



Emerging Landscapes of Tumor Immunity and Metabolism

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The metabolic reprogramming of cancer tissue has higher metabolic activity than surrounding tissues. At the same time, the local infiltration of immunosuppressive cells is also significantly increased, resulting in a significant decrease in tumor immunity. During the progression of cancer cells, immunosuppressive tumor microenvironment is formed around the tumor due to their metabolic reprogramming. In addition, it is the changes in metabolic patterns that make tumor cells resistant to certain drugs, impeding cancer treatment. This article reviews the mechanisms of immune escape caused by metabolic reprogramming, and aims to provide new ideas for clinical tumor immunotherapy combined with metabolic intervention for tumor treatment.

Keywords: cancer, metabolism, immunity, reprogram, drug resistance

INTRODUCTION

Current research on the immune system's defense against cancer has led to the rapid development of cancer immunotherapy. Some cancer cells are immunogenic due to their high mutation rate, leading to immune escape (1). Immune escape is considered a marker of cancer progression, highlighting the direct involvement of immune cells (2). Immune cells affect all aspects of cancer progression, including survival, proliferation, angiogenesis, and metastasis (3). The immune escape produced by cancer cells is accomplished by reediting the immune system. Immune editing is a dynamic process that includes elimination, balance, and escape. First, tumor cells interfere with the immune system to eliminate rejection of cancer cells.

Abbreviations: ACC1, acetyl-CoA carboxylase 1; ARG, arginase; Arg, arginine; ARG1, arginase 1; ASM, acid sphingomyelinase; cc-RCC, renal clear cell carcinoma; CIC, citric acid carrier; CSC, cancer stem cells; CTL, cytotoxic T cells; DC, Dendritic cells; EMT, Epithelial to mesenchymal transition; ER, endoplasmic reticulum; FA, fatty acids; FAO, fatty acids beta oxidation; FASN, Fatty acid synthase; GLS, glutaminase; Glut-1, glucose transporter 1; GRP78, glucose-regulated protein 78; HDAC6, histone deacetylase 6; HIF1 α , hypoxia-inducible factor 1 α ; HSP90, heat shock protein 90; IDO, Indoleamine 2,3 dioxxygenase; ITGB4, integrin β 4; ITIM, immunoreceptor tyrosine-based inhibitory motif; JAK, tyrosine kinase; Kyn, kynurenine; LAO, L-amino acid oxidase; l-Arg, l-arginine; LILRB, Leukocyte immunoglobulin-like receptor B; LILRB1, leukocyte immunoglobulin-like receptors B1; LSD1, lysine-specific demethylase 1; MAPK, mitogen Protein kinase; MDSCs, myeloid-derived suppressor cells; NOS2, nitric oxide synthase 2; NSCLC, non-small cell lung cancer; PD-1, programmed cell death protein 1; PKC ζ , protein kinase C ζ ; PLA2, phospholipase A2; PPAR, peroxisome proliferator-activated receptor; PPP, Pentose Phosphate Pathway; PTPN, phosphatase protein tyrosine phosphatase; ROS, reactive oxygen species; SL, Sphingomyelin; TCA cycle, tricarboxylic acid cycle; tDC, tumor-associated DC; TDO, tryptophan dioxxygenase; TIDC, tumor infiltration DC; Tm, memory T cells; TME, tumor microenvironment; TNBC, triple negative breast cancer; Treg, regulatory T cells; Trp, tryptophan; VHL, von Hippel-Lindau.

Then, the immune system cannot completely eliminate the tumor cells to reach a state of equilibrium. Finally, with the emergence of new tumor cell variants, an immunogen was selected. Cells with low resistance or immune resistance reach the final immune escape stage (2). Meanwhile, recent studies have shown that immune cells have unique metabolic characteristics that affect their immune function, and metabolic reprogramming is an important step in activating immune cells (4). It is these metabolic changes that further influence the immune system during cancer development, which promote the progression of cancer.

REPROGRAMMING OF METABOLISM FOR CANCER PROGRESSION

Cancer cells are well-known for their faster growth and proliferation than normal cells, and in order to meet such demands, they must reprogram cell's metabolism (5). Glucose metabolism produces ATP mainly through the oxidation of its carbon bonds. The end product can be lactic acid (anaerobic glycolysis pathway) or carbon dioxide (oxidative phosphorylation pathway) after glucose is completely oxidized by mitochondrial respiration. In tumor cells, even in the presence of oxygen and fully functioning mitochondria, glucose uptake rates increase dramatically and lactic acid is produced, known as the Warburg effect (6). Although the amount of ATP produced by glycolysis is small, its production rate is much faster than that of oxidative phosphorylation (7). In addition, the Warburg effect of tumor cells leads to increased production of lactic acid and extracellular pH of tumor microenvironment (TME), which is conducive to the processes of metastasis, angiogenesis, and immunosuppression (8). The Warburg effect is caused by a number of mechanisms. For example, glucose transporters mediate glucose transport, the first step in glycolysis, while PTEN and GLUT1 expression in the tumor cytoplasm is inversely correlated. Increased membrane expression and glucose uptake GLUT1, enhancing the Warburg effect (9). In addition, in renal cancer cells lacking von Hippel-Lindau tumor suppressor (VHL), HIF-1 also inhibits metabolism in the tricarboxylic acid (TCA) cycle by directly activating PDK1 (10).

In order to meet the rapid proliferation of cancer cells, the demand for amino acids increased significantly. Increased glutamine metabolism is a common metabolic change. Glutamine catabolism is catalyzed by glutaminase (GLS) to produce glutamic acid. Oncogenic transcription factor cMyc activates GLS expression and metabolism in tumor cells (11).

In cancer cells, the biosynthesis of fatty acids (FA) is more active, and cancer cells typically achieve higher lipid accumulation in the form of lipid droplets than normal cells. After the citric acid is produced by TCA cycle in mitochondria, the citric acid carrier (CIC) is transferred from the inner membrane of mitochondria to the cytoplasm and then enters *de novo* synthesis. CIC levels are elevated in many cancer cells, and its activity is necessary for tumor proliferation *in vitro* and tumorigenesis *in vivo* (12). In summary, tumor cells have reprogrammed their metabolism to affect normal cell

metabolism while gaining much greater proliferation capacity than normal cells.

GLUCOSE METABOLISM AND TUMOR IMMUNITY

T cells are one of the important cells of tumor immunity, and it is necessary to express specific antigen in tumor. The anti-tumor activity of T cells is greatly influenced by cell metabolism. Therefore, in the process of tumor development, metabolic reprogramming of cells inevitably affects the anti-tumor activity of T cells (13). Normally, anaerobic glycolysis is the key to maintaining T-cell immune function (14). When blood glucose is normal, T cells up-regulate glucose transporter 1 and then promote glucose uptake and anaerobic glycolysis when stimulated by antigens (15). In acute infection, apoptotic T cells and memory T cells independent of anaerobic glycolysis are produced and undergo aerobic glycolysis (16).

As previously mentioned, the Warburg effect of tumor cells significantly increases the content of lactic acid in TME, a pro-inflammatory agent that activates the IL-23/IL-17 pathway, leading to inflammation, angiogenesis, and cell remodeling. Meanwhile, the increase of lactic acid in TME leads to the decrease of pH value, and the expression of arginase I (ARG1) in macrophages increases after the acidification of TME, thus inhibiting the proliferation and activation of T cells (17).

It is well known that programmed death ligand 1 (PD-L1, also known as CD274, and B7-H1) binds to its receptor PD-1 to produce effects. PD-1 is a cell surface protein that is widely present on the surface of T cells, NK cells and dendritic cells (DC) (18). The combination of PD-L1 and PD-1 triggers inhibitory signaling, thereby suppressing the role of T cells (19). Shaojia Wang et al. found that overexpression of PD-L1 in cervical cancer cells increases glucose metabolism and is associated with tumor metastasis. From a mechanistic perspective, PD-L1 directly binds to integrin $\beta 4$ (ITGB4) and activates the AKT/GSK3 β signaling pathway to induce the expression of the transcriptional repressor SNAI1. SNAI1 can affect the epithelial-mesenchymal transition and the expression of genes regulating glucose metabolism by inhibiting the activity of SIRT3 promoter, thereby inhibiting T cell action and promoting tumor immune escape. The high expression of PD-L1 and ITGB4 in human cervical cancer is closely related to T cell function inhibition, tumor lymph node metastasis and poor prognosis (20). Siska Peter J et al. discovered that in patients with B-cell leukemia, the expression of PD-1 and TIM3 will increase, which will cause the activation of T cells, but will also lead to a decrease in T cell reactivity at the same time. Due to the increased expression of PD-1 and TIM3, it can genetically cause a decrease in Akt/mTORC1 signaling or Glut1 expression, resulting in impaired T cell metabolism and inhibiting T cell function (21). Co-stimulation and inhibitory signals jointly regulate the anti-tumor ability of tumor antigen-specific T cells. In the past, we always tried to restore the function of unresponsive T cells by blocking the inhibitory pathway. On the contrast, there have been opinions that provide T cells with extra co-stimulation signals can also enhance its anti-tumor

function recently. Polesso Fanny et al. demonstrated a synergistic effect of targeted blockade of PD-L1 and the provision of a co-stimulatory agonist to OX40, which can increase the glucose metabolism of CD8⁺ T cells and the acquisition of granzyme B by regulatory T cells, which increase the existence and function of tumor antigen-specific CD8⁺ T cells (22).

MicroRNA is an important substance regulating T cell immunity (23). Zhang Tengfei et al. examined the effect of miR-143 on the differentiation and function of T cells, and found that in esophageal cancer cell lines, overexpression of miR-143 inhibited the glucose transporter 1 (Glut-1) in T cells, inhibiting the glucose uptake and glycolysis of T cells, thereby regulating the differentiation of T cells and inhibiting the antitumor effect of T cells (24). In addition, Zhao Ende et al. found that ovarian cancer cells restrict the glucose uptake of T cells by maintaining the high expression of miR-101 and miR-26a, which weaken their function and thereby limit their methyltransferase EZH2 expression. Under normal circumstances, EZH2 can inhibit the Notch repressors Numb and Fbxw7 by trimethylating the histone H3 located at Lys27, and then further activate the Notch pathway to stimulate the expression of T cell multi-factors and transmit Bcl-2 signal to promote their survival (25).

Generally speaking, as a part of immune cells, neutrophils are important to provide immune protection to the body. However, in cancer, neutrophils can destroy the function of T cells through reactive oxygen species (ROS), thereby promoting tumor progression. We generally believe that neutrophils rely entirely on glycolysis to produce energy. Research by Rice Christopher M et al. revealed that immature c-Kit neutrophil subsets can participate in oxidative mitochondrial metabolism. In the TME, due to insufficient glucose supply, oxidative neutrophils can oxidize mitochondrial FA to generate NADPH oxidase-dependent ROS, and then inhibit the role of T cells to maintain local immune suppression. Consistent with this, neutrophils in peripheral blood of cancer patients generally show immature status, and the content of mitochondria and the degree of oxidative phosphorylation have increased (26).

A molecule called TIGIT exists on the surface of T cells, which is an immune checkpoint molecule that inhibits T cell responses. He Weiling et al. evaluated the role of TIGIT checkpoints in the occurrence and development of gastric cancer. They found that the proportion of CD8⁺ T cells expressing TIGIT on the surface of gastric cancer patients increased. In addition, gastric cancer tissues and cell lines also expressed CD155, which combined with TIGIT to restrict the glucose uptake of CD8⁺ T cells and then weaken the function of CD8⁺ T cell effector molecules, causing these cells to exhibit functional failure and impairing their activation, proliferation, cytokine production, and metabolism. Once CD155 is silenced, T cell metabolism in gastric cancer tumor cells is more active than before, and IFN- γ production is increased. Similarly, targeting CD155/TIGIT can enhance CD8⁺ T cell response and improve the survival rate of experimental animals (27).

In tumor immunotherapy, the biggest obstacle is the immunosuppressive microenvironment induced by regulatory T (Treg) cells. Treg can induce normal cell death and suppress effector T cells by mediating accelerated glucose depletion. Li

Lingyun et al. discovered that TLR8 signal transduction can selectively inhibit glucose uptake and glycolysis in Treg, thereby reversing Treg's inhibitory function, which can be a feasible method to promote tumor immunotherapy (28).

A large number of clinical evidences show that T cell immunotherapy is of great benefit to the prognosis of tumor patients. However, many studies have found that in solid cancers, this type of immunotherapy is often limited due to down-regulation of MHC I antigen presentation. In view of this, the relevant experiments designed by Marijt Cohen et al. showed that the phosphorylation signal transducer STAT1 failed to express itself in tumor cells for the reason that time was an anoxic environment and glucose deficiency, which resulted in a decrease in MHC class speech antigen even in the presence of sufficient stimulating cytokine IFN- γ . In cancer cells under this TME, the activity of PI3K in tumor cells increased, leading to the decreased sensitivity of CD8⁺ T cells to tumor recognition (29). Catalan Elena et al. also found that the deficiency of ERK5 expression and the decrease of MHC I expression in tumor cells made tumor cells more prone to glycolysis, which would help tumor cells to escape the immune monitoring of cytotoxic T cells (CTL). Furthermore, through further research on leukemia EL4 cells and L929-transformed fibroblasts, they also concluded that tumor cells are sensitive to CTL when MHC-1 is at a low expression level in tumor cells. At the same time, the sensitivity to NK cells has been improved. However, when its MHC-1 expression is completely deleted, tumor cells can promote mitochondrial oxidative phosphorylation to increase the efficacy of tumor immunotherapy (30).

Whether fighting infection or defending against cancer, CD8⁺ memory T cells (Tm) are the basis of immunity, whose activity is controlled by metabolic activity. Under normal circumstances, CD8⁺ Tm up-regulates PCK1 in the cytoplasm -a key molecule that regulates glycolysis, tricarboxylic acid cycle, and gluconeogenesis, increases glycolysis and promotes the breakdown of glycogen to glucose 6-phosphate, and then generates a large amount of NADPH through Pentose Phosphate Pathway (PPP) to ensure that glutathione is at a high level in Tm. Ma Ruihua et al. found that the pathway mentioned above were inhibited during the development of tumors, causing the GSH/GSSG ratio in Tm decreased, which result in obstacles to Tm formation and impaired function (31).

As shown in **Table 1**, these molecules are all associated with glucose metabolism and tumor immunity. Glucose-related metabolic abnormalities in tumor cells can affect the TME. At the same time, tumor cells competitively absorb glucose from the extracellular environment, resulting in decrease in glucose in T cells, thereby inhibiting T cell energy supply, blocking synthesis and affecting T cell function (**Figure 1**).

FATTY ACID METABOLISM AND TUMOR IMMUNITY

Macrophages and Fatty Acid Metabolism

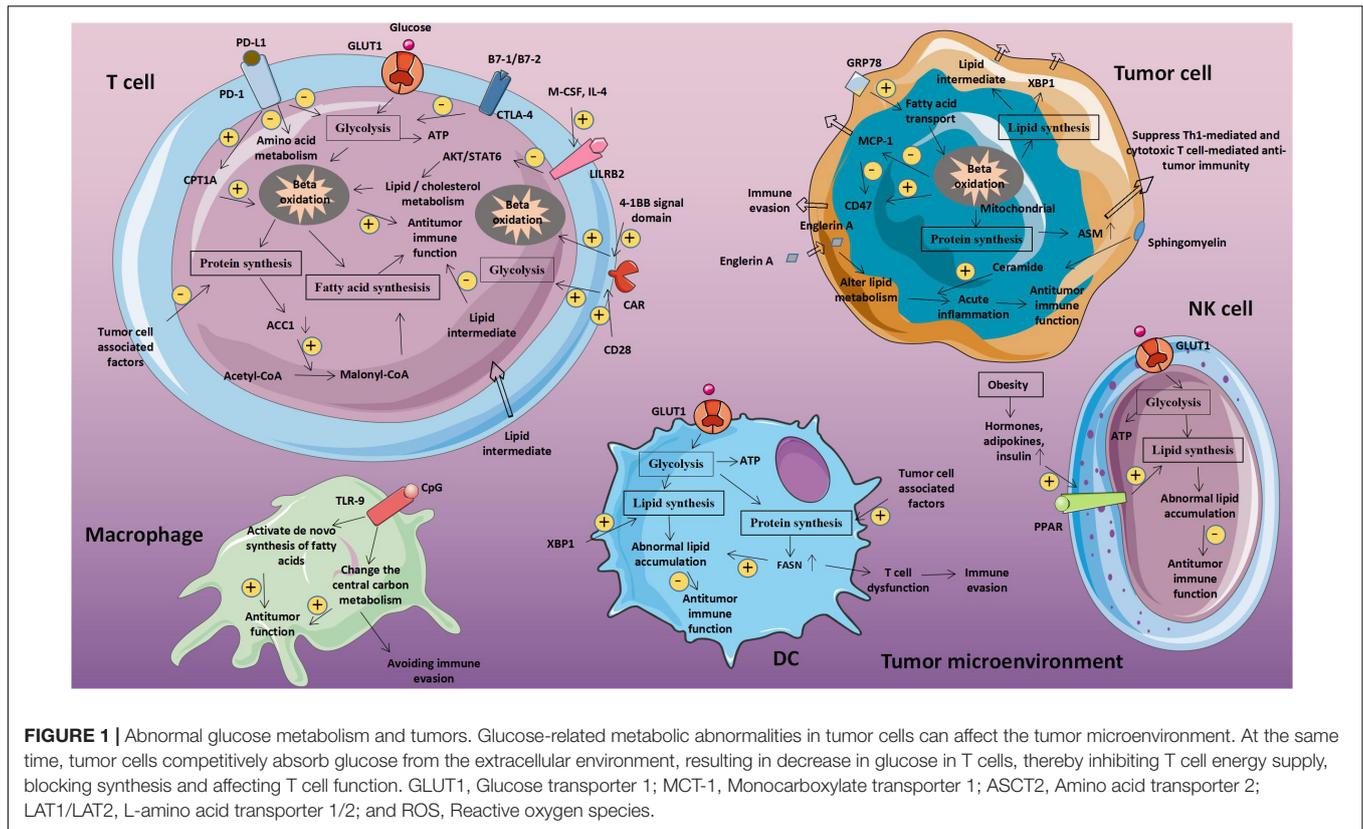
Macrophages are widely present in all tissues, and have strong plasticity and functional diversity. Macrophages are involved

TABLE 1 | Glucose metabolism and tumor immunity.

Molecules/drugs	Status	Major effects	Pathway	Tumor types	Type of Immune cells	References
PD-L1	Up	Promote tumor cell glycolysis impede T cell glycolysis and IFN- γ production	AKT/MTOR pathway	Ovarian cancer	T cells	(25)
STAT3 Wnt- β -catenin	Down	Improve long-term survival and anti-tumor activity of T cell	Reduce glycolysis, increase fatty acid oxidation	–	T cells	(88, 89)
HIF	Up	T cell dysfunction	Increase glucose transporter expression, and mTOR activation	–	T cells	(90)
GAPD	Up	T cell dysfunction	Block translation of IFN- γ from mRNA	–	T cells	(91)
Foxp3	Up	TCR-stimulated T cells preferentially differentiate into Tregs	Reduce the expression of Myc, leading to reduced glycolysis and increased oxidative phosphorylation	–	T cells	(92)
CTLA-4	Up	Preventing activation and differentiation of naive CTLs	CTLA-4 competes for the same ligands as CD28	–	T cells	(93)
Oxamate	–	Arrest the growth of tumor cells	Inhibit LDH production	–	T cells	(94)
AMPK	–	Protect CTLs from apoptosis and promote effector functions	Down-regulate glycolytic gene expression	Colon cancer	T cells	(95)
PD-1 TIM3	Up	T cell dysfunction	Defective Akt/mTORC1 signaling, reduced expression of Glut1 and hexokinase 2, and decreased glucose metabolism	B cell leukemia	T cells	(21)
IRE1 α -XBP1	Up	Decrease the ability of T cells to infiltrate tumor tissues and reduce the expression of IFNG mRNA	Inhibit activity of mitochondrial	Ovarian cancer	T cells	(58)
miR-143	Up	Inhibit T cell glucose uptake and glycolysis	Glut-1	Esophageal cancer	T cells	(24)
miR-101 miR-26a	Up	Restrict glucose uptake by T cells	Notch	Ovarian cancer	T cells	(25)
ROS	–	Disrupt the function of T cells	Oxidized mitochondrial fatty acid	–	T cells	(26)
STAT1	Down	CD 8 T cells are not sensitive to tumor recognition	Down-regulation of MHC I antigen presentation	–	CD8 ⁺ T cells	(29)
PD-L1	Block	Increase the presence and function of tumor antigen-specific CD8 T cells	Glucose metabolism of strong CD8 T cells	–	CD8 ⁺ T cells	(22)
Lactic acid	Up	Inhibition of T cell proliferation and activation	Increased expression of ARG1 in macrophages	–	T cells	(17)
ERK5 MHC I	Down	Helps tumor cells escape immune surveillance of CTL	Promote glycolysis of tumor cells	–	T cells	(30)
PD-L1 ITGB4	–	Inhibit T cell	AKT/GSK3 β	Cervical cancer	T cells	(20)
TIGIT	Up	Limiting glucose uptake by CD8 T cells	CD155 binds TIGIT receptor	Gastric cancer	CD8 ⁺ T cells	(27)
Pck1	Down	Tm formation obstacle	Reduced GSH/GSSG ratio in Tm	–	Tm cells	(31)
TLR8	–	Reverse Treg inhibition	Selective inhibition of glucose uptake and glycolysis in Treg	–	Tregs	(28)

in the initiation and development of a variety of diseases, and therefore have become important intervention targets for diseases. Macrophages mainly depend on glycolytic metabolism capacity, but fatty acid levels in cells can also significantly affect

cell function. The protein chaperone glucose-regulated protein 78 (GRP78) can mediate the endoplasmic reticulum (ER) stress pathway and cause an unfolded protein response. Studies on breast cancer cells showed that after the expression of GRP78



on the surface of cancer cells is silenced, fatty acid transport in mitochondria is inhibited, which reduces fatty acid oxidation and increases the concentration of unsaturated FA in the cell. Animal experiments by Cook Katherine L et al. showed that inhibiting GRP78 or reducing linoleic acid content in cells could increase MCP-1 in serum and reduce CD47 expression, thus increasing macrophage infiltration (32).

Macrophages enhance the body's anti-tumor immunity by phagocytosing and killing tumor cells. Liu Mingren et al. found that cancer cells express CD47 to achieve immune escape, which can be avoided by CpG oligodeoxynucleotides—a Toll-like receptor 9 agonist. CpG oligodeoxynucleotides can change the central carbon metabolism of macrophages. It can enhance the anti-tumor immune activity of macrophages and promote the phagocytosis of CD47 expressing cancer cells by macrophages. Since CpG activates the *de novo* synthesis of FA, it gives macrophages anti-cancer potential (33).

T Cells and Fatty Acid Metabolism

Studies have shown that the energy supply of T cells mainly depends on anabolic metabolism, such as aerobic glycolysis. But fatty acid metabolism can regulate the immune function activity of T cells, including the balance between effector T cells (Teff) and T cells (34). At the same time, Treg is also involved in the up-regulation of FAO gene expression, and the increase in FAO levels can further promote the generation of Treg cells (35). In addition, FAO plays an important role in the production and maintenance of Tm cells (36).

The development of cancer will lead to changes in lipid metabolism, causing a change in the proportion of metabolic intermediates, which will have a certain impact on the immune system. Wefers Christina et al. collected cancerous ascites from patients with ovarian cancer and studied it. It was found that T cells obtained from cancerous ascites could not proliferate normally after antigen stimulation, and lymphocytes could not proliferate in the acellular area of ascites. They compared cancerous ascites with normal ascites and found the difference between them is in lipid regulation, which indicates that lipid intermediates are present in ascites of ovarian cancer patients, leading to T cell dysfunction (37).

Tumor-associated bone marrow cells create an immunosuppressive microenvironment within the tumor. Leukocyte immunoglobulin-like receptor B (LILRB) family members are negative regulators of myeloid cell activation. Chen Hui-Ming et al. regulate tumor-associated myeloid cells through LILRB. In the presence of M-CSF and IL-4, LILRB2 inhibits the activation of AKT and STAT6, alters lipid/cholesterol metabolism, inhibits the infiltration of granulocyte MDSC and Treg, and significantly enhances the immune activity of T cells and promotes anti-tumor immunity (38).

Tumor cells cause metabolic reprogramming of T cells. Patsoukis Nikolaos et al. found that when PD-1 is connected, although activated T cells cannot perform glycolysis and amino acid metabolism, in this state, PD-1 can increase its fatty acids beta oxidation (FAO) rate by increasing the expression of CPT1A. At the same time, they also found that CTLA-4 can inhibit T

cell glycolysis without increasing FAO, because it maintains an unactivated state and inhibits T cell antitumor immunity (39).

The conversion of cell membrane sphingomyelin (SLs) to ceramide requires the participation of acid sphingomyelinase (ASM). In cancer cells, ASM-mediated production of ceramide is essential for cell apoptosis, proliferation, and immune regulation. Kachler Katerina et al. demonstrated that in patients with non-small cell lung cancer (NSCLC), ASM activity is increased in TME and serum, and its increase can significantly inhibit Th1-mediated and CTL-mediated anti-tumor immunity, which promotes the development of tumors (40). In addition, Batova Ayse et al. discovered that Englerin A in renal clear cell carcinoma (cc-RCC) significantly changes its lipid metabolism, and ceramide may be a mediator of Englerin A production, helping Englerin A to induce acute inflammatory response and mediate anti-tumor immunity (41). FA are important components of cell membranes, signal molecules, and bioenergy substrates. Accompanying the functional and metabolic changes that occur during the activation and differentiation of CD8⁺ T cells, fatty acid metabolism will also have corresponding changes. Lee JangEun et al. found that the tumorigenesis process is often accompanied by the loss of T cell-specific acetyl-CoA carboxylase 1 (ACC1). ACC1 catalyzes the conversion of acetyl-CoA to malonyl-CoA, which is a carbon donor in the process of long-chain fatty acid synthesis. Thus the lack of ACC1 will cause serious defects in CD8⁺T cells and promote tumor immune escape (42).

CARs are widely used clinically to redirect T cells to the cytotoxicity of cancer cells. However, the CAR's co-stimulatory domain that affects CAR-T cell persistence and effector capacity is still uncertain. Kawalekar Omkar U et al. reported the effect of co-receptor CD28 and 4-1BB signaling domains on the metabolic characteristics of human CAR-T cells. Among them, 4-1BB increases the fatty acid oxidation of CD8⁺ T cells and mitochondrial biogenesis to promote its growth, while CD28 enhances the glycolysis of CAR-T cells, which provides a theoretical basis for the future application of CAR-T cell therapy (43).

Dendritic Cells and Fatty Acid Metabolism

Fatty acid metabolism connects innate and adaptive immune responses by regulating DC function. In addition, DC cells are necessary to initiate and maintain T-cell-dependent anti-tumor immunity. Tumor cells usually evade immunosuppression by weakening normal DC function. Cubillos-Ruiz Juan R et al. found that the ER stress response factor XBP1 can directly promote tumor growth. In ovarian cancer, XBP1, which is promoted by lipid peroxidation byproducts, is activated to induce tumor-associated DC (tDC) to initiate triglyceride biosynthesis procedures, leading to abnormal lipid accumulation and subsequently inhibit tDC's ability to support anti-tumor T cells, thereby achieving the purpose of inactivating anti-tumor immunity and promoting tumor development (44).

Fatty acid synthase (FASN), a key metabolic enzyme for fatty acid synthesis, can directly promote tumor proliferation and

metastasis. In the study by Jiang Li et al., it was described that the later the clinical stage of ovarian cancer, the more obvious the increase of FASN expression is, and it is related to the state of immune suppression. They proposed that the intrinsic FASN of tumor cells promotes the development of ovarian cancer by weakening anti-tumor immunity, and found that the activation of FASN in cancer cells can lead to an increase in lipid concentration in TME, and the accumulation of abnormal lipids inhibits the ability of tumor infiltration DC (TIDC) to support anti-tumor T cells. DC fail to present antigens and primary T cell is disability when they are cultured in the ascites of ovarian cancer patients with activated FASN, which further support this view. In short, ovarian cancer endogenous FASN can induce tumor cells' immune escape through lipid accumulation in TIDC and subsequent T cell rejection and dysfunction (45).

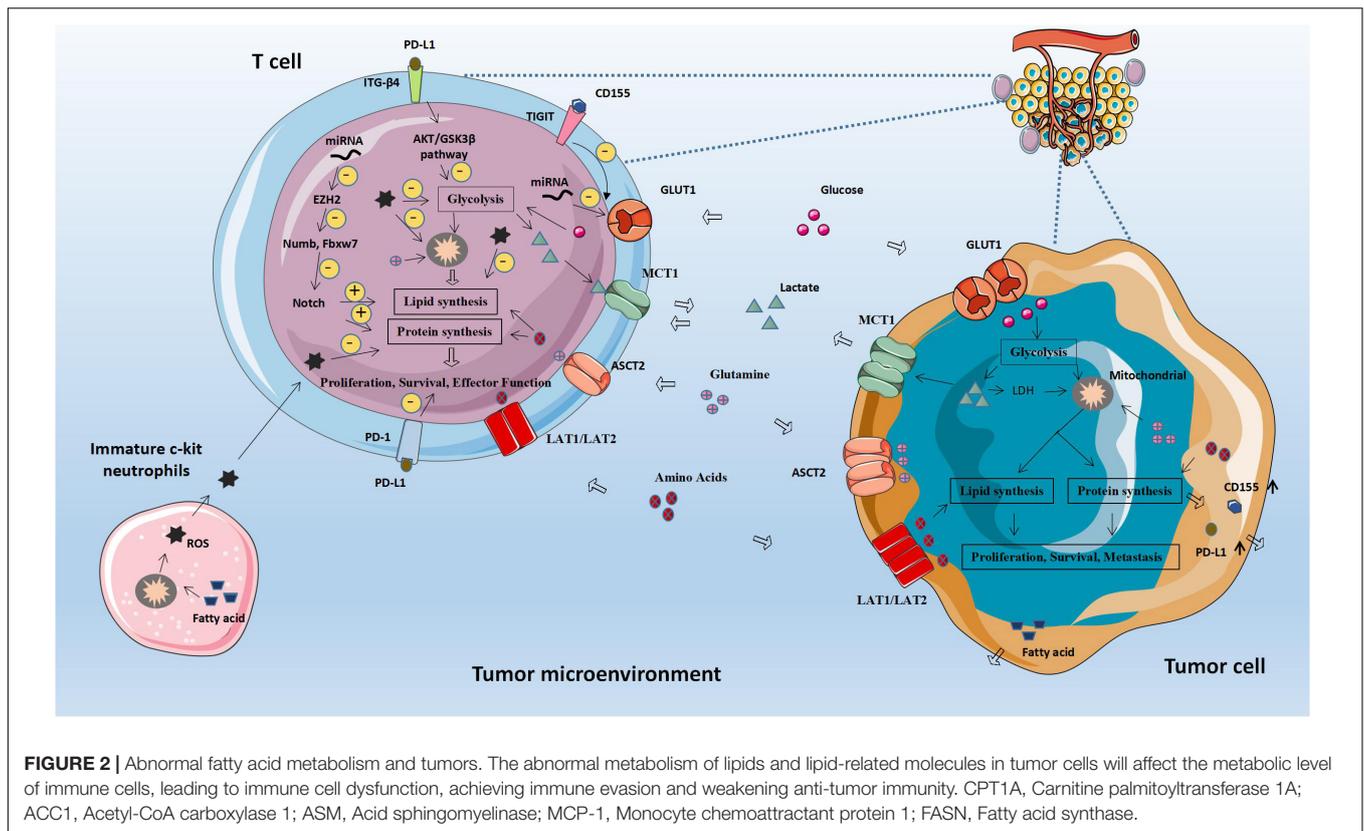
NK Cells and Fatty Acid Metabolism

In some cancers, more than 49% is attributed to obesity, which may because of excessive production of hormones, adipokines and insulin. Cytotoxic immune cells are essential for immunodetection. Michelet Xavier et al. proposed that obesity-induced peroxisome proliferator-activated receptor (PPAR) drive lipid accumulation in NK cells and then leads to impaired cell metabolism and transport, which weakens the antitumor response of NK cells (46). Therefore, the abnormal metabolism of lipids and lipid-related molecules in tumor cells will affect the metabolic level of immune cells, leading to immune cell dysfunction, achieving immune evasion and weakening anti-tumor immunity (Figure 2 and Table 2).

AMINO ACID METABOLISM AND TUMOR IMMUNITY

T lymphocyte metabolism changes with its functional status (47). For resting T cells, only low oxidative phosphorylation is required to maintain their normal life activities. When T cells are activated, they must proliferate in large numbers to produce sufficient effector cells. At this time, the metabolic requirements of T cells are significantly increased, and the main pathway of energy production also changes from low levels of oxidative phosphorylation to high levels of glycolysis and amino acid metabolism to support the synthesis of nucleotide and lipid, which is necessary for its growth and proliferation (48).

During the tumorigenesis process, due to many physiological changes, some new immune checkpoints will be generated, and these physiological changes can reprogram the inflammation, immune and metabolic processes in malignant lesions and local lymphoid tissues, thus constituting a TME that suppresses immune effects. Elevated catabolism of tryptophan (Trp) and arginine (Arg) is a common TME marker in the clinical manifestations of cancer. Indoleamine 2,3 dioxygenase (IDO) and arginase 1 (ARG1) break down Trp and Arg, respectively, and respond to inflammatory signals including interferon and TGFβ cytokines (49). Amino acid degradation reactions mediated by IDO and ARG1 have become key factors in regulating tumor-induced immune tolerance. Tryptophan



degrading enzymes and arginine degrading enzymes expressed by tumors and tumor infiltrating cells can effectively impede cancer-specific immune responses (50).

Originally, tryptophan dioxygenase (TDO) was considered to be the only enzyme capable of metabolizing L-tryptophan, which is an essential amino acid. However, IDO was later found in rabbits and proved to be able to metabolize both L-tryptophan and D-tryptophan at the same time (51). IDO is associated with a variety of immune diseases such as cancer, allergies, autoimmunity, and inflammation. In some tumors, there is abundant lymphocyte infiltration around IDO1-expressing tumor cells, which means that IDO expression may be the result of IFN- γ expression and drug resistance mechanisms. In other cancers, IDO1 expression is constitutive, while tumor cells expressing IDO1 are surrounded by fewer lymphocytes (52).

Indoleamine 2,3 dioxygenase 1 and TDO contain a group of enzymes that are required for the first step in catalyzing the decomposition of Trp into kynurenine (Kyn), and also the rate-limiting step of this reaction. The Kyn generated by this reaction is further converted into the high-energy substrate NAD (+) and ATP, which energize cell activity, and in tumor cells, IDO activity significantly increases, which causes the lack of Trp in TME and the accumulation of downstream product Kyn, while the depletion of Trp and the excessive accumulation of Kyn induce effects T cell apoptosis, dysfunction and induction of immunosuppressive regulatory T cells. In short, tryptophan metabolism is essential for cell proliferation, inflammatory response and immune regulation,

and accelerated tryptophan breakdown promotes immune escape of tumors (53–55).

As described previously, the catabolism of arginine is significantly increased in tumor tissues, which can lead to a decrease in the intracellular L-arginine concentration. L-arginine levels are closely related to the activation and maintenance of T cells. High levels of L-arginine can promote the metabolism of T cells from glycolysis to oxidative phosphorylation, thereby activating T cells and promoting the production of central memory cells. In contrast, low L-arginine concentrations in tumor tissues hinder T cell activation and inhibit T cell function (56). And myeloid-derived suppressor cells (MDSCs) are heterogeneous populations of immature cells that expand during the inflammatory process caused by tumor tissues and then increase the metabolism of L-arginine (L-Arg) by ARG1 and nitric oxide synthase 2 (NOS2), thereby suppressing the immune capacity of T cells (57).

Tumors can create a microenvironment that interferes with metabolism and effector functions of T cell to escape immune control. Ovarian cancer tissue can induce ER stress and activate the IRE1 α -XBP1 arm of T cells involved in protein expansion response, thereby controlling the mitochondrial function and antitumor ability of T cells. The study of T cells isolated from ovarian cancer patients found that up-regulation of XBP1 would reduce the ability of T cells to infiltrate tumor tissues and reduce the expression of IFNG mRNA. Tumor tissue can inhibit the uptake of glucose in T cells and cause defects in intracellular N-catenin glycosylation,

TABLE 2 | Fatty acid metabolism and tumor immunity.

Molecules/drugs	Status	Major effects	Pathway	Tumor types	Type of Immune cells	References
PD-L1	Up	Reduces cytokine secretion by activated CTLs	Up-regulating fatty acid oxidation through increased expression of CPT-I	–	T cells	(39)
Fenofibrate		Induce T cells to engage fatty acid catabolism	PPAR α	–	T cells	(96)
CD47	Up	Avoidance of metabolic changes in central carbon of macrophages	CpG oligodeoxynucleotide	–	Macrophages	(33)
GRP78	–	Increased macrophage infiltration	Increase MCP-1 serum levels and decrease CD47 expression	–	Macrophages	(32)
LILRB	–	Enhance the immune activity of T cells	Inhibits AKT and STAT6 activation	–	T cells	(38)
ASM	Up	Inhibition of Th1-mediated and cytotoxic T cell-mediated anti-tumor immunity		NSCLC		(40)
XBP1	–	Inhibition of tDC support against tumor T cells	Induction of tDC initiates triglyceride biosynthesis program	Ovarian cancer	DC	(44)
ACC1	Down	Severe defects in CD8 T cells	Catalyzes the conversion of acetyl-CoA to malonyl-CoA	–	CD8 T cells	(42)
CD28 4-1BB	–	Promote the growth of CD8 T cells	Increases fatty acid oxidation and mitochondrial biogenesis in CD8 T cells	–	CD8 T cells	(43)
PPAR	–	NK cell metabolism and transport disorders	Drives NK cell lipid accumulation	–	NK cells	(46)
FASN	Up	Inhibits the ability of T1DC-supported anti-tumor T cells	Causes increased lipid concentration in TME	–	T cells	(45)

which triggers the activation of IRE1 α -XBP1. The induction of XBP1 regulates the abundance of glutamine carriers on T cell membranes, which prevents glutamine from entering mitochondria under conditions of glucose deficiency. And glutamine is necessary for mitochondrial respiration. Thus XBP1 ultimately inhibits the activity of mitochondria and hinders the production of IFN- γ (58). One of the hallmarks of renal clear cell carcinoma is glutamine addiction. Excessive consumption of glutamine caused by glutamine addiction can result in local deprivation of glutamine outside the cell, which can induce macrophages to secrete IL23 through activation of hypoxia-inducible factor 1 α (HIF1 α), and IL23 activates the proliferation of Treg cells, promotes the expression of IL10 and TGF β , thereby inhibiting cytotoxic lymphocytes from killing tumor cells and coordinating immune escape (59).

It was reported that DC-HIL binds to syndecan-4 on effector T cells and produces an inhibitory effect on T cells. The concentrations of IL-1 β and IFN- γ in melanoma tissues are

higher than those in normal tissues. Both of them can induce the expression of DC-HIL through tumor-infiltrating CD11b (+) Gr1 (+) cells. DC-HIL can promote intracellular immune receptor tyrosine activation phosphorylation, induce intracellular expression of IFN- γ and nitric oxide synthase, and further inhibit T cell function (60).

L-amino acid oxidase (LAAO) is a flavin adenine dinucleotide-dependent enzyme, the most typical of which is IL4I1, which mainly oxidizes L-phenylalanine. IL4I1 can inhibit T cell proliferation and cytokine production by limiting the ability of T cells to respond to the stimulation of cloned receptors. In addition, IL4I1 can also promote the differentiation of naive CD4⁺T cells into regulatory T cells, thereby suppressing effector T cells' function (61). The metabolism of abnormal amino acids and amino acids related molecules in tumor cells will affect the expression of metabolism-related genes in immune cells, thus leading to the increased expression of molecules that promote tumor proliferation and weaken anti-tumor immune effects (**Figure 3** and **Table 3**).

DRUG RESISTANCE AND METABOLISM

Many drugs were originally designed to inhibit certain specific targets, and later experiments have shown that their effects are related to metabolism. And metabolic reprogramming may also be a way for cancer cells to escape from the selective inhibition of target drugs and become resistant.

Amino Acid Metabolism and Drug Resistance

Immunotherapy has become the main means of fighting cancer. However, for breast cancer, its responsiveness to immunotherapy is low, so it is necessary to find effective strategies to overcome the resistance of immunotherapy. Among them, triple negative breast cancer (TNBC) is the most difficult Type, which is largely related to the plasticity of tumor cells and the persistence of cancer stem cells (CSC). Conventional chemotherapy methods have enriched CSC, leading to drug resistance and disease recurrence. Showalter Lorale E et al. found that the expression of histone lysine-specific demethylase 1 (LSD1) is inversely proportional to chemokine CCL5 levels that attract CTLs, while the use of LSD1 inhibitors combined with PD-1 antibodies can significantly increase the infiltration of CD8⁺ T cells and reduce the tolerance of TNBC to chemotherapy drugs (62, 63). In addition, Chen Weilong et al. found that during

the taxane-containing chemotherapy, the CC motif chemokine ligand 20 (CCL20) was significantly elevated, which is activated by protein kinase C ζ (PKC ζ) or p38 mitogen Protein kinase (MAPK) -mediated NF- κ B activation to promote self-renewal and maintenance of CSC or breast cancer stem-like cells, while NF- κ B activation increases CCL20 expression, forming a positive feedback loop between the NF- κ B and CCL20 pathways, providing continuous momentum for chemo-resistance in breast cancer cells (64–66). Yu Shiyi et al. found that heat shock protein 90 (HSP90) and histone deacetylase 6 (HDAC6) are promising anticancer drug targets. Anti-HDAC6 can effectively improve the resistance of TNBC to tamoxifen (67, 68). In HER2 (+) breast cancer, the targeted anticancer drug lapatinib can directly interfere with HER-2 signaling to inhibit cancer cell proliferation. When patients show resistance to lapatinib, combined application of Th1 cytokines can greatly inhibit the metabolism of cancer cells, enhance the metabolic inhibition induced by lapatinib, and almost abolish drug resistance (62).

Over-activation of tyrosine kinase (JAK) and related transcription factors STAT3 and STAT5 in the cytoplasm of tumor cells can be found in most of the malignant tumors. JAK/STAT3 signal transduction has the ability to suppress tumor immunity, and the application of JAK inhibitors in colon cancer can suppress sporadic colon cancer caused by mutations in APC inhibitory genes, and it may also provide treatment opportunities for other oncogenes with resistance (69). Inhibitory LILRB1-5

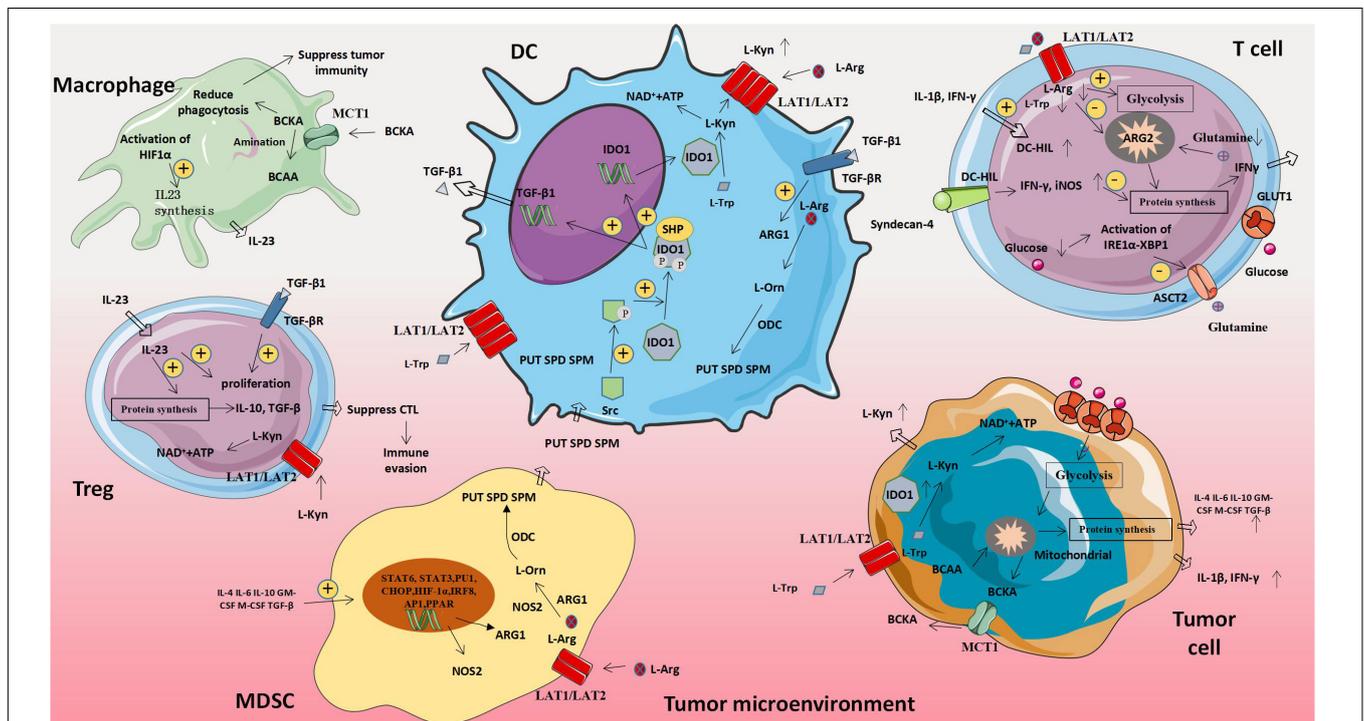


FIGURE 3 | Amino acid-related metabolic abnormalities and tumors. The metabolism of abnormal amino acids and amino acids related molecules in tumor cells will affect the expression of metabolism-related genes in immune cells, thus leading to the increased expression of molecules that promote tumor proliferation and weaken anti-tumor immune effects. MDSC, Myeloid-derived suppressor cell; ARG1, Arginase 1; L-Orn, L-Ornithine; L-Arg, L-Arginine; L-Trp, L-Tryptophan; L-Kyn, L-Kynurenine; PUT, Putrescine; SPD, Spermidine; SPM, Spermine; ODC, Ornithine decarboxylase; NOS2, Nitric oxide synthase 2; BCAA, Branched chain amino acid; and BCKA, Branched keto acid.

TABLE 3 | Amino acid metabolism and tumor immunity.

Molecules/drugs	Status	Major effects	Pathway	Tumor types	Type of Immune cells	References
SLC1A5	Up	Impairs proliferation and the release of INF-g by activated murine splenic T cells	Reduce extracellular glutamine concentration	–	T cells	(97)
IDO	Up	Induce cell cycle arrest, anergy and apoptosis in T cells	Catalyze the conversion of tryptophan to kynurenine	–	T cells	(98)
Rapamycin	–	Activate glutamate dehydrogenase and stimulate the glutamine mitochondrial uptake; favor the generation of memory-like T cells	mTORC1	–	T cells	(99)
ASCT2	Down	Block the induction of T helper 1 (Th1) and Th17 cells	Reduce T-cell glutamine uptake	–	T cells	(100)
Myc	Mutate	Reduced extracellular glutamine concentration	Tumor cell's high glutamine uptake	–	T cells	(101)
IL-1 β IFN- γ	Up	Inhibit T cell function	Induce DC-HIL expression by tumor infiltrating CD11b (+) Gr1 (+) cells	–	T cells	(60)
MDSC	Up	Suppress T-cell immunity	Increased L-Arg metabolism through arginase 1 and NOS2	–	T cells	(57)
L-arginine	Down	Suppress T-cell function	Prevents T cell metabolism from glycolysis to oxidative phosphorylation	–	T cells	(56)

signal through their immunoreceptor tyrosine-based inhibitory motif (ITIM) in their intracellular domain and recruit the phosphatase protein tyrosine phosphatase (PTPN), which can directly regulate the development, drug resistance and recurrence of cancer, and when PTPN is missing, it can induce the resistance

of CD 8 T cells to the inhibitory effect of TGF β , which can improve the sensitivity of tumor treatment (70–72). Tyrosine kinase inhibitor (EGFR-TKI) has achieved good clinical results in the treatment of patients with NSCLC. However, recent clinical studies have shown that Adenine nucleotide translocase-2

TABLE 4 | Drug resistance and metabolism.

Molecules/drugs	Status	Major effects	Pathway	Tumor types	Type of Immune cells	References
LSD1	Up	Decreases TNBC tolerance to chemotherapy drugs	LSD1 inhibitor combined with PD-1 antibody can significantly increase CD8 ⁺ T cell infiltration	TNBC	CD8 ⁺ T cells	(62)
CCL20	Up	Promote self-renewal of CSC or breast cancer stem-like cells	PKC ζ /MAPK	TNBC	–	(66)
JAK	Up	Promote colon cancer tolerance to chemotherapy drugs	APC	colon cancer	–	(69)
PTPN	Down	Improve the sensitivity of tumor treatment	Induces resistance of CD8 ⁺ T cells to TGF β inhibition	–	CD8 ⁺ T cells	(70)
ANT2	–	Promote tumor cell resistance to EGFR-TKI	–	NSCLC	–	(73)
IDO1	Up	Causes chemical and immune evasion	JAK1/STAT1 JAK1/STAT3	–	–	(75)
HIF1	Up	Promote tumor resistance to chemotherapy drugs	Promotes dissociation between glycolysis and the TCA cycle	–	–	(77)
PLA2	–	Restore cancer cells' sensitivity to chemicals	PI3K-AKT-mTOR	–	–	(82)

(ANT2) can promote tumor cells to EGFR-TKI resistance, in addition, the generation of EGFR-TKI function involves the ErbB receptor pathway, however, in cancer tissues that are resistant to EGFR-TKI, ErbB receptor-independent oncogenic pathway genes are overexpressed and the biosynthesis of partially inflammatory cytokines is too active, so it is speculated that using EGFR-TKI with antibody inhibitors may have a better chance of avoiding drug resistance (73, 74). In addition to being able to escape the cytotoxic effects of chemotherapy, multidrug-resistant cancer cells bypass the anti-cancer drug-induced immunogenicity. In their research, it was found that intracellular IDO1 activity and expression are both higher, JAK1/STAT1 and JAK1/STAT3 signaling have higher basic activities, and the STAT3 inhibitor PIAS3 is down-regulated. Campia Ivana et al. proposed that due to Constitutive activation of JAK/STAT/IDO1 axis, multidrug-resistant cells have a stronger degree of immunosuppression than chemically sensitive cells, leading to chemical and immune evasion, so destroying this axis may significantly improve chemoimmunotherapy regimens for tumors' drug-resistant (75).

Glucose Metabolism and Drug Resistance

In glucose metabolism, the TCA cycle is considered to be an internal clean metabolic pathway, which is essential for energy production and biosynthetic intermediates. Changes in the TCA cycle play a key role in tumorigenesis and inflammation, and have a certain relationship with tumor drug resistance mechanisms (76). Among the Warburg effects caused by tumors, HIF1 is the main hypoxia-induced transcription factor, which promotes dissociation between glycolysis and the TCA cycle, restricts the effective production of ATP and citric acid to prevent glycolysis. And the Warburg effect causes the accumulation of lactic acid, which will promote tumor progression, inhibit T cell function, and make it resist to some anti-tumor therapies. Therefore, the design of new anti-tumor drugs against HIF1 can solve the problem of tumor resistance to chemotherapeutics to a certain extent (77–80).

Fatty Acid Metabolism and Drug Resistance

Sphingomyelin is a necessary class of biologically active lipids, which are key components of cell membranes and are involved in cell differentiation, apoptosis, aging and other processes. Cancer cells usually show increased growth effects and escape from the cell death process. Studies have shown that enzymes involved in SL synthesis and catabolism can change in cancer cells, allowing cancer cells to acquire resistance properties (81).

Epithelial to mesenchymal transition (EMT) is a manifestation of malignant tumors, characterized by invasion and metastasis, enhanced chemical resistance, and escape from host immunity. We found that the inhibitory effect of PI3K-AKT-mTOR signal significantly reduced glycolysis and fatty acid oxidation and inhibited tumor growth, while phospholipase A2 (PLA2) can mobilize lysophospholipids and free FA to maintain fatty acid oxidation and oxidation phosphorylation, which reduces the inhibitory effect of PI3K-AKT-mTOR signaling, provides a new strategy for cancer treatment. In addition, the mTOR inhibitor PP242 can restore EMT, increase the expression of PD-L1 in cancer cells, and restore the sensitivity of cancer cells to chemical drugs (82–87). As shown in **Table 4**, these molecules are linked with drug resistance and metabolism.

CONCLUSION AND FUTURE PERSPECTIVES

The occurrence and development of tumors are accompanied by metabolic reprogramming. The effect of metabolism on immunity cannot be ignored. In this review, we provide a comprehensive overview of molecular, cellular, and microenvironmental mechanisms that together help understand how tumors can alter their own metabolism to achieve immune escape. Changes in the metabolism of sugar, fat, and amino acids affect immune cells. In order to use these metabolic characteristics to increase the efficacy of existing therapies, reduce the drug resistance of tumors or discover new treatments, many studies have been conducted in the field of tumor metabolic reprogramming. These studies describe the latest developments in the field and predict the problems that need to be solved.

AUTHOR CONTRIBUTIONS

FW, YC, and LW were responsible for gathering information of the related research and designing the review. WeZ, WuZ, and QW were responsible for language editing. WT, XP, and HC has contributed to information interpretation, editing, and critical revision of the manuscript. All authors read and approved the final manuscript.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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