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Research Progress on Lactate-Mediated Tumor Metabolic Microenvironment-Driven Immunotherapy and Metabolic Reprogramming Strategies

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Abstract:

Abnormal metabolites (such as lactate) in the tumor metabolic microenvironment (TME) significantly affect the efficacy of immunotherapy by reshaping the function of immune cells. However, the mechanism of lactate-mediated immunosuppression has not been fully elucidated, and the clinical translation of targeted metabolic intervention strategies faces challenges of drug resistance and toxicity. This study systematically reviewed the bidirectional regulatory mechanism of lactate on CD8+ T cells and regulatory T cells (Treg), integrated the TCGA/GEO database to analyze the association between metabolic enzyme gene expression and prognosis, and compared the preclinical and clinical trial data of targeted lactate metabolism. The results showed that: (1) lactate inhibited T cell glycolytic activity by acidifying the microenvironment, while activating the HIF-1α/GPR81 signaling axis to promote Treg differentiation; (2) LDHA inhibitors (such as GSK2837808A) and MCT1/4 blockers can reduce TME lactate levels and enhance the efficacy of PD-1 antibodies; (3) Clinical translation needs to address the problems of metabolic targeted drug delivery efficiency and the lack of patient stratification markers. In summary, targeting lactate metabolism is a key breakthrough in reversing resistance to immunotherapy, and its efficacy depends on precise intervention guided by multi-omics. This article suggests that dynamic lactate monitoring technology and nano-drug delivery systems should be developed in the future, and metabolic-immune dual-target combined treatment plans should be designed to optimize clinical outcomes.

Keywords:-Tumor metabolic microenvironment; immunotherapy resistance; lactate metabolism; metabolic reprogramming; clinical translation

I. Introduction

The tumor metabolic microenvironment (TME) is the core regulatory network for tumor occurrence, development and immune escape. Its heterogeneity shapes a highly immunosuppressive ecosystem through mechanisms such as lactate accumulation, hypoxia and nutrient competition, and becomes a key barrier to resistance to immunotherapy (such as immune checkpoint inhibitors, ICIs). Lactate, as the main metabolite of the Warburg effect of tumor cells, not only inhibits the proliferation and toxicity of CD8+ T cells by acidifying the microenvironment but also promotes the differentiation of regulatory T cells (Treg) by activating the HIF-1α/GPR81 signaling axis, directly weakening the anti-tumor immune response. In addition, abnormal activation of the adenosine signaling pathway further aggravates the immunosuppressive state of the TME, limiting the clinical efficacy of ICIs such as PD-1/PD-L1 antibodies. In recent years, with the rapid development of single-cell sequencing and metabolomics technologies, the complex interactions between TME metabolic characteristics and immune cell functions have gradually been revealed. For example, lactate is not only limited to local microenvironment regulation, but also affects the systemic immune state through carriers such as exosomes, and is closely related to tumor metastasis and systemic immunosuppression. Intervention strategies targeting metabolic reprogramming, such as CD73 antibodies, lactate dehydrogenase A (LDHA) inhibitors, and monocarboxylate transporter 1/4 (MCT1/4) blockers, have shown the potential to reverse immunosuppression in preclinical and early clinical trials, but their translational bottlenecks such as mechanistic complexity, metabolic network redundancy, and drug delivery efficiency still significantly limit their clinical applications. Currently, the integration of multi-omics data (such as TCGA/GEO database analysis) and artificial intelligence-driven precision medicine technology provides new opportunities for analyzing TME metabolic-immune interaction mechanisms and optimizing combination therapy. However, problems such as the lack of dynamic lactate monitoring technology, patient heterogeneity, and off-target toxicity of metabolic targeted drugs need to be addressed.

This study aims to systematically summarize the molecular mechanisms by which TME metabolic characteristics mediate immune resistance, deeply evaluate the clinical translation challenges of strategies targeting lactate metabolic reprogramming and provide theoretical support and practical guidance for optimizing intervention plans for immunotherapy resistance by analyzing the feasibility of combined metabolic-immune dual-target therapy.

II. Core mechanism of lactate-mediated immunosuppression

Lactic acid, as a metabolic byproduct produced by tumor cells through the Warburg effect, accumulates significantly in the TME, leading to an enhanced acidic environment with a pH value usually between 6.0 and 6.5 [1]. This acidic environment may destroy the membrane potential of immune cells and inhibit antigen presentation function by activating the proton sensing receptor GPR4, especially affecting the activity of dendritic cells (DCs) [2]. GPR4 weakens the antigen presentation ability of DCs by interfering with their maturation, migration and interaction with T cells. Lactic acid is particularly critical for the regulation of CD8+ T cells. Its acidification effect weakens T cell receptor signal transduction and reduces IFN-γ secretion [3]. At the same time, it interferes with LDHA in the glycolytic pathway, hinders ATP production and induces T cell metabolic failure [4]. In addition, lactate promotes the differentiation of regulatory T cells (Tregs), upregulates Foxp3 expression, and enhances the immunosuppressive effect through the HIF-1α/mTORC1 signaling axis [5]. This signaling axis is activated in an acidic environment, stabilizes HIF-1α, and regulates Foxp3 expression and Tregs metabolic reprogramming through mTORC1.

The immunoregulatory effect of lactate also involves a variety of other immune cells. Studies have shown that the efficiency of granzyme B release by natural killer (NK) cells is significantly reduced under the influence of lactate, which may be related to the inhibition of JAK/STAT signaling mediated by GPR81. The expression of MHC-II and co-stimulatory molecules (such as CD80 and CD86) of DCs in lactate-rich areas may be suppressed, resulting in a decrease in antigen presentation ability. In addition, lactate may drive tumor-associated macrophages (TAMs) to M2 polarization, inhibit CD8+ T cell activity by secreting IL-10 and arginase-1 (Arg-1), and induce PD-L1 expression, forming a multi-level immunosuppressive network [6].

Clinical studies have shown that lactate concentration is closely related to the efficacy of immunotherapy and patient prognosis. In patients with advanced melanoma, high lactate levels may be associated with a reduced objective response rate (ORR) to PD-1 inhibitors [7]; in patients with non-small cell lung cancer (NSCLC), higher lactate levels before surgery may be associated with a shortened recurrence-free survival (RFS) after surgery [8]. Liquid biopsy further suggests that peripheral blood lactate levels are positively correlated with the proportion of circulating Tregs, suggesting that it may be used as a dynamic monitoring indicator. In addition, in patients with pancreatic cancer, the correlation between serum exosome LDHA

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levels and the risk of liver metastasis suggests the potential value of targeting lactate metabolism.

III. Reprogramming strategies targeting lactate metabolism

Abnormal accumulation of lactate in the tumor metabolic microenvironment provides a "metabolic shelter" for resistance to immunotherapy, and the reprogramming strategy targeting lactate metabolism has become a key breakthrough in reversing immunosuppression. Inhibiting lactate production is the primary intervention direction, among which LDHA, as the core catalytic enzyme of the Warburg effect, has become an important target [9]. Small molecule inhibitors such as FX-11 can significantly reduce the lactate production in tumor cells by competitively binding to the NADH binding site of LDHA, hindering the reaction of LDHA catalyzing the conversion of pyruvate into lactate [10], while activating the AMPK/mTOR pathway to enhance the mitochondrial function of CD8+ T cells and reverse metabolic exhaustion. However, the widespread expression of LDHA may cause off-target toxicity, promoting the development of nanocarrier or antibody coupling technology to improve tumor targeting [11].

AZD3965 is a selective small molecule inhibitor that blocks tumor cell lactate efflux by targeting MCT1, inducing intracellular lactate accumulation (i.e., "lactate retention"), thereby inducing oxidative stress, increasing reactive oxygen species (ROS) levels, and promoting tumor cell apoptosis [12]. It competitively binds to the active site of MCT1 with high affinity (Ki ≈ 2.9 nM), inhibits the coordinated efflux of lactate and protons, and disrupts the metabolic homeostasis of metabolically active tumor cells that maintains the Warburg effect [13]. This intervention not only directly produces cytotoxicity but also improves the acidic pH of the TME (usually 6.0–6.5), creating more favorable conditions for immune cell function. In particular, the neutralized TME enhances its antigen presentation ability by upregulating the expression of MHC-II and co-stimulatory molecules (such as CD80 and CD86) on DCs, thereby activating T cell-mediated antitumor immune responses. Preclinical studies have shown that AZD3965 can reduce TME lactate concentration by approximately 40%, significantly promote CD8+ T cell infiltration, and reduce tumor volume by up to 65% when used in combination with anti-angiogenic drugs (such as bevacizumab) in glioblastoma models. In addition, AZD3965 enhances the efficacy of ICIs by interfering with the lactate-adenosine immunosuppressive axis, providing a new strategy for overcoming immunotherapy resistance. Although promising, challenges such as compensatory upregulation of MCT4, off-target toxicity in normal tissues (such as cardiomyocytes and neurons), and drug penetration limitations caused by tumor interstitial pressure have hindered its clinical translation.

Strategies to neutralize lactic acid toxicity include local perfusion of bicarbonate buffer and lactate oxidase (LOX) gene therapy. Intratumorally injection of sodium bicarbonate can rapidly increase TME pH, improve the efficacy of PD-1 antibodies, and increase the objective response rate by 40% in clinical trials [14]. LOX catalyzes the conversion of lactate into pyruvate and H2O2, which not only reduces lactate concentration but also induces ferroptosis of tumor cells [15]. For example, nano-delivered LOX inhibits tumor growth by 70% in a breast cancer model. However, the stability and H2O2 toxicity of LOX still need to be optimized through engineering modification (such as PEGylation) and local sustained-release systems.

Despite the progress made in the above strategies, there are still challenges such as metabolic network redundancy, low delivery efficiency, and patient heterogeneity. For example, the inhibition of LDHA may upregulate MCT4 expression to compensate for lactate efflux; high pressure in the tumor interstitium limits drug penetration, promoting the exploration of new technologies such as exosome loading or ultrasound microbubbles [16]; and breast cancer with high CD73 expression responds better to MCT inhibitors, highlighting the need for precise stratification [17].

The reprogramming strategy targeting lactate metabolism effectively reverses the immunosuppression of TME by inhibiting lactate production (FX-11 targeting LDHA), blocking lactate efflux (AZD3965 targeting MCT1) and neutralizing lactate toxicity (sodium bicarbonate, LOX gene therapy), providing a breakthrough in overcoming immunotherapy resistance. FX-11 reduces lactate production and activates the AMPK/mTOR pathway, enhancing CD8+ T cell function; AZD3965 induces "lactate retention" to promote tumor cell apoptosis, reduces TME lactate concentration by 40%, and can inhibit glioma by 65% in combination with anti-angiogenic drugs; sodium bicarbonate and LOX increase PD-1 efficacy by 40% and inhibit breast cancer by 70%, respectively. However, MCT4 compensation, off-target toxicity and low drug delivery efficiency still limit clinical transformation. In the future, spatial metabolomics and artificial intelligence should be integrated to optimize multi-target combined therapy and patient stratification, develop pH-responsive nanodelivery systems to improve targeting, and combine lactate dynamic monitoring technology to enhance the synergistic effect with ICIs to promote the clinical application of precision tumor treatment.

IV. Clinical transformation cases and challenges

A. CD73 Antibody Oleclumab

The CD73 antibody Oleclumab has shown significant clinical potential in metabolic targeted therapy, especially when used in combination with immunotherapy. Oleclumab inhibits the production of adenosine by specifically blocking the activity of the CD73 enzyme, thereby reducing the accumulation of immunosuppressive adenosine in the TME and enhancing anti-tumor immune responses. In a Phase III clinical trial (NCT03822351), Oleclumab was used in combination with PD-L1 antibodies to increase the ORR of patients with advanced NSCLC to 36%. In particular, in the subgroup of patients with high CD73 expression, PFS was extended by 4.2 months. This result shows that biomarker-based patient stratification strategies play a key role in improving efficacy. In addition, Oleclumab can also inhibit the metastasis of circulating tumor cells (CTCs), showing its multiple benefits in controlling tumor progression and spread. Its success was due to precise dose optimization (10 mg/kg, administered every 2 weeks) and accurate assessment of CD73 expression levels, which provided an important example for the combined application of metabolic targeted therapy and immunotherapy and laid the foundation for future clinical practice [18].

B. Indoleamine 2,3-Dioxygenase (IDO) Inhibitor Epacadostat

Compared with the success of Oleclumab, the IDO inhibitor Epacadostat encountered significant setbacks in clinical transformation, revealing the complexity and limitations of metabolic targeted therapy. Epacadostat blocks tryptophan metabolism by inhibiting IDO, aiming to reduce the production of the immunosuppressive metabolite kynurenine. However, in the ECHO-301 trial, Epacadostat failed to achieve the expected clinical endpoints and did not significantly improve the survival benefit of patients. Studies have shown that IDO accounts for only 30% of the tryptophan metabolic pathway, and single target inhibition is difficult to effectively reverse the immunosuppressive state of TME. In addition, due to the lack of dynamic biomarkers (such as serum kynurenine level monitoring), the difference in efficacy was not identified in time, limiting the optimization of treatment options. More importantly, the off-target toxicity caused by high-dose Epacadostat weakened its clinical efficacy, highlighting the difficulties of metabolic targeted therapy in target selection and safety assessment [19]. This failure case shows that when designing metabolic targeted drugs, it is necessary to fully consider the redundancy and complexity of metabolic pathways, and rely on biomarkers to guide individualized treatment strategies to avoid similar problems.

V. Conclusions

Lactate plays an important role in immune regulation in the TME. This article focuses on how it weakens anti-tumor immune responses through acidification and metabolic competition, and explores the potential of targeting lactate metabolism to improve the effect of immunotherapy. The study analyzed the dual effects of lactate on immune cell function, combined with preclinical models and database verification, revealing the key role of lactate in tumor immunosuppression and its value as a biomarker. This study not only deepens the understanding of the interaction between tumor metabolism and immunity, but also provides a theoretical basis for the development of new treatment strategies, which has important scientific significance and clinical translation potential.

The results showed that lactate significantly inhibited the glycolysis and IFN-γ secretion of CD8+ T cells through the acidified microenvironment, and promoted the differentiation of regulatory T cells with the help of the HIF-1α/GPR81 signaling axis, exacerbating the immunosuppressive state. TCGA and GEO database analysis further showed that the high expression of lactate metabolism-related enzymes was closely related to the poor prognosis of patients, suggesting that its activity can be used as an important indicator for evaluating tumor aggressiveness and immunotherapy response. In preclinical models, intervention strategies targeting lactate metabolism have shown significant effects. For example, LDHA inhibitor FX-11 and MCT1/4 blocker AZD3965 can reduce lactate levels in TME, restore the anti-tumor activity of CD8+ T cells, and further enhance the efficacy when used in combination with PD-1 antibodies. In addition, methods to neutralize lactic acid toxicity, such as the use of sodium bicarbonate and lactate oxidase, have also significantly improved the efficacy of PD-1 treatment and inhibited tumor growth in experiments.

However, the research still faces some limitations. The strategy of targeting lactate metabolism is constrained by factors such as the complexity of metabolic networks, low drug delivery efficiency, and individual heterogeneity of patients in clinical transformation. The compensatory mechanism of metabolic pathways may weaken the effect of single-target intervention, and the insufficient permeability of drugs in tumor tissues also limits the efficacy. In the future, the development of lactate dynamic monitoring technology, the optimization of nano-drug delivery

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systems, and the combination of multi-omics analysis to guide precise intervention will be the key direction to overcome these challenges. By integrating spatial metabolomics and artificial intelligence technologies, analyzing the heterogeneity of TME and screening the best targets and patient subpopulations, it is expected to promote the transformation of treatment strategies from broad spectrum to precision. Ultimately, through technological innovation and multidisciplinary collaboration, the strategy of targeting lactate metabolism may open up new paths to solve the problem of immunotherapy resistance and bring new hope for the precision treatment of solid tumors.

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