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# Metabolic modulation and immune checkpoint therapy: overcoming CD8+ T cell exhaustion in the tumor microenvironment

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**Abstract.** CD8+ T cells play a crucial role in tumor immunotherapy, especially in immune checkpoint therapy, and therefore have become the focus of cancer research. However, although immune checkpoint treatment has shown some efficacy in clinical trials, its effect is still limited by tumor immune escape. Tumors weaken CD8+ T cell function by adapting to immune stress, while mechanisms such as metabolic reprogramming and regulation of immunosuppressive factors further reduce their anti-tumor activity. Based on existing research and data, this paper discusses CD8+ T cell exhaustion, immune checkpoint regulation Programmed Death-1/ Cytotoxic T-Lymphocyte-Associated Protein 4 (PD-1/CTLA-4), and tumor microenvironment metabolism, and summarizes strategies to enhance the effect of immunotherapy. Studies have shown that by inhibiting T cell exhaustion, blocking immune checkpoint signaling pathways, and optimizing metabolism, CD8+ T cell function can be significantly enhanced and the overall therapeutic effect can be improved. However, while metabolic intervention appears promising, its clinical feasibility and safety require further validation. This study provides a theoretical basis for optimizing T cell immunotherapy and provides new ideas for clinical treatment.

**Keywords:** tumour, T cell exhaustion, immunosuppression, immune checkpoint, metabolism

## 1. Introduction

CD8+ T cells, as an important part of the immune system, have the ability to recognise and fight cancer cells, and play a vital role in cancer immunotherapy [1]. However, although functional T cells can effectively inhibit tumour growth in the early stages, continuous immune pressure may promote the evolution of tumour cells into subpopulations with stronger immune escape capabilities, which is known as the "Hellstrom paradox" [2]. This phenomenon highlights the gradual decline of $CD8^+$ T cell function in the immunosuppressive Tumor Micro-Environment (TME). In TME, metabolic stress, chronic antigen stimulation, and immune checkpoint signaling jointly drive $CD8^+$ T cell exhaustion, resulting in reduced cytokine production, decreased cytotoxicity and limited self-renewal ability. In addition, upregulation of inhibitory receptors including Programmed Death-1 (PD-1) and Cytotoxic T-Lymphocyte-Associated Protein 4 (CTLA-4) further inhibits T cells function, while metabolic limitations such as lactic acid accumulation and glucose consumption exacerbate T cell dysfunction [3]. Latest research shows that overcoming these obstacles requires a comprehensive strategy combining Immune Checkpoint Blockade (ICB) with metabolic reprogramming to restore T cell activity and enhance its anti-tumor effect [4]. Based on existing studies and data, this study focuses on the differentiation and dysfunction of $CD8^+$ T cells in the tumor microenvironment, especially the mechanism of T cell exhaustion, and analyzes the molecules that regulate T cell function, such as how transcription limits T cell activity. Through these analyses, this paper highlights the challenge of overcoming tumor-induced immunosuppression and looks forward to the future direction of T cell therapy. In addition, major immunotherapy strategies, such as ICB, are analyzed in this paper to optimize T cells' persistence, functionality, and their adaptability in the inhibitory tumor microenvironment. By identifying modulated molecular targets and revealing the core mechanisms that affect the durability and efficacy of T cells, this study provides new ideas for further improving the therapeutic potential of immunotherapy and lays a theoretical foundation for future innovation in cancer treatment.

 

## 2. Overview of tumor immunosuppression mechanisms

Tumor immune evasion refers to the survival and development of tumor cells in the host body through a variety of mechanisms to evade immune surveillance and eradication by the immune system. It mainly works through the following mechanisms.

### 2.1. Impairment of Major Histocompatibility Complex Class I (MHC-1) antigen presentation

Down-regulating MHC-1 molecule expression diminishes antigen presentation, resulting in CD8+ T lymphocytes' inability to identify and eradicate tumor cells, hence promoting immune evasion.

### 2.2. Immunosuppressive cells in the tumor microenvironment

In the tumor microenvironment, there are many immunosuppressive cells that help the tumor achieve immune escape, such as regulatory T cells, Tumor-Associated Macrophages (TAMs), and Myeloid-Derived Suppressor Cells (MDSCs). Tregs express high levels of CD25 (IL-2 receptor), thereby consuming IL-2 and secreting IL-10 and TGF-β to inhibit the CD8+T cell activation and proliferation. Tumor associated Macrophages are M2 type, they can secrete IL-10 and TGF-β, showing immunosuppression. TAMs can be attracted to tumor by hypoxic environment, releasing factors such as vascular endothelial growth factor, driving tumor expansion and promoting metastasis. Myeloid derived suppressor cells are also important players in tumor immune evasion. They can secrete IL-6 and prostaglandin E2 to promote the expression of FOXP3, thereby promoting Tregs proliferation and improving its immunosuppressive ability, or inhibiting CD8+ T cell activation.

## 3. Metabolic adaptations and immunosuppression

### 3.1. Tumor cell hyperglycolysis and lactic acid accumulation

In addition, tumor cells tend to hyperglycolysis, producing large amounts of lactate, leading to acidification of the tumor microenvironment. However, Tregs rely primarily on Oxidative Phosphorylation (OXPHOS) rather than glycolysis, and Tregs are better adapted to the acidic environment. FOXP3 is a fate-determining transcription factor in Treg cells, and high lactate enhances the stability of the transcription factor FOXP3, thereby enhancing the immunosuppressive effect of Treg cells [5].

### 3.2. Lactate-mediated PD-1 upregulation in Tregs

Kumagai's research indicates that lactate can enhance the expression of the PD-1 molecule on regulatory T cells (Tregs) and significantly boost their immunosuppressive capacity in the environment of high lactate. Within the tumor microenvironment, where elevated glycolysis leads to excessive lactic acid production, Treg cells can absorb lactate via the MCT1 transporter. Once inside Treg cells, lactate is metabolized into Phosphoenolpyruvate (PEP), which increases intracellular calcium ion levels and activates calmodulin. Calmodulin can additionally activate calcineurin and the NFAT1 transcription factor, hence promoting the production of genes such as the immunological checkpoint protein PD-1. The increase of PD-1 expression can augment the immunosuppressive effect of Treg cells [6].

## 4. CD8+ T cell exhaustion

$CD8^+$ T cells, often known as cytotoxic T lymphocytes, are integral to the anti-tumor immune response. The T Cell Receptor (TCR) is utilized to identify antigen peptides displayed by Major Histocompatibility Complex Class I (MHC I) molecules, facilitating the targeting and destruction of virus-infected or tumor cells. $CD8^+$ T cells can utilize perforin and granzymes to disrupt cell membranes, engage the Fas/FasL pathway to induce tumor cell apoptosis, and secrete cytokines to inhibit tumor growth while activating other immune cells [1]. Tumor cells frequently hinder the functionality of $CD8^+$ T cells via immune evasion strategies, including the upregulation of PD-L1, which binds to PD-1 on $CD8^+$ T cells, resulting in the inhibition of their proliferation, cytokine secretion, and cytotoxic activity. In addition, Long-term antigenic stimulation promotes the progression of T cells into an exhausted phenotype. T cell exhaustion can be divided into two subsets; precursor-exhausted T cells with moderate PD-1 expression and low T Cell Immunoglobulin Domain and Mucin Domain-3 (TIM-3) expression and terminally exhausted T cells with high PD1 expression and high TIM-3 expression [7]. Precursor-exhausted T cells rely on TCF-1 to maintain their self-renewal ability and are able to partially maintain anti-tumor effects [8].

Nonetheless, terminal exhausted T cells (Tex cells) progressively diminish their anti-tumor efficacy with sustained antigen stimulation. This is correlated with the upregulation of immune checkpoint molecules, including PD-1, CTLA-4, and TIM-3, which contribute to T cell exhaustion. Consequently, this exhaustion leads to a decreased expression of effector cytokines, such as IL-2, TNF-α, and IFN-γ. Hypoxic stimulation will further cause exhausted T cells to lose their anti-tumor immunity. These

exhausted T cells eventually accumulate in the tumor microenvironment, further promoting immune escape. In the tumor microenvironment, the accumulation of lactate hinders the efflux of $CD8^+$ T cells, thereby inhibiting their glycolytic metabolism. After CD8 + is activated, in order to provide sufficient energy for their rapid expansion and effector responses, $CD8^+$ T cells mainly rely on glycolysis. The normal discharge of lactate depends on MonoCarboxylic Acid Transporter 1 (MCT-1) to maintain the continuous progress of glycolysis and prevent metabolic blockage. However, when the lactic acid concentration in the tumor microenvironment is too high, the gradient of lactate concentration in and out of the cells decreases, resulting in MCT-1-mediated lactic acid efflux, causing lactic acid to accumulate in T cells and causing intracellular pH to decrease. This metabolic disorder not only weakens the glycolytic energy supply capacity of T cells, but also further inhibits the proliferation, cytokine secretion and killing functions of T cells by affecting enzyme activities, limiting its role in the anti-tumor immune response. Therefore, lactic acid metabolism imbalance is one of the important mechanisms of tumor immune escape, indicating that regulating lactic acid metabolism may become a potential strategy for enhancing anti-tumor immunity [9].

## 5. Major immunotherapy strategies

### 5.1. Mechanism of immune checkpoint blockade

Immune Checkpoint Blockade (ICB) is one of the main immunotherapies for cancer treatment. ICBs restore the anti-tumor activity of T cells by targeting inhibitory immune checkpoints such as Cytotoxic T-Lymphocyte-Associated Protein 4 (CTLA-4), Programmed Death-1/Programmed Cell Death Ligand 1 (PD-1/PD-L1), Lymphocyte Activation Gene-3 (LAG-3), and T Cell Immunoglobulin Domain and Mucin Domain-3 (TIM-3) to enhance the body's immune response. Among them, CTLA-4 blockade, such as Ipilimumab, can inhibit the binding of CTLA-4 to CD80/CD86 and enhance the activation of T cells, which mainly acts on the naïve T cell stage in the lymph nodes. Programmed Death-1 (PD-1) is an immunological checkpoint molecule mostly expressed on T cells, B cells, NK cells, and certain myeloid cells. PD-1 reduces T cell activation by attaching to its ligand, PD-L1, hence avoiding excessive immune system responses. However, many tumors overexpress PD-L1, which uses this pathway to evade immune system attack and thus reduce the anti-tumor immune response. In addition, LAG-3 and TIM-3 are also emerging immune checkpoint targets, which have become important directions in ICB research.

### 5.2. Challenges and limitations of PD-1/PD-L1 therapy

In particular, PD-1/PD-L1 inhibitors have made important breakthroughs in clinical practice, but their efficacy is still limited by many factors, especially drug resistance has become one of the main challenges limiting the efficacy of ICB. The data indicates that the overall response rate for patients receiving PD-1/PD-L1 inhibitors ranges from 10% to 20%, signifying that the majority of patients do not get benefit from the medication. It has been established that the tumor microenvironment (TME) is a major factor impacting the effectiveness of PD-1/PD-L1 immunotherapy, including the increase of immunosuppressive factors such as Tregs and MDSCs, resulting in inhibition of $CD8^+$ T cell function.

### 5.3. Role of metabolic dysregulation in ICB resistance

Metabolic disorders, such as lactate accumulation, alter the pH of the tumor microenvironment and inhibit T cell function. Ronald M. Peralta found that terminal exhausted T cells (Tex cells) were significantly activated by the gene Slc16a11 in the tumor microenvironment, thereby upregulating the expression of Mono-Carboxylic Acid Transporter 11 (MCT11). Tex cells utilize MCT11 to augment lactate absorption and metabolism, hence intensifying the dysfunction of Tex cells and resulting in a diminished anti-tumor immune response. The application of an Anti-MCT11 monoclonal antibody (αMCT11) in a tumor-bearing murine model demonstrated that αMCT11 effectively decreased lactate uptake by Tex cells, thus enhancing the effector function of Tex cells and markedly suppressing tumor growth. In addition, αMCT11 in combination with anti-PD-1 increased complete response rates and significantly enhanced the effector function of Tex cells in the TME [10]. Ting Y's study showed that melanoma cells significantly upregulated the SLC16A3 gene encoding MCT4 in a state of hyperglycolysis. MCT4 is the main transporter of lactate efflux, so high expression of MCT4 promotes rapid excretion of lactate, thereby acidifying the Tumor Micro-Environment (TME), resulting in a decrease in pH, thereby inhibiting $CD8^+$ T cell effector functions such as reduced expression of granzyme B and IFN-γ. In his experiments, CRISPR-Cas9 technology was used to knock out Solute Carrier Family 16 Member 3 Gene (SLC16A3). SLC16A3 knockdown tumors showed a stronger response to PD-1 inhibitors. Furthermore, in a murine model, the conjunction of the MCT4 inhibitor (Lonidamine) and anti-PD-1 therapy led to a substantial decrease in tumor volume and an augmented capacity of $CD8^+$ T cells within the tumor microenvironment to secrete IFN-γ and granzyme B relative to the monotherapy cohort, thereby markedly improving their cytotoxic efficacy [11]. These investigations underscore the capacity of metabolic control to diminish lactate buildup in the tumor microenvironment, thus boosting the therapeutic potential of PD-1 blockade.

## 6. Discussion

This study explored the exhaustion of $CD8^+$ T cells in the Tumor Micro-Environment (TME), and analyzed the limitations and optimization strategies of Immune Checkpoint inhibition (ICB) therapy. Although immunotherapy has made significant progress in cancer treatment, current ICB therapy still has difficulty in achieving lasting efficacy in most patients (response rate is only 10%-20%), indicating the need for a deeper understanding of T cell dysfunction and the development of innovative treatment strategies. Metabolic disorders in the TME are key factors affecting T cell function. High glycolysis leads to lactate accumulation, inhibits $CD8^+$ T cell glycolysis, damages mitochondria and increases reactive oxygen species (ROS) production, accelerating T cell exhaustion. Existing studies have found that MCT11 is highly expressed in terminally exhausted T cells (Tex), promotes lactate uptake, and further weakens anti-tumor function. Monoclonal antibodies targeting MCT11 (αMCT11) can reduce lactate uptake, enhance T cell immune function, and synergize with PD-1 inhibitors to improve efficacy [10]. In addition, MCT4 promotes lactate efflux, aggravates TME acidification, and weakens $CD8^+$ T cell function. Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR-Cas9) knockout of SLC16A3 (MCT4 encoding gene) can increase $CD8^+$ T cell activity and enhance the response rate of PD-1 inhibitors [11]. It can be concluded that the molecular mechanism of T cell exhaustion is closely related to TME metabolic disorders, and metabolic intervention may become an important breakthrough in optimizing the efficacy of ICB. Future research must concentrate on elucidating the fundamental molecular mechanisms underlying T cell exhaustion, identifying targets for reactivating T cell functionality, and formulating combinatorial treatment techniques to enhance the efficacy and longevity of T cell therapy. These explorations will promote more efficient cancer immunotherapy and lay the foundation for future therapeutic breakthroughs.

## 7. Conclusion

This study explored the mechanism of $CD8^+$ T cell exhaustion in the Tumor Micro-Environment (TME) and its impact on immunotherapy, analyzed the limitations of Immune Checkpoint Blockade (ICB) therapy, and proposed the potential value of metabolic intervention as an optimization strategy. Elevated lactate levels, decreased pH, and metabolic diseases can expedite the functional deterioration of $CD8^+$ T cells, whereas precise metabolic modulation can augment T cell functionality and boost the effectiveness of PD-1 drugs. However, this study mainly draws on existing review literature to draw conclusions, lacks the support of specific experimental data, and the actual mechanism of action of combined metabolic regulation and immune checkpoint therapy still needs to be further verified in the future. Additionally, there are differences in TME characteristics of different tumor types, and the clinical feasibility and safety of metabolic intervention need to be further explored. Future research should focus on specific experimental studies, delve further into the molecular underpinnings of T cell exhaustion, and explore the optimization strategy of metabolic regulation combined with ICB therapy to promote more precise and efficient cancer immunotherapy.

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