Biomedicine & Pharmacotherapy 124 (2020) 109821

Contents lists available at ScienceDirect

Biomedicine & Pharmacotherapy

journal homepage: www.elsevier.com/locate/biopha

Review

Cancer immunotherapy: Pros, cons and beyond

Shuzhen Tan[a,b,c], Dongpei Li[b,*], Xiao Zhu[a,b,*]

[a] Guangdong Key Laboratory for Research and Development of Natural Drugs, Guangdong Medical University, Zhanjiang, 524023, China
[b] The Marine Biomedical Research Institute, Southern Marine Science and Engineering Guangdong Laboratory Zhanjiang, Guangdong Medical University, Zhanjiang 524023, China
[c] Cancer Center, The Affiliated Hospital, Guangdong Medical University, Zhanjiang 524023, China

ARTICLE INFO

Keywords:
Cancer immunotherapy
Immune checkpoint inhibitors
Tumor microenvironment
CAR-T
PD-1

ABSTRACT

Cancer immunotherapy is an innovative treatment for tumors today. In various experiments and clinical studies, it has been found that immunotherapy does have incomparable advantages over traditional anti-tumor therapy, which can prolong progression-free survival (PFS) and overall survival (OS). However, immunotherapy has obvious complexity and uncertainty. Immunotherapy may also cause severe adverse reactions due to an over-active immune system. More effective and fewer adverse reactions immunological checkpoints are still under further exploration. This review gives an overview of recent developments in immunotherapy and indicates a new direction of tumor treatment through analyzing the pros and cons of immunotherapy coupled with keeping a close watch on the development trend of the immunotherapy future.

1. Introduction

Unlike traditional cancer treatments such as radiotherapy and chemotherapy, immunotherapy is an innovative treatment that dynamically modulates the immune system to attack cancer cells in multiple targets and directions [1]. Immunotherapy is mainly used to strengthen the immune system by regulating the immune microenvironment, so that immune cells can attack and clear tumor cells at several important nodes [2]. In combination with traditional anti-tumor therapy or multiple immunocheckpoint inhibitors (ICIs), most of the effects will be significantly enhanced, but the specific situation remains to be further studied. The research of related anti-tumor drugs is gradually deepening, and the market and application of drugs are increasing gradually. At present, the gap with international research level is gradually narrowing, which greatly promotes the development of tumor immunotherapy. This review introduces all aspects of immunotherapy in detail, and analyzes the literature related to tumor immunity to reveals the mysterious veil of immunotherapy.

2. Cellular immunotherapy for tumors

Immune cells can identify and kill tumors. By stimulating immune cells and using the body's own tumor-specific immune response to overcome tumor escape, immune cells can once again play a role in tumor surveillance and clearance. Cell immunotherapy is now effective in hematologic tumors, but due to the heterogeneity within solid tumors and external microenvironment, the efficacy for solid tumors is not as expected [3].

Abbreviations: ACI, adoptive cellular Immunotherapy; aeTSAs, aberrantly expressed tumor-specific antigens; APCs, antigen presenting cells; ADCC, antibody dependentcell-mediated cytotoxicity; BCMA, B Cell Maturation Antigen; BiTE, Bispecific T Cell Engager; bTMB, blood tumor mutation burden; CIK, cytokine-induced killer cells; CAR-T, chimeric antigen receptor T-cell immunotherapy; CRS, cytokine release syndrome; CyTOF, Cytometry by Time-Of-Flight; CAF, cancer-associated fibroblasts; CTL, cytotoxic T lymphocyte; DC, dendritic cells; DAMPs, damage associated molecular patterns; hTERT, Human telomerase reverse transcriptase; HPD, hyperprogressive disease; iUPD, immunity uncomfirmed progressive disease; imRECIST, immune-modified Response Evaluation Sriteria In Solid Tumors; ICIs, immune checkpoint inhibitors; ITH, intratumoral heterogeneity; irAE, immune related adverse events; KARs, killer activation receptors; KIRs, killer inhibitory receptors; LAK, lymphocyte activated killer cells; LTSCP, subcutaneous panniculitis T lymphoma; MAK, macrophages activated killer cells; MDSCs, Myeloid-derived suppressor cells; MM, Multiple myeloma; MSI, microsatellite instability; MSI-H, high microsatellite instability; mTSAs, mutated tumor-specific antigens; MHC, major histocompatibility complex; NKC, natural killer cells; OS, overall survival; PD, progressive disease; PFS, progression-free survival; RECIST, response evaluation criterion in solid tumor; TIL, tumor infiltrating lymphocyte; Tregs, regulatory T cells; TCR-T, T cell receptor; TME, tumor microenvironment; TMB, tumor mutation burden; TAMs, tumor-associated macrophages; TAA, tumor associated antigen; TAPC, tumor antigen presenting cells; TGR, tumor growth rate

* Corresponding authors at: Guangdong Key Laboratory for Research and Development of Natural Drugs, Guangdong Medical University, Zhanjiang, 524023, China and The Marine Biomedical Research Institute, Southern Marine Science and Engineering Guangdong Laboratory Zhanjiang, Guangdong Medical University, Zhanjiang 524023, China.

E-mail addresses: dliimmag@gmail.com (D. Li), bioxzhu@yahoo.com, xzhu@gdmu.edu.cn (X. Zhu).

https://doi.org/10.1016/j.biopha.2020.109821
Received 5 November 2019; Received in revised form 12 December 2019; Accepted 18 December 2019

2.1. Adoptive cellular immunotherapy (ACI)

ACI refers to the treatment of killing tumor cells by injecting immunologic effector cells modified and amplified by genes, which has become a hot research direction and important means of tumor treatment because of its strong specificity, easy preservation, and no drug resistance. ACI can be divided into nonspecific ACI and specific ACI. The immune cells in nonspecific ACI are activated by lymphocytes or cytokines in the peripheral blood and have the ability to kill a variety of tumors. However, due to poor tumor targeting and weak killing ability, they are only used for adjuvant therapy. Immunologic effector cells in nonspecific ACI include dendritic cells (DC), natural killer cells (NKC), cytokine-induced killer cells (CIK), tumor-infiltrating lymphocyte (TIL), lymphocyte activated killer cells (LAK), macrophages activated killer cells (MAK), etc. The immune cells in specific ACI are induced by specific tumor antigen stimulation and specific stimulating factors, including TIL therapy, T cell receptor -T (TCR-T) and Chimeric Antigen Receptor T-Cell Immunotherapy (CAR-T) [4]. The main effector cells are CD8 + T cells and CD4 + T cells. This kind of therapy has strong specificity, strong targeting, high lethality, small side effects, and no drug resistance, so it can be used in some advanced patients or patients with no response to other curative effects. TIL therapy is only used for melanoma temporarily due to its difficulty in separating and collecting, and CAR-T therapy is mostly used for blood tumor treatment [5].

2.2. NK cell therapy

NK cells are toxic natural immune cells whose surface is mainly composed of activated killer activation receptors (KARs) and killer inhibitory receptors (KIRs). NK cells recognize that normal cells are generally dominated by inhibitory receptors and avoid killing, while NK cells can quickly respond to virus infection and tumor occurrence. Even without an antibody, NK cells do not need to be activated to kill the immune system and trigger an overall immune system defense and attack. The killing effect of NK cells on tumor cells without MHC-1 receptor and tumor cells with up-regulated expression of activated ligand was activated, especially for metastatic tumors and blood tumors [6]. In addition, activated cytokines such as IL-2 and IL-5 mediate and promote the activation of NK cells and antibody-dependent cell-mediated cytotoxicity (ADCC) mediates NK cells to recognize and kill antibody-coated tumor cells. Newly developed BiKE and TriKE molecule could improve the effectiveness of ADCC [7]. However, tumor cells still have the mechanisms of inhibiting NK cells to achieve immune escape [8]. Firstly, tumor cells secrete MICA and MICB proteins, and relevant targeted antibodies have been developed and achieved certain results, eg.mAb 7C6 [9]. Secondly, tumor cells inhibit the identification and killing of NKC by raising the expression of HLA-G [10] and binding with the NK cells inhibitory receptor LIR-1 [11]. Thirdly, tumor cells secrete and shed the soluble activated NKG2D ligand, which not only makes it difficult for NK cells to bind to the NKG2D ligand on the tumors, but also enables the continuous activation of NK cells near the tumor, reducing the sensitivity of recognition [12]. Fourthly, inhibitory immune cells such as myeloid-derived suppressor cells (MDSCs) and regulatory T cells (Tregs) and other inhibitory immune cells can inhibit anti-tumor activity of NK cells by secreting cytokines or by direct contact [13]. By inhibiting NK cells inhibitory signaling pathways and activating NK cell activation signaling pathways, or by combining targeted drugs to promote NK cells to reach the specific tumor site, the treatment of NK cells on tumors can be achieved, thereby improving the anti-tumor effect and reducing side effects [14]. At present, NK cells combined with immune checkpoint inhibitors, NK cells combined with CAR [15] and NK cell-based immunotherapy have emerged in medical research (Fig. 1).

2.3. Chimeric antigen receptor T-cell (CAR-T) immunotherapy

CAR-T refers to the chimeric antigen receptor T-cell immunotherapy, which is efficient adoptive cell therapy. It mainly extracts the patient's body T cells through leukocyte reduction procedures, and transformed into the surface CAR-T by genetic engineering means, and then transferred to the tumor of patients to achieve tumor-specific killing. The therapy has a high remission rate for tumors expressing CD19 proteins, such as B-cell acute leukemia and large B-cell lymphoma. The drugs currently approved by the FDA include Novartis's tisagenlecleucel-T (Kymriah) and Kite/Gilead's axicabagene ciloleucel (Yescarta). Kymriah can be used to treat recurrent or refractory B-cell acute lymphoblastic leukemia [16]. Yescarta works in relapsed or refractory adult large B-cell lymphoma, but its associated side effects include cytokine release syndrome (CRS) and neurotoxicity [17]. Although CAR-T therapy can be formally applied to leukemia and lymphoma, not only with very few tumor-specific molecules, and inhibition of immune environment and T-cell depletion is also strongly related.

There has also been great progress in the study of T-cell depletion. The main direction is to control and inhibit T cell depletion, effectively treat tumors and expand the beneficiary population [18]. a. The absence of TET2 protein can prolong the time of T cells in the central memory state, prevent cell-targeted failure, increase muscle memory T cell, improve perforated enzyme and granule enzyme levels, and improve the effectiveness of CAR-T therapy and reduce the production cost after the treatment of TET2 protein or gene through drug mediation or gene-editing technologies [19]. b. Nr4a transcription factors are highly expressed in CD8 + T cells of chronic viral infection and cancer, and can significantly improve the efficacy of CAR-T when they are not expressed. In animal experiments, Mice in which CAR T cells did not express Nr4a showed significantly reduced tumor size and prolonged survival. Inhibiting Nr4a transcription factor expression in the future is expected to be an important strategy to combat T-cell depletion [20]. c. Epigenetic drug decitabine inhibits DNA methylation, acts on depleted T-cells associated with epigenetics [21,22], enables depleted T-cells to be reversed as long-lasting functional memory T-cells, inhibits the obstruction of depleted T-cells in immune system control infections and tumors, and limits the efficacy of immunosuppressants [23–25]. In addition, PD-1/PD-L1 immune checkpoint inhibitors can significantly control tumor growth [26]. This method is also expected to be effective in treating a variety of cancers.

3. Immune checkpoint inhibitors (ICIs)

The immune checkpoint is located on the surface of T cells or tumor cells as the acting target for inhibiting the over-activation of T cells. Inhibitory checkpoint protein under normal circumstances to prevent autoimmune disease damage, but when encountering a tumor, it will prevent T cells from approaching the tumor, weakening the ability of the immune system to recognize and destroy tumor cells [27]. By using ICIs, the immune response of T cells can be largely activated, and re-establish the immune effect of anti-tumor (Fig. 2). A large number of studies have used immunosuppressive checkpoints as one of the means of immunotherapy, and the number of effective immune checkpoint available for immunotherapy is enormous, but more specific sites are still in exploring. ICIs efficacy is associated with biomarkers expression, such as PD - L1 expression quantity, tumor mutation burden (TMB) and microsatellite instability (MSI) [28].

3.1. Improve the curative effect of ICIs

Clinically, the effective rate of PD-1 / PD-L1 inhibitors is approximately 80 % in lymphoma, 60 % in high microsatellite instability (MSI-H) tumors, and the efficiency fluctuates between 10 % and 30 % in other common solid tumors [29]. However, immunotherapy not only costs a lot but also may delay the disease if the treatment fails. Therefore, improving the efficacy of ICIs to achieve precision anti-tumor therapy is a major direction of immunotherapy research.

a. Detecting therapeutic response and prognostic biomarkers

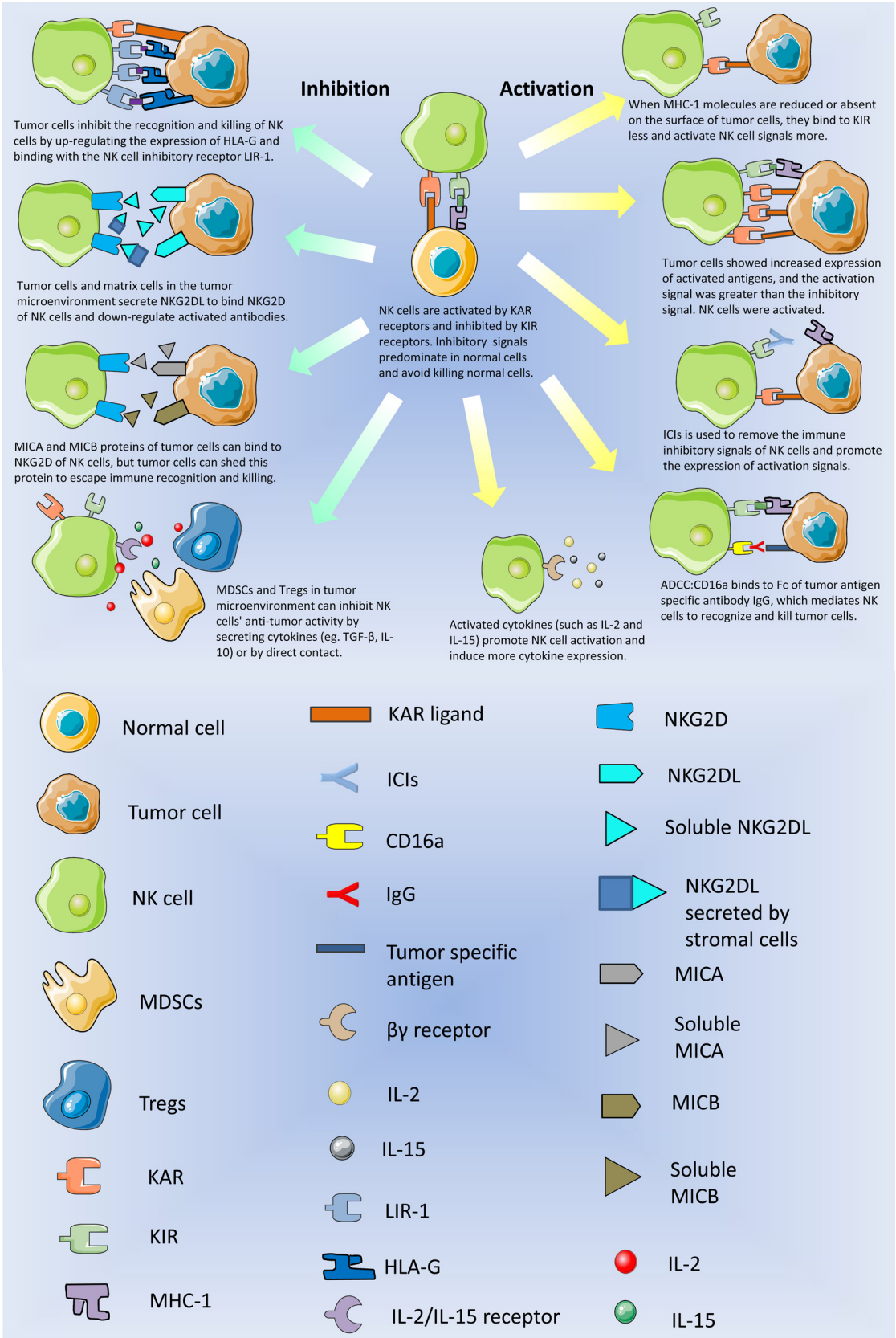

Fig. 1. The mechanisms of activation and inhibition of NK cells. NK cells are composed of KAR and KIR. The activation and inhibition signals of NK cells determine their response to tumor cells. The mechanisms of NK cell activation include: (1) Reducing the binding of MHC-1 molecules to inhibitory receptor KIR. (2) Increasing binding to activated antigens. (3) Immunosuppression signals were removed using ICIs. (4) ADCC mediates the recognition and killing of tumor cells. (5) Cytokines promote the activation of NK cells. The mechanisms of NK cell inhibition: (1) Tumor cells up-regulate the expression of HLA-G and increase the binding to inhibitory receptor LIR-1. (2) The bond between the tumor cell (NKG2DL) and NK cell (NKG2D) leads to downregulation of antibodies activity. (3) Tumor cells shed MICA and MICB proteins to avoid killing. (4) MDSC and Tregs secrete cytokines to inhibit the killing effect.

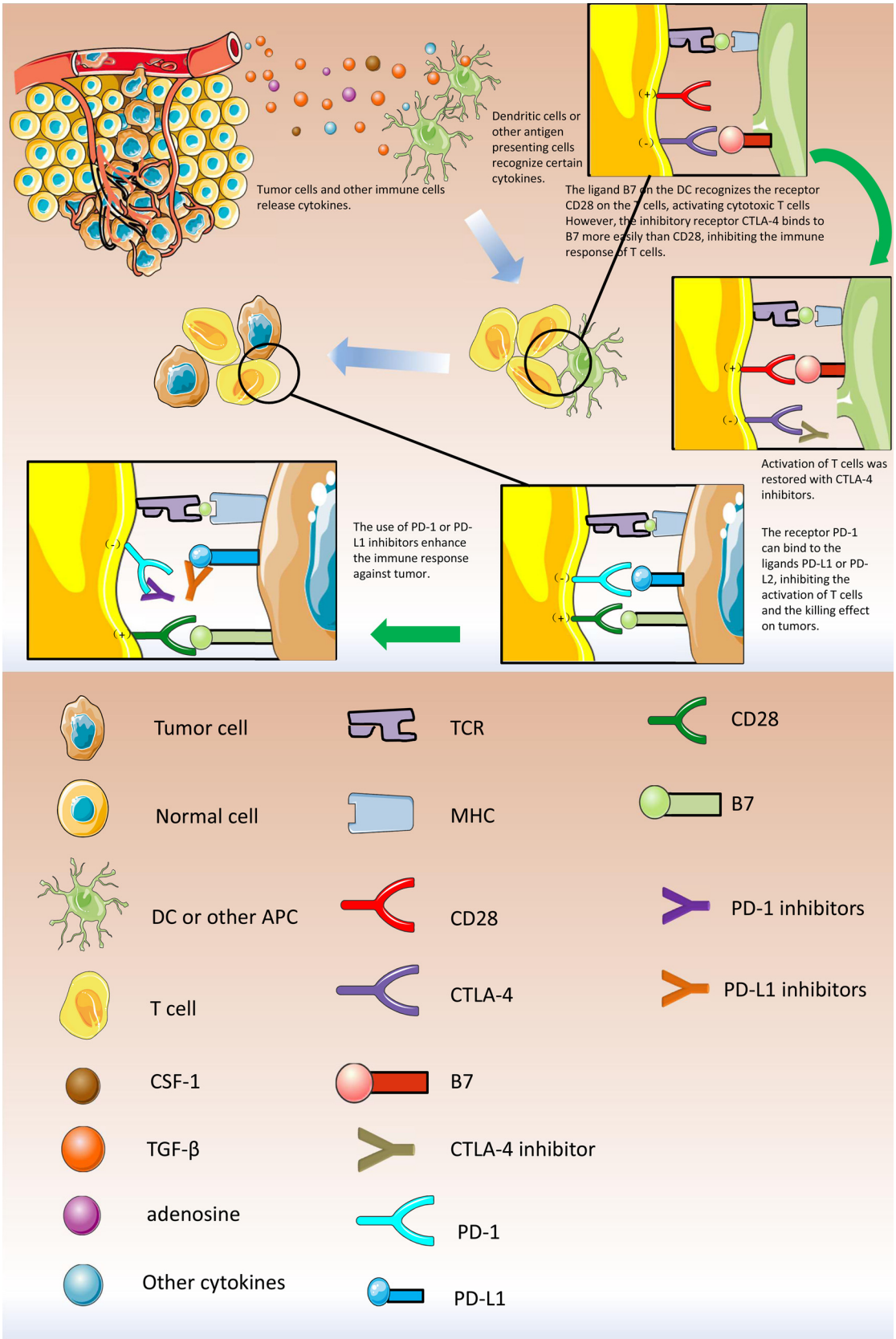

Fig. 2. The use of ICIs can enhance the body's immune resistance to cancer. In the immune microenvironment, tumor cells and other immune cells release cytokines, such as CSF-1, TGF-β, adenosine, etc. Dendritic cells (DC) or other antigen presenting cells recognize cytokines. The ligand B7 on the DC recognizes the receptor CD28 on the T cells, activating cytotoxic T cells and promoting the proliferation and migration of T cells to tumors. Nevertheless, in activated T cells, the inhibitory receptor CTLA-4 binds to B7 more easily than CD28, thus inhibiting the immune response of T cells. Activation of T cells was restored with CTLA-4 inhibitors. Activated T cells act on tumor cells. The receptor PD-1 in T cells can bind to the ligands PD-L1 or PD-L2 in tumor cells, inhibiting the activation of T cells and the killing effect on tumors. The use of PD-1 or PD-L1 inhibitors *in vivo* can enhance the immune response of T cells against tumors, inhibit tumor proliferation, and prolong the survival of patients.

Table 1
Summary of major listed immune checkpoint inhibitors in China. ICIs, Immune Checkpoint Inhibitors; NK cell, natural killer cells.

Immune Checkpoint Inhibitors	Immune checkpoint expression site	English generic name for inhibitors	Inhibitor trade name	The type of tumor being treated	Adverse reactions
PD-1 ICIs	T cell, B cell, NK cell, Monocytes, Dendritic cell, Tumor cell	Pembrolizumab	Keytruda	Non-small cell lung cancer, malignant melanoma, etc	Diarrhea, itching, fatigue, etc.
		Nivolumab	Opdivo	Breast cancer, malignant melanoma, etc	
		Cemiplimab	Libtayo	Breast cancer, malignant melanoma, etc	
		Toripalimab	Toripalimab Injection	Breast cancer, lymphatic ccancer, melanoma, etc	
		Sintilimab	Sintilimab Injection	Hodgkin's lymphoma, Lymphoma, Bladder cancer, non-small cell lung cancer	
		Pidilizumab	CT-011		
PD-L1 ICIs	Dendritic cell, macrophages, Tumor cell	Pidilizumab	CT-011		
		Atezolizumab	Tecentriq	Bladder cancer, non-small cell lung cancer	Fatigue, loss of appetite, cough, nausea, musculoskeletal pain and constipation, etc.
		Durvalumab	Imfinzi	Advanced or metastatic urothelial carcinoma	
		Avelumab	Bavencio	Merkel Cell Carcinoma	
CTLA-4 ICIs	Activated T cell, NK cell	Avelumab	Bavencio	Merkel Cell Carcinoma	
		Ipilimumab	Yervoy	Metastatic melanoma	Dermatitis, enterocolitis, hepatitis, colitis, thyroiditis, etc.

Before treatment with PD-1 / PD-L1 inhibitors, CyTOF can be used to detect various cells in the patient's blood. The number of CD14 + CD16HLA-DRhi monocytes in the blood is the most accurate indicator for predicting progression-free survival and overall survival, while the proportion of monocytes in the peripheral blood mononuclear cells is expected to be the standard for predicting patients' response to PD-1 / PD-L1 inhibitors [30].

b. A combination of two or more ICIs.

The method can avoid neutralizing the antitumor effect of other inhibitory pathways

after suppressing single immune checkpoints such as increased PD-1 expression of tumor cells and the activation of PD-L1+/VISTA+T cells, and CD68 + macrophages after the use of CTLA-4 ICIs alone. In combination, anti-CTLA-4 promotes early activation of T cells in lymphatic tissue, while anti-PD-1 mainly plays a role in tumor tissue to inhibit T-cell failure during the effect stage [31–34]. The combination of multiple ICIs significantly improves the anti-tumor effect, and the number of its potential combinations is immeasurable, providing another direction for more effective anti-tumor treatment.

c. Establishing a model for predicting the efficacy of ICIs [35]

From clinical experience, the efficacy of inhibitor is not determined by the single biomarker, but requires a combination of variables, including the host phylogenetics, tumor genomics, PD-1 and PD-L1′s levels, tumor microenvironment and gut microbiota, which ultimately affect tumor-host interactions. Patients can benefit the most by continually updating and evaluating predictive models.

d. Converting Tregs into inflammatory cells [36]

In the process of tumor development, Tregs promote tumor growth by inhibiting effector T cells, which also affects the efficacy of tumor immunotherapy [37]. The present study has found that by blocking the CARMA1-BCL10-MALT1 (CBM) signalosome [38], inhibitory Tregs can be transformed into inflammatory cells secreting IFN-γ, thereby activating the inflammatory response in the tumor, inhibiting the tumor growth, and improving the sensitivity of tumor cells to immunotherapy. The combination of anti PD-1 ICI and MALT1 inhibitor Mepazine can significantly slow down the growth rate of tumor.

3.2. Classification of common ICIs

PD-1 receptors are distributed on the surface of antigen-stimulated T-cells, linked to T-cells and tumor cells, and can be combined with PDL-1 and PDL-2 ligands to inhibit T-cell activation [39]. The use of PD-1/PD-L1 receptor antagonists in the body not only enhances the immune response of T cells against tumors but also acts on tumor-associated macrophages (TAMs), restores the ability of macrophages to phagocytosis of tumors, inhibits tumor proliferation, and prolongs patient survival [40]. PD-1/PD-L1 inhibitors are more selective, have fewer side effects and are safer to apply than CTLA-4 inhibitors. PD-1/PD-L1 monoclonal antibodies have been widely used in melanoma, non-small cell lung cancer, head and neck cancer, Hodgkin's lymphoma, urinary epithelial cancer, gastric cancer, kidney cancer, liver cancer and so on [41–45].

Antagonists targeting PD-1 receptor include PD-1 monoclonal antibody and PD-L1 monoclonal antibody, which represent the following drugs [44]: a. Keytruda (Pembrolizumab). It had a higher response rate in non-small cell cancers, and KEYNOTE results showed that Pembrolizumab improved overall survival (OS) and progression-free survival (PFS) in patients with solid tumors and significantly prolonged the life of patients with locally advanced or metastatic non-small cell lung cancer compared to platinum chemotherapy. b. Tecentriq (Atezolizumab). Chemotherapy drugs combined with Tecentriq increased the objective remission rate by 17 %, prolonged PFS and significantly improved the therapeutic effect. c. Opdivo (Nivolumab). Opdivo works better in gastric cancer and squamous cell carcinoma of the head and neck. In one trial, 12 % of patients responded to Opdivo treatment without taking into account the level of expression of PD-L1.

In addition, CTLA-4 is widely distributed on T cells. Blocking CTLA-4 activates the immune system and causes severe reactions, including hepatitis, colitis and thyroiditis. Unlike other therapies that directly attack cancer cells to reduce tumor size, Yervoy (ipilimumab)'s efficacy will take several months to show. Due to these two limitations, the antibody is currently only used in the treatment of advanced melanoma. More information about ICIs can be found in the summary table of major listed ICIs in Table 1.

Siglec-15 is the latest target discovered this year, and the researches about it are getting increasingly deep. Siglec-15 can down-regulate the immune activity of T cells, so that the anti-tumor immune mechanism of the body is suppressed, and tumor cells can achieve immune escape. Siglec-15 is increased in a variety of tumor cells, such as bladder, kidney, liver and lung cancer. By knocking out the siglec-15 or using the siglec-15 inhibitor, people can relieve immunosuppression and achieve specific killing of the tumor. Some studies have pointed out that the combination of siglec-15 inhibitor and PD-1 / PD-L1 inhibitor can eliminate the resistance of tumors to PD-1 / PD-L1 inhibitor, improving the success rate of treatment [46,47].

4. Factors influencing tumor immunotherapy

The effect of tumor immunotherapy is influenced by many factors. First, it is related to human immunity, which is closely related to genetics and internal microflora [48,49]. Second, it is related to tumor cells. Intra-tumor heterogeneity of tumor neoantigen, the number of clone-derived new antigens, tumor cell mutation target, tumor mutation load significantly affect the therapeutic effect, among which patients with low intra-tumor heterogeneity of tumor neoantigen and a large number of clonal source neoantigen have more therapeutic advantages [50]. Third, it is related to environmental factors, such as daily routine, diet, bacterial infection, and drug use.

4.1. Effect of tumor type on efficacy

According to the immune characteristics of the tumor, the tumor can be divided into three types: the first is “immunosuppressed”, also known as “immune desert type”, the central and marginal area of which lack of T cells, or although there are lymphocytes, the number and density of cells is not large. Tumor specific killer T cells are the main cause of this type of immunity inhibition. PD-1/PD-L1 therapy is basically ineffective for this type in the clinical. The second is "immune excluded", also known as immune exemption type, which has a large number of CD3+ and CD8+ lymphocytes on the edge of the tumor. However, these cells can't immerse in the tumor center. The main reason why the immune response is suppressed is the escape of T cells. The third is known as immune inflammatory type, which contains PD-L1, pro-inflammatory factors and effectors around the tumor, but the escape of the tumor inhibits the immune response [51]. For immunosuppressive and immune exclusive tumors, T cell transport regulators, soluble factor regulators, and physical barrier-destroying methods can be used for treatment [52].

4.2. Effect of tumor microenvironment on the efficacy

Tumor microenvironment includes tumor cells, peripheral immune cells, neovascularization, endothelial cells, fibroblasts, and extracellular matrix [53]. In clinical practice, by measuring the composition, number and other factors of immune cells in the tumor center and surrounding microenvironment, the degree of tumor deterioration, inevitability and the effect of immunotherapy drugs can be preliminarily determined. Meanwhile, the immunotherapy of inflammatory tumor can be predicted by combining genetic and environmental factors. The inflammatory cells, inflammatory mediators and important proteins in inflammatory signaling pathways can be used as drug targets [54]. Although the efficacy is still random, it lays a foundation for improving the efficacy and is conducive to providing personalized treatment for patients.

The tumor cells with high expression of PD-1 or presence of IFN-γ, granzyme, CXCL9/CXCL10 and other markers or with high mutation load generally respond well to PD-1 / PD-L1 inhibitors. Immunosuppressive drivers in the tumor microenvironment include MDSCs and macrophages, which deplete extracellular arginine and promote tryptophan degradation, while cancer-associated fibroblasts (CAF) mediate T cell apoptosis after binding to T cells [55]. In addition, acidic and hypoxic conditions in the tumor microenvironment are conducive to tumor growth and reproduction, inhibit the activation and toxicity of T-cells, and severely inhibit the anti-tumor immune response [56,57].

4.3. The effect of intestinal bacteria

The number and type of intestinal flora affect not only the incidence of cancer but also the sensitivity to chemotherapy and immunotherapy. Studies have shown that intestinal symbiosis acts to activate the congenital immune system and that the intestinal symbiotic flora spontaneously activates the immune system to fight the tumor when T cells are immersed in the tumors [48,58]. Matson et al. have proved that immune checkpoint inhibitors have no significant effect on cancer mice with intestinal microbiome deficiency [58]. They found that the higher the abundance of good bacteria group, the more CD4+ and CD8+ cells in the surrounding blood, the better the effect of anti-PD-1 treatment on melanoma. These findings are expected to be applied to clinical practice and improve the efficacy of immunotherapy by improving patients' lifestyle or supplementing good intestinal microflora. In addition, taking antibiotics seriously affects the balance of intestinal flora, resulting in decreased efficacy of immunotherapy, consequently antibiotics should be avoided in immunotherapy [59].

4.4. Neoantigens

The intratumoral heterogeneity (ITH) of neoantigen, too few clonal neoantigens, and the increase of subclonal neoantigens are the fundamental reasons for the decreased efficacy of anti-PD1/CTLA4 immunotherapy [60]. The more clone-derived new antigens and the lower the heterogeneity in the tumor, the patient can achieve a significantly longer total survival time. The lower the heterogeneity in neoantigen tumor, the more the number of clonal neoantigens, and the higher the expression of pro-inflammatory genes such as PD-L1 and IL-6, IFN-γ in tumor, suggesting that clonogenic neoantigens may be correlated with activation effector T cells in the environment of inflammatory tumor, or induced by immune checkpoint molecules and their ligands [61]. When the cloned new antigen is higher, the lower the ITH, the more significant the patient's immunotherapy effect increases. Patients with obvious efficacy can be tested for cloned new antigens that can be identified by T cells for peripheral blood analysis.

In addition, some patients may produce multiple subclonal neoantigens in the tumor due to multi-line radiotherapy, which may eventually lead to a decrease in the proportion of clonal neoantigens and a decline in the efficacy of immunotherapy [62]. Therefore, although the total number of mutations in these patients is high, the efficacy of immunotherapy is poor. The specific mechanism is still under further study and discussion.

4.5. Tumor mutational burden (TMB)

TMB has a great effect on the immunotherapy of tumor. With the increase of tumor mutation load, the more new antigens are released, and the neoantigens trigger T cell response at the same time. The effect of immunotherapy is more obvious, the more suitable for immunotherapy [63]. The PFS and OS are prolonged after treatment. There have even been studies suggesting that the number of mutations

in tumor mutation load or tumor DNA can be used as immune markers to predict the effect of immunotherapy and guide clinical trials using immunotherapy [64,65].

Using a liquid biopsy to detect the number of mutations in tumor DNA in blood samples [66], the number of ctDNA changes in the blood can reflect an increase in the mutation load. Changes in mutation burden are associated with the therapeutic effect of immune checkpoint inhibitor therapy, including overall response, PFS, and OS. Studies have shown that 45 % of patients respond to immune checkpoint inhibitor therapy when there are more than three unidentified genomic changes in the circulating tumor DNA. When the genome was less altered, only 15 % of patients responded. The median response time for patients who responded to immunotherapy within two months with a large number of genomic changes in their blood samples was approximately two years [67]. Today, blood TMB (bTMB) based on blood ctDNA and SNVs-based calculations can better predict immunotherapy outcomes [68].

5. The mechanism of drug resistance in immunotherapy

Cancer immunity includes immune surveillance, balance, and escape [69]. Tumor cells can evade the recognition and attack of the immune system by recruiting immune regulatory cells, down-regulating tumor antigen expression, releasing immune inhibitory factors and other immune escape mechanisms in the host, so as to continue to and metastasis, and eventually form visible tumor lesions. Tumor proliferation can also be achieved by selectively amplifying proteins that escape immunity, including PD-L1, arachidonic acid lipoxygenase, IDO1/IDO-2 [70]. The mechanisms of resistance is detailed in Fig. 3

5.1. Mechanisms of the primary immune resistance

Tumor-specific T cells induce antitumor effects by producing interferon-γ that recognizes tumor cells and corresponding antibodies in antigen-presenting cells (APCs). This effect can directly inhibit tumor cell proliferation and promote tumor cell apoptosis, recruit other immune cells, enhance tumor antigen presentation and increase protein expression of antigen presentation (e.g. major histocompatibility complex (MHC) molecule [71]. If the pathway is mutated, PD-L1 expression is exposed [72], and the expression of anti-PD-L1 of cancer cells increases, blocking the immunotherapy of PD-L1 or PD-1 will be ineffective. Or tumor cells directly express PD-L1, bind with T cell surface PD-1 to inhibit activated cytotoxic T lymphocyte (CTL), inhibit the activation of cytotoxic T cells, suppress the immune response, and cause depletion of T cells, thus leading to primary drug resistance [73,74].

5.2. The mechanisms of the acquired immune resistance

When the body has an anti-tumor immune response, lymphocytes infiltrated by tumor cells can secrete a large number of IFN-γ mediated tumor cells to express PD-L1 [75]. PD-L1 in combination with PD1 of CTL can inhibit the immune killing effect of effector T cells on tumor [74,76].

5.3. The internal and external mechanisms of resistance to immunotherapy

Resistance to immunotherapy can be divided into two mechanisms, internal and external. In the internal mechanism, antigen mutation, tumor antigen expression, HLA expression deficiency and change of antigen survival process mechanism can lead to primary resistance [77]. Mechanism changes of antigen generation process include activation of the MAPK pathway, enhancement of PI3K pathway caused by PTEN expression loss, continuous expression of WNT/β-catenin signal pathway or high expression of mixed PD-L1. Loss of target antigens, HLA, interferon signaling, and T cell function can lead to acquired resistance. The extrinsic mechanism may be due to changes in CTLA-4, PD-1 or other immune checkpoints, T-cell failure and phenotypes changes, immune-suppressive cell groups such as Tregs, MDSC, type II macrophages and tumor microenvironmental cytokines and metabolites such as CSF-1, tryptophan metabolites, TGF-β, adenosine and so on [78].

5.4. The self-neutralization of tumor cells

There are clinical findings that even though PD-1 is highly expressed in tumor cells in some patients, the effect of PD-1/PD-L1 ICIs is still poor. Studies have shown that this situation occurs because these tumor cells express both PD-L1 and PD-1. Before PD-1/PD-L1 ICIs act on PD-L1 of tumor cells, PD-L1 has been bound to its own PD-1, resulting in the loss of the target of PD-1/PD-L1 ICIs. This mechanism is called the PD-1 and PD-L1″self-neutralization" of PD-1 pathways [79].

5.5. Self-neutralization of antigen-presenting cells

APC also weakens the ability of T cells to conduct PD-1 signals through self-binding of PD-1 and PD-L1, and eventually the anti-tumor immune response of T cells is weakened [80].

5.6. The mechanisms of exosome release inhibits immunity

Cancer cells suppress the immune response by releasing exosomes [81], which carry PD-L1 protein and inhibit T cells from reaching the tumor. Metastatic melanoma, breast cancer, colorectal cancer, and lung cancer all release exosomes with PD-L1 [82–84] (Fig. 3). The immune system, through a variety of immune escape mechanisms, leads to the failure of PD-1 / PD-L1 inhibitors to bind to the target or to have ineffective effects on the target, thus losing its effect [85]. In summary, the complete escape of the immune system is the result of the combination of the intrinsic characteristics of PD-1/PD-L1 co-expression, cytokine composition, degree of mutation and other external environmental factors such as intestinal flora and infectious microorganisms.

5.7. Treatment measures against tumor resistance

In the process of treating tumors, the emergence of tumor cell resistance is difficult to avoid, but patients can get the best treatment results through appropriate means. First, priority should be given to the appropriate population for immunotherapy before treatment. The type and number of tumor markers, even the presence of PBRM1 gene defects [86,87] and intestinal flora, are tested to determine whether the patient was a suitable individual for treatment. Then, individualized treatment strategies and combination therapy are developed for patients to improveFi the sensitivity of tumor cells to immunotherapy, accelerate the killing of tumor cells, and reduce the emergence of drug resistance of tumor cells [88].

6. Conclusions and future perspectives

Nowadays, anti-tumor immunotherapy is playing an increasingly important role in the field of tumor therapy. Encouraging results have been obtained in the treatment trials of various malignant tumors, and improves the efficacy of immunotherapy and reduces adverse reactions by finding new targets and new methods such as combination therapy. However, there is still some controversy immunotherapy, such as some treatments with blindness, empirical and limitation, individual cases with severe adverse reactions and even life-threatening, the randomness of therapeutic effect and high cost of treatment. The advantages and disadvantages of immunotherapy are detailed in Table 2. It would be fully realize that the occurrence of tumor is a dynamic and complex process, fully design an individually designed immunotherapy scheme based on the characteristics of the tumor and the individual immune status of patients, and conduct the immunotherapy in a targeted way, so as to achieve the optimal therapeutic effect and recover the health of

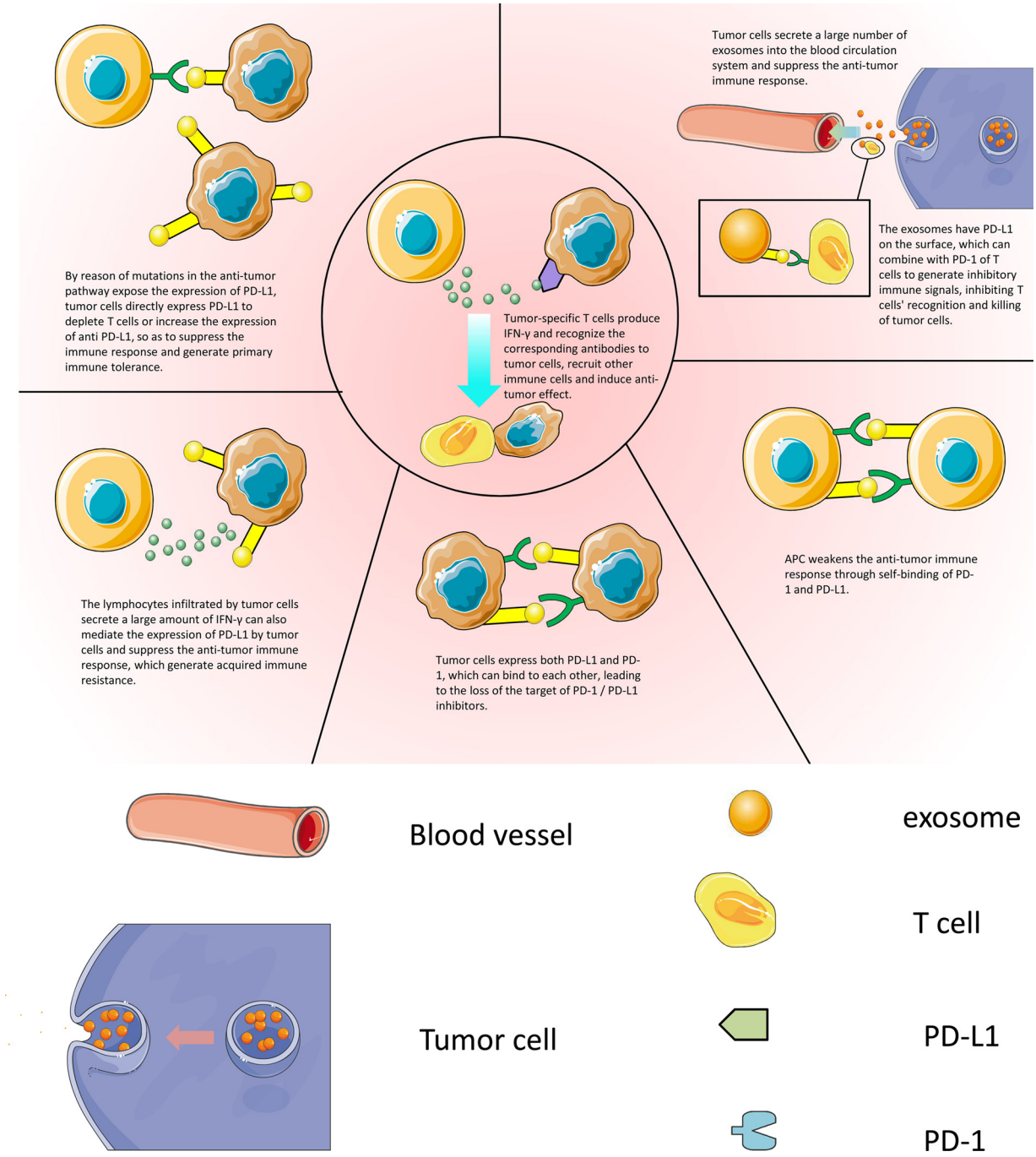

Fig. 3. The mechanism of drug resistance in immunotherapy. The escape of anti-tumor drugs can be realized by the primary immune resistance mechanism and the secondary immune mechanism of tumors. In addition, the self-neutralization of tumor cell targets, antigen-presenting cell targets and tumor release of exosomes to suppress immunity are another way to resist the anti-tumor drugs, making the effect of immunotargeted drugs reduced or even ineffective.

tumor patients.

Immunotherapy is a promising new type of advanced cancer treatment, is the great breakthrough to now existing tumor treatment. The future should focus on the recovery of specific immune immunosuppressive pathway in the anti-tumor process, not simply to enhance the broad and untargeted systemic immune response, including three principles: determining that the immunosuppressive microenvironment is caused by the tumor, focusing the immunosuppression on the tumor microenvironment, and identifying new targets acting on the main functional pathways [89,90]. On the basis of these, identify the most suitable targets for different target mechanisms, while improving the targeting of treatment by improving treatment regimens and reduce the toxic and side effects, so as to challenge the huge problems of postoperative recurrence and metastasis. The path of immunotherapy faces great challenges and opportunities, and will also mature.

Authors' contributions

ST and DL performed the literature search and wrote the first draft of the manuscript. ST, DL and XZ revised and edited the final version of the manuscript. All authors read and approved the final manuscript.

Table 2
The pros and cons of immunotherapy.

The advantages of immunotherapy	The disadvantages of immunotherapy
1. The treatment effect of "immunoinflammatory" tumor is good, and the long-term survival rate is significantly improved.、 2. High accuracy, specificity and targeting of immunotherapy. 3. Immunotherapy is effective for a long time. 4. Wide adaptability. The treatment can control and kill multiple types of tumors. 5. Be persistent. The treatment initiate the body's immune system to restore immune function and kill tumor cells for a long time. 6. Be comprehensive. It can restore and improve the body's immune function, fully identify, search and kill tumor cells, and effectively prevent tumor recurrence and metastasis. 7. With thoroughness. It can thoroughly remove residual tumor cells and microscopic lesions from the body. 8. The side effects are less than the traditional. treatment.	1. There are limitations in the treatment objects and high selectivity for the users. When the type of tumor is "immune suppression type" and "immune exclusion type", the effect of immunotherapy is poor. 2. The use of immunocheckpoint inhibitors can produce negative regulation, leading to autoimmune diseases and even death. 3. A variety of non-specific toxic and side effects may occur after use in some patients, and even hyperprogressive disease may occur, accelerating the death of patients. 4. The effect of immunotherapy is affected by many factors. The survival rate and prognosis of patients are uncertain. 5. Treatment costs are high.

Funding

This work was supported by This work was supported partly by National Natural Science Foundation of China (81541153); Guangdong Provincial Science and Technology Department (2016A050503046, 2015A050502048 and 2016B030309002), and The Public Service Platform of South China Sea for R&D Marine Biomedicine Resources (GDMUK201808); Southern Marine Science and Engineering Guangdong Laboratory Zhanjiang (ZJW-2019-07); Zhanjiang Science and Technology Plan (2017A06012); and “Group-type” Special Supporting Project for Educational Talents in Universities (4SG19057G).

Declaration of Competing Interest

The authors declare that they have no competing interests.

References

[1] J. Couzin-Frankel, Breakthrough of the year 2013. Cancer immunotherapy, Science 342 (6165) (2013) 1432–1433.
[2] I. Chevolet, R. Speeckaert, M. Schreuer, B. Neyns, O. Krysko, C. Bachert, B. Hennart, D. Allorge, N. van Geel, M. Van Gele, L. Brochez, Characterization of the in vivo immune network of IDO, tryptophan metabolism, PD-L1, and CTLA-4 in circulating immune cells in melanoma, Oncoimmunology 4 (3) (2015) e982382.
[3] H. Ikeda, H. Shiku, Immunotherapy of solid tumor: perspectives on vaccine and cell therapy, Nihon Rinsho 70 (12) (2012) 2043–2050.
[4] H.E. Marei, A. Althani, T. Caceci, R. Arriga, T. Sconocchia, A. Ottaviani, G. Lanzilli, M. Roselli, S. Caratelli, C. Cenciarelli, G. Sconocchia, Recent perspective on CAR and Fcgamma-CR T cell immunotherapy for cancers: preclinical evidence versus clinical outcomes, Biochem. Pharmacol. 166 (2019) 335–346.
[5] A. Panda, A. Betigeri, K. Subramanian, J.S. Ross, D.C. Pavlick, S. Ali, P. Markowski, A. Silk, H.L. Kaufman, E. Lattime, J.M. Mehnert, R. Sullivan, C.M. Lovly, J. Sosman, D.B. Johnson, G. Bhanot, S. Ganesan, Identifying a Clinically Applicable Mutational Burden Threshold as a Potential Biomarker of Response to Immune Checkpoint Therapy in Solid Tumors, JCO Precis Oncol 2017 (2017).
[6] M. Shevtsov, G. Multhoff, Immunological and translational aspects of NK cell-based antitumor immunotherapies, Front. Immunol. 7 (2016) 492.
[7] Z.B. Davis, D.A. Vallera, J.S. Miller, M. Felices, Natural killer cells unleashed: checkpoint receptor blockade and BiKE/TriKE utilization in NK-mediated anti-tumor immunotherapy, Semin. Immunol. 31 (2017) 64–75.
[8] C. Cantoni, L. Huergo-Zapico, M. Parodi, M. Pedrazzi, M.C. Mingari, A. Moretta, B. Sparatore, S. Gonzalez, D. Olive, C. Bottino, R. Castriconi, M. Vitale, N.K. Cells, Tumor Cell Transition, and Tumor Progression in Solid Malignancies: New Hints for NK-Based Immunotherapy? J. Immunol. Res. 2016 (2016) 4684268.
[9] L. Ferrari de Andrade, R.E. Tay, D. Pan, A.M. Luoma, Y. Ito, S. Badrinath, D. Tsoucas, B. Franz, K.F. May Jr., C.J. Harvey, S. Kobold, J.W. Pyrdol, C. Yoon, G.C. Yuan, F.S. Hodi, G. Dranoff, K.W. Wucherpfennig, Antibody-mediated inhibition of MICA and MICB shedding promotes NK cell-driven tumor immunity, Science 359 (6383) (2018) 1537–1542.
[10] W.H. Yan, HLA-G expression in cancers: potential role in diagnosis, prognosis and therapy, Endocr. Metab. Immune Disord. Drug Targets 11 (1) (2011) 76–89.
[11] T.L. Chapman, A.P. Heikeman, P.J. Bjorkman, The inhibitory receptor LIR-1 uses a common binding interaction to recognize class I MHC molecules and the viral homolog UL18, Immunity 11 (5) (1999) 603–613.
[12] H. Saito, T. Osaki, M. Ikeguchi, Decreased NKG2D expression on NK cells correlates with impaired NK cell function in patients with gastric cancer, Gastric Cancer 15 (1) (2012) 27–33.
[13] I. Mellman, G. Coukos, G. Dranoff, Cancer immunotherapy comes of age, Nature 480 (7378) (2011) 480–489.
[14] M.G. Morvan, L.L. Lanier, NK cells and cancer: you can teach innate cells new tricks, Nat. Rev. Cancer 16 (1) (2016) 7–19.
[15] E.L. Siegler, Y. Zhu, P. Wang, L. Yang, Off-the-Shelf CAR-NK cells for Cancer immunotherapy, Cell Stem Cell 23 (2) (2018) 160–161.
[16] G. Wei, J. Wang, H. Huang, Y. Zhao, Novel immunotherapies for adult patients with B-lineage acute lymphoblastic leukemia, J. Hematol. Oncol. 10 (1) (2017) 150.
[17] F. Kroschinsky, F. Stolzel, S. von Bonin, G. Beutel, M. Kochanek, M. Kiehl, P. Schellongowski, H. Intensive Care in, G. Oncological Patients Collaborative, New drugs, new toxicities: severe side effects of modern targeted and immunotherapy of cancer and their management, Crit Care 21 (1) (2017) 89.
[18] E.J. Wherry, M. Kurachi, Molecular and cellular insights into T cell exhaustion, Nat. Rev. Immunol. 15 (8) (2015) 486–499.
[19] J.A. Fraietta, C.L. Nobles, M.A. Sammons, S. Lundh, S.A. Carty, T.J. Reich, A.P. Cogdill, J.J.D. Morrissette, J.E. DeNizio, S. Reddy, Y. Hwang, M. Gohil, I. Kulikovskaya, F. Nazimuddin, M. Gupta, F. Chen, J.K. Everett, K.A. Alexander, E. Lin-Shiao, M.H. Gee, X. Liu, R.M. Young, D. Ambrose, Y. Wang, J. Xu, M.S. Jordan, K.T. Marcucci, B.L. Levine, K.C. Garcia, Y. Zhao, M. Kalos, D.L. Porter, R.M. Kohli, S.F. Lacey, S.L. Berger, F.D. Bushman, C.H. June, J.J. Melenhorst, Disruption of TET2 promotes the therapeutic efficacy of CD19-targeted T cells, Nature 558 (7709) (2018) 307–312.
[20] J. Chen, I.F. Lopez-Moyado, H. Seo, C.J. Lio, L.J. Hempleman, T. Sekiya, A. Yoshimura, J.P. Scott-Browne, A. Rao, NR4A transcription factors limit CAR T cell function in solid tumours, Nature 567 (7749) (2019) 530–534.
[21] A.L. Xia, J.C. Wang, K. Yang, D. Ji, Z.M. Huang, Y. Xu, Genomic and epigenomic perspectives of T-cell exhaustion in cancer, Brief. Funct. Genomics 18 (2) (2019) 113–118.
[22] D.R. Sen, J. Kaminski, R.A. Barnitz, M. Kurachi, U. Gerdemann, K.B. Yates, H.W. Tsao, J. Godec, M.W. LaFleur, F.D. Brown, P. Tonnerre, R.T. Chung, D.C. Tully, T.M. Allen, N. Frahm, G.M. Lauer, E.J. Wherry, N. Yosef, W.N. Haining, The epigenetic landscape of T cell exhaustion, Science 354 (6316) (2016) 1165–1169.
[23] K.E. Pauken, M.A. Sammons, P.M. Odorizzi, S. Manne, J. Godec, O. Khan, A.M. Drake, Z. Chen, D.R. Sen, M. Kurachi, R.A. Barnitz, C. Bartman, B. Bengsch, A.C. Huang, J.M. Schenkel, G. Vahedi, W.N. Haining, S.L. Berger, E.J. Wherry, Epigenetic stability of exhausted T cells limits durability of reinvigoration by PD-1 blockade, Science 354 (6316) (2016) 1160–1165.
[24] H.E. Ghoneim, Y. Fan, A. Moustaki, H.A. Abdelsamed, P. Dash, P. Dogra, R. Carter, W. Awad, G. Neale, P.G. Thomas, B. Youngblood, De novo epigenetic programs inhibit PD-1 blockade-mediated t cell rejuvenation, Cell 170 (1) (2017) 142–157 e19.
[25] S. Mardiana, B.J. Solomon, P.K. Darcy, P.A. Beavis, Supercharging adoptive T cell therapy to overcome solid tumor-induced immunosuppression, Sci. Transl. Med. 11 (495) (2019).
[26] S. Rafiq, O.O. Yeku, H.J. Jackson, T.J. Purdon, D.G. van Leeuwen, D.J. Drakes, M. Song, M.M. Miele, Z. Li, P. Wang, S. Yan, J. Xiang, X. Ma, V.E. Seshan, R.C. Hendrickson, C. Liu, R.J. Brentjens, Targeted delivery of a PD-1-blocking scFv by CAR-T cells enhances anti-tumor efficacy in vivo, Nat. Biotechnol. 36 (9) (2018) 847–856.
[27] A.G. Ramsay, Immune checkpoint blockade immunotherapy to activate anti-tumour T-cell immunity, Br. J. Haematol. 162 (3) (2013) 313–325.
[28] K. Buder-Bakhaya, J.C. Hassel, Biomarkers for clinical benefit of immune checkpoint inhibitor Treatment-A review from the melanoma perspective and beyond, Front. Immunol. 9 (2018) 1474.
[29] Y. Yu, Molecular classification and precision therapy of cancer: immune checkpoint inhibitors, Front. Med. 12 (2) (2018) 229–235.
[30] C. Krieg, M. Nowicka, S. Guglietta, S. Schindler, F.J. Hartmann, L.M. Weber, R. Dummer, M.D. Robinson, M.P. Levesque, B. Becher, High-dimensional single-cell analysis predicts response to anti-PD-1 immunotherapy, Nat. Med. 24 (2) (2018) 144–153.
[31] D.T. Proctor, Z. Patel, S. Lama, L. Resch, G. van Marle, G.R. Sutherland,

Identification of PD-L2, B7-H3 and CTLA-4 immune checkpoint proteins in genetic subtypes of meningioma, Oncoimmunology 8 (1) (2019) e1512943.
[32] V. Genoud, E. Marinari, S.I. Nikolaev, J.C. Castle, V. Bukur, P.Y. Dietrich, H. Okada, P.R. Walker, Responsiveness to anti-PD-1 and anti-CTLA-4 immune checkpoint blockade in SB28 and GL261 mouse glioma models, Oncoimmunology 7 (12) (2018) e1501137.
[33] D.L. Bajor, R. Mick, M.J. Riese, A.C. Huang, B. Sullivan, L.P. Richman, D.A. Torigian, S.M. George, E. Stelekati, F. Chen, J.J. Melenhorst, S.F. Lacey, X. Xu, E.J. Wherry, T.C. Gangadhar, R.K. Amaravadi, L.M. Schuchter, R.H. Vonderheide, Long-term outcomes of a phase I study of agonist CD40 antibody and CTLA-4 blockade in patients with metastatic melanoma, Oncoimmunology 7 (10) (2018) e1468956.
[34] X. Wu, A. Giobbie-Hurder, E.M. Connolly, J. Li, X. Liao, M. Severgnini, J. Zhou, S. Rodig, F.S. Hodi, Anti-CTLA-4 based therapy elicits humoral immunity to galectin-3 in patients with metastatic melanoma, Oncoimmunology 7 (7) (2018) e1440930.
[35] J.J. Havel, D. Chowell, T.A. Chan, The evolving landscape of biomarkers for checkpoint inhibitor immunotherapy, Nat. Rev. Cancer 19 (3) (2019) 133–150.
[36] M. Di Pilato, E.Y. Kim, B.L. Cadilha, J.N. Prussmann, M.N. Nasrallah, D. Seruggia, S.M. Usmani, S. Misale, V. Zappulli, E. Carrizosa, V. Mani, M. Ligorio, R.D. Warner, B.D. Medoff, F. Marangoni, A.C. Villani, T.R. Mempel, Targeting the CBM complex causes Treg cells to prime tumours for immune checkpoint therapy, Nature 570 (7759) (2019) 112–116.
[37] P.A. Savage, D.S. Leventhal, S. Malchow, Shaping the repertoire of tumor-infiltrating effector and regulatory T cells, Immunol. Rev. 259 (1) (2014) 245–258.
[38] I. Meininger, D. Krappmann, Lymphocyte signaling and activation by the CARMA1-BCL10-MALT1 signalosome, Biol. Chem. 397 (12) (2016) 1315–1333.
[39] D.M. Pardoll, The blockade of immune checkpoints in cancer immunotherapy, Nat. Rev. Cancer 12 (4) (2012) 252–264.
[40] M. Katoh, FGFR inhibitors: effects on cancer cells, tumor microenvironment and whole-body homeostasis (Review), Int. J. Mol. Med. 38 (1) (2016) 3–15.
[41] H.K. Angell, J. Lee, K.M. Kim, K. Kim, S.T. Kim, S.H. Park, W.K. Kang, A. Sharpe, J. Ogden, A. Davenport, D.R. Hodgson, J.C. Barrett, E. Kilgour, PD-L1 and immune infiltrates are differentially expressed in distinct subgroups of gastric cancer, Oncoimmunology 8 (2) (2019) e1544442.
[42] B. Bian, D. Fanale, N. Dusetti, J. Roque, S. Pastor, A.S. Chretien, L. Incorvaia, A. Russo, D. Olive, J. Iovanna, Prognostic significance of circulating PD-1, PD-L1, pan-BTN3As, BTN3A1 and BTLA in patients with pancreatic adenocarcinoma, Oncoimmunology 8 (4) (2019) e1561120.
[43] S.H. Kang, B. Keam, Y.O. Ahn, H.R. Park, M. Kim, T.M. Kim, D.W. Kim, D.S. Heo, Inhibition of MEK with trametinib enhances the efficacy of anti-PD-L1 inhibitor by regulating anti-tumor immunity in head and neck squamous cell carcinoma, Oncoimmunology 8 (1) (2019) e1515057.
[44] N. Mohan, S. Hosain, J. Zhao, Y. Shen, X. Luo, J. Jiang, Y. Endo, W.J. Wu, Atezolizumab potentiates Tcell-mediated cytotoxicity and coordinates with FAK to suppress cell invasion and motility in PD-L1(+) triple negative breast cancer cells, Oncoimmunology 8 (9) (2019) e1624128.
[45] Y. Pan, Q. Fei, P. Xiong, J. Yang, Z. Zhang, X. Lin, M. Pan, F. Lu, H. Huang, Synergistic inhibition of pancreatic cancer with anti-PD-L1 and c-Myc inhibitor JQ1, Oncoimmunology 8 (5) (2019) e1581529.
[46] J. Wang, J. Sun, L.N. Liu, D.B. Flies, X. Nie, M. Toki, J. Zhang, C. Song, M. Zarr, X. Zhou, X. Han, K.A. Archer, T. O'Neill, R.S. Herbst, A.N. Boto, M.F. Sanmamed, S. Langermann, D.L. Rimm, L. Chen, Siglec-15 as an immune suppressor and potential target for normalization cancer immunotherapy, Nat. Med. 25 (4) (2019) 656–666.
[47] G. Cao, Z. Xiao, Z. Yin, Normalization cancer immunotherapy: blocking Siglec-15!, Signal Transduct. Target. Ther. 4 (2019) 10.
[48] A. Sivan, L. Corrales, N. Hubert, J.B. Williams, K. Aquino-Michaels, Z.M. Earley, F.W. Benyamin, Y.M. Lei, B. Jabri, M.L. Alegre, E.B. Chang, T.F. Gajewski, Commensal Bifidobacterium promotes antitumor immunity and facilitates anti-PD-L1 efficacy, Science 350 (6264) (2015) 1084–1089.
[49] J. Tang, Z. Xu, L. Huang, H. Luo, X. Zhu, Transcriptional regulation in model organisms: recent progress and clinical implications, Open Biol. 9 (11) (2019) 190183.
[50] N. McGranahan, A.J. Furness, R. Rosenthal, S. Ramskov, R. Lyngaa, S.K. Saini, M. Jamal-Hanjani, G.A. Wilson, N.J. Birkbak, C.T. Hiley, T.B. Watkins, S. Shafi, N. Murugaesu, R. Mitter, A.U. Akarca, J. Linares, T. Marafioti, J.Y. Henry, E.M. Van Allen, D. Miao, B. Schilling, D. Schadendorf, L.A. Garraway, V. Makarov, N.A. Rizvi, A. Snyder, M.D. Hellmann, T. Merghoub, J.D. Wolchok, S.A. Shukla, C.J. Wu, K.S. Peggs, T.A. Chan, S.R. Hadrup, S.A. Quezada, C. Swanton, Clonal neoantigens elicit T cell immunoreactivity and sensitivity to immune checkpoint blockade, Science 351 (6280) (2016) 1463–1469.
[51] T. Riegger, S. Conrad, H.J. Schluesener, H.P. Kaps, A. Badke, C. Baron, J. Gerstein, K. Dietz, M. Abdizahdeh, J.M. Schwab, Immune depression syndrome following human spinal cord injury (SCI): a pilot study, Neuroscience 158 (3) (2009) 1194–1199.
[52] J. Galon, D. Bruni, Approaches to treat immune hot, altered and cold tumours with combination immunotherapies, Nat. Rev. Drug Discov. 18 (3) (2019) 197–218.
[53] X. Zhu, H. Luo, Y. Xu, Transcriptome analysis reveals an important candidate gene involved in both nodal metastasis and prognosis in lung adenocarcinoma, Cell Biosci. 9 (1) (2019).
[54] X. Zhu, M.C.M. Lin, W. Fan, L. Tian, J. Wang, S.S. Ng, M. Wang, H. Kung, D. Li, An intronic polymorphism in GRP78 improves chemotherapeutic prediction in non-small cell lung cancer, Chest 141 (6) (2012) 1466–1472.
[55] S. Kim, S.J. Nam, C. Park, D. Kwon, J. Yim, S.G. Song, C.Y. Ock, Y.A. Kim, S.H. Park, T.M. Kim, Y.K. Jeon, High tumoral PD-L1 expression and low PD-1(+) or CD8(+) tumor-infiltrating lymphocytes are predictive of a poor prognosis in primary diffuse large B-cell lymphoma of the central nervous system, Oncoimmunology 8 (9) (2019) e1626653.
[56] Y. Sun, R. Wang, M. Qiao, Y. Xu, W. Guan, L. Wang, Cancer associated fibroblasts tailored tumor microenvironment of therapy resistance in gastrointestinal cancers, J. Cell. Physiol. 233 (9) (2018) 6359–6369.
[57] Z. Benson, S.H. Manjili, M. Habibi, G. Guruli, A.A. Toor, K.K. Payne, M.H. Manjili, Conditioning neoadjuvant therapies for improved immunotherapy of cancer, Biochem. Pharmacol. 145 (2017) 12–17.
[58] V. Matson, J. Fessler, R. Bao, T. Chongsuwat, Y. Zha, M.L. Alegre, J.J. Luke, T.F. Gajewski, The commensal microbiome is associated with anti-PD-1 efficacy in metastatic melanoma patients, Science 359 (6371) (2018) 104–108.
[59] B. Routy, E. Le Chatelier, L. Derosa, C.P.M. Duong, M.T. Alou, R. Daillere, A. Fluckiger, M. Messaoudene, C. Rauber, M.P. Roberti, M. Fidelle, C. Flament, V. Poirier-Colame, P. Opolon, C. Klein, K. Iribarren, L. Mondragon, N. Jacquelot, B. Qu, G. Ferrere, C. Clemenson, L. Mezquita, J.R. Masip, C. Naltet, S. Brosseau, C. Kaderbhai, C. Richard, H. Rizvi, F. Levenez, N. Galleron, B. Quinquis, N. Pons, B. Ryffel, V. Minard-Colin, P. Gonin, J.C. Soria, E. Deutsch, Y. Loriot, F. Ghiringhelli, G. Zalcman, F. Goldwasser, B. Escudier, M.D. Hellmann, A. Eggermont, D. Raoult, L. Albiges, G. Kroemer, L. Zitvogel, Gut microbiome influences efficacy of PD-1-based immunotherapy against epithelial tumors, Science 359 (6371) (2018) 91–97.
[60] G.P. Linette, M. Becker-Hapak, Z.L. Skidmore, M.L. Baroja, C. Xu, J. Hundal, D.H. Spencer, W. Fu, C. Cummins, M. Robnett, S. Kaabinejadian, W.H. Hildebrand, V. Magrini, R. Demeter, A.S. Krupnick, O.L. Griffith, M. Griffith, E.R. Mardis, B.M. Carreno, Immunological ignorance is an enabling feature of the oligo-clonal T cell response to melanoma neoantigens, Proc Natl Acad Sci U S A 116 (47) (2019) 23662–23670.
[61] J. Liu, D. Li, H. Luo, X. Zhu, Circular RNAs: The star molecules in cancer, Mol. Aspects Med. 70 (2019) 141–152.
[62] O. Franzese, F. Battaini, G. Graziani, L. Tentori, M.L. Barbaccia, A. Aquino, M. Roselli, M.P. Fuggetta, E. Bonmassar, F. Torino, Drug-induced xenogenization of tumors: A possible role in the immune control of malignant cell growth in the brain? Pharmacol. Res. 131 (2018) 1–6.
[63] C. Jensen, D.H. Madsen, M. Hansen, H. Schmidt, I.M. Svane, M.A. Karsdal, N. Willumsen, Non-invasive biomarkers derived from the extracellular matrix associate with response to immune checkpoint blockade (anti-CTLA-4) in metastatic melanoma patients, J. Immunother. Cancer 6 (1) (2018) 152.
[64] M. Yarchoan, A. Hopkins, E.M. Jaffee, Tumor mutational burden and response rate to PD-1 inhibition, N. Engl. J. Med. 377 (25) (2017) 2500–2501.
[65] X. Tang, Y. Huang, J. Lei, H. Luo, X. Zhu, The single-cell sequencing: new developments and medical applications, Cell Biosci. 9 (1) (2019).
[66] N. Ramalingam, S.S. Jeffrey, Future of liquid biopsies with growing technological and bioinformatics studies: opportunities and challenges in discovering tumor heterogeneity with single-cell level analysis, Cancer J. 24 (2) (2018) 104–108.
[67] M. Alexander, J. Galeas, H. Cheng, Tumor mutation burden in lung cancer: a new predictive biomarker for immunotherapy or too soon to tell? J. Thorac. Dis. 10 (Suppl 33) (2018) S3994–S3998.
[68] D.R. Gandara, S.M. Paul, M. Kowanetz, E. Schleifman, W. Zou, Y. Li, A. Rittmeyer, L. Fehrenbacher, G. Otto, C. Malboeuf, D.S. Lieber, D. Lipson, J. Silterra, L. Amler, T. Riehl, C.A. Cummings, P.S. Hegde, A. Sandler, M. Ballinger, D. Fabrizio, T. Mok, D.S. Shames, Blood-based tumor mutational burden as a predictor of clinical benefit in non-small-cell lung cancer patients treated with atezolizumab, Nat. Med. 24 (9) (2018) 1441–1448.
[69] P. Sharma, S. Hu-Lieskovan, J.A. Wargo, A. Ribas, Primary, Adaptive, and Acquired Resistance to Cancer Immunotherapy, Cell 168 (4) (2017) 707–723.
[70] M.S. Rooney, S.A. Shukla, C.J. Wu, G. Getz, N. Hacohen, Molecular and genetic properties of tumors associated with local immune cytolytic activity, Cell 160 (1-2) (2015) 48–61.
[71] J. Gao, L.Z. Shi, H. Zhao, J. Chen, L. Xiong, Q. He, T. Chen, J. Roszik, C. Bernatchez, S.E. Woodman, P.L. Chen, P. Hwu, J.P. Allison, A. Futreal, J.A. Wargo, P. Sharma, Loss of IFN-gamma pathway genes in tumor cells as a mechanism of resistance to Anti-CTLA-4 therapy, Cell 167 (2) (2016) 397–404 e9.
[72] H. Kronig, L. Kremmler, B. Haller, C. Englert, C. Peschel, R. Andreesen, C.U. Blank, Interferon-induced programmed death-ligand 1 (PD-L1/B7-H1) expression increases on human acute myeloid leukemia blast cells during treatment, Eur. J. Haematol. 92 (3) (2014) 195–203.
[73] P. Ranji, T. Salmani Kesejini, S. Saeedikhoo, A.M. Alizadeh, Targeting cancer stem cell-specific markers and/or associated signaling pathways for overcoming cancer drug resistance, Tumour Biol. 37 (10) (2016) 13059–13075.
[74] T. Seto, D. Sam, M. Pan, Mechanisms of primary and secondary resistance to immune checkpoint inhibitors in Cancer, Med. Sci. Basel (Basel) 7 (2) (2019).
[75] C. Liu, A.C. Gao, IFNgamma, a Double-Edged Sword in Cancer Immunity and Metastasis, Cancer Res. 79 (6) (2019) 1032–1033.
[76] E. Alspach, D.M. Lussier, R.D. Schreiber, Interferon gamma and its important roles in promoting and inhibiting spontaneous and therapeutic Cancer immunity, Cold Spring Harb. Perspect. Biol. 11 (3) (2019).
[77] J. Rieth, S. Subramanian, Mechanisms of intrinsic tumor resistance to immunotherapy, Int. J. Mol. Sci. 19 (5) (2018).
[78] I. Kozar, C. Margue, S. Rothengatter, C. Haan, S. Kreis, Many ways to resistance: how melanoma cells evade targeted therapies, Biochim. Biophys. Acta Rev. Cancer 1871 (2) (2019) 313–322.
[79] C. Dezutter-Dambuyant, I. Durand, L. Alberti, N. Bendriss-Vermare, J. Valladeau-Guilemond, A. Duc, A. Magron, A.P. Morel, V. Sisirak, C. Rodriguez, D. Cox, D. Olive, C. Caux, A novel regulation of PD-1 ligands on mesenchymal stromal cells through MMP-mediated proteolytic cleavage, Oncoimmunology 5 (3) (2016)

e1091146.
[80] Y. Zhao, D.L. Harrison, Y. Song, J. Ji, J. Huang, E. Hui, Antigen-presenting cell-intrinsic PD-1 neutralizes PD-L1 in cis to attenuate PD-1 signaling in t cells, Cell Rep. 24 (2) (2018) 379–390 e6.
[81] Z. Tang, D. Li, S. Hou, X. Zhu, The cancer exosomes: clinical implications, applications and challenges, Int. J. Cancer (31 October) (2019), https://doi.org/10.1002/ijc.32762 [Epub ahead of print].
[82] W. Gu, L. Wang, Y. Wu, J.P. Liu, Undo the brake of tumour immune tolerance with antibodies, peptide mimetics and small molecule compounds targeting PD-1/PD-L1 checkpoint at different locations for acceleration of cytotoxic immunity to cancer cells, Clin. Exp. Pharmacol. Physiol. 46 (2) (2019) 105–115.
[83] N. Chaput, C. Thery, Exosomes: immune properties and potential clinical implementations, Semin. Immunopathol. 33 (5) (2011) 419–440.
[84] J. Zhou, X.L. Li, Z.R. Chen, W.J. Chng, Tumor-derived exosomes in colorectal cancer progression and their clinical applications, Oncotarget 8 (59) (2017) 100781–100790.
[85] R. Boldrini, M.D. De Pasquale, O. Melaiu, M. Chierici, G. Jurman, M.C. Benedetti, N.C. Salfi, A. Castellano, P. Collini, C. Furlanello, V. Pistoia, L. Cifaldi, M. Terenziani, D. Fruci, Tumor-infiltrating T cells and PD-L1 expression in childhood malignant extracranial germ-cell tumors, Oncoimmunology 8 (2) (2019) e1542245.
[86] D. Pan, A. Kobayashi, P. Jiang, L. Ferrari de Andrade, R.E. Tay, A.M. Luoma, D. Tsoucas, X. Qiu, K. Lim, P. Rao, H.W. Long, G.C. Yuan, J. Doench, M. Brown, X.S. Liu, K.W. Wucherpfennig, A major chromatin regulator determines resistance of tumor cells to T cell-mediated killing, Science 359 (6377) (2018) 770–775.
[87] D. Miao, C.A. Margolis, W. Gao, M.H. Voss, W. Li, D.J. Martini, C. Norton, D. Bosse, S.M. Wankowicz, D. Cullen, C. Horak, M. Wind-Rotolo, A. Tracy, M. Giannakis, F.S. Hodi, C.G. Drake, M.W. Ball, M.E. Allaf, A. Snyder, M.D. Hellmann, T. Ho, R.J. Motzer, S. Signoretti, W.G. Kaelin, T.K. Choueiri, E.M. Van Allen, Genomic correlates of response to immune checkpoint therapies in clear cell renal cell carcinoma, Science 359 (6377) (2018) 801–806.
[88] L. Schultz, R. Gardner, Mechanisms of and approaches to overcoming resistance to immunotherapy, Hematology Am. Soc. Hematol. Educ. Program 2019 (1) (2019) 226–232.
[89] M.F. Sanmamed, L. Chen, A Paradigm Shift in Cancer Immunotherapy: From Enhancement to Normalization, Cell 176 (3) (2019) 677.
[90] S.S. Kim, J.B. Harford, M. Moghe, T. Slaughter, C. Doherty, E.H. Chang, A tumor-targeting nanomedicine carrying the p53 gene crosses the blood-brain barrier and enhances anti-PD-1 immunotherapy in mouse models of glioblastoma, Int. J. Cancer 145 (9) (2019) 2535–2546.