
The Role of Amino Acid Metabolic Reprogramming in Tumor Development and Immunotherapy

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Abstract: Many amino acid transporters are solvent carrier proteins, which are membrane transport proteins. In order for cells of all kinds to thrive, including cancerous ones, they need a constant supply of amino acids, which are important for growth and development. Tumor cells exhibit considerable metabolic reprogramming as one of their distinguishing characteristics. A growing number of studies have shown that the Warburg effect is just one of several factors that influence the development and occurrence of cancers and the tumor microenvironment, immunological response, and cell activity in the gained and innate immune systems. Metabolism reprogramming is required for both cancer growth and the induction of efficient immune systems in the tumor microenvironment. The amino acid metabolism of different cells and their interaction with one another influence tumor immunity and therapeutic efficacy in cancer patients. Therefore, amino acid metabolism has received more attention. Amino acid metabolism is extensively involved in regulating the immune response in the tumor microenvironment. Tumor immunotherapy helps the immune system kill tumor cells by targeting specific molecules and abnormal metabolic processes to change the tumor microenvironment. Amino acid metabolizable energy regulates tumor microenvironment and anti-tumor immune response from signal transduction, tumor inflammatory environment, angiogenesis, tumor cell invasion, and metastasis. It is a crucial intervention target in tumor immunotherapy. This review summarizes the most recent developments in amino acid metabolic reprogramming in tumorigenesis and immunotherapy.

Keywords: Amino Acid Metabolic Reprogramming, Tumor Immunotherapy, Tumorigenesis

1. Introduction

According to Otto Warburg, the most notable change in both tumor cells and normal cells is converting glucose metabolism from aerobic to anaerobic glycolysis [1]. Malignant tumor cells frequently undergo metabolic reprogramming that affects the energy pathways of the cell and the metabolic pathways of amino acids, lipids, and other compounds (such as polyamines). Metabolic phenotypes and metabolic dependence of adjacent stroma and immune cells in the tumor microenvironment (TME) are changed during the development of tumor cells from precancerous tissue to local invasion and metastasis. Therefore, metabolic reprogramming is an indirect response to cell proliferation and survival signals and is a carcinogenic pathway [2–4]. Cancer development and progression are integrally tied to the

regulation of glucose, lipids, and amino acid metabolism due to the degrading tumor microenvironment. As early as the 1920s, WARBURG hypothesized that the significant difference among normal and tumor cells is the glucose metabolism pathway. The transition to aerobic glycolysis provides sufficient energy and necessary macromolecular precursors for tumor cell proliferation. Lactic acid generated by glycolysis pathway metabolism in the tumor microenvironment can not only serve as "fuel" for tumor-adjacent cells but also assist tumor cells in escaping immune suppression by "feeding" regulatory T cells (Tregs) [4, 5]. In addition, to maintain their rapid proliferation and provide necessary energy sources under the condition of metabolic stress, tumor cells, after lipid reprogramming, gradually increased their dependence on de novo synthesis of fatty acid (fatty acid) and the uptake of exogenous fatty acids. Additionally, immune cells in the TME can modify their lipid

metabolism in response to various micro environmental stimulation [6]. It has been discovered that tumor and Treg cells influence the anti-tumor immune response by increasing the expression of phospholipase A2-IVa, which results in lipid metabolism reprogramming and aging in T cells [7]. Therefore, the expression changes of some multifunctional metabolic enzymes and abnormal accumulation of tumor metabolites also promote tumorigenesis [8, 9]. Recent investigations have demonstrated that amino acid metabolism plays a significant role in forming and expanding cancers. Protein synthesis relies on amino acids for energy production, nucleoside production, and maintaining cell REDOX equilibrium, which provides resources for tumor cells and immune cell populations in the body [10]. Metabolic reprogramming systematically affects physiological changes and the course of an immune response. Recent studies have found a specific nutrient distribution mechanism in TME, where immune cells and tumor cells preferentially obtain glucose and Glutamine [11]. Rapidly proliferating tumor cells compete with T cells for amino acids through high expression of relevant transport proteins and poor vascular development in tumors, leading to depletion of amino acids and nutrients in TME, which damages the TCR activation signaling pathway, T cell glycolysis metabolism, and its anti-tumor effect function [6]. Researchers reported that excessive activation of T cells in PD1 knockout mice could also lead to the systematic reduction of tryptophan and tyrosine, resulting in a deficiency of brain neurotransmitters serotonin and dopamine, and ultimately anxiety and fear responses [12]. Influenza virus infection causes metabolic reprogramming of epithelial cells and immune cells, causing epithelial cells to become dependent on glucose and Glutamine and inducing activation and differentiation of immune cells, resulting in antiviral immunosuppression [13]. Various cells in inflammatory sites can release enzymes that consume amino acid metabolites in the local microenvironment, including arginine and indoleamine-2,3-dioxygenase (IDO), which consume arginine (IDO), respectively. Arg and tryptophan [14]. Energy metabolism also interacts with natural immune response pathways. Glycolysis and lactic acid bind to the antiviral pathway protein MAVS and negatively regulate the expression of the type I interferon gene, directly affecting the antiviral response [15, 16]. Correspondingly, EGFR anti-tumor drugs can activate the interferon pathway, leading to drug resistance of tumor cells [17]. Several studies have indicated that tumor immunotherapy can remodel the TME's amino acid metabolism, initiate and sustain the tumor immune circulatory microenvironment, restore the body's anti-tumor immune response, and subsequently affect the therapeutic effect. As a result, tumor cells utilize amino acids with their own proliferating and invading and employ the imbalance of amino acid metabolism in TME to avoid immune monitoring. The function of aberrant amino acid metabolism in the emergence and growth of tumors is explored in this work. The relevance of amino acid metabolic processes programming in modulating anti-tumor immune

response and immunotherapy.

2. Molecular Reprogramming of Amino Acids in Cancer and Development

T-cells and macrophages are the leading representatives of the lymphoid system and myeloid system in the immune system. On the one hand, amino acid metabolism can drive the activation and proliferation of T cells; on the other hand, Glutamine promotes the polarization of M2 macrophages through the GLN-UDPGICNAC pathway and the α -ketoglutaric acid produced by glutamine decomposition [18]. Polarized macrophages have different arginine metabolism patterns, and to support tumor growth, IL-4-induced macrophages up regulate arg1-mediated polyamine production, which results in increased cellular proliferation and collagen formation [6]. The ability of tumor cells to grow and proliferate is fueled by the availability of amino acids in the tumor microenvironment. Due to metabolic changes, tumor tissue gradually forms an acidic and anoxic microenvironment [19]. Metabolic reprogramming of tumor cells can be accomplished by using exosomes generated from cancer-associated fibroblast (CAF) to supply amino acids, metabolic precursors, and other metabolites for the speedy growth and reproduction of tumor cells [18]. Since tumor cells can control ROS levels through glutathione and NADPH produced by glutamine (Gln) metabolism and prevent chromosomal instability caused by high ROS levels, tumor cells need to increase extracellular uptake and up regulate the auto synthesis of Gln. Maintain the survival of tumor cells [18]. Tumor cells can absorb Gln from CAFs, and the increased Gln replenishment in tumor cells leads to increased ammonia release, resulting in increased CAFs autophagy. This autophagy phenotype provides a rich source of Gln for tumor cells. Tumor-associated macrophage (TAM) mediated regulation of amino acid supply also controls T cell activation and proliferation through paracrine metabolic coupling. For example, macrophages can take up cysteine (Cys-Cys) and reduce it to cysteine (Cys), which is secreted out of the cell and transported to T cells, thus regulating the REDOX balance and proliferation of T cells [20]. Therefore, amino acid metabolism regulates tumor cell growth and proliferation from multiple aspects and participates in the response process of anti-tumor immunity [21].

2.1. Glutamine

When it comes to protein, lipid, and nucleic acid synthesis, Glutamine is the most significant non-essential amino acid inside the body. For many tumor cells, Glutamine is a conditionally necessary amino acid. In order to meet the energy needed for cell proliferation, tumor cells use a large number of intermediate glycolysis metabolites for anabolism, so they need to consume a large amount of glucose. These two primary sources of energy, glucose and Glutamine, are used by tumor cells and healthy tissue growing at a rate that usually exceeds their energy and biosynthesis needs. The

"glutamine addiction" of tumor cells provides carbon and nitrogen to supplement the tricarboxylic acid cycle (TCA) intermediate α -ketoglutarate donor. It promotes the biosynthesis of nucleotides [22], thus significantly enhancing glutamine uptake and dissociation metabolism in many tumor cells. Experiments with cells demonstrated that glutamine supplementation could improve cell proliferation and enhance cells' ability to fight and metastasize [23].

Glutamic acid, in addition, is an important immune system regulator since it affects lymphocyte proliferation and function. When administered to critically ill patients, exogenous Glutamine can considerably boost the total number of lymphocytes, T cells, and the circulating CD4/CD8 ratio, in addition to enhancing the body's overall immunity [24]. Experimental evidence on mice has demonstrated that inhibiting glutamine metabolism reduces tumor growth and improves anti-tumor immunity [25]. Glutamate metabolism in mice with cancer slowed the growth and spread of their tumors and led to a massive drop in the number of myeloid derived suppressor cells (MDSC), which can help fight cancer. MDSC was transformed into proinflammatory and antitumor M1 macrophages. Although the total number of tumor-associated macrophages remained unchanged, TAM reprogrammed into M1 macrophages could promote tumor antigenic cross-presentation, leading to enhanced activation, proliferation, and efferent function of CD8+ T cells. Therefore, blocking glutamine metabolism has a potential advantage as a tumor disease-free therapy.

2.2. Tryptophan

TRP (tryptophan) is an essential amino acid that plays a role in various physiological functions. There are two enzymes involved in catabolism, IDO and Tryptophan-2, 3-Dioxygenase (TDO), and the primary byproduct, kynurenine (Kyn), has immunosuppressive properties. By inhibiting the function of DC cells, inhibition of rejection during implantation of fertilized egg and embryo development [26]. In addition, tumor cells generally have high levels of tryptophan decomposition enzymes. Several clinical studies have demonstrated that elevated IDO1 and TDO levels are related to a worse prognosis in lung cancer, acute myeloid leukemia (AML), and gastric cancer [27, 28]. Upregulated expression of IDO1 and TDO in malignant tumors leads to tryptophan depletion and accumulation of downstream products, resulting in an immunosuppressive microenvironment by inhibiting the mTOR pathway and activation of GCN-2 and Kynurenine pathway (KP) [29]. Tryptophan depletion inhibits mTOR mediated molecular stress response and induces autophagy of effector T cells (Teff). At the same time, the activation of GCN-2 kinase is triggered, which attenuates its downstream target EIF-2 due to phosphorylation, and ultimately leads to the stagnation of Teff proliferation in the G1 cycle [29]. As a result of the breakdown of tryptophan, canisurine is produced, which acts as an endogenous stimulator of the aryl hydrocarbon receptor (AHR). Embryogenesis, metamorphosis, and inflammation are all affected by AHR activation [30]. AHR signal is

closely related to tumorigenesis due to its influence on oncogenic expression, angiogenesis, cell survival, and immune cell function [27]. Tumor cells block CD4+ and CD8+ T cell proliferation through paracrine to facilitate tumor immune evasion and enhance cell existence and migration via autocrine via the TDOkyn-AHR pathway (Figure 1) [30]. It is also possible that metabolites such as 3-hydroxykynurenine (3HK) and 3-hydroxyanthranilic acid (HAA) produced downstream of Kyn have immunosuppressive effects. In addition to being used in protein synthesis and KP substrate, tryptophan is also used in the production of neurotransmitters (5-hydroxytryptamine) and neuromodulators (tryptamine) [31]. Upregulation of the KP pathway leads to decreased 5-hydroxytryptamine (5-HT) levels, which negatively affects mood and behavior. Since 5-HT receptors are expressed by various tumor cells and cell lines, many cancer patients often suffer from cancer complications such as chronic pain, depression, behavioral disorders, and fatigue [32]. 5-HT signaling can also affect tumor growth, metastasis, and angiogenesis, so targeting Trp catabolic therapy to treat neurological dysfunction in cancer patients may contribute to the treatment of tumors [33].

2.3. Asparagine, Aspartic Acid

In addition to being a non-essential amino acid, formaldehyde (Asn) is a crucial modulator of the amino acid regulatory database and the proliferation of malignant cells. In vivo, ASNS can produce it. Asparagine is the real key that intracellular asparagine does. It helps balance other intracellular and extracellular amino acids, like glycine, histidine, threonine, and serine [34]. During nutrient depletion, KRAS induced the ATF4 pathway, and the expression of asparagine synthase was upregulated. ATF4-targeting ASNS leads to the prevention of apoptosis, protein production, and stimulation of mTORC1, thereby maintaining cell proliferation and reducing ATF4-mediated cell apoptosis. PI3K-Akt regulates ASNS, and inhibiting the KRAS-ATF4-ASNS pathway through AKT, in combination with extracellular asparagine depletion, can decrease tumor growth in KRAS-driven non-small cell lung cancer (NCLC). Patients with NSCLC provide insight on a possible treatment [35]. Furthermore, Extracellular asparagine is necessary for maintaining activity, proliferation, and initiating activation and biochemical remodeling in the early stages of CD8+ T cell activation. [36]. Aspartate can also be degraded by asparagine. Maintaining the homeostasis of asparagine and aspartic acid is essential for tumor cell growth. We found that aspartic acid and asparagine directly bind to kinase LKB1 and affect the kinase activity of LKB1 and signal transduction of downstream AMPK signaling pathways. The binding of asparagine to LKB1 inhibited the activity of LKB1, while aspartic acid enhanced the kinase activity of LKB1 to a certain extent. Therefore, tumor cells regulate asparagine metabolism to control the LKB1-AMPK signaling pathway and affect the survival and proliferation of tumor cells [37]. Aspartic acid is one of the lowest concentrations of amino acids in our blood, and most mammalian cells cannot

absorb aspartic acid from the environment. Aspartic acid inhibits tumor cell growth by controlling nucleotide and protein synthesis under hypoxia. Therefore, pathways related to aspartic acid availability may target cancer therapy [38].

Negative control of T cell activation by CTLA4 and PD-1 checkpoint receptors through restricting amino acid intake and catabolism. By altering T cell amino acid metabolism, immune checkpoint blockade increases T cell effector performance.

While immunotherapy-induced IFN- γ reduces cystine uptake by tumor cells, leading to lipid peroxidation and tumor iron death. Extracellular Trp depletion and Kyn accumulation caused by TRP-KYN metabolism can inhibit T cell activation, reduce its proliferation and effector function, and promote tumor cell growth and migration. The red top arrow indicates an increase or enhancement, and the blue down arrow indicates a decrease.

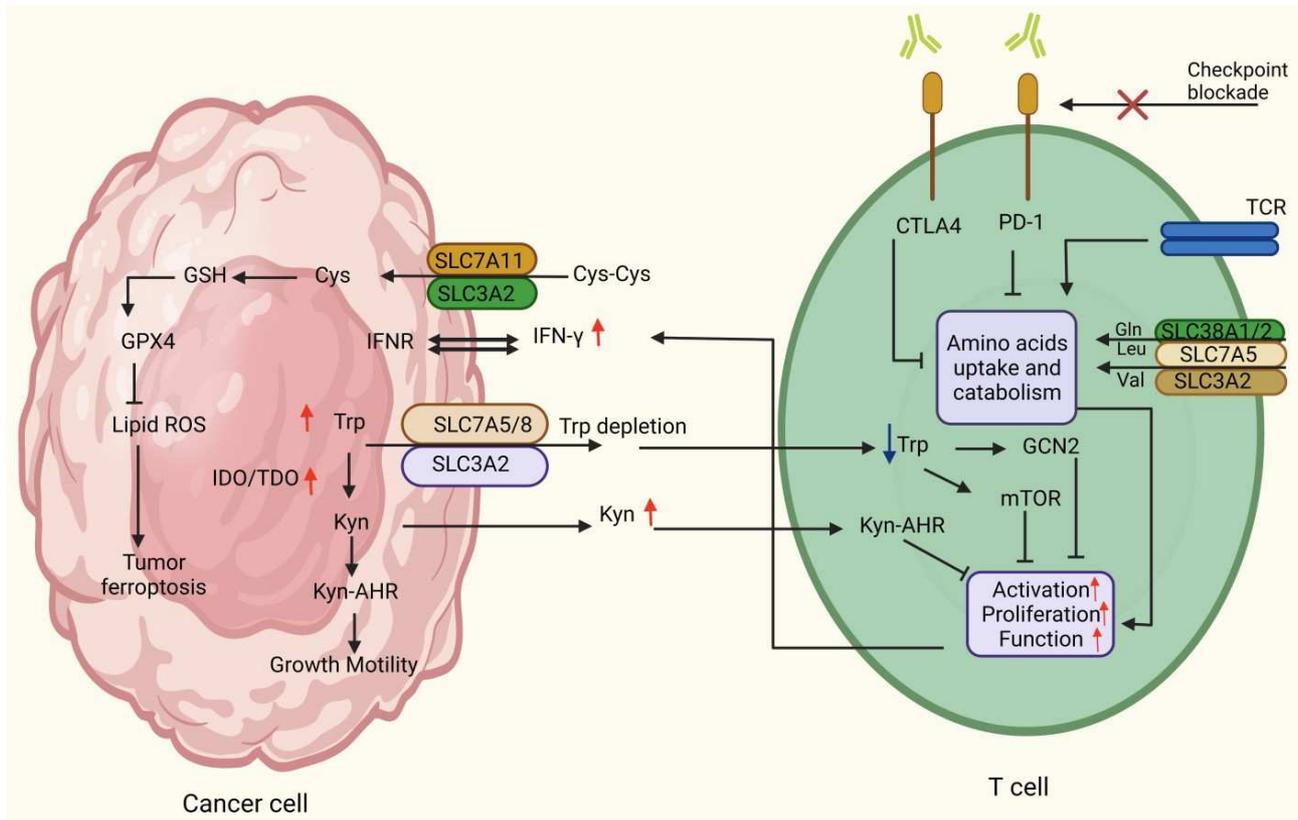


Figure 1. Reprogramming amino acid metabolism and immunecheckpoint treatment (based on the reference 37and 21).

2.4. Arginine

The amino acid arginine involves various processes. Aside from being a building block for protein synthesis, arginine is also a precursor for nitric oxide, polyamines, creatine, and range of other amino acids, among many others. Because it is a semi-essential amino acid, in some situations but not in others, it is required. Two enzymes in most cells can synthesize and degrade arginine: arginine succinate lyase (ASL) in addition to Arginino succinate synthase 1 (ASS1). Citrulline and aspartic acid are catalyzed by ASS1 and converted to arginine succinate, which ASL then lyses to arginine and fumarate [39]. Arginine metabolism is relatively complex, among which arginine enzyme, arginine deiminase, and arginine decarboxylase are arginine metabolizing enzymes. Mitochondrial arginase 2 (ARG2) or arginase 1 (ARG1) hydrolyze arginine to urea and ornithine inside the cytoplasm. It results in reduced local arginine concentrations. Although arginine can be synthesized in the liver, due to the abundance of endogenous arginase, arginine can immediately

catalyze the production of urea and ornithine in the urea cycle. Therefore, the level of organic acid in liver cells (0.03-0.10 mmol/L) is much lower than the concentration of other amino acids (0.5-10.0 mmol/L) [40]. A high arginine concentration has been shown to alter cell metabolism, activate T cells, enhance the formation of anti-tumor T cells, and increase T cell survival [41]. Thus, ASS1 expression is deficient in many malignancies, including melanomas, prostate cancer, hepatocellular carcinoma, mesothelioma, and bladder cancer. ARG1 and ARG2 arginase expression is increased in gastric, breast, prostate, colorectal, and AML cancers. Proliferating tumors activate macrophages that produce ARG1 and suppress T-cell activation by eating arginine, which creates an environment hostile to T-cell activation. [42]. A recent study states that tumor cells use extracellular vesicles to deliver ARG1 over long distances to immune cells, inhibiting anti-tumor immune response by affecting arginine metabolism [43]. Small molecule suppressor CB1158 selectively inhibits arginase ARG1, promotes T-cell proliferation, alleviates myeloid cell-

mediated immune try to break out and inhibits tumor growth [44]. 6-gingerol, an extract of Traditional Chinese medicine, can inhibit arginase and lead to M1 chemotaxis of macrophages through reprogramming, affecting cancer progression [45, 46].

3. Tumor Immunotherapy and Metabolic Reprogramming

Tumor immunotherapy is an anti-tumor therapy that assists the body's immune system in killing tumor cells by changing the immune microenvironment of tumor tissue. It has become the fourth anti-tumor therapy method after surgery, chemotherapy, and radiotherapy. Traditional immunotherapy is mainly divided into non-specific and specific immunotherapy [45]. Immune system modulators and cellular immunotherapy belong to non-specific immunotherapy. In clinical practice, Lentinan, cytokines, and other immune modulators are often used as adjuvant drugs combined with other chemotherapy drugs. Cellular immunotherapy takes the body's immune cells outside the body for modification to have a more effective and accurate immune ability. Specific immunotherapy mainly includes tumor vaccine therapy and monoclonal antibody therapy. Tumor vaccine treatment stimulates the body's anti-tumor immune response by introducing specific antigens on the surface of tumor cells into the patient to strengthen the body's defense function. By marking tumor cells, monoclonal antibodies aid the immune system's fight against cancer. CTLA4 antibody, CYTotoxic T-lymphocyte-associated protein 4 (CYTotoxic T-lymphocyte-associated protein 4), and PD-1 (Programmed cell death protein 1) represent a new age of immune checkpoint therapy [47]. Immune checkpoints act as inhibiting receptors on the cell surface of immune cells, preventing an over-reactive immune system, and tumor cells can use this mechanism to evade immune surveillance. Immune checkpoint therapy is specific immunotherapy that stimulates the anti-tumor immune response by altering the immunosuppressive pathway activated by tumor cells. Due to the remarkable effect of immune checkpoint inhibitors in the clinical treatment of various cancers, immune checkpoint therapy has gradually become a promising therapeutic strategy in cancer immunotherapy.

Tissue-dependent metabolic phenotypes of tumor cells constantly change as the disease progresses [3]. It means that modification in metabolic activity could be used to diagnose and monitor cancer and effectively cure it [3]. An anti-tumor immune response can be restored by using tumor immunotherapy's metabolic reprogramming to rebalance nutrition usage in the tumor microenvironment (TME). As a result, tumor immunotherapy can influence metabolic transmission and conflict among tumor cells and T cells in the tumor microenvironment. Here we introduce the immune checkpoint therapy as a representative. T cell activation, effector T cell activity, and memory T cell formation all

depend on the ability of T cells to switch to aerobic glycolysis biochemical mode [48]. Activation of checkpoint receptors on the surface of T cells, such as Pd-1, CTLA4, and others, results in immunosuppression by inhibiting changes in T cell energy consumption. [49]. Rapid cell proliferation re-quires a large number of free fatty acids. Linear fatty acid oxidation (FAO) is known to be slowed by the enzyme Carnitine palmitoyl transferase 1A (CPT1A). In T cells, Pd-1 upregulates the production of CPT1A, which enhances endogenous lipid oxidation [21], and induces lipid lysis by increasing the release of esterase ATGL, direct target glycerol fatty acids, and ultimately inhibits the proliferation and differentiation of T cells [49]. Therefore, immune checkpoint receptors assist tumor cells in evading immune surveillance through glucose and lipid metabolism [50]. The local immune effect that mediates immune surveillance in the tumor microenvironment is gradually transformed into immune tolerance, thus promoting tumor growth and angiogenesis while inhibiting anti-tumor immunity [27]. For example, in the B16 mouse melanoma model, the PD-1 and IDO pathways potentially work together to calm Tregs. The immune checkpoint is one of the primary causes of changes in the immune microenvironment, and amino acid catabolism is thought to enhance the immune checkpoint pathway. Rate-limiting enzymes such as IDO1 and TDO in the tryptophan metabolic pathway mentioned above and immune checkpoint receptors such as CTLA4 and PD1 can be involved in the immune tolerance process of tumors. The combination of trypanoic acid depletion in TME and Trpcatabolites creates a powerful barrier to anti-tumor immunity from CTLA4 and PD-1-PD-L1 pathway-mediated immune checkpoints in T cells. In some immune checkpoint therapies targeting adaptive T-cell activation, the activated immune cells themselves also secrete IFN- γ and other interferons to enhance IDO expression [51]. Therefore, IDO inhibitors may be adjunctive to immunotherapy that induces an inflammatory response.

Tumor immunotherapy was initially designed to enhance the signaling pathway activated by T cells. In addition to tumor immunotherapy targeting glucose and lipid metabolism, immune checkpoint blocking therapy also enhances T cells' invasion and effector function by reprogramming amino acid metabolism [52]. For example, glutamine uptake increases during T cell activation, while PD-1 signal leads to decreased expression of corresponding transporters SLC38A1 and SLC38A2 and catabolism of branched amino acids (including valine and leucine) in T cells [21]. Therefore, blocking the immune checkpoint receptor removes the differentiation inhibition of T cells by reprogramming glutamine metabolism. In patients treated with immune checkpoint Blocker (ICB), T cell infiltration is not only increased.

Moreover, interferon regulatory gene expression is also upregulated [53]. IFN- γ can down-regulate the expression of SLC7A11 and SLC3A2 transporters in tumor cells, inhibit the input of cysteine required for glutathione synthesis, and cause intracellular glutathione depletion, which indirectly

leads to glutathione peroxidase-4. GPX4 is inactivated and ultimately induces iron death in tumor cells [54]. Cancer therapy is increasingly addressing amino acid metabolic reprogramming as a viable treatment method in light of the close relationship between amino acid metabolism and T-cell immunity.

4. Conclusion

To a large extent, the metabolism of amino acids affects the immune response in the tumor cells. Unlike the traditional cancer treatment model, immunotherapy reverses the immune balance in the tumor microenvironment by restoring the proliferation and effectors function of immune cells and ultimately assisting the immune system in killing tumor cells. Clinical investigation shows that the efficacy of immunotherapy is closely related to the heterogeneity, individual differences, and complexity of tumor pathogenesis. Therefore, further research on the role of metabolic reprogramming in TME formation and maintenance is significant for improving tumor immunotherapy. Metabolic phenotypes develop with the evolution of cancer, and new dependencies appear in treatment resistance and metastasis. Far reaching implications for clinical treatment arise from the use of medications that target the reprogramming of amino acid metabolism in tumor microenvironments in conjunction with cancer immunotherapy [3].

Author's Contribution

All authors contributed to drafting and revising the article and agree to be accountable for all aspects of the work. All authors read and approved the final manuscript.

Declaration of Interest

The authors declare that they have no competing interests.

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