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Mechanisms of Resistance to Immunotherapy and Optimization Strategies in Driving Gene-Positive NSCLC

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Abstract. Non-small cell lung cancer (NSCLC) poses a huge threat to people's health and immunotherapy, especially ICIS (immune checkpoint inhibitors), plays an important role in the therapy of this cancer. Although ICIs have made significant progress in the treatment of NSCLC, most patients still have drug resistance problems, especially the group of patients with positive driver genes. Thus, the therapeutic outcomes are heavily restricted, and it is necessary to explore the mechanism of drug resistance in driving gene-positive NSCLC patients. This paper primarily talks about the mechanism of drug resistance for these patients. After that, some optimized therapeutic strategies are proposed to deal with the problem of drug resistance based on the mechanisms. This paper finds that the mechanisms of drug resistance can be divided into two layers: intrinsic and extrinsic aspects. In the intrinsic layer, there are four factors that induce drug resistance: low immunogenicity, antigen presentation disorder, abnormal interferon signaling and dynamic immune phenotypes. In the extrinsic layer, abnormal angiogenesis and hypoxia, reshaped ECM and inhibitory cells in TME also make a huge difference to drug resistance. Based on these factors, some optimized therapeutic strategies that make a combination of ICIS and other therapy methods, such as radiotherapy and chemotherapy, are proposed to deal with the problem of drug resistance.

Keywords: Drug resistance, driving gene-positive NSCLC, optimized therapy strategies, biomarkers

1. Introduction

Non-small cell lung cancer is the most common type of lung cancer in the world, accounting for over 50% of all lung cancer cases. Immunotherapy plays an important part in the comprehensive treatment of NSCLC. As a breakthrough treatment strategy, immune checkpoint inhibitors (ICIs) have made remarkable progress in clinical practice, especially in PD-1/PD-L1 blocking treatment. However, clinical practice shows that not all patients can benefit from stable and lasting survival from ICIs because of drug resistance to ICIS, especially for driving gene-positive NSCLC patients. It suggests that these patients have a more specialized molecular background and immunobiological characteristics, so it is difficult to simply apply the immunotherapy strategy of general NSCLC. It has been mentioned that the driving gene-positive NSCLC is a special population with obvious heterogeneity. Its immunotherapy value and optimization path still need to be judged in combination

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with specific molecular types [1]. Thus, it is necessary to explore the mechanism of drug resistance regarding driving gene-positive NSCLC and propose some optimized therapeutic strategies to deal with drug resistance based on the mechanism mentioned in this paper.

Recent research has found that for driving gene-positive NSCLC, different driving gene subtypes have obvious differences in tumor immunogenicity, tumor microenvironmental state and response to immune checkpoint inhibitors [2]. For example, driving genes such as EGFR, ALK, ROS1, RET, HER2, METex14 and KRAS not only determine the molecular type of tumors, but also shape different immunobiological characteristics to a certain extent, resulting in inconsistent benefits of their immunotherapy. This feature is one of the essential reasons for continuous exploration in this field. For the mechanisms of drug resistance to ICIS, it has been summarized into two major levels: tumor-intrinsic and tumor-extrinsic [3]. These two aspects promote drug resistance together. But at present, there is no clear explanation about these two levels. Because of the restriction of immunotherapy, recent research has gradually shifted from single-drug treatment to combined intervention to overcome the difficulties of drug resistance to ICIS and it has been verified that the combined therapy strategies are effective methods to deal with drug resistance [4].

This paper primarily explores the mechanism of drug resistance from two levels: tumor-intrinsic and tumor-extrinsic. And then, biomarkers that can be applied to guide treatment selection and monitor therapeutic outcomes are discussed. Based on these two aspects, some optimized therapy strategies are proposed to deal with the problem of drug resistance. This paper mainly aims to overcome the difficulties of drug resistance in driving gene-positive NSCLC patients. As a result, the survival rate of these patients can be improved significantly.

2. Clinical characteristics of immunotherapy for driving gene-positive NSCLC

ICIS plays an important role in NSCLC. However, in patients with positive driving genes, the overall benefit of single-drug ICIs in driving gene-positive NSCLC patients is limited, and the effect is not as good as that of people with negative driving genes. It has been shown that in nivolumab monotherapy, the objective response rate (ORR) of EGFR-mutated NSCLC is only 14%, while EGFR wild-type patients can reach 30%, which further supports the low sensitivity of EGFR mutation to ICIs [5]. Different driving gene subtypes are not exactly the same. To illustrate, patients with different driving genes are not the same in immune status, PD-L1 expression, tumor mutation burden (TMB) and clinical response. Thus, driving gene-positive NSCLC patients cannot be regarded as a completely unified population. It suggests that there is a special immunological and molecular biological basis behind driving gene-positive NSCLC and it is necessary to further analyze the mechanism of their low response to ICIs and drug resistance.

3. Mechanism for driving gene-positive NSCLC hyporesponsiveness and drug resistance to ICIS

3.1. Intrinsic mechanism of NSCLC

It refers to the molecular and functional abnormalities of tumor cells themselves, which determine whether the tumor can be easily recognized by the immune system and whether the immune system can really initiate an effective anti-tumor immune response and make a difference.

Firstly, driving gene-positive NSCLC, especially EGFR and ALK mutations, usually shows low immunogenicity. In these patients, the overall mutation load of the tumor is low and there are few new antigens formed, making these tumors not easily recognized by the immune system. The

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analysis of EGFR mutation lung cancer shows that the TMB (tumor mutation burden) of EGFR mutation tumors is largely lower than that of EGFR wild-type NSCLC, with a median value of 56 vs 181 mut/exome, respectively [6]. This is why in NSCLC, driving gene-positive patients are often more difficult to benefit from single-drug ICIs than driving gene-negative patients. Other studies have also shown that the TMB of ALK-mutated NSCLC is also lower than that of wild-type, while some studies have found that a small number of EGFR-mutated patients with high TMB may still benefit from ICIs [6].

Secondly, driving gene-positive NSCLC usually shows an antigen presentation disorder. In other words, these driving genes often inhibit MHC-1 expression, thus reducing recognition by CD8+ T cells. It has been verified that the EGFR mutation makes use of the MEK-ERK pathway to reduce MHI-C expression. It affects CXCL10, CCL5 and other chemokine signals, making it difficult for CD8+ T cells to enter the tumor. As a result, the tumor itself is not easily recognized, so that even if ICIS are widely used, T cells are not capable of making a great difference.

In addition, abnormal interferon signaling and weak molecular response to immune effects are also an important source of inherent drug resistance to ICIs. Although PD-1/PD-L1 is blocked, whether the tumor can really be removed depends not only on whether T cells can be activated, but also on whether the tumor cells are still sensitive to immune effect signals such as IFN-γ. These driving gene-positive tumor cells can alter the response to immune cytokines. Thus, even if immune recognition has happened, it is still possible to avoid immune killing. Abnormal interferon signaling mainly manifests as the downregulation of IFN-γ receptor expression and the inhibition of the JAK-STAT signaling pathway in driving gene-positive NSCLC. It weakens the response of tumor cells to IFN-γ and other immune effect signals, thus avoiding immune killing.

Finally, the internal immune phenotype of the tumor is not stationary, but will evolve dynamically during the treatment process. That is to say, specific factors such as types of previous treatment and intensity of immune pressure can induce driving gene-positive tumor cells to adjust their immune-related molecular expression, antigen presentation ability and inflammatory signal status, which can further develop in the direction of immune escape. In other words, the driving gene-positive NSCLC is not a fixed target, but a molecular subtype with continuous adaptability, which also explains why single immune checkpoint blocking is often difficult to bring lasting efficacy, and the median PFS is significantly shorter than that in driving gene-negative patients.

3.2. Mechanism of tumor microenvironment

In addition to the intrinsic molecular abnormalities of tumor cells themselves, the tumor microenvironment, as the external environment for tumor growth and development, also plays a key role in inducing ICIs resistance in driving gene-positive NSCLC. The tumor microenvironment determines whether the immune response can reach the tumor and make a difference. Tumor microenvironment (TME) is an important element that promotes immune resistance to drugs. TME is composed of tumor cells, immune cells, fibroblasts, endothelial cells, extracellular matrix, cytokines and metabolic factors, which evolve dynamically and reshape continuously. It plays an essential role in driving gene-positive NSCLC and induces continuous resistance to ICIS.

Firstly, Abnormal angiogenesis and hypoxia will bring limitations to the immune response. It has been shown in the review of EGFR mutation lung cancer, which clearly lists ECM (extracellular Matrix) and tumor blood vessels as the core observation dimensions [7]. TME can promote the formation of abnormal blood vessels through VEGF and other factors promoted by driving genes. These blood vessels are often structurally disordered and have abnormal permeability, which not only affects drug delivery but also hinders immune cells from effectively entering the core area of

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the tumor. At the same time, the hypoxia can induce a series of adaptive changes that are conducive to tumor survival and metastasis. In other words, tumor blood vessels are also an important structural basis for regulating the entry and distribution of immune cells. For driving gene-positive patients, it is difficult for effective immune cells to reach the position where they need to play a role. Therefore, even if ICI plays an activation role, it may be restricted by TME.

Secondly, in the layer of immune cells, the EGFR mutation in NSCLC shows a more inhibitory cell composition. The TME in driving gene-positive NSCLC is often filled with a variety of cell groups that can inhibit the activity of T cells, such as regulatory T cells (Treg), bone marrow-source inhibitory cells (MDSC) and macrophage subgroups with tumor-promoting functions. These cells weaken the anti-tumor immune response by competing for nutrition, secreting inhibitory factors, inhibiting antigen presentation and interfering with T cell activation. It has been demonstrated that the number of CD39+, CD8+, PD-1 and T cells in EGFR mutation NSCLC is less than that of wild-type EGFR lung cancer [8]. At the same time, EGFR signals can recruit regulatory T cells through CCL22 and inhibit CD8+ T cell infiltration by reducing CXCL10/CCL5. That is to say, the low reaction to ICIS and the generation of drug resistance is not only related to the reduction of T cells, but also the increase of cells generating a series of negative effects on anti-tumor immune response.

Finally, ECM (extracellular Matrix) also makes a huge difference. ECM is not only a supporting component of tissue structure, but also an important factor affecting immune cell infiltration, T cell activity and ICI efficacy. ECM in tumors is often reshaped, becoming more dense, rigid and abnormally arranged. This structural change can form a significant physical barrier and prevent T cells and drugs from entering the tumor. At the same time, ECM can also regulate the signal conduction of tumor cells and immune cells by interacting with cell surface receptors, further affecting the immunosuppressive state.

3.3. The synergy between these two aspects

In summary, the restriction of ICIS treatment in driving gene-positive NSCLC is caused by the intrinsic and microenvironmental characteristics of tumors. On the one hand, low immunogenicity, antigen presentation disorder, abnormal interferon signaling and dynamic immune phenotype, all of which are promoted by driving genes such as EGFR and ALK, reduce the response to ICIS and engender drug resistance. On the other hand, abnormal angiogenesis and hypoxia, reshaped ECM and inhibitory cells in TME, also make a big difference to ICIS resistance. In the clinical aspect, this double restriction is ultimately manifested as EGFR/ALK-driven NSCLC, ORR and PFS are obviously not ideal under single-drug ICIs, while the benefits of driver-negative NSCLC are relatively clear.

4. Biomarkers in immunotherapy

4.1. Applications and limitations of classic biomarkers

Biomarkers play a central role in cancer immunotherapy. They can be applied to predict which patients are more likely to respond, guide treatment selection, and monitor therapeutic outcomes. Some classic biomarkers have already been used to guide treatment selection and monitor outcomes in NSCLC, such as PD-L1 and TMB (tumor mutation burden). PD-L1 is one of the most commonly used biomarkers. However, in the driving gene-positive NSCLC, its explanatory power is significantly reduced. It has been shown that though some EGFR or ALK-driven tumors can also have an increase in PD-L1, this increase sometimes reflects the expression changes induced by the

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oncogene pathway, which does not necessarily mean that there is a real active anti-tumor immune response in the tumor [9]. Therefore, high expression of PD-L1 is not the same as high sensitivity to ICIs, and relying on PD-L1 alone is easy to overestimate the benefits of treatment. TMB also has similar problems. It is widely thought that the higher the TMB, the more potential new antigens there are, and the more likely the tumor is to be recognized by the immune system. However, TMB is not a universal indicator. On the one hand, different testing platforms and thresholds are not uniform. On the other hand, even if TMB is low, it can explain the overall low sensitivity, which may not be enough to distinguish who may still benefit from treatment among individuals. As a result, compared with general NSCLC, the predictive value of these classic biomarkers in driving gene-positive NSCLC is limited.

4.2. Research progress of new biomarkers

These classic biomarkers cannot be used as the only indicator to predict therapeutic outcomes in driving gene-positive NSCLC. From the discussion regarding drug resistance to ICIS above, it is clear that what really determines whether ICIs can be effective in driving gene expression is often not only what is expressed on the surface of the tumor, but also whether there is not enough effect inside the tumor to immune cells, whether these cells are inhibited, and whether they can really enter the core area of the tumor. Thus, TME-related biomarkers will play an important role in predicting therapeutic results in driving gene-positive patients. Biomarkers for ICIs are expanding from PD-L1/TMB/microsatellite instability (MSI) to TME-related markers [9]. TME-related biomarkers mainly include tumor-infiltrating lymphocytes (TILs), tertiary lymphoid structures (TLS), CD8+ T cell infiltration level, and inhibitory immune cell ratio, all of which can be applied as indicators to predict therapeutic outcomes and guide treatment selection. In addition, liquid biopsy-related markers, especially circulating tumor DNA (ctDNA)/cell-free DNA (cfDNA), are also meaningful in driving gene-positive NSCLC. As verified earlier, driving gene-positive NSCLC has the characteristic of dynamic molecular evolution. The advantage of liquid biopsy is that it can be detected repeatedly and dynamically monitored, which is more suitable for monitoring molecular changes and drug resistance trends before and after treatment. ctDNA dynamic monitoring can timely capture the changes of tumor immune phenotype and drug resistance signals, which are consistent with the dynamic evolution characteristics of driving gene-positive NSCLC. Thus, ctDNA can not only assist molecular typing but also may help predict ICI efficacy and detect drug resistance signals. Compared with PD-L1 and TMB, TME-related biomarkers can more accurately reflect the local immune status of tumors and better predict the efficacy of ICIs in driving gene-positive patients.

4.3. From single indicators to a composite prediction model

A single indicator can only reflect one side of the tumor. For example, TMB is more inclined to reflect the potential immunogenicity of tumors, while TME markers reflect the infiltration and inhibition of local immune cells and ctDNA reflects dynamic molecular changes. It has been mentioned above that some driving gene-positive NSCLC patients have high PD-L1, but the therapeutic outcomes of ICIS are still average, meaning that the prediction of therapy results cannot be determined by only one indicator. Thus, it is necessary to combine these indicators to further predict therapeutic results and guide treatment selection. The addition of dynamic liquid biopsy information, such as ctDNA, can compensate for the lack of static indicators and predict the risk of drug resistance effectively.

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5. Optimized therapy strategies

Based on the above analysis, it can be seen that for the driving gene-positive NSCLC patients, it is often difficult to obtain stable benefits from single-drug treatment (ICIS). Therefore, the key to treatment optimization is not to simply strengthen treatment, but to stratify patients according to the driving genotyping, tumor microenvironment status, classic and new biomarker results, and choose a more suitable combined scheme. The value of combined treatment lies in the collaborative intervention for different links of tumor biology. It includes enhancing antigen release, improving immune cell infiltration, removing inhibitory cells, alleviating immunosuppressive microenvironment, and improving the sensitivity of tumors to effective immune attacks.

At present, there are five kinds of combined therapy schemes that can be applied to driving gene-positive NSCLC patients. These therapeutic schemes are shown in Table 1. Immune combined chemotherapy can promote the death of tumor cells and increase tumor antigen release. Thus, it can enhance the recognition of tumors by the immune system. It makes a great difference to patients with insufficient immunogenicity and single-drug ICIs are not easy to take effect. An immune combined angiogenesis inhibitor helps to improve the tumor microenvironment through the normalization of blood vessels, making it easier for immune cells to enter the tumor tissue and increase immune infiltration. Immune combined radiotherapy can enhance the death of tumor cells and promote the release of tumor antigen. Meanwhile, it can promote the activation of T cells to improve TME. Immune combined targeted therapy can not only inhibit abnormal driving pathways, but also help reshape the tumor microenvironment by reducing hypoxia, improving the condition of local blood vessels, and promoting T cell infiltration. An immune combined novel immunomodulator enhances T cell activation and relieves immunosuppression to improve the immune system.

Table 1. Therapy schemes for driving gene-positive NSCLC patients [10]

	Target location	Main effect	Limitations
ICIS+ chemotherapy	Tumor cells	Increases antigen release & promotes tumor	Systemic toxicity, non-specific effects
ICIS+ targeted therapy	TME	Improves T cell infiltration by reducing hypoxia & normalizing vasculature	Resistance, limited to specific targets
ICIS+ novel immunomodulator	Immune system	Enhances T cell activation& relieves immunosuppression adverse	Risk of immune-related
ICIS+ radiotherapy	Tumor cells & TME	Increase antigen release & T cell activation	Limited anti-tumor response
ICIS+ radiotherapy	Tumor vasculature & TME	Normalize antigen & increase immune infiltration	Improved efficacy

It must be mentioned that not all patients are suitable for the same combined strategy. It needs to be judged according to the driving gene subtype, PD-L1, TMB, TME biomarkers, ctDNA dynamic changes, and the patient's clinical status, etc. [11]. For example, when the biomarker test shows low TMB, low CD8+ T cell infiltration and insufficient TLS level, it often suggests that the tumor is in a relatively cold immune state, and the benefit of single-drug ICIs is limited. It is more suitable to consider ICI combined chemotherapy to improve the treatment response by increasing antigen release, enhancing tumor recognition and improving TME. It is capable of helping patients to find the most suitable combined therapy schemes for themselves.

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6. Conclusion

This paper systematically elaborates the mechanisms underlying ICIs' resistance and corresponding combination treatment strategies for driver gene-positive NSCLC, aiming to overcome clinical immunotherapy resistance. The ICIs' resistance mechanisms are divided into intrinsic and extrinsic types. Intrinsic resistance arises from low tumor immunogenicity, defective antigen presentation, abnormal interferon signaling and dynamic immune phenotypes, whereas extrinsic resistance is mainly attributed to abnormal angiogenesis, hypoxia, remodeled extracellular matrix and inhibitory immune cells in the TME. Based on these resistance mechanisms and multiple biomarkers, including PD-L1, TMB, TME features and dynamic ctDNA changes, this paper summarizes five effective ICIs combination regimens. It is highlighted that treatment regimens should be selected individually based on gene subtypes, microenvironmental characteristics and patients' clinical conditions to reverse ICIs resistance. This work clarifies the systematic resistance mechanisms and feasible optimized therapeutic strategies, providing theoretical support for improving immunotherapy efficacy and NSCLC patients' survival outcomes. However, the proposed combination regimens still possess several unresolved clinical limitations. Traditional analytical methods are insufficient to process complex and heterogeneous tumor multi-group data, restricting accurate prediction of treatment response. In the future, artificial intelligence can be adopted to integrate multidimensional data, precisely predict immunotherapy efficacy and optimize individualized treatment plans. Existing studies have validated that AI models can significantly improve the accuracy of PD-L1 status prediction, showing promising prospects in assisting precise clinical decision-making for NSCLC immunotherapy.

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