Reshaping the dynamic tumor immune microenvironment of liver cancer: From treatment-induced evolution to Novel combined strategies

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Abstract: In the treatment of liver cancer, the remodeling of the tumor immune microenvironment is of great significance. The research focuses on the evolution of the dynamic tumor immune microenvironment of liver cancer induced by treatment, and analyzes the influence of different treatment methods on its cell composition, cytokines and other aspects. Based on this evolution feature, exploring new combined strategies to enhance the anti-tumor immune effect and overcome immune escape can provide new ideas for the treatment of liver cancer and is expected to improve the prognosis of patients.

Key words: Liver cancer Dynamic tumor immune microenvironment Treatment-induced evolution; New joint strategy

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Introduction

Liver cancer is a common and highly fatal malignant tumor, and the effectiveness of traditional treatments is limited. The tumor immune microenvironment plays a key role in tumor occurrence, development and treatment response. In recent years, research on its dynamic changes has gradually deepened. Understanding the evolution law of the dynamic tumor immune microenvironment of liver cancer induced by treatment and developing new combined strategies have become important directions for improving the therapeutic effect of liver cancer.

1 Overview of the dynamic Tumor Immune Microenvironment of Liver Cancer

1.1 Basic Concepts of the tumor immune microenvironment

The tumor immune microenvironment is a complex ecosystem composed of tumor cells, immune cells, stromal components and various signaling molecules. It is not static but in a dynamic equilibrium state, which profoundly influences the occurrence, development and outcome of tumors. During the transformation of normal tissues into malignant tumors, the local microenvironment is gradually modified, forming a special environment that is conducive to tumor growth while suppressing the body's anti-tumor immune response. It contains various types of immune cells, such as T lymphocytes, B lymphocytes, natural killer cells, macrophages and dendritic cells, etc., each of which plays different functional roles. Meanwhile, fibroblasts and vascular endothelial cells in the extracellular matrix are also involved, promoting tumor angiogenesis, invasion and metastasis by secreting growth factors, cytokines and other means. In addition, various soluble mediators such as chemokines and inflammatory factors interweave into a complex network regulatory system in this environment, maintaining the delicate relationship between tumors and the immune system. Understanding this concept is crucial for revealing the progression mechanism of liver cancer and formulating effective intervention measures.

1.2 Unique Characteristics of the immune microenvironment in liver cancer

Liver cancer, as a highly heterogeneous type of malignant tumor, exhibits unique properties in its immune microenvironment that distinguish it from other types of cancer. The liver itself has a unique anatomical structure and physiological functions, making it an important metabolic organ and immune tolerance site in the human body. This characteristic leads to a more complex and challenging immune microenvironment in which liver cancer is located. On the one hand, there are a large number of resident macrophages in the liver - kupfer cells. While they recognize and clear pathogens, they may also be domesticated by tumors and transform into tumor-promoting M2-type macrophages. On the other hand, as the portal vein system directly connects the intestine and the liver, the intestinal flora and their products can continuously influence the level of inflammation and immune response patterns within the liver. In addition, the background of chronic liver diseases caused by factors such as hepatitis B virus infection has further shaped a special microenvironment based on chronic inflammation and dominated by immunosuppression. In this environment, effector CD8+ T cells often become functionally exhausted, the proportion of regulatory T cells increases, and the activity of natural killer cells is inhibited. Together, they form an important barrier for liver cancer to evade immune surveillance.

1.3 Dynamic Changing Influencing Factors

The dynamic changes of the immune microenvironment of liver cancer are driven by multiple factors. The first is the genetic alterations of the tumor itself, including the activation of oncogenes and the inactivation of tumor suppressor genes. These mutations not only give tumor cells an advantage in proliferation but also interfere with the immune recognition process by secreting specific ligands. Secondly, there is the existence of tumor stem cells. These subpopulations of cells with self-renewal capabilities can reshape the surrounding microenvironment by secreting various factors and enhance their own survival ability. The third is the impact of therapeutic intervention. Whether it is surgical resection, radiotherapy and chemotherapy, or the use of targeted drugs, they will all disrupt the original immune homeostasis and induce new adaptive responses. For instance, radiotherapy may lead to an increase in the release of tumor antigens, which theoretically should stimulate a stronger anti-tumor immune response. However, in reality, it may exacerbate local inflammatory responses due to radiation damage to normal tissues, which is instead detrimental to the recovery of immune function. Finally, individual differences among patients are also a factor that cannot be ignored. The genotypes, underlying health conditions, nutritional status, etc. of different patients will all affect their response patterns and degrees to treatment, and thereby influence the evolution trajectory of the immune microenvironment.

2 Evolution of the tumor immune microenvironment induced by treatment

2.1 Changes in the immune microenvironment after surgical treatment

Surgical operation, as one of the main cure methods for early-stage liver cancer, can directly remove the primary lesion, but it also has a profound impact on the immune landscape within the remaining liver tissue. In the short term after surgery, the molecular patterns related to tissue damage released during the wound healing process will activate the innate immune system and trigger an acute inflammatory response. However, this seemingly positive immune activation is actually a double-edged sword: moderate inflammation helps eliminate residual tiny lesions, while excessive or persistent inflammation may promote the formation of new blood vessels and create conditions for recurrence. More importantly, the surgical operation itself disrupts the original anatomical barrier, which may lead to tumor cells entering the circulatory system and increase the risk of distant metastasis. At the same time, surgical stress can also alter hormone levels throughout the body. In particular, elevated cortisol can inhibit the proliferation and differentiation of lymphocytes, weakening the overall immunity of the body. Therefore, how to balance the relationship between surgical trauma and immune protection has become a key issue that needs to be addressed in clinical practice.

2.2 Immune microenvironment remodeling caused by chemotherapy and radiotherapy

Traditional cytotoxic chemotherapy drugs mainly act on rapidly dividing tumor cells, but they inevitably also damage the normally proliferating and active healthy cell population, including bone marrow hematopoietic stem cells and lymphoid precursor cells. This not only reduces the number of white blood cells in the peripheral blood, lowering the body's ability to resist infection, but also indirectly affects the degree of immune infiltration at the tumor site. Some chemotherapy drugs can

even directly act on the surface receptors of immune cells, interfering with their normal functioning. Radiotherapy also has a dual effect: Although high-dose radiation can effectively kill tumor cells in the radiation field, it can also cause radioactive damage to the surrounding normal tissues, induce the production of a large number of pro-inflammatory factors and free radicals, and form secondary inflammatory foci. This chronic low-grade inflammatory state may instead stimulate the surviving tumor cells to acquire stronger invasiveness and drug resistance. It is worth noting that recent studies have found that the application of low-dose beat chemotherapy or precise radiotherapy techniques is expected to alleviate the above-mentioned side effects while retaining a certain degree of immune stimulation, which provides new ideas for optimizing treatment plans.

2.3 Regulation of the immune microenvironment by immunotherapy

With the successful application of immune checkpoint inhibitors, immunotherapy represented by the PD-1/PD-L1 pathway has completely transformed the treatment landscape of advanced liver cancer. This type of drug reactivates the previously suppressed T-cell response by blocking negative regulatory signals, enabling some patients to achieve long-term survival benefits. However, the effectiveness of single immunotherapy remains limited. The reason lies in the existence of multi-level and multi-link immune escape mechanisms within tumors. For instance, tumors can compensate for blocked pathways by upregulating the expression of other inhibitory molecules; Or recruit immunosuppressive subsets such as myeloid-derived suppressor cells and regulatory T cells to settle in the tumor bed, and build a physical shielding layer to prevent effector cells from approaching the target. Therefore, it is particularly important to deeply analyze the specific changing patterns of the immune microenvironment during immunotherapy, search for markers that predict therapeutic efficacy, and develop new strategies to overcome drug resistance. The current research focuses include exploring combination therapy regimens, the selection of sequential administration timing, and precise stratified treatment based on biomarkers, among other directions.

3 Exploration of New Joint Strategies

3.1 Combination of immunotherapy and traditional treatment

Combining immunotherapy with traditional treatment methods has become a hot trend in the current field of liver cancer treatment. Theoretically speaking, the death of tumor cells caused by chemotherapy or radiotherapy releases a large amount of tumor-associated antigens, thereby enhancing the efficiency of antigen presentation and improving immunogenicity. Immunotherapy, on the other hand, can relieve the immune brake and amplify this effect. In practice, numerous clinical trials have confirmed that this combination therapy can indeed achieve a synergistic effect in some populations. For instance, in unresectable locally advanced cases, the application of transarterial chemoembolization combined with PD-1 antibody therapy not only takes advantage of the regional control benefits of interventional methods but also leverages the systemic anti-cancer potential of immune drugs, achieving an effect of "1+1>2". However, the optimal combination mode of the two therapies still needs to be adjusted individually based on the specific conditions of the patients, including further optimization in aspects such as the selection of drug types, the design of the administration sequence, and the control of dosage intensity.

3.2 Combined application of different immunotherapy methods

In addition to the combination with conventional therapies, the mutual cooperation among various immunotherapy methods also shows great potential. For instance, when CAR-T cell therapy is combined with oncolytic virus vectors, the former is responsible for specifically recognizing and eliminating tumor cells expressing specific antigens, while the latter releases more antigenic substances by lysing tumor cells, thereby activating the endogenous immune response. Another promising strategy is the application of bispecific antibodies, which can simultaneously bind to two different targets. They can not only directly activate the T-cell killing function but also block the tumor escape mechanism. In addition, the research and development of tumor vaccines is also constantly advancing, aiming to actively induce the body to generate a lasting memory immune response. The integrated application of these emerging technologies is expected to break through the existing bottlenecks and achieve more efficient and safer therapeutic effects. Of course, how to ensure good compatibility

and security among different components remains an urgent problem to be solved.

3.3 Personalized Joint Strategies Based on the evolution of the immune microenvironment

Given the significant differences in the biological behavior of tumors among each patient, the future direction is bound to be towards greater refinement and personalization. By conducting a comprehensive omics analysis of the patient (including genomics, transcriptomics, proteomics, etc.), combined with imaging features and clinical information, we can draw a detailed "immune map", based on which to determine which pathways are dominant and which nodes are the most ideal intervention targets. Based on this, the multi-dimensional intervention plan designed will no longer be limited to a single treatment model, but will flexibly adjust the treatment strategy according to the real-time monitored dynamic changes in the immune system. For instance, when an increase in a certain type of immunosuppressive cells is detected, the corresponding antagonists should be added in a timely manner. If a specific signaling pathway is found to be abnormally active, targeted small molecule inhibitors should be selected to curb it.

4 Clinical Practice and Challenges

4.1 Exploration and Application of Biomarkers

In the research related to the immune microenvironment of liver cancer, it is crucial to search for reliable biomarkers. The ideal biomarker should be able to accurately reflect the tumor immune status, predict the treatment response and prognosis. At present, researchers are dedicated to screening specific molecular indicators in blood and tissue samples, such as changes in certain cytokine levels and differences in the expression of surface receptors on immune cells. These markers not only help to identify in advance the patient groups that may benefit from the new combination strategy, but also can monitor the treatment effect in real time and guide the adjustment of treatment plans. However, due to the high heterogeneity of liver cancer, a single biomarker often fails to comprehensively cover the complex immune dynamic processes. Therefore, it is necessary to establish a multi-dimensional biomarker combination system to improve the prediction accuracy. Meanwhile, standardized detection methods and data analysis processes are also key to ensuring the wide application of biomarkers.

4.2 Optimization Directions for Clinical Trial Design

To verify the safety and efficacy of the new combination strategy, well-designed clinical trials are indispensable. Future trials should adopt adaptive designs, allowing for flexible modification of the trial protocol based on interim analysis results, such as adjusting enrollment criteria, changing treatment arm Settings, or dose exploration ranges. Stratified randomization can reduce the influence of confounding factors and ensure balanced comparability among subgroups. The adaptive enrichment strategy can quickly screen out the dominant population and accelerate the clinical application of effective therapies. In the clinical trials of novel combined strategies for liver cancer treatment, the selection of included endpoints is extremely crucial. The objective response rate in short-term efficacy indicators can directly reflect the tumor shrinkage situation, allowing researchers to quickly understand the initial effect of the drug on the lesion. However, focusing only on the short term is not enough. Long-term survival benefits are the core criterion for measuring the therapeutic effect, which reflects the actual clinical benefits that patients obtain. At the same time, the assessment of quality of life should not be ignored, covering multiple aspects such as the patient's physical functions and psychological state. After all, the treatment goal is to enable the patient to prolong their life with quality. Innovative experimental design can adopt adaptive design, flexibly adjusting the plan based on early data. Set multiple time points for phased assessment to comprehensively capture changes in therapeutic effects. In this way, not only can the therapeutic effect information at different stages be obtained in a timely manner, but also evidence can be accumulated efficiently, providing a solid support for the clinical application of the new combined strategy and promoting its transition from trial to routine treatment.

4.3 Interdisciplinary Collaboration from the Perspective of Translational Medicine

To promote breakthroughs in liver cancer treatment, it is necessary to closely integrate basic research with clinical practice. The translational medicine platform has built a bridge to promote in-depth collaboration among biologists,

pathologists, imaging experts and clinicians. For instance, organoid models can be used to simulate patient-specific tumor growth characteristics and test the effects of different drug combinations; Combining artificial intelligence algorithms to analyze massive medical big data, potential correlation patterns are mined to assist in decision-making. In today's medical field, interdisciplinary integration has become a powerful engine driving scientific research progress and clinical transformation. In terms of liver cancer treatment, biologists have delved deeply into the molecular mechanisms of tumor cells, providing a theoretical basis for precise targeting. Pathologists, with their rich experience in tissue sample analysis, accurately interpret the characteristics of disease progression. Imaging experts use advanced imaging techniques to achieve dynamic monitoring and assessment of lesions. Clinicians, based on their first-hand practical experience, provide feedback on the problems and demands in actual treatment. All parties work closely together, such as integrating multi-source data resources by establishing a shared database and using bioinformatics tools to identify potential therapeutic targets. The industry-university-research-medical collaborative innovation network brings together the strengths of universities, research institutions, pharmaceutical enterprises and medical institutions to accelerate the process of new drug research and development and conduct multi-center clinical trials to verify therapeutic effects. This all-round and multi-level cooperation model is constantly breaking through the limitations of traditional diagnosis and treatment, opening up new paths for the conquest of liver cancer and bringing more hope for a cure.

Conclusion: In-depth research on the evolution of the dynamic tumor immune microenvironment of liver cancer induced by treatment provides theoretical support for the formulation of new combined strategies. Through reasonable combined therapy, it is expected to break immune tolerance, enhance immune killing, and improve the survival status of liver cancer patients. In the future, strategies still need to be further optimized in the field of liver cancer immunotherapy. On the one hand, it is necessary to deeply explore the complex mechanisms of the tumor microenvironment, precisely screen the advantageous population, and achieve individualized medication. On the other hand, actively carry out multi-center and large-sample clinical trials, strictly follow scientific research norms, and collect detailed data to verify efficacy and safety. At the same time, it is necessary to strengthen the close connection between basic research and clinical application, and explore comprehensive treatment plans in combination with other treatment methods, such as the synergistic effect with targeted drugs and radiotherapy. Through continuous innovation and practice, we constantly break through bottlenecks, bringing new hope to more liver cancer patients, promoting this field to new heights, and ultimately improving the prognosis and quality of life of patients.

References

[1]Yang Zhihui, Miao Jingxiaguang, Liao Rongrong. Key words of tumor immunotherapy nursing related research: Open visualization analysis [J]. Journal of Nursing, 2023,30 (1) : 12-16.
[2] Yang He, Zhang Sheng, Xin Yanfei. Research Progress of Tumor Immunotherapy [J]. Chinese Journal of Clinical Pharmacology and Therapeutics, 2016,21 (9) : 1074-1080.
[3] Zhang Sihan (Review) Xu Bin (Proofreading). The Current Development Status and Prospect of Tumor Immunotherapy Drugs [J]. International Journal of Pathology and Clinical Practice, 2021, 41(10):2447-2460.
[4] Li Youbing, Jiang Jiaji. New Advances in Systemic Therapy for Primary Liver Cancer [J] Liver,2021,26(4):349-352.
[5] Liu Lin, Qin Shukui. Research Status and Progress of Molecular Targeted Drugs and immune checkpoint Inhibitors in the treatment of advanced hepatocellular carcinoma [J]. Journal of Clinical Oncology,2019,24(9):839-849.

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