Proceedings of the 4th International Conference on Biological Engineering and Medical Science
DOI: 10.54254/2753-8818/59/20241396

# Mechanisms of resistance to immune checkpoint inhibitors and solutions to the problem

**Yibo Xia**

The Second Clinical College, China Medical University, Shenyang, 110000, China

2019341407@stu.cmu.edu.cn

**Abstract.** Immune checkpoint inhibitors (ICIs) have now become one of the major clinical treatments for tumors, which can inhibit the negative immunomodulation and thus enable the immune system to function to treat tumors. However, as with other treatments, patients develop clinical resistance to ICIs, which is an important cause of ICI treatment failure and tumor recurrence. The body acquires resistance to ICIs through pathways such as regulatory T cells (Treg) that increase the expression of other immune checkpoints to resist immunity, Wnt/β-catenin that affect the secretion of IFNα and IFNβ and thus suppress T-cell activation, and the NF-κB pathway that induces B cells to arrest in the G2/M phase and thus inhibit the differentiation of B cells into germinal center B cells. Targeting Tregs at targets such as OX40, using the Wnt/β-catenin inhibitor XAV-939, and combining ICIs with radiotherapy and chemotherapy can resolve the issue of resistance to ICIs. In this paper, we review the specific mechanisms by which ICIs develop resistance and possible future solutions, with the purpose of discovering ways to the efficiency of ICIs in addressing cancer and exploring new avenues for future cancer therapy. In the future era of individualized medicine, the application of precision medicine in the treatment of cancer with ICIs is equally worthy of consideration.

**Keywords:** Immune checkpoint inhibitors, regulatory T cells, Wnt/β-catenin pathway, NF-κB pathway, drug resistance.

## 1. Introduction

ICIs are used to treat tumors by inhibiting the negative immunomodulation, thereby allowing the immune system to function. Currently, ICIs, including corresponding to CTLA-4 and PD-1/PD-L1, are heavily employed in healthcare settings and have achieved breakthroughs in the therapy of renal cancer, melanoma and lung cancer [1]. However, as with other therapies, patients develop resistance to ICIs, which is an important reason for ICIs treatment failure and tumor recurrence. Clinical studies have shown that the patients' response rate to PD-1/PD-L1 treatment varies widely, with less than 20% of patients having an effective response to its immunotherapy [2]. Research has revealed that during immunotherapy with ICIs, the expression of other ICs on the surface of Treg cells in the patient's body increases, thereby inhibiting the activation of effective T cells (Teff) [3]. Besides this mechanism, apoptotic Treg under the action of ICIs promotes immune escape through the adenylate metabolic pathway, which can also lead to resistance to ICIs [3]. Elsewhere, Wnt/β-catenin inhibits T-cell infiltration and block immunotherapy [4]. Tumor-infiltrating immune cells regulate cell cycle progression through aberrant activation of the NF-κB pathway, inhibit the differentiation of B cells in

DOI: 10.54254/2753-8818/59/20241396

the germinal center, inhibit the transcription of genes related to cytotoxicity in NK cells, and regulate the expression of monocyte/macrophage chemokines and AREG, which indirectly affects the outcome of the ICI therapy [5]. So far, a better solution to the problem of resistance to ICIs has not been found in the clinic, which makes the use of ICIs to treat tumors still not a first-line treatment. This paper will analyze the specific mechanisms of resistance to ICIs in terms of the three mechanisms mentioned above and explore the corresponding solutions by targeting Treg cell therapy, Wnt/β-catenin inhibitors, and combining ICIs with other therapeutic approaches, and hypothesize about future treatment modalities that are likely to be feasible.

## 2. ICIs and drug resistance

ICs are a type of molecules with negative immunoregulatory effects, consisting of programmed death receptors and their ligands, which inhibit the activation of the immune system. Common ICs include CTLA-4 and PD-1/PD-L1. Due to their immunosuppressive effects, their monoclonal antibodies, also known as ICIs, can be used to inhibit the immunosuppressive effects of ICs in the treatment of tumors. However, when ICIs are used to treat tumors, patient resistance makes the treatment less effective. Drug resistance is categorized into primary resistance, adaptive resistance and acquired resistance. The first time a patient is treated with ICIs without response is called primary resistance, and the development of resistance after a period of effective treatment is called acquired resistance. Adaptive resistance refers to the immune escape of tumors that the immune system has the capacity to identify and attack through a series of adaptive changes that result in resistance of the organism. It can manifest as primary or acquired immunity or a mixture of both [6]. There are no clear experimental results proving that the body's resistance to ICIs belongs to one of the above categories. How the body develops resistance to ICIs and how to solve the problem of the body developing resistance to ICIs is the key to explore in this paper.

## 3. Mechanisms associated with Treg-mediated generation of resistance to ICIs

### *3.1. Mechanisms of Treg action and the effect of ICs on it*

Treg is an immunosuppressive cell that diminishes the immune system’s function in the fight against tumors by inhibiting the activation and proliferation of CD4+T and CD8+T cells. It has been found that in a variety of tumor diseases, Tregs are recruited in response to fatty acid metabolism and a variety of chemokines, and differentiate in response to TGF-β. This increases the proportion of Treg in the TME and promotes tumor growth and multiplication [7]. In addition, Treg can reduce the antigen presentation capacity of antigen presentation cells (APC) and enhance immune escape of tumors. The ICs can be expressed on the surface of Treg. CTLA-4 on the surface of Treg binds to B7 ligand on APC, regulates APC, inhibits Teff proliferation and activation, and promotes Treg growth. ICIs positively regulate the immune system by inhibiting the action of ICs on the surface of Treg thereby inhibiting the growth of Treg. Figure 1 shows the mechanisms by which Treg has been confirmed to play a role in TME, and there are still many undiscovered mechanisms that still need to be further explored. Through these mechanisms, it can play an important role in TME, but at the same time, it can cause the body to be resistant to ICIs, affecting the positive effect of TME.

### *3.2. Mechanisms of Treg-mediated acquisition of resistance to ICIs*

Studies have shown that after treatment with ICIs, there is a compensatory increase in the expression of other checkpoints in Treg that inhibit Teff activity. These checkpoints include T cell immunoglobulin and TIM-3, LAG-3, T cell immunoreceptor with immunoglobulin and TIGIT, and VISTA et al [8]. Blockade of Teff cell activation can occur when lactobacillus-9 on the surface of tumor cells interacts with TIM-3 and LAG-3, or when lactobacillus-3 on the surface of tumor cells binds to MHC II on dendritic cells (DCs), CD155/CD122 on DCs binds to TIGIT, and VISTA binds to VSIG-3 on CD4+T and CD8+T cells. On Tregs, the action of ICs such as TIM-3 can increase the production of TGF-β, IL-10, granzymes and perforins. Granzymes and perforins lead to the decomposition of Teff cells, while

DOI: 10.54254/2753-8818/59/20241396

TGF-β and IL-10 enhance the immunosuppressive function of Tregs and their differentiation and survival ability. The levels of IL-10, granzymes and perforins in tumor tissues of mouse melanoma and colon cancer models show that Treg cells expressing TIM-3 have a stronger ability to suppress immune cell activity than those not expressing TIM-3 [9]. However, Tregs also trigger an adenosine inhibitory pathway mediated by CD39 and CD73 enzymes, converting extracellular ATP into adenosine, thereby changing the mode of action of the mediator from inflammation to immunosuppression and enhancing tumor escape [8]. The Treg-mediated mechanism is related to the inhibition of Teff cells, so restoring the immune function of Teff cells is an important entry point for solving ICIs resistance in the future. In addition, whether reducing the production of substances such as TGF-β can avoid immunosuppression is also worthy of further discussion. At the same time, how to block the adenosine-mediated immunosuppressive pathway and whether it can have an effect by regulating enzymes such as CD39 also need to be explored in subsequent experiments. The Treg-mediated body's resistance to ICIs involves a variety of substances in the TME, which play an important role in the mechanism and provide us with a research direction for solving drug resistance. These mechanisms suggest that restoring the immune function of Teff cells and reducing the production of TGF-β currently have potential applications in solving the problem of ICIs resistance. Future studies need to further explore the effects of blocking adenosine-mediated immunosuppression pathways and their effects on ICIs resistance.

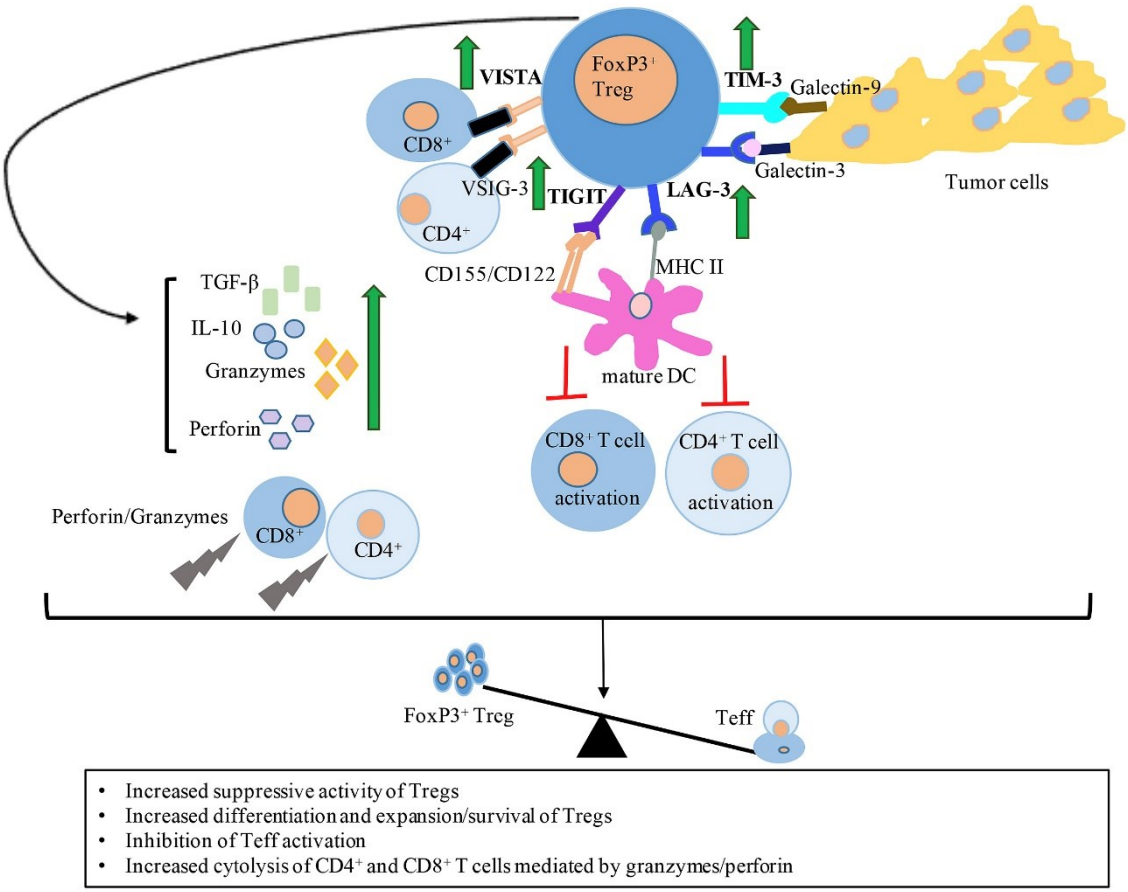


**Figure 1.** Compensatory elevation of other ICs on Treg after treatment with ICIs [8].

### *3.3. Strategies to address resistance to ICIs by targeting Treg-related pathways*

From the above, it can be seen that the drug resistance of ICIs is closely related to Treg, so taking the means of targeting Treg can solve the problem of drug resistance of ICIs. Currently, OX40, ICOS and GITR can be used to targeted Treg [9]. Nevertheless, given that Treg is crucial to the immune system's regular function in the body, if a therapeutic strategy of targeting Treg is adopted, it will inevitably affect

DOI: 10.54254/2753-8818/59/20241396

the normal operation of the body's immune system. In the future, a substantial quantity of clinical trial data is still needed to explore the way to address the issue of drug resistance of ICIs with as few adverse effects as possible. All of these approaches are expected to be put into clinical use in the future to address drug resistance caused by Treg.

## 4. Mechanisms associated with the Wnt/β-catenin pathway and ICIs

### *4.1. Mechanism of action of Wnt/β-catenin with PD-1/PD-L1 and CTLA-4*

Without Wnt signaling, intracellular β-catenin is captured by specific protein complexes (APC, Axin, and GSK-3β) and phosphorylated and then ubiquitinated and degraded. β-catenin is stabilized and no longer phosphorylated when Wnt signaling is triggered. It then enters the nucleus to bind to Tcf/Lef and stimulate the transcription of target genes. When the pathway is aberrantly activated in tumor cells, it can block tumor antigen release and presentation, as well as tumor cell elimination and T-cell activation and infiltration [10]. As β-Catenin reaches the nucleus, it combines with the transcription factor TCF/LEF to form a complex, and binds to the promoter region of CD274, inducing the expression of PD-L1, thereby inducing tumor immune escape [4] In clinical trials, this pathway was found to be activated and CTLA-4 expression was significantly increased in melanoma. Wnt/β-catenin signaling can be demonstrated by RT-PCR and flow cytometry to induce CTLA-4 expression in melanoma cells at the level of both transcription and translation [11]. It is thus clear that in some tumors, aberrant activation of this pathway plays an important role in tumor growth and reproduction.

### *4.2. Mechanisms of Wnt/β-catenin-mediated drug resistance*

Activation of the Wnt/β-catenin pathway inhibits the aggregation of chemokine CCL4 and DCs, affects the recruitment of T cells, thereby promoting non-T cell infiltration in the TME and reducing the therapeutic effect of PD-1/PD-L1. In a genetically engineered melanoma mouse model, studies have found that the reduced infiltration level of CD8+ T cells in the tumor microenvironment is associated with the activation of β-catenin. In mice with the β-catenin pathway deleted, the infiltration level of CD8+ T cells is higher. Further experiments showed that the activation of β-catenin increased the expression of the transcriptional repressor ATF3 and reduced the expression level of the chemokine CCL4, resulting in a decrease in the production of IFNα and IFNβ, inhibiting the activation of T cells and reducing the immune system's response to ICIs. In melanoma, studies using mouse models have confirmed that anti-PD-1 and anti-CTLA-4 antibodies are not effective in mice with activated β-catenin pathways, but are significantly effective in mice with inhibited pathways, indicating that the activation of this pathway is associated with ICI resistance [12]. Although current experimental studies have shown that this pathway is associated with ICIs resistance, its specific mechanism has not yet been fully elucidated. Future studies need to further explore how to overcome ICIs resistance by regulating the pathway. This may include developing new inhibitors or combining other treatments to enhance the immune response. In addition, the role of this pathway in different types of tumors should be studied to develop more widely applicable treatment strategies. By deeply understanding the mechanism of it, we hope to improve the clinical efficacy of ICIs and increase the success rate of cancer treatment.

### *4.3. Strategies to address ICIs resistance by targeting the Wnt/β-catenin pathway*

Given that activation of the Wnt/β-catenin pathway can downregulate the immune system, inhibiting this pathway is a viable solution to counteract ICI resistance [13]. Specific inhibitors such as XAV-939 and Wnt-C59 have been shown to effectively inhibit PD-L1 expression in tumor cells [4]. In experiments using cell-derived xenograft (CDX) mice, treatment outcomes were significantly improved when XAV-939 was combined with anti-PD-L1 antibodies, reinforcing the potential of pathway inhibitors to overcome ICI resistance. In the mouse mammary tumor virus (MMTV)-Wnt1 model, the selective Wnt/β-catenin pathway inhibitor E7386 also significantly enhanced the therapeutic effect and reduced resistance when paired with anti-PD-1 antibodies [14].

DOI: 10.54254/2753-8818/59/20241396

Feng et al. showed that hs BCL9CT-24 can prevent ICI resistance by blocking the interaction between β-catenin and BCL9, thereby increasing immune cell infiltration, reducing the proportion of Tregs, increasing the proportion of DCs, and inhibiting BCL9/BCL9L and transforming growth factor [15]. This study also provides a theoretical basis for the combination of inhibitors of this pathway with targeted Treg. Another inhibitor, C59, targets membrane-bound O-acyltransferase (PORCN), a key enzyme in Wnt biosynthesis. Its combination with anti-CTLA-4 antibodies has been shown to activate tumor-infiltrating CD8+ T cells and expand tumor antigen-specific CD8+ T cells, thereby inhibiting melanoma growth [16].

Although these findings suggest that this pathway can regulate drug resistance by modulating the immune system, clinical trials are still needed to determine their applicability in treating cancer patients and addressing drug resistance. In addition, since it affects the production of IFNα and IFNβ, further studies are needed to evaluate whether the combination of ICIs and IFN can alleviate drug resistance. The relationship between this pathway and DCs suggests that modulation of DCs may also be a potential approach that requires further experimental exploration.

## 5. Mechanism of ICIs action by aberrant activation of NF-κB pathway

### *5.1. Mechanisms of the NF-κB pathway*

NF-κB is a transcription factor protein that controls the production of other transcription factors. When there is no signal stimulation, most of the NF-kB dimers are bound to the inhibitory factor IκB protein in the cytoplasm, and there is an anchor protein region on the κB protein that can inactivate the dimers and not transmit signals. The NF-κB dimer, which can enter the nucleus, bind target genes, and enhance target gene transcription, is released when the inhibitory factor IκB protein is destroyed in response to a signal.NF-κB consists of transactivation domains (TADs): NF-κB1(P50), NF-κB2(P52), and subunits containing TAD: RelA(P65), RelB, c-Rel.NF-κB forms homo- or heterodimers in cells to activate downstream gene transcription, and the most common dimeric form is the P50-P65 heterodimer [5]. The family of NF-κB inhibitors (IKB), including NFKBIA, NFKBBIB, NFKBIZ, and BCL3, bind to extra-nuclear Heterodimer binding, and inhibits dimerization to the nucleus. Aberrant activation of the NF-κB pathway can be found in B cells, NK cells and monocytes/macrophages surrounding triple-negative breast cancer tumors. The "Seurat" package was used to calculate, and by comparing the NF-κB expression in the PR group and SD group around the tumor, it was known that most of the tumor-infiltrating immune cells activated the pathway, and that the abnormal activation of it promotes the tumor drug resistance [5]. From the results of single-cell analysis, the aberrant activation of it could inhibit the formation of cateninB1-CDK1 in B cells by up-regulation of GADD45β, thus inhibiting the differentiation of B cells into germinal center B cells. Aberrant activation of this pathway in triple-negative breast cancer TME plays an important role in suppressing immune effects. However, whether this pathway can play the same role in other tumors needs to be supported by subsequent experimental data.

### *5.2. Relationship between the NF-κB pathway and resistance to ICIs*

The pathway generates resistance to ICIs in B cells, NK cells and monocytes/macrophages through different mechanisms. In B cells, aberrant activation of the pathway was found to inhibit the formation of cateninB1-CDK1 through the upregulation of DNA damage-inducible protein β (GADD45β), which induced B cells to arrest in the G2/M phase and thus inhibited the differentiation of B cells into germinal center B cells by pseudotime analysis [5]. In a pseudotime analysis of monocytes/macrophages, AREG was found to be expressed only when both BCL3 and NF-κB were upregulated. The results of the pseudotime analysis suggested that the transcription of AREG may require the involvement of BCL3 in regulation. AREG amphiregulin is involved in the replication, invasion, and apoptosis inhibition of tumor cells, and up-regulates the expression of PD-L1 on the surface of tumors to play the role of immune escape. By methods such as functional calculations and single-cell sequencing, it was found that the pathway inhibits the expression of GNLY genes in NK cells, and NK cells with low expression

DOI: 10.54254/2753-8818/59/20241396

of GNLY under-express cytotoxicity-associated genes, such as GZMB, GZMH, FGFBP2, and FCGR3A, indicating that, compared to normal GNLY-expressing NK cells, the antibody-dependent and non the dependent cytotoxic effects are all attenuated, reducing the immune role of NK cells, which contributes to the development of resistance to ICIs in the body. Since NK cells with low GNLY expression can highly express (P50)2 and AREG is only highly expressed when BCL3 is upregulated, it is inferred that AREG transcription may be regulated by the (P50)2-BCL3 complex, and that the formation of the (P50)2-BCL3 complex is associated with the aberrant activation of this pathway, and affects the emergence of resistance to ICIs [5]. This pathway plays an important role in different cells of the TME through different mechanisms, and overall, it causes suppression of the immune system, which allows the organism to acquire drug resistance.

### *5.3. Approaches to addressing resistance to ICIs*

Currently, there are clinical therapeutic options to treat inflammatory diseases by inhibiting the pathway through inhibition of IKK and proteasome, but caution is still needed in treating cancer. A large amount of data suggests that the NF-κB pathway can enhance the sensitivity of tumor cells to apoptosis and senescence, so whether we should take the treatment of tumors by inhibiting it and what dosage can be efficiently treated still need to be explored in more experiments. However, for the NF-κB pathway, the (P50)2-BCL3 complex affects the resistance of ICIs. By detecting the expression levels of peritumoral immune cells (P50)2 and BCL3, they can be used as cofactors to predict resistance to ICIs. The mechanism of this pathway in other tumor cells is still unknown, and a great deal of research is still needed to identify specific ways to address drug resistance. This is one of the future directions for research on TME.

## 6. Combination of ICIs with other treatments

### *6.1. ICIs combined with radiotherapy*

The body produces cytokines as a result of radiation therapy, which lead to T cell accumulation in TME. This raises the expression of specific molecules on the surface of tumor cells, which raises the expression of tumor antigens and strengthens the immune system's ability to combat tumors. In a mouse model, anti-PD-1 antibody treatment combined with radiotherapy resulted in a decrease in the body's resistance to PD-1 antibodies [17]. This combination therapy has also produced different degrees of effect in patients with non-small cell lung cancer (NSCLC), malignant melanoma and renal cell carcinoma. However, in the clinical testing of NSCLC patients treated with ICIs in combination with radiotherapy, it was found that although the condition of some patients improved in a brief amount of time, in the long run, they still developed systemic diseases and the mortality rate did not change significantly. The antigens on the surface of patients' tumor cells still need to be identified more precisely, which also provides a direction for the subsequent research of ICIs in precision therapy. Radiotherapy is the current mainstream treatment for cancer in clinical practice, and if its combination with ICIs have good results in subsequent clinical trials,it can change the difficulty of treating tumors, reduce the number of radiotherapy cycles for patients, and improve their quality of life due to prolonged radiotherapy.

### *6.2. ICIs combined with chemotherapy*

It has been shown that high-frequency, low-dose chemotherapy can activate a substantial amount of cytotoxic T cells and inhibit immunosuppressive cells in TME, promote the action of ICIs on TME, and solve the problem of drug resistance of ICIs [18]. In the treatment of advanced NSCLC, ICIs combined with carboplatin/cisplatin and pemetrexed as well as ICIs combined with carboplatin+paclitaxel have good efficacy, which can solve the problem of resistance to some ICIs. The combination of ICIs with antiangiogenic drugs has also been experimentally proven to have some efficacy. However, the incidence of adverse reactions of ICIs combination chemotherapy was found to be high in clinical trials, and how to better solve the adverse reactions produced by ICIs combination chemotherapy is the direction that needs to be explored in the subsequent research. In precision medicine, chemotherapy-

DOI: 10.54254/2753-8818/59/20241396

targeted treatment protocols have matured. Then in the future, for different tumors or different patients, whether different chemotherapy combined with ICIs can be arranged through big data and AI technology to efficiently solve the tumors is the direction of future medical development.

## 7. Conclusion

This paper introduces the mechanisms of Treg cells, Wnt/β-catenin pathway and NF-κB pathway to suppress the immune system, and analyzes the specific mechanisms of their resistance to ICIs through clinical trials, mouse models, and pseudotime analysis, etc., and puts forward a plan to solve the related resistance problems, in the regulation of Treg cells, it is possible to target OX40 for targeted Treg therapy, and in obstruting the Wnt/β-catenin pathway, inhibitors such as XAV-939 can be used to address the resistance of ICIs. But because the number of clinical samples is still relatively small, we can't get the accurate effect of ICIs resistance. Because these pathways all play important roles in the normal immune microenvironment, so what dosage can be used to solve the problem of ICIs resistance without affecting the normal functioning of immune system is also a topic to be explored in the future. Current clinical trials have also revealed more cases of severe adverse reactions following the use of ICIs, and more research is needed on how to minimize adverse effects while improving therapeutic effectiveness. Whether the combination of multiple ICIs can improve the therapeutic efficacy and whether more substances similar to the (P50)2-BCL3 complex, which can detect resistance to ICIs, can be found are also issues that need to be further explored. In other aspects, ICIs are currently used to treat fewer types of tumors, and more research is needed to broaden the scope of treatment and to investigate whether the mechanism of resistance to ICIs exists in more tumors. It is hoped that in the future, large sample data can be obtained in the clinic, and the effect of each solution can be specifically analyzed to come up with the most efficient therapy, so that ICIs can be more efficiently applied to the treatment of tumors to improve the prognosis as well as overall survival rate of patients and make the tumor no longer as the biggest problem for patients.

## References

[1] Zhang H. Bi Y. Wei Y. et al. 2021 Blocking Wnt/ß-catenin signal amplifies anti-PD-1 therapeutic efficacy by inhibiting tumor growth migration and promoting immune infiltration in glioblastomas Molecular Cancer Therapeutics 20 7 1305-1315

[2] Huang T. Li F. Cheng X. Wang J. et al. 2021. Wnt inhibition sensitizes PD-L1 blockade therapy by overcoming bone marrow-derived myofibroblasts-mediated immune resistance in tumors. Frontiers in Immunology 12 619209

[3] Oweida A. Hararah M. K. Phan A. et al. 2018. Resistance to radiotherapy and PD-L1 blockade is mediated by TIM-3 upregulation and regulatory T-cell infiltration. Clinical Cancer Research 24 21 5368-5380

[4] Wang C. Wu L. Tang C. et al. 2023 Research progress on the role of Wnt/β-catenin pathway in immune checkpoint inhibitor resistance. Journal of Shanghai University Natural Science Edition 29 02 224-233

[5] Li R. 2024 Single-cell analysis of potential mechanisms of immune checkpoint inhibitor resistance in advanced triple-negative breast cancer Master's thesis China Medical University

[6] Sharma P. Hu-Lieskovan S. Wargo J. A. & Ribas A. 2017 Primary adaptive and acquired resistance to cancer immunotherapy Cell 168 4 707-723

[7] Alissafi T. Hatziioannou A. Legaki A. I. et al. 2019 Balancing cancer immunotherapy and immune-related adverse events: The emerging role of regulatory T cells Journal of Autoimmunity 104 102310

[8] Saleh R. & Elkord E. 2019 Treg-mediated acquired resistance to immune checkpoint inhibitors Cancer Letters 457 168-179

[9] Yuan W. & Deng D. 2022 Research progress on the mechanism of regulatory T-cell mediated acquired resistance to immune checkpoint inhibitors Chinese Journal of Immunology 38 22 2804-2808

[10] Wang B. J. Tian T. Kalland K. H. et al. 2018 Targeting Wnt/β-catenin signaling for cancer immunotherapy Trends in Pharmacological Sciences 39 7 648-658
[11] Shan K. V. Chien A. J. Yee C. et al. 2008 CTLA-4 is a direct target of Wnt/β-catenin signaling and is expressed in human melanoma tumors Journal of Investigative Dermatology 128 12 2870-2879
[12] Spranger S. Bao R. & Gajewski T. F. 2015 Melanoma-intrinsic β-catenin signaling prevents antitumor immunity Nature 523 7559 231-235
[13] Wen X. L. Wu Y. L. Awadasseid A. et al. 2020 New advances in canonical Wnt/β-catenin signaling in cancer Cancer Management and Research 12 6987-6998
[14] Yamada K. Hori Y. Inoue S. et al. 2021 E7386 a selective inhibitor of the interaction between β-catenin and CBP exerts antitumor activity in tumor models with activated canonical Wnt signaling Cancer Research 81 4 1052-1062
[15] Feng M. Jin J. Q. Xia L. et al. 2019 Pharmacological inhibition of β-catenin/BCL9 interaction overcomes resistance to immune checkpoint blockades by modulating Treg cells Science Advances 5 5 eaau5240
[16] Holtzhausen A. Zhao F. Evans K. S. et al. 2015 Melanoma-derived Wnt5a promotes local dendritic-cell expression of IDO and immunotolerance: Opportunities for pharmacologic enhancement of immunotherapy Cancer Immunology Research 3 9 1082-1095
[17] Deng L. Liang H. Burnette B. et al. 2014 Irradiation and anti-PD-L1 treatment synergistically promote antitumor immunity in mice Journal of Clinical Investigation 124 2 687-695
[18] Kareva I. 2017. A combination of immune checkpoint inhibition with metronomic chemotherapy as a way of targeting therapy-resistant cancer cells International Journal of Molecular Sciences 18 10 2134