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# Metabolism-related cells, pathways, and molecules in tumor microenvironment immunosuppression

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**Abstract.** Metabolic reprogramming in the Tumor Micro-Environment (TME) is one of the core mechanisms driving tumor immunosuppression. This paper systematically explores the functions and regulatory pathways of metabolism-related cells in the TME, such as Tumor-Associated Macrophages (TAMs), eosinophils, and basophils, and analyzes their potential impact on immunotherapy. TAMs polarize into pro-tumor M2 phenotypes through metabolic reprogramming, including enhanced glycolysis, arginine metabolism imbalance (High Expression of Arginase (ARG1)), and Fatty Acid Oxidation (FAO dependence), secreting immunosuppressive factors such as Interleukin-10 (IL-10) and Transforming Growth Factor-β (TGF-β), which inhibit T cell function. In addition, eosinophils and basophils participate in the immune regulation of the TME by releasing cytokines (Interleukin-4 (IL-4), Interleukin-6 (IL-6)) and bioactive molecules (histamine, heparin), but their roles are highly microenvironment-dependent. Immunotherapy strategies targeting TAMs include polarization regulation (blocking Colony Stimulating Factor 1 Receptor, (CSF-1R) or activating Toll-Like Receptor (TLR) pathways), metabolic intervention (inhibiting ARG1/ Indoleamine-Pyrrole 2,3-Dioxygenase Inhibitors (IDO)), and targeting the CD47-SIRPα axis, which can synergistically enhance the efficacy of immune checkpoint inhibitors (such as Programmed Death 1/ Programmed Death Ligand 1 (PD-1/PD-L1)) and Chimeric Antigen Receptor T-Cell (CAR-T) therapies. This paper further summarizes the principles, advantages, and processes of current immunotherapy methods and proposes a personalized strategy of combined targeting of metabolic pathways and immune checkpoints to overcome TME heterogeneity and resistance. Future research should delve into the dynamic metabolic networks of the TME, develop novel combination therapies, and provide theoretical and clinical pathways to break through the tumor immunosuppressive barrier.

**Keywords:** tumor microenvironment, metabolic reprogramming, tumor-associated macrophages (TAMs), immunosuppression, combination therapy

## 1. Introduction

The immunosuppressive characteristics of the Tumor Micro-Environment (TME) are the core mechanisms through which tumors escape host immune surveillance and continue to progress. Recent research has revealed that metabolic reprogramming is not only a key strategy for tumor cells to adapt to the harsh microenvironment but also a core driving force for regulating immune cell function. Features such as hypoxia, acidity, and nutrient competition in the TME force immune cells (such as tumor-associated macrophages and T cells) to undergo metabolic adaptive changes, thereby forming an immunosuppressive network. Among these, Tumor-Associated Macrophages (TAMs), the most abundant immune cell population in the TME, polarize into pro-tumor M2 phenotypes through metabolic reprogramming, including enhanced glycolysis, arginine metabolism imbalance, and lipid oxidation dependence, secreting immunosuppressive factors (such as Interleukin-10 (IL-10), Transforming Growth Factor-β (TGF-β)), and directly inhibiting T cell activity, becoming an important barrier to immune therapy resistance. Meanwhile, granulocyte subpopulations such as eosinophils and basophils participate in regulating the immune balance of the TME by releasing cytokines Interleukin-4, Interleukin-6, (IL-4, IL-6) and bioactive mediators (histamine, heparin), but their roles are highly microenvironment-dependent, and the mechanisms remain incompletely elucidated. Although immune checkpoint inhibitors (such as Programmed Death 1/ Programmed Death Ligand 1 (PD-1/PD-L1)) and Chimeric Antigen Receptor T-Cell (CAR-T) therapies have shown significant efficacy in clinical settings, the metabolic heterogeneity and dynamic adaptability of the TME still lead to primary or secondary resistance in most patients. Therefore, understanding the regulatory networks of metabolism-related cells and pathways and developing combination strategies targeting metabolic reprogramming and immune checkpoints have become key directions

 

to overcome current therapeutic bottlenecks. This paper systematically reviews the interactive mechanisms between metabolic abnormalities and immunosuppression in the TME, focuses on the core pathways of TAMs metabolic reprogramming, and discusses new strategies for immunotherapy based on metabolic interventions, aiming to provide theoretical support and translational ideas for optimizing tumor immunotherapy [1].

## 2. Overview of cells and extracellular matrix in the tumor microenvironment

### 2.1. Tumor cells

As the core component of the Tumor Micro-Environment (TME), tumor cells exhibit high genomic instability compared to normal cells, with numerous gene mutations and chromosomal abnormalities. These genetic alterations enable tumor cells to acquire uncontrolled proliferative capacity, allowing them to continuously divide and grow. For example, many tumor cells exhibit activation of proto-oncogenes or inactivation of tumor suppressor genes, such as the common EGFR gene mutations seen in lung cancer, which make tumor cells overly sensitive to growth signals and allow them to proliferate even under limited nutrient conditions. At the same time, tumor cells also possess the ability to evade apoptosis. While normal cells initiate apoptosis in response to DNA damage or abnormal growth to maintain homeostasis, tumor cells can block apoptosis signaling pathways through various mechanisms, such as upregulating the expression of the anti-apoptotic protein Bcl-2, enabling them to survive and accumulate [2].

### 2.2. Immune cells

The tumor microenvironment is home to a diverse range of immune cells that interact in complex ways with tumor cells. Macrophages are one of the most important types of immune cells in this environment. Depending on their functional state, macrophages can be classified into classically activated M1 macrophages and alternatively activated M2 macrophages. M1 macrophages have strong anti-tumor activity and can secrete a variety of cytokines, such as Tumor Necrosis Factor-Alpha (TNF-α) and Interleukin-12 (IL-12). These cytokines activate other immune cells, directly kill tumor cells, or inhibit tumor angiogenesis. However, in the tumor microenvironment, macrophages are often induced to polarize into M2 macrophages. M2 macrophages promote tumor growth, angiogenesis, and immune suppression by secreting cytokines such as Interleukin-10 (IL-10), which inhibit the anti-tumor activity of immune cells while promoting tumor cell proliferation and metastasis. Additionally, T lymphocytes are key participants in the tumor immune response. $CD8^+$ T cells (cytotoxic T cells) can recognize and kill tumor cells that express tumor antigens, while $CD4^+$ T cells assist other immune cells' activation and functional performance by secreting cytokines. However, in the tumor microenvironment, tumor cells can suppress T cell functions through various mechanisms, such as expressing PD-L1 to bind with PD-1 on the surface of T cells, thereby inhibiting T cell activation and proliferation and enabling tumor cells to escape immune surveillance.

### 2.3. Stromal cells

Cancer-Associated Fibroblasts (CAFs) are one of the main types of stromal cells. CAFs differ significantly from normal fibroblasts in morphology, phenotype, and function. They secrete large amounts of extracellular matrix components, such as collagen and fibronectin, remodeling the tumor microenvironment's structure to provide physical support and growth signals for tumor cells. At the same time, CAFs can secrete various growth factors and cytokines, such as Transforming Growth Factor-Beta (TGF-β) and Platelet-Derived Growth Factor (PDGF), which promote tumor cell proliferation, migration, and invasion, regulate tumor angiogenesis, and suppress immune cells' anti-tumor activity. Furthermore, adipocytes are also part of the stromal cells in the tumor microenvironment. Adipocytes can influence tumor cell metabolism and growth by secreting fatty acids, cytokines, and other substances. For example, breast cancer cells can take up fatty acids released by adipocytes for membrane synthesis and energy supply, thereby promoting tumor cell growth and metastasis.

### 2.4. Extracellular matrix

The Extra-Cellular Matrix (ECM) is an important component of the tumor microenvironment, composed of various macromolecules, including collagen, elastin, glycosaminoglycans, and fibronectin. The ECM not only provides physical support for tumor cells and other cells but also regulates cell proliferation, differentiation, migration, and survival through interactions with receptors on the cell surface. During tumorigenesis and progression, the composition and structure of the ECM undergo significant changes. For example, tumor cells can secrete Matrix Metallo-Proteinases (MMPs) to degrade ECM components, creating conditions for tumor cell migration and invasion. Additionally, ECM remodeling can affect signaling pathways within the tumor microenvironment, promoting tumor cell growth and metastasis. The ECM can also regulate the biological behavior of tumor cells by storing and releasing growth factors and other bioactive molecules.

## 3. Overview of cell metabolism in the tumor microenvironment

### 3.1. Metabolic reprogramming in tumor cells

To meet the demands of rapid proliferation and survival, tumor cells undergo significant metabolic changes, known as metabolic reprogramming. The most typical example is the Warburg effect, where tumor cells preferentially convert glucose into lactate through glycolysis, even under aerobic conditions, rather than using the more efficient oxidative phosphorylation pathway to generate energy. Although this metabolic strategy is less energy-efficient, it provides tumor cells with a large amount of intermediate metabolites for the synthesis of macromolecules such as nucleotides, amino acids, and fatty acids, supporting the rapid proliferation of tumor cells. Additionally, tumor cells reprogram glutamine metabolism, where glutamine not only serves as a nitrogen source for nucleotide and amino acid synthesis but also enters the TriCarboxylic Acid (TCA) cycle through a series of metabolic reactions, providing energy to the tumor cells. At the same time, tumor cells adjust fatty acid metabolism by upregulating the expression of genes related to fatty acid uptake and synthesis, thereby taking up more fatty acids for membrane synthesis and energy supply.

### 3.2. Changes in immune cell metabolism and function

The metabolic state of immune cells is closely linked to their function. For example, M1 macrophages undergo metabolic reprogramming upon activation, shifting from oxidative phosphorylation to glycolysis as the predominant metabolic pathway. This metabolic change provides M1 macrophages with sufficient energy and metabolic intermediates to support the production of pro-inflammatory cytokines and Reactive Oxygen Species (ROS), thus exerting anti-tumor effects. In contrast, M2 macrophages mainly rely on fatty acid oxidation for energy, a metabolic process that supports their immune suppressive function and promotion of tumor growth. For T lymphocytes, naïve T cells primarily rely on fatty acid oxidation to maintain basic metabolic levels, while activated T cells, especially effector T cells, rapidly upregulate glycolysis and glutamine metabolism to meet their energy needs for proliferation and execution of effector functions. However, in the tumor microenvironment, tumor cells interfere with immune cell metabolic reprogramming by secreting immunosuppressive factors or altering the nutrient concentration in the microenvironment, thereby inhibiting immune cell function. For example, tumor cells consume large amounts of glucose, reducing glucose levels in the tumor microenvironment and limiting glycolysis in infiltrating T cells, thereby suppressing T cell activation and proliferation.

### 3.3. The impact of stromal cell metabolism on the tumor microenvironment

Stromal cell metabolism also influences the metabolic state of the tumor microenvironment. For example, Cancer-Associated Fibroblasts (CAFs) exhibit high glycolytic activity, producing large amounts of lactate through glycolysis, leading to acidification of the tumor microenvironment. This acidic environment not only promotes tumor cell invasion and metastasis but also suppresses immune cell function. Meanwhile, CAFs can regulate the metabolism of tumor cells and immune cells through the secretion of metabolic products and cytokines. For instance, TGF-β secreted by CAFs can induce epithelial-mesenchymal transition (EMT) in tumor cells, enhancing their migration and invasion abilities, while also influencing the metabolism of tumor cells, making them more dependent on fatty acid oxidation. Additionally, adipocytes in the tumor microenvironment can release fatty acids through lipolysis, providing an energy source for tumor cells and promoting their growth and metastasis.

## 4. Major signaling pathways and molecules in the tumor immunosuppressive microenvironment

### 4.1. Hypoxia-Inducible Factor (HIF) signaling pathway

**Activation of HIF-1α:** Under hypoxic conditions in the Tumor Micro-Environment (TME), HIF-1α in tumor-associated macrophages (TAMs) is upregulated. Hypoxia stabilizes HIF-1α, which then translocates to the nucleus and acts as a transcription factor to regulate numerous genes associated with TAM metabolism and function.

**Immunosuppressive Consequences:** HIF-1α induces TAMs to express genes like Transferrin Receptor 1 (TfR1), increasing iron supply to cancer cells and promoting their proliferation. At the same time, HIF-1α drives metabolic reprogramming in TAMs towards oxidative metabolism, reducing their own glucose uptake and supplying more glucose to the cancer cells, which rely on high glycolysis. This limits the function of immune effector cells, creating an immunosuppressive environment.

### 4.2. Lactate-mediated signaling pathway

**Key Role of Lactate:** In the TME, the large amounts of lactate produced by glycolytic cancer cells can induce TAMs to polarize towards an immunosuppressive M2-like phenotype.

**GPR81 Signaling:** Lactate binds to G Protein-coupled Receptor 81 (GPR81) on TAMs, activating downstream signaling pathways that upregulate anti-inflammatory and pro-tumor cytokines, such as InterLeukin-10 (IL-10) and Vascular Endothelial Growth Factor (VEGF). IL-10 inhibits T cell and dendritic cell activation, while VEGF promotes angiogenesis, both contributing to immunosuppression.

**Inhibition of Antigen Presentation:** Lactate-induced M2-like TAMs also reduce antigen presentation ability by downregulating the expression of Major Histocompatibility Complex Class II (MHC-II) molecules and co-stimulatory molecules, preventing T cells from effectively recognizing and attacking cancer cells, thereby weakening the anti-tumor immune response.

### 4.3. Glutamine molecules

**Glutamine Transporters and Enzymes:** Solute Carrier Family 1 Member 5 (SLC1A5) and Glutaminase (GLS): In M2-like TAMs, the expression of glutamine transporter SLC1A5 and glutamine metabolic enzyme GLS is increased. SLC1A5 facilitates the uptake of glutamine into TAMs, and GLS converts glutamine into glutamate, initiating subsequent metabolic pathways.

**Immunoregulatory Role:** Glutamine metabolism is closely linked to the polarization and immunoregulatory functions of TAMs. Glutamine Synthetase (GS) supports TAM polarization towards the M2 phenotype, while inhibiting GS can promote the conversion of M2-like TAMs into a more immune-stimulatory M1-like phenotype, indicating that glutamine metabolism-related molecules are potential targets for regulating TAM-mediated immunosuppression.

### 4.4. Fatty acids

Fatty Acid Transporter Proteins (FATP) and Fatty Acid-Binding Protein (FABP): TAMs can uptake extracellular fatty acids via FATP and FABP. In the tumor microenvironment, TAMs increase fatty acid uptake, which is crucial for maintaining their M2-like phenotype and immunosuppressive function.

Peroxisome Proliferator-Activated Receptor γ (PPARγ): PPARγ is a key regulator of fatty acid metabolism, highly expressed in TAMs. Activation of PPARγ promotes TAM polarization towards the M2-like phenotype, enhancing their immunosuppressive functions and regulating the expression of genes associated with immunosuppression.

### 4.5. Purine metabolism-related pathways

Adenosine Receptor Signaling Pathway: In the tumor microenvironment, ATP is gradually hydrolyzed into adenosine by extracellular nucleotidases. Adenosine binds to adenosine receptors on TAMs, activating downstream signaling pathways that promote TAM production of immunosuppressive cytokines, inhibiting T cell proliferation and function.

IDO Signaling Pathway: Indoleamine 2,3-DiOxygenase (IDO) is often highly expressed in TAMs. IDO catalyzes the catabolism of tryptophan, leading to local tryptophan depletion and kynurenine accumulation, which suppresses T cell proliferation and function, promotes the differentiation and expansion of regulatory T cells (Tregs), and induces immunosuppression.

## 5. Advanced therapeutic approaches targeting tumor immunosuppression – PD1/PDL1 and related CAR-T therapies

### 5.1. PD1/PDL1 therapy

#### *5.1.1. Normal immune status*

Under normal physiological conditions, PD-1 is an immune checkpoint protein expressed on the surface of T cells, while PD-L1 is typically expressed on the surface of tumor cells and some normal cells. When PD-1 on T cells binds with PD-L1 on normal cells, it transmits inhibitory signals to T cells, suppressing their activity and preventing the immune system from generating an excessive immune response against the body's own tissues, thereby maintaining immune homeostasis [3].

#### *5.1.2. Tumor evasion mechanism*

Tumor cells exploit the PD-1/PD-L1 immune checkpoint mechanism to evade recognition and attack by the immune system. Tumor cells overexpress PD-L1, which binds with PD-1 on T cells, inhibiting T cell activation, proliferation, and cytokine secretion, preventing T cells from effectively killing tumor cells, thereby enabling immune evasion by the tumor cells.

*5.1.3. Therapeutic principle*

The function of PD-1/PD-L1 inhibitors is to block the interaction between PD-1 and PD-L1, thereby relieving the immune suppression and restoring T cell recognition and cytotoxicity against tumor cells, thereby activating the body's own anti-tumor immune response.

*5.1.4. Advantages and limitations of PD1/PDL1 therapy*

Advantages: Compared to traditional chemotherapy and radiotherapy, PD-1/PD-L1 inhibitors offer advantages such as stronger specificity and relatively fewer side effects. They can precisely target tumor cells with minimal damage to normal cells, and some patients can achieve long-term survival benefits.

Limitations: Not all patients respond to PD-1/PD-L1 inhibitors, and the effectiveness varies. Response rates may depend on factors such as tumor cell PD-L1 expression levels, tumor mutation burden, and microsatellite instability. Additionally, long-term use may induce immune-related adverse effects, such as immune-related pneumonitis, hepatitis, and colitis.

### 5.2. CAR-T Cell therapy

*5.2.1. Mechanism of action*

**Preparation of CAR-T Cells:** First, T cells are isolated from the patient's blood. Then, through genetic engineering, a Chimeric Antigen Receptor (CAR) gene, which specifically recognizes tumor cell surface antigens, is introduced into the T cells, causing them to express CAR and transforming them into CAR-T cells with directed tumor-killing capabilities.

**Tumor Cell Killing Process:** After the modified CAR-T cells are infused back into the patient, the CAR on their surface specifically recognizes tumor cell surface antigens. This triggers the activation and proliferation of CAR-T cells through signaling pathways inside the T cells, leading to the release of cytotoxic substances such as perforin and granzymes, which directly kill tumor cells. Additionally, CAR-T cells secrete cytokines that recruit and activate other immune cells to work together in the anti-tumor response.

*5.2.2. Common targets and clinical applications*

**Common Targets:** Currently, commonly used CAR-T cell therapy targets include CD19 and BCMA. CD19 is mainly expressed on the surface of B cells, and CAR-T cells targeting CD19 have shown significant efficacy in treating B-cell malignancies such as acute lymphoblastic leukemia and non-Hodgkin lymphoma. BCMA is primarily expressed on the surface of multiple myeloma cells, and CAR-T cells targeting BCMA have also shown good effects in the treatment of multiple myeloma [4].

**Clinical Applications:** CAR-T cell therapy has made breakthrough progress in the treatment of hematologic malignancies, achieving high remission rates in patients with refractory and relapsed blood cancers. However, in solid tumors, the efficacy is relatively limited due to issues such as tumor heterogeneity and an immunosuppressive microenvironment, and it remains under investigation.

*5.2.3. Advantages and limitations*

**Advantages:** CAR-T cell therapy offers high specificity and targeting ability, allowing precise recognition and killing of tumor cells. It has shown significant efficacy in tumors that are resistant to traditional treatments, especially in hematologic malignancies, offering new hope for patients.

**Limitations:** CAR-T cell therapy can lead to severe adverse reactions such as cytokine release syndrome (CRS) and neurotoxicity. CRS manifests as fever, chills, hypotension, respiratory failure, and can be life-threatening in severe cases. Neurotoxicity may lead to cognitive dysfunction, seizures, and other symptoms. Additionally, CAR-T cell therapy is expensive, the preparation process is complex, and there is a risk of tumor relapse.

## 6. Summary

Various cells and the stroma within tumors work together to form an immunosuppressive microenvironment, which involves cellular reprogramming and the expression and alteration of various cells and signaling molecules, presenting a dynamic and spiraling change.

Metabolic reprogramming in the tumor microenvironment regulates the functions of immune cells (such as TAMs and eosinophils), creating an immunosuppressive barrier. Strategies targeting metabolic pathways (such as HIF-1α, ARG1) and immune checkpoints (such as PD-1/PD-L1) can significantly enhance the effectiveness of immunotherapy. Future research should

further explore TME heterogeneity and dynamic changes, and develop personalized combination therapies (such as CAR-T combined with TAM polarization regulation) to optimize clinical outcomes [3, 5].

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