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The Feasibility of Combining Immune Checkpoint Inhibitors with Cancer-related Fibroblasts for the Treatment of Tumors

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Abstract: In tumor therapy, immune checkpoint inhibitors (ICIs) are widely utilized. However, in most cases, patients with colorectal cancer and breast cancer have a low response rate to ICIs monotherapy. By directly or indirectly inhibiting T cells, Cancer-associated fibroblasts (CAFs) impact the immune response against tumors and immune cells' sensitivity to immune checkpoints. At present, the research on targeted CAFs for tumor treatment has become a hot topic. This paper analyzed the mechanism of immune resistance to ICIs in some tumor patients, found that CAFs promoted the formation of immune resistance in patients, and analyzed two ways of targeting CAFs to inhibit tumor progression and found that the drug GKT137831 could restore the sensitivity of patients to ICIs by inhibiting CAFs. The combined treatment of ICIs and CAFs provides a reference for the clinical treatment of tumors. However, CAFs are a highly heterogeneous cell population, so it is necessary to find more precise CAFs targeting drugs to enhance tumor immunogenicity and improve tumor sensitivity to ICIs through combination therapy.

Keywords: Immune checkpoint inhibitors, immune resistance, cancer-associated fibroblasts, immune blockade, targeted therapy.

1. Introduction

In recent years, Clinical practice has been extensively using immunotherapy. Among various immunotherapies, ICIs have attracted much attention. Compared with traditional treatment methods for tumors, ICIs have shown higher survival rates, providing a new weapon for combating tumors [1]. The treatment of solid tumors has resulted in significant therapeutic effects. Some patients are achieving lasting benefits and improving disease prognosis. However, even though immunotherapy is more efficient and tolerable than conventional and targeted therapies, several patients exhibit innate or acquired drug resistance [2]. ICIs are ineffective in treating colorectal cancer and breast cancer patients, and some patients begin to develop immune resistance immediately after treatment [3].

It is believed that the tumor micro-environment (TME) plays a significant role in immunotherapy. One of the most important components of TME is CAFs, which can produce a series of effects by secreting many effector molecules, and finally allow tumor cells to escape the attack of immune cells [4]. CAFs are associated with almost all the main characteristics of tumors, so they play a huge role in predicting the development of tumors [5]. It has been proven in numerous studies that CAFs interact with immune cells and other immune components to control TME. CAFs are becoming increasingly important in tumor immune evasion, which inhibits anti-tumor immune responses [6].

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Therefore, reducing the inhibitory effect of CAFs on immune cells and overcoming immune resistance has become a new way to treat tumors. This article mainly introduces the contents of ICIs and immune resistance, CAFs and immune resistance, and CAFs and T cells. In addition, this paper will also explore the impact of ICIs combined with CAFs targeting on tumor immunotherapy, promote the recovery of sensitivity to ICIs in tumor patients receiving treatment, and effectively improve the quality of immunotherapy.

2. ICIs and immune resistance

Immunotherapy has created a new way of tumor treatment. The principle of using immunotherapy to treat diseases is to utilize the active and passive immunity of the host to fight the tumor. At present, immunotherapy has gradually become a new way of clinical tumor treatment. Different immunotherapies have different mechanisms of action, The key to using ICIs to treat tumors is the integrity of all stages of the cancer immune cycle, if any link in this stage is destroyed, then the use of immunotherapy to treat tumors will not be satisfactory results. At present, several ICIs have been approved for clinical treatment and have achieved satisfactory results, but some tumor patients have no obvious response to ICIs or even produce immune resistance. ICIs mainly blocks immune checkpoint molecules to further relieve immune suppression, activate the killing effect of immune cells in the immune response on tumor cells, and eventually lead to the apoptosis of tumor cells to complete an effective anti-tumor immune response [7]. Although the use of ICIs is becoming more widespread, this treatment is only effective for a small percentage of patients, and there are still many patients who are unable to express satisfaction with ICIs treatment. Understanding the mechanism of ICIs resistance in cancer patients is helpful to improve the therapeutic effect of ICIs and increase the cure rate of cancer. Sreya et al. indicated that resistance to checkpoint therapy may occur if the tumor's immune response is disrupted [7].

Tumor immune response is mainly mediated by T cells, which can play the killing role of tumor cells through a series of processes. However, if any stage of the immune response involved in T cells is broken, immune resistance can occur. There are many factors in TME that can affect immune blocking therapy, and tumor cells promote their own occurrence and development through interaction with components in TME, leading to the emergence of immune resistance [6].

3. CAFs and immune resistance

CAFs activate signaling pathways such as JAK/STAT, TGF-β and Wnt by secreting a variety of cytokines, promoting the proliferation and malignant transformation of epithelial cells as well as the proliferation, invasion, migration, angiogenesis and drug resistance of tumor cells [8].

ICIs are one of the main drugs in tumor immunotherapy. It plays a role in killing tumors by regulating the immune response in which immune cells participate. The immune response relies heavily on T cells, and the absence of T cells in TME is the ultimate cause of immunotherapy failure [1]. The anti-tumor immune response that T cells participate in can be inhibited by CAFs, as confirmed by relevant studies and its specific mechanism of action on T cells. The success of the anti-tumor immune response depends on the integrity of the immune cycle, and CAFs in TME can reduce the ability to kill tumors by interfering with multiple stages of the immune cycle in multiple ways. Therefore, when ICIs are applied to patients, CAFs in TME play a role in affecting the anti-tumor immune response induced by ICIs, resulting in ICIS being unable to achieve its full efficacy. In addition, some patients with immunosuppression due to genetic factors and previous treatment factors are subjected to inhibitory anti-tumor reactions involving CAFs, and their immune function will be more strongly suppressed, and their reactivity to ICIs will be lower and eventually produce immune resistance.

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4. CAFs and T cells

CAFs affect the function of immune cells by secreting various cytokines and products, and reduce the effectiveness of ICIs in the treatment of tumors [9]. When T cells perform anti-tumor immune response, CAFs inhibit immune cells from killing tumor cells by secreting cytokines such as TGF-β, IL-6, CXCL12 and vascular endothelial growth factor [8]. In conclusion, the high expression of CAFs can affect the development of tumors. Through direct and indirect effects on immune cells, CAFs can have a negative impact on the anti-tumor immunity of immune cells by inhibiting the anti-tumor immune response and encouraging tumor development. T cells involved in immune regulation include cytotoxic T cells (CD8+T cells) and Tregs. CD8+T cells release perforin and other substances through contact with tumor cells, leading to the death of tumor cells. Tregs are lymphocytes that negatively regulate the body's immune response by secreting immunosuppressive factors such as IL-10 and TGF-β to suppress excessive immune response.

4.1. Indirect effects of CAFs on T cells

CAFs can cause Tregs to infiltrate, leading to the formation of immunosuppressive T cells, which allows cancer cells to evade detection by the immune system. Studies have shown that Foxp3 (a transcriptional regulatory factor that is specifically expressed on the surface of CD4+CD25+Tregs and is essential for the development and functional maintenance of Tregs) with high expression of Tregs plays an important role in inhibiting anti-tumor immunity, while CAFs can not only promote the recruitment and infiltration of Tregs, but also promote the retention of Tregs. It can also promote the transformation of Tregs and eventually induce immunosuppression [6]. Athina et al. found that CAFs exist in a variety of subtypes, one of which can phagocytose and process tumor antigens and exhibit a tolerant phenotype that acts on Tregs in an antigen-specific manner and blocks T cell responses [9].

CD8+T cells and Tregs are both important components of T lymphocytes, which work together in the immune system. CD8+T cells are primarily responsible for the direct killing effect, while Tregs maintain the immune balance by suppressing excessive immune responses. The proper function of Tregs is essential for the proper functioning of CD8+T cells. CAFs promote the recruitment, infiltration and activation of Tregs, and then inhibit the killing process of tumor cells participated by CD8+T cells, and finally produce immunosuppression.

4.2. Direct effects of CAFs on T cells

T cells can be directly inhibited by CAFs through the promotion of Tregs, but they can also be indirectly inhibited by CAFs through interaction with them, causing them to participate in anti-tumor immunity [6]. The direct inhibitory effect of CAFs on T cells is mainly through the following three ways: inhibiting the transport and recruitment of T cells in tumors; Reduce T cell infiltration in TME; Inhibition of cytotoxic function of T cells [10].

CAFs can prevent T cells from transporting and recruiting to the tumor site, decreasing the number of T cells present in the tumor site, and not activating the anti-tumor immune response fully. Recruitment of immune cells involves a large system, and if any stage of the process is disrupted, T cells cannot be recruited to the diseased site. Research has revealed that recruitment chemokines and their chemokine receptors are responsible for activating the recruitment dependent system, while CAFs have the ability to regulate the recruitment of peripheral T cells to tumors by secreting many cytokines and chemokines [10].

The success of immunotherapy against the tumor depends on the number of T cells infiltrating the tumor. However, the presence of CAFs preferentially infiltrates T cells in loose collagen fibers, reduces the infiltration of T cells in tumors, and reduces the effect of immune response. It has been

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found that CAFs can act as a biophysical barrier to reduce the contact between T cells and tumor cells and inhibit the immune killing effect of T cells [10]. Ford et al. discovered that CAFs had a significant impact on the distribution of CD8+T cells, which gather near the tumor and are excluded from the center of the tumor [11]. The reduction of CD8+T cells make it impossible for patients treated with ICIs to produce the anti-immune response of the tumor, and the tumor patients cannot be satisfactorily cured.

CAFs inhibit the cytotoxic function of T cells present in TME by directly or indirectly up-regulating immune checkpoint molecules. Studies have shown that up-regulation of CAFs not only enhances inhibitory immune checkpoint molecules, but also plays an indirect role through paracrine [10]. CD8+T cells can be inhibited from killing tumors by CAFs. When patients are treated with ICIs, CAFs play a role in inhibiting CD8+T cells, which in turn inhibits the immune response of tumors, and ultimately leads to the unsatisfactory response of patients to ICIs.

All in all, through the above studies, this paper found that CAFs can directly inhibit T cells through some mechanisms. The key to the success of ICIs in the treatment of tumors is that T cells can recognize and kill tumor cells, and CAFs in TME can inhibit the anti-tumor immune response participated by T cells in the above three ways, resulting in patients receiving ICIs treatment can not show a good cure effect, and even develop drug resistance. There is evidence that CAFs can directly affect patients' sensitivity to ICIs [12].

The mechanism of action between CAFs and T cells is very complex, and it is necessary to further explore more clear pathways of action to uncover the fog of immunosuppression, so that cancer patients can better receive the effect of ICIs therapy.

5. Feasibility of ICIs combined with CAFs in the treatment of tumors

ICIs alone do not have a good response rate in some tumor patients, and to improve the sensitivity of patients to immunotherapy and prevent patients from developing immune resistance, combination therapy is needed to treat the tumor. The development of immune resistance is largely influenced by CAFs, and they are highly promising in clinical research as a potential target for tumor treatment. Studies have shown that targeting CAFs can block their function in a variety of ways. Liu et al. studied the function of CAFs in immunotherapy and found that CAFs could be inhibited by targeting the direct consumption of CAFs and effector molecules secreted by CAFs to slow down the progression of tumors, so as to realize the treatment of patients [4].

5.1. Direct consumption of targeted CAFs

Different types of CAFs have different roles. Understanding the functions of different CAFs in tumors and then targeted consumption are of certain reference value in clinical practice. Different types of CAFs also have different roles in the occurrence and development of tumors. In addition, CAFs also have rich and diverse biomarkers, and CAFs with different markers have different roles. Studies have shown that targeting FAP+CAFs consumption can inhibit tumor growth [4].

5.2. Effector molecules targeting CAFs secretion

Targeting cytokines, chemokines, and growth factors secreted by CAFs is believed to be effective in inhibiting CAFs [4]. A large number of cytokines, chemokines and growth factors secreted by CAFs can promote tumor growth, proliferation, migration, invasion and metastasis. Therefore, it is feasible to target CAFs by inhibiting the above factors. In conclusion, the anti-tumor immune process involved in CAFs can be inhibited by directly targeting CAFs or indirectly acting on CAFs secreted effector molecules.

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In addition, Kirsty Ford et al. focused on NOX4, the enzyme that produces ROS, to investigate the feasibility of targeting CAFs. In many human cancers, CAFs increase NOX4, which is an enzyme that can be inhibited to overcome immunotherapy resistance and improve outcomes [11]. Several human cancers use NOX4 as a key regulator of the CAF phenotype, with its downstream target TGF-β1. Therefore, inhibiting the function of CAFs can be accomplished by targeting NOX4. As shown in Figure 1, NOX4 inhibitor GKT137831 can resensitize tumors to ICIs. Studies have shown that after applying GKT137831, an inhibitor of NOX4, to mice, CD8+T cells in the tumor center increased, and CD8+T cells in the tumor margin decreased, and the mice's sensitivity to ICIs was significantly improved [11]. Therefore, this paper found that the phenomenon of immune resistance can be inhibited by using GKT137831 to inhibit NOX4, so as to achieve the purpose of inhibiting CAFs. GKT137831 is a clinical trial drug with good safety. A large part of solid cancers are CAFS-rich, and NOX4 inhibition combined with immunotherapy has great feasibility in the clinical treatment of tumors.

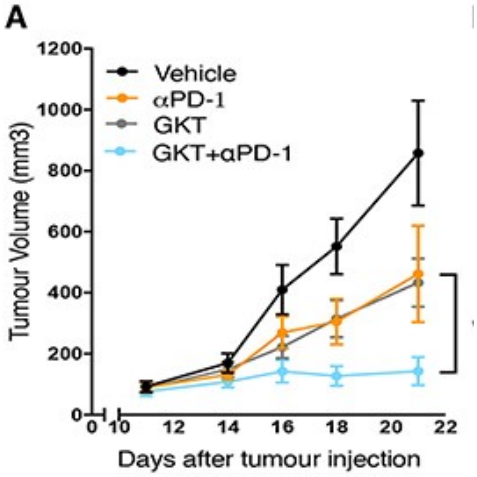

Figure 1: NOX4 inhibition re-sensitizes CAFS-rich tumors against PD-1 checkpoint therapy [11].

6. Discussion

With the progress of society and the development of science and technology, immunotherapy has completely changed the way of tumor treatment and brought new ideas for the treatment of tumors. In a variety of immunotherapies, ICIs have received more and more attention and have been widely used in clinical practice. However, only some tumor patients who received ICIs received good results, and other patients were insensitive to ICIs and even developed drug resistance. T cells play a significant role in tumor immunotherapy and the clinical prognosis of patients, and they are the main factor in the success of ICIs in the treatment of tumors. CAFs inhibit the tumor immune response by inhibiting the transport and recruitment of T cells to the tumor, inhibiting the infiltration of immune cells (CD8+T cells), and inhibiting the cytotoxic function of T cells present in the tumor environment. The release of various inflammatory and growth factors by CAFs found in tumor lesions affects TME and plays an immunomodulatory role. Therefore, immunotherapy strategies targeting CAFs have important clinical significance for the treatment of tumors. There are two main ways to target CAFs. The first approach can directly target different types and subtypes of CAFs present in TME, or target different biomarkers of CAFs. The second pathway can indirectly inhibit the function of CAFs by acting on effector molecules secreted by CAFs.NOX4 enzyme plays a key role in the formation of CAFs. Targeting CAFs through NOX4 enzyme inhibitor (GKT137831) is expected to prevent the infiltration process of immune cells (CD8+T cells) involved in CAFs, increase the number of immune

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cells (CD8+T cells) in the tumor center, and improve the sensitivity of patients to ICIs. To enhance the response of tumor patients to ICIs. However, CAF targeting methods need to be more precise and personalized due to the heterogeneity of CAFs, and the inhibitory role of certain subpopulations in tumor growth [13]. Therefore, it is urgent to explore more accurate targeting methods, and the combined application of ICIs and CAFs targeting drugs to treat diseases is expected to solve the dilemma of immune resistance in patients.

7. Conclusion

This paper introduces the relationship between ICIs, immune resistance, CAFs and T cells. It is mainly aimed at the problem of poor treatment effects due to immune resistance of tumor patients after receiving ICIs treatment, and to explore better treatment measures, so that the number of patients with good effects on ICIs can be increased. Through the above analysis, we found that CAFS-rich tumors were significantly less sensitive to ICIs, and the sensitivity of tumors to ICIs could be restored by using the inhibitor GKT137831. Therefore, the combination of ICIs and CAFs in the treatment of tumors has certain feasibility. However, CAFs are highly heterogeneous. In some cases, the development of tumors will inhibit the number of CAFs, and CAFs do not always play a role in promoting tumor progression. If we blindly inhibit the function of CAFs, it may have the opposite consequence and accelerate the development of patients' disease. So there's a need to find more precise and personalized ways to treat tumors, It is believed that in the near future, the treatment of ICIs and CAFs will be widely used in clinical practice, and more and more patients receiving ICIs treatment will have better therapeutic effects.

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