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Research on the Metabolism of Immune Cells and Immune Escape Mechanisms in the Tumor Immune Microenvironment

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Abstract:

The tumor microenvironment (TME) is a complex and dynamic system consisting of tumor cells, immune cells, stromal cells, and extracellular matrix, whose internal metabolic state and other characteristics have a profound impact on the proliferation, invasion, metastasis and treatment response of tumors. Currently, there is a problem of poor treatment efficiency for tumors due to immune escape. So, analyzing the internal relationship between the metabolism of immune cells and the mechanism of immune escape in TME is a goal for improving treatment outcomes. This study involved analyzing the changes in immune cell metabolites and investigating the impact of metabolic pathways on immune function. Firstly, the metabolic changes of different immune cells ($CD8^+$T cells, NK cells, Tregs, TAMs) were described, and it was found there was a significant metabolic disorder in TME. The reprogramming of sugar metabolism inhibits immune activity, the fatty acid metabolism promotes immune evasion, and the disorder of amino acid metabolism seizes key amino acids leading to the immune cells being in a "nutritional deficiency" state. Meanwhile, the abnormal accumulation of metabolites such as lactic acid and ketone bodies jointly creates an immunosuppressive microenvironment. However, some immune functions can be restored and the growth of tumors can be inhibited by regulating certain metabolic pathways. Treating the metabolic disorders in TME is expected to become a breakthrough in tumor immune suppression. It provides experimental evidence for developing the combined strategy of "metabolic regulation + immunotherapy" and opens up a new direction for the design of tumor treatment plans.

Keywords: Tumor microenvironment; Immune cells; Immune escape; Immune cell metabolism; Mechanism of immune escape.

1. Introduction

Nowadays, tumors have become a complex disease to overcome due to their rapid mutation, difficulty in treatment, high fatality and disability rates, and other characteristics. Tumor immune escape is one of the key factors leading to poor treatment outcomes, whose causes include the downregulation of tumor cell antigens and the activation of immune checkpoints. Among them, TME, as a special unit closely related to immune escape, is gradually becoming a research focus. TME is not a single cell cluster, but rather a dynamic network composed of tumor cells, immune cells (such as $CD8^+$ cytotoxic T cells, regulatory T cells (Tregs), tumor-associated macrophages (TAMs), natural killer cells (NK cells), etc.), stromal cells (endothelial cells, fibroblasts, etc.), as well as extracellular matrix and a large number of soluble factors (such as cytokines, growth factors, chemokines, etc) [1]. In TME, the glucose deficiency caused by tumor cell metabolism, the abnormal accumulation of metabolites such as lactic acid, and the hypoxia and low pH conditions resulting from abnormal blood vessels all contribute to the immunosuppressive state, which lead to immune escape.

The unique metabolic environment within TME can lead to alterations in the tumor‘s metabolic process. Among them, tumors rely on glycolysis for energy supply under aerobic conditions [2]. This abnormal metabolism not only meets the energy requirements for its rapid proliferation, but also competes with the microenvironment to consume glucose and deprives immune cells of their nutrient supply. At the same time, the imbalance in amino acid metabolism leads to the disorderly breakdown of glutamine and arginine, weakening the anti-tumor ability of immune cells [3]. Additionally, when the nutrition of the TME changes, the internal cells will form a special lipid metabolism pattern characterized by fatty acid oxidation. These metabolic abnormalities do not exist independently but affect tumor progression through cross-regulation.

Tumor metabolic changes also directly contribute to immune evasion: some tumor cells evade immune recognition by down-regulating MHC-I molecules, or up-regulating MHC-I molecules to resist NK cell killing, thereby inhibiting T cell activation through abnormal antigen expression [4]. Moreover, these metabolic disorders can also suppress the immune response.

However, the mechanism how the metabolic changes in the TME lead to immune escape remains not fully clear. Based on this, this article aims to analyze the mechanisms of metabolic changes in the TME and abnormal regulation of immune cells to clarify how the two work together to cause immune escape, and explore related treatment strategies. The goal is to theoretically deepen the understanding of the interaction between TME metabolism and immune escape and improve the theory of tumor immunology, and provide a basis for the development of new anti-tumor drugs from a clinical perspective, facilitate the exploration of potential targets, and promote the development of tumor treatment.

2. The Metabolism of Tumor Microenvironment and Immune Cells

TME is a complex tumor system composed of immune cells, tumor cells, stromal cells, and extracellular matrix. Immune cells include innate immune cells (TAM, DC cells, monocytes, mast cells, eosinophils, platelets) and adaptive immune cells (T cells, B cells). This section mainly elaborates on the functions of TAM, NK cells, T cells, and B cells in the tumor microenvironment.

TAM cells regulate the immune tumor microenvironment through phenotypic polarization, promoting tumor angiogenesis and nutrient supply, and accelerating tumor cell invasion and metastasis. Based on their functions, they can be classified into the anti-tumor M1 type and the pro-tumor M2 type. M1 is usually activated by cytokines such as lipopolysaccharide and tumor necrosis factor and plays a significant role in phagocytosis and killing during the early stage of tumor immunity. M2 macrophages (alternatively activated macrophages) are usually activated by anti-inflammatory factors such as interleukin-4, interleukin-13, interleukin-10 and M-CSF. They have the functions of maintaining tissue homeostasis, repair, remodeling, angiogenesis, and promoting cell invasion and migration [5]. In TME, the mitochondrial division of M1 type macrophages is enhanced and the tricarboxylic acid cycle is impaired. The expressions of two TCA-limiting enzymes, isocitrate dehydrogenase and succinate dehydrogenase are significantly downregulated which result in the accumulation of metabolic products such as citrate, fumarate, isocitrate and succinate. This can be enhanced by hypoxia-inducible factor-1α to increase the expression of pro-inflammatory factor IL-1β. Besides, LPS stimulation upregulated the expression of enzymes related to glycolysis in macrophages, resulting in increased glucose consumption and higher lactate production. In contrast, M2 macrophages exhibited the characteristic of enhanced mitochondrial fusion and complete TCA cycle, promoting cellular oxidative phosphorylation and metabolic energy production through enhanced electron transfer efficiency [5].

NK cells are an important component of innate immunity. In TME, they have both direct killing and immune regulatory effects. Through dual regulation of „activation receptor - ligand binding“ and „inhibition of receptor signal absence“, they precisely identify tumor cells and initiate the killing process. It plays a role in immune regulation

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both in the normal metabolic regulation of the body and in pathological immune responses, including anti-microbial, anti-infection, participation in hypersensitivity reactions and anti-tumor activities [6]. Under normal circumstances, NK cells need to undergo a series of regulatory actions by cellular signaling molecules to exert their cytotoxicity and immune regulatory functions, such as the regulation by the system of phosphorylation of signal transducers and activators of transcription [7]. In TME, NK cells often exhibit low effector activity, which leads to abnormal receptor expression and blockade of the ligand spectrum. The activity of NK cells is often suppressed by tumors, resulting in weakening or losting activity [7].

T cells are an important component of the adaptive immune system. However, some T cells can promote tumor formation, while others can limit tumors, such as CD8+ memory T cells, which can promote a favorable cancer prognosis by killing tumor cells. And CD8+ T cells are often supported by CD4+ T helper 1 cells, which can release interleukin-2 and interferon-γ to support CD8+ cells. Other types of CD4+ T cells, Th2 cells, support the immune response of B cells by secreting IL-4, IL-5, and IL-13. Meanwhile, Th17 cells can promote the inflammation of the antibacterial tissues by secreting IL-17, IL-21 and IL-22, thereby facilitating tumor growth. In addition, there is a type of T cells known as regulatory T cells (Tregs) in the body. These cells can suppress the immune response and promote tumor growth, leading to immune escape [5]. Studies have shown that in patients with ovarian cancer and pancreatic ductal adenocarcinoma, there is an excessive accumulation of FoxP3+ Tregs in the tumor microenvironment, which may indicate a poorer prognosis for cancer patients. Moreover, Tregs depletion can induce the regression of metastatic lesions in patients with advanced melanoma [8]. Under normal circumstances, T cells obtain energy and raw materials for biosynthesis through glycolysis and rely on oxidative phosphorylation as the main process when in a resting state, thereby exerting their immune functions. However, in TME, immune cells compete with tumor cells for nutrients. Due to local hypoxia, lack of nutrients, and accumulation of metabolic products such as lactic acid, T cells face dual metabolic stresses of oxygen deficiency and sugar scarcity and subsequently undergo adaptive metabolic changes to maintain the normal functioning of their immune functions [9].

The B cells present in the adjacent lymph nodes to the TME and invasive tumors are also crucial in the TME. They play a key role in regulating the survival, proliferation of tumor cells, and in studying the drug resistance of tumor cells. B cells play a crucial role as a key link in the „anti-tumor immune network“ of the tumor microenvironment by differentiating into plasma cells to secrete specific antibodies, or by activating T cell immune responses through antigen presentation, and secreting cytokines to shape the anti-tumor microenvironment. At the same time, the role of B cells in controlling the immunosuppression of tumors cannot be ignored. Bregs cells can inhibit T cell activation, as well as suppress DC cells and NK cells. It will also promote tumor metastasis. For instance, FoxP3+ cells rely on TGF-β to promote the metastasis of tumor cells [10]. Under normal physiological conditions, B cells are mainly oxidative phosphorylation in the resting state and switch to glycolysis rapidly in the active state. However, B cells in the TME cannot freely adjust as needed and will encounter problems such as limited glycolytic capacity.

3. Abnormal Metabolism in Tumor Cells

3.1 Glycometabolism

Anderson et al. discovered that some cancer cells largely rely on the TCA cycle to generate energy and synthesize biological macromolecules. At the same time, some researchers found that the activity of glycolysis in cancer samples was significantly enhanced, indicating that tumor cells reprogrammed their glycolytic process to promote the progression of cancer [11, 12]. In TME, the usage of glucose significantly increases. Tumors obtain additional glucose by upregulating high-affinity glucose transporters. This not only enhances the glucose utilization rate of cancer cells but also causes a difference in the metabolism of normal glucose compared to cancer. Most cancer cells break down glucose to produce lactic acid, so the TME will show high levels of lactic acid and low levels of glucose. Taking hepatocellular carcinoma as an example, in HCC patients, the levels of sugar metabolism markers such as 6-phosphoglucose in the circulating serum are significantly elevated. During the process of tumor invasion and metastasis, the contents of metabolic markers such as glucose and lactic acid in the sugar metabolism pathway change significantly, which is related to the increased energy consumption of the tumor tissue. In HCC (hepatocellular carcinoma) tissues, the contents of substances such as malic acid and succinic acid related to the tricarboxylic acid cycle are decreased, and the glycolysis pathway is inhibited while the gluconeogenesis pathway is highly active. This abnormal sugar metabolism provides energy and raw materials for the growth, proliferation, and invasion and metastasis of tumor cells. However, this metabolic process leads to a reduction in energy. To meet the higher energy demands, cancer cells need other energy sources, such as glutamine [12].

3.2 Llipid Metabolism

In TME, overexpressed FA transporters, specific oncogene expression, and the induction of tumor cells to regulate stromal cells (including adipocytes and fibroblasts) due to hypoxia in tumor cells, tumor cells absorb extracellular FAs and generate mitogenic signals to maintain tumor cell proliferation. Secondly, in normal tissues, fat production is limited to liver cells and adipocytes. However, in TME, the high metabolism required by cancer cells stimulates the generation of adipocytes. The integration and mutual regulation between oncogenic signals and lipid metabolism promote the growth, survival, proliferation, migration, infiltration and metastasis of cancer cells [13]. For instance, in breast cancer patients, estrogen activates the transcription of FASN and ACC through the ER receptor, then promoting fatty acid synthesis; and fatty acids (such as oleic acid) can in turn enhance the activity of ER, driving the continuous proliferation of the tumor.

3.3 Amino Acid Metabolism

Amino acids are one of the important nutrients for the human body. They can serve as carbon and oxygen donors to provide raw materials for the synthesis of necessary biological macromolecules and can also be utilized by immune cells in the TME to exert anti-tumor effects. Therefore, they play a significant role in tumor differentiation. For example, the amide group can regulate the function of T cells in tumor immunity. However, blocking glutamine does not weaken the function of T cells, but instead increases the anti-tumor activity of T cells. Tryptophan can be decomposed into 3-aminofuranic piperidine, which can pass through T cells via SLC7A5 or SLC7A8 and upregulate the programmed death receptors of CD8+ to initiate the differentiation and production of Tregs. Tregs are closely related to the development and immune escape of tumors. Therefore, abnormal amino acid metabolism can lead to tumor escape [1].

4. Interaction between Immune Cell Metabolism and Immune Escape

4.1 Buildup of Glucose and Lactic Acid

Warburg et al. observed that compared with normal cells, malignant tumor cells absorb significantly more glucose, and this provides the metabolic substrates necessary for the rapid proliferation of malignant cells, including amino acids, nucleotides, lipids, etc. In terms of the biological metabolism of cancer cells, its characteristics include increased glucose uptake, excessive lactate secretion, and alterations in the tricarboxylic acid cycle. In TME, cancer cells require more glucose and thus compete with normal immune cells (most notably CD8+ cytotoxic T lymphocytes). The active glycolysis in cancer cells is not only associated with the upregulation of PD-L1 and the recruitment of cytokines by GM-CSF and M-CSF, which are bone marrow immunosuppressive cells, but also related to the recruitment of CTLs and the reduction of the pro-inflammatory chemokine CXCL10 [14].

Meanwhile, the accumulation of lactic acid is associated with various tumor immunosuppression. This is because lactic acid has been proven to inhibit the cytotoxicity of CTL cells by restricting the TCA cycle through pyruvate carboxylase, leading to the accumulation of pyruvate dehydrogenase and limiting the secretion of succinate; moreover, lactic acid can also inhibit the proliferation of effector T cells by blocking glycerol-3-phosphate dehydrogenase (GAPDH) and phosphoglycerate dehydrogenase (PHGDH) [14].

4.2 Llipid Metabolism

In TME, cancer cells typically exhibit an increase in FA fatty acids and an increase in endogenous fatty acid synthesis. On one hand, the expression of MHC I molecules on the surface of cancer cells increases, enhancing the recognition ability of CTLs (cytotoxic T lymphocytes) for them. However, this enhanced recognition ability may be counteracted by subsequent compensatory mechanisms, allowing the tumor to evade detection, ultimately serving as a means of escape. On the other hand, the expression of the CD47 molecule in cancer cells is upregulated. This molecule can prevent bone marrow cells from engulfing and absorbing tumor cells, thereby hindering the clearance of tumors by the innate immune system. Furthermore, abnormal metabolism also inhibits the normal death process of immune cells, weakens the antigen presentation function, and leads to an enhanced inhibitory effect of regulatory T cells (Tregs), further exacerbating the immunosuppressive state. These effects work together, making abnormal metabolism in the tumor microenvironment become an important factor for tumor evasion of immune system surveillance [14].

4.3 Amino Acid

Glutamine is an important source of energy and metabolite for rapidly proliferating cancer cells and immune cells. Most cancer cells consume glutamine at a faster rate than glucose. For instance, basal-like breast cancer exhibits a high transcriptional signature of glutamine metabolism, which is characterized by scarce immune infiltration and is associated with poor disease outcomes. This indicates that this metabolic adaptation has an immunosuppressive function [15]. In TME, cancer cells compete with immune cells for essential amino acid - methionine by expressing high levels of methionine transporters [16]. Tryptophan

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is an essential amino acid, but its deficiency does not fall below the limit threshold of TME, so the deficiency of tryptophan does not cause immunosuppression in tumors [14].

5. Therapies for Immune Evasion

5.1 Regarding Immune Cells and Tumor Cells

Direct removal of tumor tissue through surgery is an important treatment method for early-stage tumors, localized solid tumors, or certain specific types of tumors. There are various types of surgeries. Radical surgery aims to completely remove the tumor and the surrounding tissues that may be invaded, in order to achieve the goal of cure; debulking surgery is used when it is impossible to completely remove the tumor, and as much of the tumor tissue as possible is removed to alleviate symptoms; palliative surgery is performed to alleviate complications caused by the tumor, such as intestinal obstruction and compression symptoms, in order to improve the quality of life of patients. Secondly, to damage the DNA of tumor cells by using high-energy rays (such as X-rays, γ-rays, etc.), their growth and division can be inhibited. This method is suitable for radical treatment of relatively localized solid tumors, such as head and neck tumors, lung cancer, esophageal cancer, skin cancer, lymphoma, etc.; it is also commonly used for preoperative, intraoperative, and postoperative adjuvant treatments of some tumors, such as breast cancer, cervical cancer, gastrointestinal tumors. Postoperative radiotherapy can eliminate residual tumor cells and improve the local control rate of the tumor. Chemotherapy drugs are used to interfere with the metabolic, proliferation, and division processes of tumor cells, thereby inhibiting tumor growth.

PD-L1 binds to the immune checkpoint receptor PD-1 on the surface of T cells, inhibiting the proliferation, cytokine secretion and cytotoxicity of T cells, which cause them to enter a state of functional exhaustion. Therefore, blocking PD-1 can effectively prevent T cell exhaustion, but the re-established T cell activity will be depleted again [17].

The most important aspect of immune escape is Tregs, which are immunocytes with strong inhibitory effects in tumor immunity. Monoclonal antibodies produced against their inhibition have been proven to reduce tumor development. Meanwhile, strategies targeting M2 macrophages and DC cells that promote tumor growth are also under development [18]. In the NANT trial, longitudinal sequencing of bulk TCR from 60 tumors and corresponding peripheral blood mononuclear cells (PBMCs) from 23 patients showed that tumor restriction was significantly reduced, and the TCR diversity was significantly decreased and clonality increased in most patients. These results collectively reveal the HRD dependence of tumor-infiltrating T cells and the complex dynamics of interfering with the tumor-reactive landscape during treatment, with the crucial immunomodulatory role of eTregs being emphasized [19].

5.2 Regarding Metabolic Disorders

Regarding the treatment strategy for TCA, glutamine, as a key metabolic substrate in the tricarboxylic acid cycle, plays a significant role in the energy metabolism of various malignant tumors. Studies have shown that tumor cells maintain the energy and biosynthetic precursors required for their rapid proliferation by enhancing the catabolism of glutamine. This metabolic characteristic makes the glutamine metabolic pathway a potential target for anti-tumor therapy. The early development strategy focused on glutamine analogues, such as 6-diamino-5-oxo-L-deoxynojirimycin (DON), inhibiting glutaminase activity by mimicking the structure of glutamine. Although these pioneering studies demonstrated the feasibility of targeted glutamine metabolism-based treatments, the compounds ultimately failed to be successfully applied in clinical treatment due to their significant systemic toxic reactions. Meanwhile, the latest research indicates that in addition to inhibiting the glutamine metabolism in the TCA cycle through glutamine synthetase (GLS), the α-ketoglutarate dehydrogenase complex (KGDHC) has also become an important metabolic weakness in various cancers, demonstrating potential therapeutic target value [12]. Finally, the mutation of the TCA cycle gene IDH2 provides a unique opportunity for therapeutic intervention. Currently, several small molecule inhibitors of mutant IDH2 are in clinical development, including AG-221 which inhibits mutant IDH2, and AG-881 which targets mutant IDH1 and IDH2. These compounds bind to the active catalytic sites of mIDH1/2 enzymes and prevent the conformational changes necessary for the conversion of α-KG to 2-HG. AG-221 is an oral inhibitor of mutant IDH2-R140 and IDH2-R172. It is currently undergoing I/II phase clinical trials as a treatment for AML and solid tumors. Preclinical data indicate that AG-221 can significantly reduce the level of 2-HG. Moreover, AG-221 causes tumor cell differentiation in a mouse xenograft model. The preliminary data from the AML clinical trial indicate that AG-221 alone resulted in a 41% response rate and a 28% complete response rate among the subjects [20]

Aiming to lipid metabolism, the combined regulation of oncogenic signals and lipid metabolism promotes the growth of cancer cells. Therefore, there is a strong emphasis on developing therapeutic drugs related to lipid metabolism to intervene in cancer, such as preclinical studies of lipid metabolism enzyme inhibitors [13]. Meanwhile, statin drugs are currently being tested as anti-cancer agents

in multiple clinical trials. Retrospective studies have shown that statin treatment prolonged the survival time of patients with multiple myeloma, colorectal cancer, and metastatic pancreatic cancer when combined with first-line chemotherapy [21]. Clinical studies have shown that the anti-tumor effect of statin drugs exhibits dose and time dependence.

To fully realize its potential as an adjunctive therapy, it is necessary to optimize the treatment plan. Based on the type of tumor and individual differences, the type, dosage, and duration of administration of statins should be precisely selected. A study on the treatment of advanced gastric cancer patients with simvastatin involved 244 patients, who were randomly assigned to the treatment group (120 patients received simvastatin, 124 patients received placebo). The median progression-free survival (PFS) for the 120 patients assigned to giscavastatin was 5.2 months (95% CI, 4.3 - 6.1), compared with 4.63 months (95% CI 3.5 - 5.7) for the 124 patients assigned to XP plus placebo (OR ratio 0.930, 95% CI 0.684 - 1.264; p = 0.642). Among the 120 patients in the simvastatin group, 63 (52.5%) and 124 patients (56.4%) experienced adverse events [22]. The conclusion was that the disease-free survival period was higher in the simvastatin group, and it is recommended to conduct low-dose simvastatin chemotherapy in the non-target population of AGC.

Aiming to amino acid metabolism, restricting the intake of certain amino acids can effectively limit the growth and activity of tumors by influencing the functions of immune cells. For instance, in colorectal cancer models, restricting the intake of sulfur-containing amino acids (such as methionine and cysteine) can inhibit the differentiation of $CD4^+$ T cells into regulatory T cells (Tregs); it can promote the infiltration of $CD8^+$ T cells into tumors; and threonine has shown significant therapeutic effects in glioblastoma models, capable of reducing tumor volume and improving survival rates [1].

6. Discussion

Immune cell metabolism plays a multi-dimensional regulatory role in tumor immune regulation. Abnormalities in glucose metabolism, lipid metabolism, and amino acid metabolism are not isolated but are interconnected in a complex network, exerting influences on various aspects of tumor immune regulation. For instance, abnormal glucose metabolism can indirectly regulate lipid synthesis by affecting the ratio of NADPH/NADP+. The lactic acid produced can also indirectly inhibit the activity of key enzymes in fatty acid β-oxidation (such as CPT1A), hindering the polarization of M1-type macrophages. FASN is the core enzyme for fatty acid de novo synthesis and is highly expressed in Tregs, maintaining their immunosuppressive phenotype by synthesizing fatty acids such as palmitic acid. Disorder in glutamine metabolism may alter the flux of the TCA cycle, thereby affecting the epigenetic modifications of immune cells. However, there is still a need for further exploration regarding the differences in metabolic characteristics of immune cells in different tumor types, and how non-immune cells (such as fibroblasts) in regulate immune escape. This kind of „metabolism-immunity“ interaction effect makes it difficult to completely break through immune evasion through a single targeted approach to a specific metabolic pathway - for instance, when only glycolysis is blocked, tumor cells can achieve „metabolic compensation“ by enhancing fatty acid synthesis or glutamine breakdown, thus maintaining an immunosuppressive state.

Immune cell metabolism offers a promising new strategy for tumor immunotherapy, but there are still some issues in its clinical application that need to be addressed. Firstly, improving the targeting ability of the drugs is of great significance. It is necessary to study techniques for targeting immune cells within the tumor microenvironment to avoid systemic metabolic disorders that may affect the metabolism of normal cells. In addition, how to achieve synergistic enhancement when combined with existing cancer treatment methods (such as CAR-T cell therapy, immune checkpoint inhibitors, etc.) is also one of the future research directions. Finally, the synergy of existing treatments is lacking. The response rate of immune checkpoint inhibitors (such as PD-1/PD-L1 antibodies) in solid tumors is only 20%-30%. Part of the reason is that metabolic abnormalities in the tumor microenvironment (such as lactic acid accumulation and hypoxia) can weaken the activity of T cells. Currently, there is a lack of standardized combined treatment regimens of „metabolic regulators + immune checkpoint inhibitors“ in clinical practice. How to enhance the efficacy of immunotherapy through metabolic intervention still requires more III-phase clinical trials to verify.

Solving these problems will be the future research direction in clinical medicine, which is conducive to maximizing the clinical therapeutic benefits of this treatment strategy and promoting the precision, individualization and maximization of cancer treatment.

7. Conclusion

This study deeply elucidated the abnormal metabolic patterns of the tumor immune microenvironment and analyzed the mechanism by which metabolic reprogramming affects the immune escape mechanism. The research confirmed that metabolic disorders in immune cells are an important link in tumor evasion of immune surveillance. Targeted regulation of key metabolic pathways (such as

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glycolysis, lipid metabolism, and amino acid metabolism) can effectively restore anti-tumor immune function.

At the level of mechanism research, it is necessary to strengthen the cross-integration of „metabolomics - immunology - epigenetics". On one hand, by using single-cell metabolomics technology, the metabolic heterogeneity of different immune cell subtypes in TME can be analyzed, and the regulatory role of key metabolic nodes in immune escape can be clarified. Traditional metabolomics can only reflect the overall levels of metabolites in the TME and cannot distinguish the metabolic characteristics of different immune cell subtypes. The subtype-specific metabolic differences need to be accurately captured through single-cell level metabolic flow analysis (such as single-cell mass spectrometry imaging, stable isotope-labeled metabolic flow detection).On the other hand, exploring the impact of metabolic disorders on the epigenetics of immune cells requires focusing on the regulatory mechanisms of metabolic disorders on the epigenetics of immune cells. This is because the functional state of immune cells is not only influenced by metabolic energy supply but is also closely related to epigenetic modifications (such as histone methylation, acetylation), and metabolites are the key link connecting these two aspects. Future research should further conduct combined analyses of epigenetic sequencing and metabolomics to clarify the epigenetic change profiles of immune cells in different metabolic disorder scenarios, then explain the specific mechanisms.

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