evaluating the efficacy and safety of exploring pembrolizumab in multiple solid tumors (NCT03797326).

Atezolizumab is a representative drug of PD-L1 inhibitor, which has been approved globally for multiple types of solid tumors, such as urothelium carcinoma, NSCLC, and others. IMvigor210 confirmed that Atelizumab has antitumor activity in platinum-resistant uroepithelial cancer. In advanced NSCLC, atezolizumab in combination with anti-angiogenic drugs (e.g. bevacizumab) proved to be effective. Analysis of the two-stage phase II trial [11] demonstrated a partial response (PR) rate of 12.5% among treated patients, and 75.0% achieved stable disease (SD). The overall disease control rate (DCR) was almost 87.5%. The majority of adverse reactions observed were mild in severity. Additionally, in patients with unresectable HCC, the combination therapy of atezolizumab and bevacizumab demonstrated prolonged OS and more favorable median PFS compared to the former first-line agent sorafenib.

These ICIs above have one thing in common. If PD-L1/PD-1 inhibitors are required, it is necessary to test the PD-L1 CPS. At present, Combination therapies are still the developing direction of ICIs.

Anti-CTLA-4 is represented by Ipilimumab, the first anti-CTLA-4 monoclonal antibody to receive FDA approval. Since receiving FDA approval in 2011, Ipilimumab demonstrated significant survival benefits in patients with advanced melanoma. In 2015, the combination of Lpilimumab and Nivolumab gained FDA approval, it has been a first-line approach to advanced melanoma. At the same time, Ipilimumab itself became a second-line approach. Ipilimumab in combination with nabulizumab has also emerged as a first-line treatment option for renal cell carcinoma (RCC). This combination has also been proven effective in treating HCC and colorectal cancer with high microsatellite instability/mismatch repair deficiency (MSI-H/dMMR).

In addition to the representative Ipilimumab and tremelimumab, the investigational Anti-CTLA-4 drugs ONC-392 (NCT04140526) and BMS-986218 have demonstrated good disease control rates in clinical trials.

Relatlimab, an anti-LAG-3 drug, was approved by the FDA in 2022 for use in advanced melanoma in combination therapy options. Its research on other cancers has entered Phase III clinical trials. Anti-TIGIT Vibostolimab, as well as ICIs drugs based on the new targets CD134 and VISTA, have also shown initial efficacy in clinical trials. In conclusion, ICIs are redefining cancer care, demonstrating remarkable efficacy across an expanding spectrum of malignancies.

4. Challenges

4.1. irAEs (immune-related adverse events)

Using ICIs has proved progressively more effective for advanced cancer, but ICIs therapy may lead to immune-related adverse events. The mechanism [12] is multiple, including antigen-specific T-cell stimulation and response, B-cell stimulation, autoantibody production, and inflammatory cytokines.

There are shared T-cell receptor sequences and/or upregulated organ-specific transcripts between tumors and non-malignant tissues affected by toxicity. Among patients receiving ICIs treatment, irAEs occur in 66%-96% of cases, with severe irAEs developing in 7%-59% [13].

IrAEs involving multiple organ systems are observed in ≤90% of patients receiving CTLA-4 inhibitors, and 70% in those treated with PD-1/PD-L1 inhibitors [14]. This indicates that while ICIs demonstrate high efficacy, the population affected by their side effects remains alarmingly high, too. IrAEs involve the skin, gastrointestinal tract, hepatic system, and endocrine system, with severe cases posing life-threatening risks.

A wide range of skin irAEs is typical since the skin is a strongly immunogenic organ containing diverse immune cell populations, such as mast cells, T cells, macrophages, and cutaneous dendritic cells [15], including maculopapular rash, pruritus, psoriasiform rash. Those skin complications are self-limiting and reversible, but some can develop into lifelong diseases, such as vitiligo.

ICIs can cause endocrine disorders, including adrenal insufficiency, thyroid disease, insulin-dependent diabetes (IDDM), and more. Hormone-secreting cells cannot recover from the inflammation induced by T cells, which leads to a lasting deficiency of hormones. Long-term research demonstrates that among the 101 patients, 55(55%) patients who received CTLA-4-based ICI, almost have undetectable levels of corticotropin and cortisol with a median follow-up of 45.5 months [16]. Additionally, among 33 IDDM patients, 58% of patients occurred diabetic ketoacidosis. A large amount of clinical experiences reveal that the endocrine system is greatly affected by ICIs. Interestingly, a positive correlation between endocrine irAEs and overall survival (OS) was observed in some research projects [17]. The incidence of irAEs was 9% in specific datasets and was associated with improved OS.

ICIs can also cause multiple neurological chronic irAEs (e.g. myasthenia gravis, encephalitis, polyneuropathy). Haem-irAEs are known to have unpredictable adverse reactions with poor prognosis but have a relatively low incidence rate.

The features of irAEs also vary throughout the various ICI classes. For instance, anti-CTLA4 is anticipated to cause hypoadrenocorticism and digestive adverse reactions more frequently, whereas anti-PD1 or PD-L1 are more commonly linked to arthralgia and pneumonia [18]. This organ specificity also complicates the event of irAEs.

Overall, irAEs are not just ordinary side effects. The mechanism of irAEs generation in different ICIs has not been fully elucidated, and the differences in the irAE risk profiles of diverse ICIs still remain a mystery, thus increasing the risk of use.

4.2. Resistance

The resistance of ICIs can be classified into two types: primary and secondary in time dimensionality, and intrinsic or extrinsic in occurrence mechanism.

In simple terms, even if the patients' tumors show high expression of PD-L1 and equip quite favorable conditions for ICIs application, patients with primary resistance show no response to ICIs from the outset of treatment. The secondary resistance is that patients show satisfactory immune reactions through using ICIs initially but subsequently occur cancer progressions, resulting in the deterioration of their conditions.

As several research demonstrate, Tumor Mutational Burden (TMB), alterations in signaling pathways, abnormal interferon signaling pathways and antigen processing, and presentation defects are all factors that lead to intrinsic resistance [19].

TMB, defining the quantity of somatic non-synonymous mutations in tumor cell genomes per million nucleotides, is a prospective biomarker that can report the total amount of mutations that happen in tumors. A higher TMB leads to more mutation-derived neoantigens. MHC molecules on cancer cells present these neoantigens, enhancing T cell recognition and attack, directly increasing ICIs' medical effects. Adversely, low TMB and lack of neoantigens are the reasons for intrinsic resistance. For instance, as a low TMB tumor, prostate cancer has a low response rate to ICIs.

Abnormal oncogenic signaling alters the immune microenvironment during cancer development, impacting immunotherapy efficacy. The loss of tumor suppressor gene PTEN can boost the activity of the PI3K-Akt pathway, which in turn can up-regulate VEGF, CCL2 and other inhibitory cytokines expressions. Additionally, because PTEN-deficient cells are unable to activate the IFN signaling pathway, PTEN loss may result in immune resistance and poor efficacy of ICIs. As known, the WNT/β-catenin pathway is involved in embryonic development and maintenance of tissue homeostasis through a complex succession of mechanisms. WNT protein determines the opening and closing of the pathway WNT/β-catenin pathway, when there is no activate signal, β-catenin is phosphorylated by the destruction complex, which consists of APC/Axin/GSK3β. Then β-catenin is degraded by the proteasome. When there is an activated signal, WNT combines with Frizzled receptor and LRP5/6 co-receptor, recruiting Dishevelled (DVL) Protein. Afterward, the destruction complex is destroyed which leads to consistent accumulation of β-catenin. Aberrant WNT/β-catenin pathway signaling activation inhibits T cell infiltration by downregulating the expression of chemokines. Otherwise, it can activate other immune-suppression pathways, which in turn complicates the mechanisms of ICIs resistance. Other Signal pathways including RAS-MAPK, ALK, and Hippo can all shape the immunosuppressive microenvironment through multiple mechanisms [20].

Defects in IFN-γ Signaling are a proven reason for ICI resistance. As a pleiotropic cytokine with an important role in anti-tumor immunity, IFN-γ directly induces apoptosis in tumor cells by activating the JAK-STAT signaling pathway. However, the loss-of-function mutations of the JAK-STAT pathway are related closely to the loss of tumor cell sensitivity to IFN-γ, with an associated lack of MHC class I and PD-L1 expression [21]. Some research shows that the change of JAK1, and JAK2 genes can lead to primary resistance to ICIs. Furthermore, patients who are resistant to ICIs frequently exhibit IFN-γ-driven resistance molecules or have molecular abnormalities in the IFN-γ signaling pathway [22]. To summarise above, genetic defects in the IFN-γ pathway may be a crucial resistance circuit shared by multiple immune checkpoint therapies.

TME consists of immune cells, fibroblasts, endothelial cells, and non-cellular components. ICIs can reinvigorate antitumoral immune by targeting the immune-related cells in TME, however, those cells have complex mechanisms that lead to medicine resistance. Based on this, a number of relevant T and B cell indicators can be used as biomarkers.

5. Conclusion

At present, ICIs have shown high therapeutic potential among many kinds of tumor therapies. However, as mentioned above, it is constrained by two factors: IrAEs and resistance, which are still sticky and limit the application of ICIs.

The interplay of pre-existing autoimmune conditions, microbiome profiles, and dynamic immune markers have all been implicated in the mechanisms of irAEs, as well as have the potential to participate in the prediction, diagnosis, and treatment of irAEs. Patient autoimmune characteristics include baseline levels of biomarkers, pre-existing abnormal antibodies, etc. Baseline levels can considered as the participant's quantifiable starting point. For instance, patients with high Basal Absolute Eosinophil Count (AEC) may have more possibility of experiencing toxic reactions. So, AEC can be used as a predictive biomarker [23]. Elevated titers of rheumatoid factor (RF), antinuclear antibodies, and antithyroglobulin are frequently detected at pre-intervention baseline and exacerbate cumulative toxicity. This results in a high probability of developing irAEs.

Many researches have proved that there was a mechanistic association between microbiome characteristics and ICI response and irAEs. One aspect is that microbial metabolites may influence T cell-mediated immune response. Also, dysbacteriosis can lead to the activation of specific immune pathways, affecting therapeutic efficacy. Despite the existence of unexplored mechanisms, the findings that a high abundance of specific microbial species demonstrates correlations with response rates to certain ICIs and exhibits specificity in the onset characteristics of tissue-specific have been

documented, especially in gastrointestinal irAEs. These discoveries indicated that irAE-associated microbiome signatures may serve as predictive biomarkers.

Beyond preventive roles, the microbiome may play a therapeutic role in irAE management. Fecal microbiota transplantation (FMT) has stepped into the application stage, diminishing the severity of specific irAEs and shortening the course of the disease. One completed clinical trial shows that a PD-1 inhibitor combined with an oral administration of a monoclonal Bifidobacterium lactis strain Improved partial remission rates in patients without severe reactions to irAEs (NCT03775850).

Dynamic immune markers include non-specific biomarkers (e.g., blood counts, cytokines, TMB, etc.), and organ tissue-specific markers. For example, elevated auto-antibodies targeting CD74 were observed in severe immune-related pneumonia cases following ICIs administration. However, there were no striking CD74 changes in patients without ICIs treatment. Similarly, in patients with endocrine irAE-induced thyroid dysfunction, thyroid peroxidase antibodies (TPOAb) exhibit aberrations and demonstrate divergent disease manifestations between anti-PD-1 and anti-PD-L1 treated cohorts, which helps both elucidate the pathogenic mechanisms of irAEs and enhances diagnostic precision.

However, fluctuations in the levels of biomarkers found so far are detected after the occurrence of irAEs and are not immediate. Although marker specificity increases diagnostic accuracy, this heterogeneity problem determines that it is difficult to have universal markers involved in the diagnosis, and the predictive efficacy is not stable within each patient. Furthermore, the intricate pathophysiological mechanisms by which heterogeneous classes of ICIs induce irAEs involve multiple pathways. This mechanistic complexity introduces substantial interpatient variability in irAE profiles, thereby creating substantial barriers to biomarker standardization and clinical validation across diverse patient cohorts. Another question is that marker levels may fluctuate with the treatment cycle, making it difficult to determine the timing of marker diagnosis. Future directions will focus on more kinds of biomarkers studies and overcoming heterogeneity to the greatest extent possible. Establishing marker libraries for tumor types, ICIs drugs, and irAEs typing, and taking into account the dynamic nature of marker monitoring is the way to precise prediction and diagnosis. Ultimately, the current therapeutic armamentarium for managing irAEs remains predominantly reliant on high-dose corticosteroid protocols, often with suboptimal response rates in steroid-refractory cases. Emerging evidence highlights the urgent need for biomarker-guided stratified interventions, also in the therapeutic area of irAEs.

How to solve the resistance is a hot research topic. Combined drug therapies have become the solution to drug resistance. For instance, ICIs combined with anti-angiogenic drugs can not only reduce oxygen and nutrient supply to tumor cells but also block vascular endothelial immunosuppressive secretion and mitigate T cell apoptosis and dysfunction. Including Axitinib, Bevacizumab, Thalidomide, etc., certain anti-angiogenic drugs are approved by FDA.

Combination therapies are multiple. Examples include ICIs combined with chemoradiotherapy, ICIs combined with targeted therapies, and dual ICI regimens. The combination of dual ICIs can block multiple immune checkpoints simultaneously [24]. The earliest case of successful combination therapy was the combination of navulizumab and ipilimumab, which was highly effective in patients with advanced melanoma. Current combinations of ICIs are no longer constrained by the more conventional PD-1/PD-L1 and CTLA-4, with new combinations moving into clinical trials and involving multiple cancer types. For instance, the combination of anti-PD-L1+TIGHT inhibitor, anti-PD-1+anti-CTLA-4. Research demonstrated that the triple combination therapy (anti-PD-1+anti-LAG-3+anti-CTLA-4) showed marked efficacy in managing both intracranial and extracranial metastases of melanoma, substantially enhancing therapeutic outcomes and prolonging response duration in melanoma brain metastases [25].

Metabolic intervention in tumor cells has received much attention in recent years. Take glucose metabolism as an example, phosphofructokinase 2/fructose-2,6-bisphosphatase 3 (PFKFB3) promotes glycolysis in tumor cells, and its inhibitor PFK-158 significantly inhibits tumor cell

proliferation and induces apoptosis. An experiment showed that PFK-158 synergistically augmented the anti-tumor efficacy of anti-CTLA-4 ICIs in melanoma-bearing murine models [26]. In addition to glucose metabolism, inhibitors interfering with amino acid, lipid, and lactate metabolism have demonstrated initial clinical progress and have generated several regimens for use in combination with ICIs. For instance, polyethylene glycol-modified arginine deiminase (ADI-PEG20) combined with anti-PD-1 ICIs is involved in the treatment of HCC. Therapeutic strategies combining ICIs with metabolic pathway antagonists demonstrate synergistic potential in remodeling the immunosuppressive TME, thereby enhancing anti-tumor immunity while notably mitigating the development of acquired resistance mechanisms. This approach achieves dual therapeutic objectives through metabolic reprogramming of immune cells and targeted blockade of immune checkpoints, effectively reversing TME-mediated immunosuppression and improving durable clinical responses. Options for ICIs combined with metabolic interventions will be explored more in the future.

In addition, as a relatively new area, the combination of ICIs with cancer vaccines and lysosomal viruses has also become a direction of development exploration to increase efficacy and reduce drug resistance.

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