

The Metabolic Reprogramming of Immune Cells in the Tumor Microenvironment and the Mechanism of Immune Therapy Resistance

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Abstract. The efficacy of immune checkpoint inhibitors (ICIs) is often limited by primary and acquired resistance induced by the tumor microenvironment (TME), with the metabolic reprogramming of immune cells being the core mechanism. This review systematically analyzes the three key metabolic stresses in the TME: glucose deprivation, lactate accumulation, and adenosine accumulation. How these metabolic stresses, by reshaping the metabolic states and functions of T cells, macrophages, and dendritic cells, jointly construct an immunosuppressive ecosystem and lead to ICIs resistance. Glucose deprivation directly weakens the activation and function of effector T cells, while lactate and adenosine further inhibit effector immune cells and support the functions of immunosuppressive cells such as regulatory T cells and M2-type macrophages, ultimately forming a treatment-tolerant microenvironment. The article further explores therapeutic strategies targeting metabolic nodes such as lactate dehydrogenase A (LDHA), CD73/CD39 - adenosine axis, to reverse immunosuppression and enhance the efficacy of ICIs, and looks forward to the future direction of using "metabolism-immunity" typing to guide individualized combination therapy.

Keywords: Immune checkpoint inhibitors, tumor microenvironment, metabolic reprogramming, immunotherapy resistance.

1. Introduction

Immune checkpoint inhibitors (ICIs), including programmed death receptor-1 (PD-1)/programmed death ligand-1 (PD-L1) and cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) inhibitors, have significantly improved the survival prognosis of patients with various advanced solid tumors [1]. However, the low clinical response rate and the prevalence of drug resistance have become the bottlenecks restricting their efficacy. Besides the intrinsic factors of tumor cells (such as antigen presentation defects), the immunosuppressive ecosystem shaped by tumor microenvironment (TME) is another core pillar leading to immune escape and treatment resistance [2].

Lately, the rapid development of immune metabolism has revealed that the functions of immune cells are closely coupled with their metabolic states, and the TME is a highly abnormal and competitive ecological niche [3]. The reprogrammed metabolic patterns of tumor cells, such as the Warburg effect, cause them to extensively absorb glucose and secrete lactic acid, resulting in the TME presenting characteristics of glucose deficiency, acidification, and hypoxia [4]. Additionally, there are immunosuppressive molecules such as adenosine and arginine in the TME. Immune cells infiltrating must adapt to this harsh metabolic environment, and their metabolic reprogramming fundamentally determines their functional fate: whether to exert anti-tumor effects or transform into a tolerant phenotype [5].

This review aims to systematically elaborate on how the three core metabolic stresses in the TME - glucose deprivation, lactate accumulation, and adenosine accumulation - through the reprogramming of the metabolism and functions of key immune cells such as T cells, macrophages, and dendritic cells (DCs), jointly promote immunosuppression and ICIs resistance. The article will analyze the molecular mechanisms and discuss the therapeutic strategies and clinical prospects based on existing evidence targeting these metabolic pathways.

2. Glucose deprivation in the TME and its immunosuppressive consequences

Glucose is the primary carbon source for cells to generate biosynthetic precursors through glycolysis and the tricarboxylic acid (TCA) cycle. In the TME, the competition for glucose between tumor cells and immune cells, especially activated effector T cells, is extremely intense.

2.1. Direct inhibition of effector T cells

Activated CD8⁺ cytotoxic T lymphocytes (CTLs) and Th1 cells heavily rely on aerobic glycolysis to fuel their rapid proliferation and the synthesis of cytokines (e.g., IFN- γ , TNF- α) and cytotoxic granules [6]. However, tumor cells highly express glucose transporters such as GLUT1, enabling them to take up glucose at an accelerated rate. As a result, glucose levels in the TME drop to below 1 mM, far lower than the physiological concentration of approximately 5 mM. Such glucose starvation exerts multiple damaging effects on effector T cells [7].

Severe glucose depletion restricts glycolytic metabolism in T cells, markedly suppressing the translation and secretion of key cytokines like IFN- γ despite abundant transcript levels [8]. Impaired glycolysis further disrupts essential biosynthesis, leading to growth arrest, reduced proliferation, and mitochondrial apoptosis. Beyond directly compromising function, limited glucose also reshapes T cell epigenetic patterns. The reduction of glucose-derived acetyl-CoA decreases histone acetylation, closing chromatin structures around effector genes and potentially causing long-term suppression of T cell function [9].

2.2. Metabolic adaptability imbalance and the dominance of Tregs

Unlike effector T cells, regulatory T cells (Tregs) have a greater survival advantage in low-glucose environments. Their functions are more dependent on oxidative phosphorylation (OXPHOS) and fatty acid oxidation (FAO) [10]. When glucose is scarce, Tregs can efficiently utilize alternative carbon sources such as fatty acids, lactic acid, or glutamine to sustain survival and inhibit functions. This enables Tregs to survive even in nutrient-poor tumor microenvironments, and their immunosuppressive functions may even be enhanced. Therefore, glucose deprivation actually creates a selective pressure that is favorable for Tregs rather than effector T cells, intensifying the immunosuppressive state.

2.3. Impact of glucose deprivation on DCs and natural killer cells

Insufficient glucose will impair the antigen processing and presentation capabilities of DCs, reduce the expression of co-stimulatory molecules (such as CD80 and CD86), and decrease the production of pro-inflammatory cytokine IL-12, resulting in the inability of DCs to effectively activate naive T cells [11]. Moreover, the cytotoxic function and cytokine production of natural killer (NK) cells also depend on glycolysis. Glucose limitation in the TME will also weaken the anti-tumor activity of NK cells.

3. The immunomodulatory roles of lactate in the tumor microenvironment

Tumor cells use monocarboxylate transporters (MCTs) to substantially export lactate, which is produced by glycolysis. This process causes a significant acidification of the TME. Accumulated lactate acts not merely as a metabolic byproduct but also functions as a critical signaling molecule that extensively remodels the local immune microenvironment. In this way, it forms a key link between metabolic reprogramming in tumors and the development of immune suppression.

3.1. The direct inhibitory effect on effector immune cells

By inhibiting the proliferation of T cells and NK cells and the secretion of their cytokines (such as IFN- γ and TNF- α), high concentrations of lactic acid directly dilute the functions of effector immune cells. The inhibitory effect primarily arises from lowered intracellular pH, which hinders signal

transduction and inhibits the activity of key enzymes in glycolysis, including phosphofructokinase [12]. Besides the acute functional impairment mentioned above, lactic acid accumulation also drives T cells into a state of chronic exhaustion. This occurs by upregulating the expression of exhaustion-associated transcription factors such as TOX and increasing PD-1 levels, ultimately resulting in the functional impairment of T cells [13].

3.2. Promotion of immunosuppressive cell survival and function

Lactic acid not only suppresses antitumor effector cells but also sustains tumor-protective immune populations. Recent data indicate that Tregs directly utilize lactate as an energy source, converting it into pyruvate to fuel TCA cycling and oxidative metabolism. This adaptive capacity enables Tregs to survive and retain potent immunosuppressive activity under acidic conditions, while lactate further stabilizes their identity epigenetically by promoting histone lactylation at the Foxp3 locus [14].

Lactate also reshapes myeloid cell function. Through HIF-1 α stabilization, it drives tumor-associated macrophages (TAMs) toward an immunosuppressive M2 phenotype, which impairs T-cell responses via cytokine secretion, elevated PD-L1 expression, arginine depletion, and proangiogenic effects [15]. Moreover, an acidified microenvironment recruits and activates Myeloid-derived suppressor cells (MDSCs), further reinforcing tumor immune suppression.

3.3. Affecting the functions and antigen presentation of DCs

Lactic acid can markedly inhibit DCs, stopping them from fully activating and maturing. Their impaired capacity for antigen presentation and pro-inflammatory cytokine secretion effectively halts the priming of adaptive immunity.

4. The immunosuppressive adenosine pathway in cancer

Extracellular adenosine accumulation is a major immunosuppressive mechanism in the TME. It is generated through a two-step cascade: CD39 produces AMP from ATP/ADP, and CD73 then converts AMP to adenosine. Both enzymes are highly expressed on various cells, including tumor cells, Tregs, and MDSCs. Hypoxia exacerbates this by upregulating CD73 via HIF-1 α , amplifying adenosine production.

Adenosine mainly activates the G protein-coupled signaling pathway by binding to its high-affinity receptor A2A (widely expressed in immune cells) and low-affinity receptor A2B, thereby increasing intracellular cAMP levels and exerting a powerful immunosuppressive effect.

4.1. Comprehensive suppression of T cell responses by adenosine

Adenosine signals can inhibit T-cell receptor (TCR) signal transduction, reduce the production of IL-2, and suppress the Ras-MAPK and PI3K-Akt-mTOR pathways, thereby completely inhibiting the activation, proliferation, and production of effector molecules (such as IFN- γ , granzyme B) of T cells. Long-term or high-concentration exposure to adenosine can also induce the apoptosis of activated T cells. In addition, adenosine can directly promote the differentiation of activated T cells into Tregs through the A2A receptor signal and enhance the inhibitory function of existing Tregs.

4.2. Adenosine-mediated regulation of innate immune cells

Adenosine inhibits the cytotoxic activity, proliferation, and cytokine production of NK cells. The adenosine signal inhibits the maturation of DCs, reduces their IL-12 production, and may induce them to develop a tolerant phenotype. At the same time, adenosine can promote the polarization of macrophages to the M2 type, enhancing their immunosuppressive and tissue repair functions.

5. Strategies and prospects for overcoming ICI resistance through targeted metabolic reprogramming

Unlike directly supplementing nutrients, reprogramming the intrinsic metabolic pathways of immune cells at the therapeutic level is a more feasible strategy. For instance, enhancing the mitochondrial adaptability of T cells by activating AMPK agents (such as metformin) or pre-treating cells in vitro with cytokines (such as IL-15 in adoptive cell therapy) can improve their anti-tumor persistence and the synergistic effect with ICIs. At the same time, inhibiting tumor glycolysis (using HK2 or PKM2 inhibitors) helps restore the availability of glucose in the tumor microenvironment. Although achieving highly tumor-selective drug delivery is crucial to avoiding systemic immune toxicity, it is important to note.

Neutralizing immunosuppressive metabolites is another key clinical direction. Targeting lactate production (LDHA inhibitors) or efflux (MCT1/4 inhibitors) can respectively alleviate the acidity of the TME or induce acidosis in tumor cells. Both have shown significant synergistic effects with anti-PD-1 therapy in preclinical studies. Systemic alkalization therapy (such as sodium bicarbonate) provides a simpler alternative, but its specificity still needs further verification. Similarly, through CD39/CD73 inhibitors (such as oleclumab), A2A/A2B receptor antagonists, or engineered adenosine deaminase to block the immunosuppressive adenosine axis, good safety and early efficacy have been demonstrated in clinical trials combining ICIs.

Furthermore, the exploration of emerging metabolic nodes has opened up new pathways for treatment. This includes developing new generation IDO1 inhibitors targeting the tryptophan-putrescine pathway, using ARG1 inhibitors or arginine supplementation to counteract arginine depletion mediated by MDSCs and TAMs, as well as optimizing T-cell receptor signal transduction by regulating cholesterol metabolism (such as statins) - although the clinical value of the latter remains controversial.

6. Challenges, biomarkers, and future directions

6.1. The severe challenge of targeted metabolism

Blocking a single metabolic pathway may be difficult to achieve the expected therapeutic effect and is prone to being compensated. Therefore, it is necessary to comprehensively analyze the metabolic network or adopt a multi-target combined strategy. The metabolic state of the TME exhibits spatiotemporal heterogeneity and dynamically changes with the disease stage and treatment process. Metabolism is the basic physiological activity of normal cells. To avoid systemic toxicity, drugs with tumor selectivity must be developed (such as targeting tumor antigens or tumor microenvironment-responsive drug delivery systems). At the same time, establishing a reliable predictive biomarker system is also a key issue that needs to be urgently addressed at present.

6.2. The future development direction

By integrating multi-omics data such as genomic, transcriptomic, proteomic, metabolomic, and immunological data, the "metabolism-immunity" classification criteria are established to achieve precise metabolic-immune typing of tumors, thereby identifying tumor subgroups that are sensitive to specific metabolic interventions.

Develop new non-invasive monitoring tools, such as using metabolic imaging (such as novel PET tracers) and liquid biopsy (such as circulating metabolite analysis) technologies to monitor the metabolic status and treatment response of the TME in real time and non-invasively, providing guidance for individualized treatment.

Optimize the combined treatment strategy, meticulously design the combined treatment plan of metabolic regulators and immune checkpoint inhibitors, chemotherapy, radiotherapy, or other immunotherapies, including exploring the optimal administration sequence, timing, and dosage, in order to achieve the maximum synergistic therapeutic effect.

7. Conclusion

Metabolic reprogramming in the TME is a pivotal node between abnormal tumor metabolism and immune therapy resistance. Metabolic stresses including glucose shortage, lactate accumulation, and excessive adenosine jointly reshape the metabolic status and function of core immune cells such as T lymphocytes, macrophages, and DCs, ultimately forming an immunosuppressive microenvironment that facilitates tumor proliferation and blocks anti-tumor immune responses. Targeting such metabolic weaknesses has exhibited promising value in preclinical and preliminary clinical trials, helping to overturn immunosuppression and strengthen the therapeutic effects of ICIs. Nevertheless, the clinical translation of such strategies remains hindered by challenges including metabolic complexity, tumor heterogeneity, and potential off-target toxicity. Moving forward, interdisciplinary cooperation combined with systems biology tools will help to further dissect the metabolic-immune network within tumors. Combined with the development of accurate biomarkers and personalized combination regimens, metabolic interventions are expected to become viable clinical approaches to reverse immunotherapy resistance, eventually bringing greater clinical benefits to cancer patients.

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