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Emerging role of metabolic reprogramming in tumor immune evasion and immunotherapy

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Mounting evidence has revealed that the therapeutic efficacy of immunotherapies is restricted to a small portion of cancer patients. A deeper understanding of how metabolic reprogramming in the tumor microenvironment (TME) regulates immunity remains a major challenge to tumor eradication. It has been suggested that metabolic reprogramming in the TME may affect metabolism in immune cells and subsequently suppress immune function. Tumor cells compete with infiltrating immune cells for nutrients and metabolites. Notably, the immunosuppressive TME is characterized by catabolic and anabolic processes that are critical for immune cell function, and elevated inhibitory signals may favor cancer immune evasion. The major energy sources that supply different immune cell subtypes also undergo reprogramming. We herein summarize the metabolic remodeling in tumor cells and different immune cell subtypes and the latest advances underlying the use of metabolic checkpoints in antitumor immunotherapies. In this context, targeting both tumor and immune cell metabolic reprogramming may enhance therapeutic efficacy.

tumor microenvironment, metabolic reprogramming, infiltrating immune cells, tumor immune evasion, antitumor immunotherapy

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Introduction

Over the past few decades, the traditional tumor treatment methods of surgery, radiotherapy, chemotherapy, and targeted therapy have made incredible progress; however, these methods also have certain limitations (Ge et al., 2020; Wang et al., 2020a; Wang et al., 2020b). In recent years, tumor immunotherapy has become a powerful and promising treatment method to promote antitumor immune response (Peng et al., 2019). In general, immunotherapy is based on adoptive transfer of modified T-cell receptor (TCR) or chimeric antigen receptor (CAR) T-cells, and immune checkpoint inhibitors (Li and Dong, 2018; Lin and Zhang, 2019;

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Papaioannou et al., 2016; Ren et al., 2020; Rosenberg et al., 2011). Although antitumor immunity has been shown to be clinically successful, the effectiveness of these treatments is limited to a small number of patients (Wu et al., 2020). Immune evasion is a major obstacle in cancer treatment. Common escape mechanisms include major histocompatibility antigen complex (MHC)-I mutations or low expression of antigens resulting in impaired antigen presentation and therefore resistance to immune checkpoint blockade therapy (McGranahan et al., 2017). CAR T-cell therapy has demonstrated strong specific targeting, and independence from MHCs (Ti et al., 2018). However, despite great progress in lymphomas and other hematological malignancies, it still faces difficulties in solid tumors (Yu et al., 2019). These methods must address the immunosuppressive microenvironment and the low immunogenicity of tumor cells (Kishton et al., 2017). Therefore, developing new methods to circumvent these challenges and improve treatment efficacy is a current focus.

Tumor-infiltrating lymphocytes (TIL) are challenged with a hostile microenvironment, which contains many immunosuppressive factors (Zhao et al., 2020). In addition to the increase of negative regulatory signals and the reduction of co-stimulatory factors, TILs are also regulated by "metabolic checkpoints" (Motz and Coukos, 2013; Scharping and Delgoffe, 2016). TILs face a lack of nutrition primarily due to competition with tumor cells for limited nutrients, and the tumor microenvironment (TME) is not conducive to the T-cell recognition of antigens and antitumor effects. It is worth noting that due to the dysregulation of metabolic activity in tumor cells, tumor-infiltrating immune cells usually undergo metabolic stress, resulting in an impaired antitumor immune response. To meet the needs of rapid growth and proliferation, tumor cells exhibit high glycolysis levels even in the presence of excess oxygen; this is referred to as "the Warburg effect" and is one of the hallmarks of cancer (Kouidhi et al., 2017). In addition to glucose metabolism, lipid metabolism and amino acid (AA) metabolism also play important roles in determining the fate and function of tumor cells and TILs. Metabolic reprogramming in the TME also has a certain plasticity, which makes it possible for metabolic checkpoints to become targets for immunotherapy.

In this review, we discussed the role of metabolic reprogramming in tumor immunity, the competition between immune and tumor cells for nutrients and metabolites, their responses to hypoxic and acidic environments, and the strategy of targeting metabolic checkpoints as antitumor therapy. We also summarized the metabolic reprogramming of various immune cell subtypes and the metabolic checkpoints used in immunotherapy. This information can be used to specifically improve antitumor efficiency and clinical immunotherapy based on the TME.

Metabolic reprogramming in the TME

Tumor cells undergo metabolic reprogramming

Changes in energy metabolism are a hallmark of cancer. Tumor cells demonstrate a greater tendency to use glycolysis for energy production rather than oxidative phosphorylation (OXPHOS), even under conditions of sufficient oxygen, and are known as "the Warburg effect" (Warburg, 1956). In this process, after glucose is taken up into cells, pyruvate is produced. Most of the pyruvate is converted to lactic acid and transported outside the cell, coupled with ATP production. At first, Warburg speculated that tumor cells must rely on glycolysis due to damaged mitochondrial function. However, further research showed that the mitochondrial function was intact (Fantin et al., 2006). Why, then, do tumor cells undergo this metabolic shift? Later studies have suggested several reasons: (i) as tumor cells need to proliferate quickly, they not only require ATP but also metabolites and intermediates as anabolic precursors or catabolism substrates (e.g., acetyl-coenzyme A (acetyl-CoA) is very important for fatty acid (FA) synthesis and protein acetylation) (DeBerardinis et al., 2007); (ii) the rate of glycolysis is in fact much higher than that of OXPHOS (Brooks, 2009); or (iii) glycolysis produces fewer reactive oxygen species (ROS), as mitochondrial OXPHOS is the main source of ROS production. By reducing OXPHOS, ROS-induced cell senescence or apoptosis is also reduced (Wang et al., 2017).

The hypoxic nature of the TME has been well described. Hypoxia-induced factor (HIF) is a nuclear transcription factor produced by tumor cells as they adapt to the hypoxic environment. It mainly influences the Warburg effect through the following means: (i) upregulation of the expression of glucose transporter (GLUT), which thereby increases glucose uptake (Starska et al., 2015); (ii) upregulation of the expression of enzymes involved in glycolysis (Parra-Bonilla et al., 2010); and (iii) inhibition of OXPHOS (Kim et al., 2006; Zhao et al., 2017). Growing evidence shows that there are some signaling pathways that affect glycolysis in tumor cells, including via the transcription factors c-Myc (Li and Simon, 2013), PI3K/Akt/mTOR, and AMPK (Okkenhaug et al., 2016; Tang et al., 2020; Thorpe et al., 2015; Troncone et al., 2017). Therefore, hypoxia does not straight forwardly induce the Warburg effect, but rather promotes glycolysis via other specific and complex signaling pathways. Moreover, this increase of glycolysis causes greater lactic acid accumulation in the TME, the acidic microenvironment of which promotes tumor progression and negatively affects TIL cells.

It is worth noting that although glycolysis is the primary pathway of tumor metabolism, mitochondrial metabolism is not damaged, so OXPHOS can and does still occur in tumor cells. Studies have shown that the metabolism in cancer stem-like cells (CSCs) differs from other tumor cells and

mainly depends on the mitochondrial tricarboxylic acid (TCA) cycle (Sancho et al., 2016). However, it is encouraging for treatment that most cancer cells depend on glycolysis and are therefore sensitive to metabolic antitumor therapies.

Abnormal lipid metabolism in tumor cells has received less attention, but its importance has been increasingly recognized in recent years. Lipids are composed of fats (including triglycerides, TG) and lipoids (mainly phospholipids, cholesterols, and cholesterol esters). Lipid metabolism involves the synthesis, degradation, and storage of lipids. In anabolic processes, acetyl-CoA is exported to the cytoplasm following the Krebs cycle, from which fatty acid synthase catalyzes the synthesis of fatty acids. In catabolic processes, fatty acids produce energy and metabolites via OXPHOS. Correspondingly, tumor cells use anabolism to form membranes, store energy, and generate signal transduction molecules, whereas under conditions of limited nutrient availability, they tend to use OXPHOS to produce energy (Luo et al., 2017).

Metabolic reprogramming of tumor-infiltrating immune cells

Metabolism in immune cells is distinct in the resting and activated states (Figure 1). Tumor-infiltrating lymphocytes, especially cytotoxic T lymphocytes (CTLs), are the main effectors of antitumor immunity; however, there are other immunosuppressive cells in the microenvironment, such as tumor-associated macrophages (TAMs), myeloid-derived suppressor cells (MDSCs), and regulatory T cells (Tregs), which hinder the antitumor immune response (Yan et al., 2019).

Tumor-infiltrating T cells

Naive $CD4^+$ T cells can differentiate into effector T cells (Teffs) Th1, Th2, and Th17 cells or into Tregs. Th1 cells assist in the activation of $CD8^+$ T cells, and Tregs play an immunosuppressive role. $CD8^+$ T cells can be divided into naive cells, memory cells, and Teff subsets, where naive $CD8^+$ T cells primarily differentiate into CTLs (Zhang et al., 2020; Zhou et al., 2020). Importantly, each immune cell subtype exhibits different metabolic characteristics.

Naive or resting T cells rely upon the oxidation of fatty acids or glucose. After encountering antigens, T-cell receptors and co-stimulatory factors will activate T cells, and the T cells will shift to glycolytic metabolism and fatty acid synthesis (FAS) to maintain the proliferation, differentiation, and function of Teffs (MacIver et al., 2013). Tregs act like brakes, playing important roles in self-tolerance and immunosuppression to prevent an excessive immune response. Unlike Teffs, Tregs obtain energy through the TCA cycle of glucose metabolism and the β-oxidation of lipids (Dang et al., 2009). In exhausted $CD8^+$ T cells, the expression of glycolysis-related genes was downregulated, while genes related to OXPHOS were upregulated (Wherry et al., 2007). Following the innate immune response, a small cluster of antigen-specific T cells will form memory T cells, so that when the same antigen is recognized, a swifter adaptive immune response can be raised. Metabolism in memory cells is similar to that in naive cells, which mainly depend on mitochondrial metabolism and fatty acid oxidation (FAO) to generate energy rather than biosynthesis (Pearce et al., 2013). However, memory T cells seem to produce energy

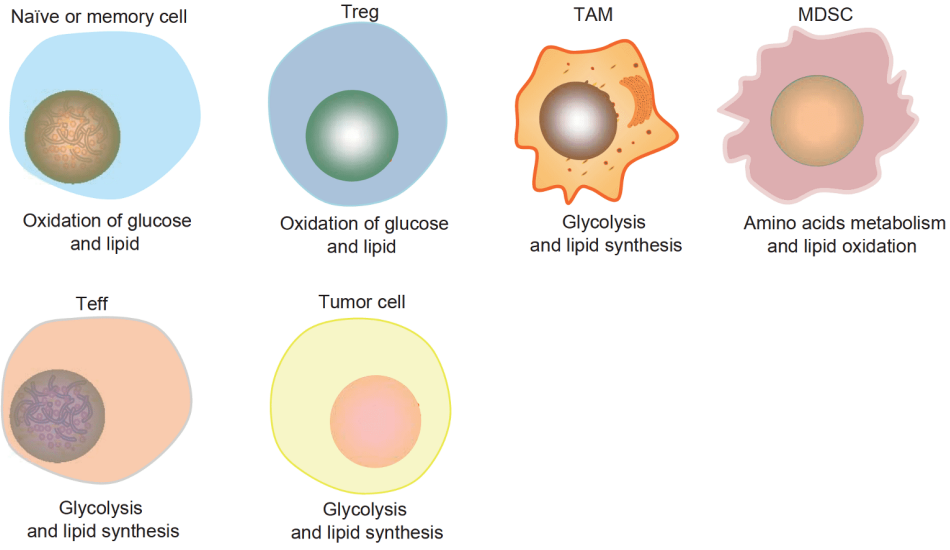

Figure 1 (Color online) Tumor cells and different immune cell subtypes have distinct metabolic characteristics. Different cells have distinct metabolic requirements due to their growth and activation status; therefore they present unique metabolic characteristics. Activated cells need to proliferate rapidly and tend toward anabolism.

more efficiently, which manifests as mitochondrial aggregation (Tennant et al., 2010). Studies have shown that Teffs, including Th1, Th2, and Th17 cells, demonstrate increased GLUT1 expression and exhibit glycolytic characteristics, while Tregs have reduced GLUT1 and glucose uptake and are mainly dependent on fatty acid oxidation. Under conditions of glucose starvation, many key genes are suppressed, and both glycolysis and effector functions are inhibited. However, when GLUT1 or hexokinase (HK) are reintroduced, the function of T cells is partially restored (Kim et al., 2007). This indicates that metabolic changes directly affect the activation, differentiation, effectors function, and exhaustion of T cells.

FAS is important for cell structures in proliferating cells and for the differentiation of effector T cells. FAO mainly provides energy and important metabolic intermediates required for $CD8^+$ T cell memory and the differentiation of $CD4^+$ Tregs. Interestingly, the inhibition of mTOR via rapamycin significantly reduced the population of Myc-mediated activated T cells, suggesting that T-cell activation depends on mTOR-dependent pathways and that the key molecules of lipid synthesis, sterol regulatory-element binding proteins (SREBPs), are very sensitive to PI3K and mTOR inhibition (Wang et al., 2011). More importantly, the inhibition of the SREBP pathway significantly inhibits the proliferation and differentiation of $CD8^+$ T cells into Teff cells. Consistent with this, the inhibition of acetyl-CoA carboxylase 1 (ACC1), the rate-limiting enzyme in FAS, impairs the formation Th17 cells and promotes Treg differentiation (Berod et al., 2014). Carnitine palmitoyltransferase I (CPT1) is a rate-limiting enzyme in FAO. AMPK inhibits FAS when ACC2 activity is decreased, which in turn relieves the allosteric inhibition of malonyl-CoA on CPT1 promoting FAO. Thus, AMPK regulates the balance between FAS and FAO (Abu-Elheiga et al., 2000). Cholesterol is essential for membrane synthesis, and liver X receptor (LXR), SREBP-2, and acyl-CoA acyltransferase (ACAT)-1 play important roles in maintaining intracellular cholesterol stability. During the activation of T cells, LXR has antiproliferative functions, and the loss of LXRβ promotes proliferation. Mice lacking LXRβ exhibited lymphoid hyperplasia and enhanced antitumor responses, suggesting that the proper regulation of LXR-dependent sterol metabolism is important for the immune response (Bensinger et al., 2008). However, whether sterol metabolism depends on FAS or FAO also relys on the cell activation and the environment. Once $CD4^+$ T cells develop into effectors and are recruited to inflammatory tissues, their metabolic fitness must also adapt (Byersdorfer et al., 2013).

Amino acids serve as nitrogen source for other metabolic pathways. While the amino acid content is generally maintained at levels required by physiology, some amino acid synthesis pathways are checkpoints for immunity and metabolism. The two most studied enzymes in amino acid metabolism are indoleamine 2,3-dioxygenase 1 (IDO1) and arginase 1 (ARG1), which are rate-limiting enzymes of the L-tryptophan (Trp) and L-arginine (Arg) synthesis pathways. These enzymes inhibit the immune response, and solid tumors can also hijack them to achieve immune escape (Mondanelli et al., 2017). The system L transporter Slc7a5 (LAT1) is an amino acid transporter, and LAT1-deficient $CD4^+$ T cells cannot proliferate and differentiate into Th1 or Th7 cells. LAT1 deficiencies in $CD8^+$ T cells also impair cellular functions, although Tregs are not affected (Sinclair et al., 2013). Glutamine can be converted to glutamate by glutaminase (GLS), entering the TCA cycle or contributing to epigenetic modification. GLS plays an important role in T-cell activation and differentiation; the absence of GLS leads to inhibition of T-cell activation and proliferation. Reduced PIK3IP1 levels in Th1 cells are very sensitive to IL-2-mediated mTORC1 signaling. T cells lacking GLS can promote Th1 cells and CTL T-cell accumulation, but not that of Th17 cells (Johnson et al., 2018). IRE1α-XBP1 signaling in T cells controls mitochondrial metabolism and antitumor response. Ascites in patients with ovarian cancer inhibit T-cell glucose absorption and N-linked protein glycosylation, resulting in the activation of IRE1α-XBP1, inhibition of mitochondrial activity, and interferon-γ (IFN-γ) production. In fact, inhibiting the activation of IRE1α-XBP1 signaling or overexpressing glutamine transporter promotes mitochondrial respiration and efficiency. Targeting IRE1α-XBP1 signaling may help restore mitochondrial respiration and promote antitumor abilities (Song et al., 2018a).

Under metabolic stress conditions, AMPK inhibits the activity of T cells by inhibiting mTOR signaling and increasing catabolism, which leads to the inhibition of glycolysis and increased OXPHOS. However, metabolic reprogramming in TILs is also plastic to some degree; for example, Th17 cells can utilize OXPHOS (Franchi et al., 2017), and Tregs can also favor glycolysis (Gerriets et al., 2016).

TAMs

Macrophages play important roles in maintaining self-tolerance and protection against foreign antigens. Chronic exposure to aggressive antigens results in activation of anti-inflammatory M2-type macrophages, creating a mutagenic environment and promoting tumor onset. TAMs account for the majority of the cells in the tumor stroma (Guilbaud et al., 2019). Metabolic reprogramming of TAMs is associated with immunosuppression and tumor progression. For example, abhydrolase domain containing 5 (ABHD5) promotes triglyceride hydrolysis. Inhibiting the expression of ABHD5 in macrophages induces the production of nuclear factor kappa B (NF-κB) p65-dependent matrix metalloproteinases (MMPs), thereby promoting tumor invasion (Shang et al.,

2019). Furthermore, FAO promotes the secretion of IL-1β in TAMs, further leading to the migration of hepatocellular carcinoma (Zhang et al., 2018). The metabolic signature of TAMs is similar to that of tumor cells, namely, increased glycolysis and fatty acid synthesis (Liu et al., 2017). Protein or amino acid-restricted TAMs elicited reduced tumor growth and promoted antitumor immune responses via ROS/mTOR signaling (Orillion et al., 2018).

MDSCs

MDSCs are the primary immunosuppressive cells inhibiting cytotoxic T-cell function. They can also suppress other immune-activating cells, such as dendritic and natural killer cells, and promote Treg activation. Mounting evidence shows that MDSCs directly promote tumor invasion, metastasis, and angiogenesis (Won et al., 2019). An increase in immune-suppressive enzyme arginase and G-CSF levels in gliomas promoted the accumulation of MDSCs and T-cell immunosuppression (Raychaudhuri et al., 2011). Migration inhibitory factor (MIF) promotes the expression of arginase-1 in MDSCs in a CXCR2-dependent manner. Knocking down MIF reduced the production of arginase-1, increased the response of toxic T cells, and prolonged the survival of tumor-bearing mice. Although MIF itself does not affect tumor growth, MIF activates and protects MDSCs through arginase-1 to promote the pro-tumor environment (Otvos et al., 2016). MDSCs maintain immune suppression by increasing fatty acid oxidation (Al-Khami et al., 2016).

A crosslink between metabolic reprogramming and immune response

There are many mechanisms by which tumors evade from immune responses. The metabolic interactions between tumor and tumor-infiltrating immune cells are primary strategies of immune escape (Wang et al., 2014). As proliferation requires a consistent pool of nutrients, the tumor and tumor-infiltrating immune cells form a competitive relationship, thus creating a hostile TME for the antitumor immune response (Figure 2).

Nutrient starvation in the TME

Due to the massive expansion of tumor cells that consume the majority of the nutrients in the TME, tumor-imposed nutrient restriction reduces TIL nutrient uptake and leads to slower TIL proliferation. However, a newly research group analyzed secretomes data from glucose-deprived cells, and revealed that multiple cytokines and chemokines were up-regulated due to starvation stress. Furthermore, glutamine deprivation, 2-deoxyglucose (2-DG) and metformin, also promoted the release of IL-6 and IL-8, leading to induced chemotaxis of B cells, macrophages, and neutrophils, suggesting that nutrient deprivation in the TME can serve as an initiator of inflammation (Püschel et al., 2020).

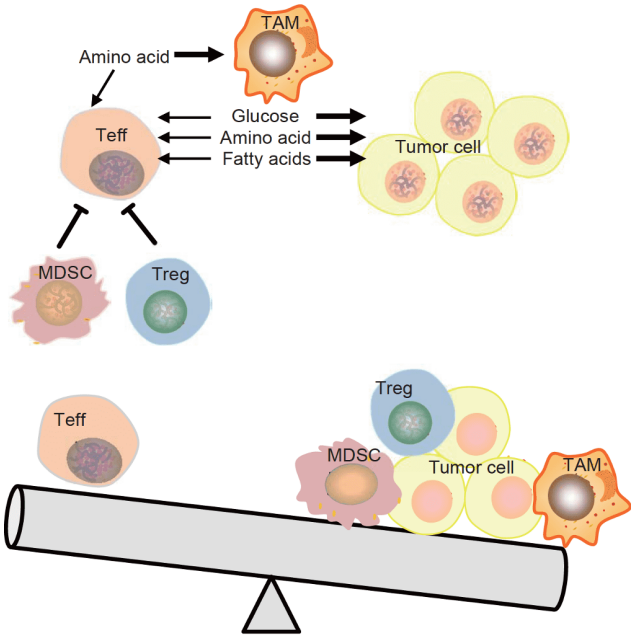

Figure 2 (Color online) The tumor microenvironment is hostile for Teff cell metabolism. Teffs need to compete with a variety of cancer and other immune cells in the TME for nutrients, some immunosuppressive cells release cytokines that inhibit the activation of and metabolism in Teffs.

Inhibiting FAS in naive T cells significantly increases production of IFN-γ, while the addition of exogenous lipids to the medium will inhibit the production of IFN-γ in all subtypes, indicating that fatty acid metabolism can directly affect the efficacy of T cells (Ecker et al., 2018). Cholesterol also regulates antitumor immunity by affecting the expression of some cytokines. $CD8^+$ T cells can be polarized to become IL-9-secreting (Tc9) cells. Cholesterol activates LXRs, leading to SUMOylation of LXRs and ultimately inhibiting the expression of IL-9, which is necessary for the antitumor effects of Tc9 cells. Therefore, cholesterol is a key regulator of the differentiation and function of Tc9 cells (Tatematsu and Kuroda, 2018).

Interestingly, during T-cell activation, AA uptake and mTORC1 activity both increase. These events are very important for the differentiation of $CD4^+$ cells into Th1 effector cells (Kolev et al., 2015). Eliminating essential AAs, especially arginine, impairs the functions of T cells, neutrophils, MDSCs, and TAMs (Liu et al., 2017). These cells inhibit T-cell proliferation and cytokine secretion in an arginase-dependent manner (Rodriguez et al., 2004). These results indicate that the competition for limited nutrients leads to a immunosuppressive TME.

Metabolites from tumors determine the fate and function of tumor-infiltrating immune cells

In addition to tumor-imposed nutrient limitations, tumor cell metabolites can also affect the function of immune cells. Lactic acid promotes stemness and tumor invasiveness (Goetze et al., 2011) and also regulates the immune escape of tumors. Exogenous lactic acid can inhibit the cell-killing function of NK cells by increasing MDSCs; in L-lactate dehydrogenase A (LDHA)-knockout xenograft models, the cell-killing function of NK cells is enhanced, manifested by the increase of perforin and granzyme and the decrease in MDSC accumulation (Husain et al., 2013). Tumor-derived lactic acid accumulation in the TME leads to metabolic inhibition and low reactivity of CTLs. However, there are also studies showing that tumor-derived lactic acid stimulates the activation of dendritic cells (DCs) and antigen expression (Gottfried et al., 2006). Activated DCs and macrophages alter the citric acid cycle, resulting in the aggregation of citrate and succinate. Citrate is exported to the cytoplasm and converted to acetyl-CoA, which is very important for fatty acid synthesis and protein acetylation (Kelly and O'Neill, 2015).

Extracellular adenylate is also an important immune regulator. Its signal is transduced by G protein-coupled adenosine receptors (Fredholm et al., 2001). Signaling via the adenylate receptor induces and regulates proliferation and differentiation of Tregs, macrophages, and MDSCs (Morello et al., 2016).

Targeting metabolic reprogramming of cancer cells or tumor-infiltrating immune cells in antitumor immunotherapy

Traditional methods of treating tumors have certain limitations. By inhibiting metabolism at certain stages, the activation and proliferation of T cells can also be inhibited; therefore, the development of new methods for modulating metabolism can also promote antitumor immunity. Metabolic reprogramming has become an attractive target for antitumor immunity. However, the interplay between tumor and immune cells should be dissected to identify more suitable targets.

Targeting glucose metabolism

Tumors characterized by high levels of glycolysis present an immunosuppressive microenvironment. Glycolytic activity is a better predictor of immune characteristics than high tumor burden or aneuploidy. In addition, glycolysis promotes the expression of death protein 1 ligand (PD-L1) in tumors, making anti-PD-L1/PD-1 (death protein 1) treatment possible (Jiang et al., 2019). Cell metabolism is targeted in two main ways: directly targeting the metabolic enzymes and metabolites or indirectly affecting related signaling pathways.

Targeting enzymes or metabolites

Adjusting the metabolism of T cells forces T cells to rely primarily on glycolysis rather than the catalyzed TCA cycle, because glycolysis can support the rapid proliferation of T cells and provide intermediate metabolites, which promotes T-cell-killing function.

Inhibiting the expression of GLUT1 in T cells reduces glucose transport and inhibits the activation, expansion, and function of Teff cells (Macintyre et al., 2014). 2-DG is a glucose analog and an inhibitor of HK that can be ingested but cannot subsequently enter the glucose metabolism pathway. Activated $CD8^+$ T cells promote the generation of memory cells and antitumor functionality in the presence of the glycolysis inhibitor 2-DG (Sukumar et al., 2013). Similarly, the proviral integration site for Moloney murine leukemia virus (PIM) kinases are a class of serine/threonine kinases that promote cell-cycle transition and regulate mTORC1 activity. Upon inhibition of PIM kinase activity (via a pan-PIM kinase inhibitor), T cells reduce glucose uptake and upregulate the expression of genes that suppress glycolysis; this antitumor effect can be accelerated in combination with anti-PD-1 therapy (Chatterjee et al., 2019). Furthermore, pyruvate dehydrogenase (PDH) is a key bifurcation point between T-cell glycolysis and oxidative metabolism. PDH function is inhibited by PDH kinases (PDHKs). Knocking down PDHK1 inhibits Th17 cell differentiation and increases Treg formation. This change in the $CD4^+$ T-cell population is partially mediated by ROS, as N-acetylcysteine (NAC) treatment restores Th17 cell production. PDHK1 is necessary for both the survival and function of Th17 cells. The metabolite phosphoenolpyruvate (PEP) is very important in maintaining T-cell receptor-mediated Ca^{2+}-NFAT signaling. Upon overexpression of phosphoenolpyruvate carboxykinase 1 (PCK1), tumor-specific $CD4^+$ and $CD8^+$ T cells increase PEP levels and improve effector function. In addition, PCK1 overexpression in T cells limits tumor growth and prolongs the survival of tumor-bearing mice (Ho et al., 2015). Dichloroacetate (DCA) can induce the conversion of glycolysis to OXPHOS and inhibit the growth of tumor cells (Vella et al., 2012). Studies have found that DCA has little effect on lymphocyte proliferation and cytotoxicity; however, DCA inhibits aerobic glycolysis and induces Treg differentiation. If DCA is used as an anticancer drug, it may lead to reduced immune surveillance, but it can be used as an immunosuppressive drug for transplantation and autoimmune diseases (Eleftheriadis et al., 2013).

Targeting the acidic microenvironment

An acidic TME environment can promote immunosuppression. Some anticancer strategies focus on neutralizing the environment by using lactate dehydrogenase (LDH) and lactic acid transporter inhibitors, monocarboxylate transporter (MCT) inhibitors, vacuolar-type H^+-ATPase (V-ATPase) inhibitors, or oral bicarbonate supplements. When lactic acid production is prevented, thereby tumor progression is inhibited (Le et al., 2010). However, reducing lactate levels may cause inhibitory effects on immune cells. When RAW 264.7 macrophages were treated with FX11 (a specific LDHA inhibitor), the levels of cytokines, inducible nitric oxide synthase (iNOS) and cyclooxygenase 2 (COX-2) was downregulated due to reduced lactate levels (Song et al., 2018b). In addition, inhibition of LDHA expression with FX11 reduced lipogenesis, proliferation and effector functions in rheumatoid arthritis CD8 (Souto-Carneiro et al., 2020). Therefore, when choosing LDH to promote antitumor immunity, the effects of tumor cells and T cells should be comprehensively considered.

In addition to LDH, targeting lactic acid transporters can also prevent acidosis. MCT can export lactic acid from tumor cells into the microenvironment. The MCT inhibitor AZD3965 is currently in phase I clinical trials (NCT01791595). Studies have shown that some new MCT inhibitors (Bola et al., 2014), including thalidomide, lenalidomide, and pomalidomide, block CD147–MCT-1 signaling (Pinheiro et al., 2010). Furthermore, in T cells, lenalidomide promotes the secretion of IL-2 and IFN-γ (Görgün et al., 2010), thus playing a dual role in inhibiting tumor cells and promoting T-cell activation. Another nonsteroidal anti-inflammatory drug, diclofenac, has also been shown to be effective in inhibiting lactic acid export. Diclofenac could reduce lactic acid production, counteract immunosuppression, and promote antitumor effects (Chirasani et al., 2013; Pantziarka et al., 2016). In addition to MCT, vacuolar H^+-ATPase (V-ATPase) can be blocked by proton pump inhibitors (PPIs). Co-treatment with PPIs in adoptive T-cell transfer in mice leads to an increase of infiltrating T cells and improves the therapeutic efficacy (Calcinotto et al., 2012). However, the interaction between PPIs and metabolic checkpoint inhibitors needs further study, as the addition of PPI to the gut microbiome may inhibit the efficacy of checkpoint inhibitors (Imhann et al., 2016). Another possible strategy for targeting tumor acidity is via bicarbonate supplements. In mice, the combination of anti-PD-1 and bicarbonate therapies significantly reduces the size and weight of tumors. In general, bicarbonate supplements neutralize the acidic TME, providing a promising immunotherapy treatment.

Targeting related signaling pathways and checkpoints

As mentioned above, PI3K-AKT-mTOR signaling plays an important role in metabolic reprogramming, and some treatments targeting mTOR have also demonstrated efficacy. An analog of rapamycin, a drug that inhibits mTOR activity, has been approved for the treatment of various cancers (Schmidt et al., 2017). However, rapamycin has been shown to promote activation of Tregs and memory T cells while inhibiting the proliferation of Teff cells (Chi, 2012). Encouragingly, the combination of rapamycin and immunotherapy increases the toxicity functions of memory T cells (Mineharu et al., 2014). Therefore, if properly combined with other therapies, rapamycin can be an attractive treatment. In addition, PI3K/Akt pathway inhibitors (e.g., Akti-1/2 and LY294002) reduce the expression of 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 3 (PFKFB3) and the production of fructose-2,6-bisphosphate and lactate (Simon-Molas et al., 2018). It is suggested that the use of PI3K/Akt activators may promote glycolysis during T cell activation.

A Treg-mediated increase in glucose consumption can cause cell senescence and suppress T-cell function. However, TLR8 signaling selectively inhibits glucose uptake in Treg cells, reducing glycolysis and leading to the reversal of the Treg inhibitory effect and improving antitumor immunity. This reprogramming of glucose metabolism has been demonstrated in a melanoma adoptive transfer T-cell therapy model (Li et al., 2019).

NAC significantly increases the survival of T cells in the TME and the ability to kill target cells *in vitro*. Mechanistically, NAC inhibits Foxo1 expression through PI3K/Akt activation, but does not affect memory cells, thereby inhibiting PD-1 and granzyme B expression (Scheffel et al., 2018).

As a metabolic regulator, CD36 is upregulated in intratumoral Treg cells. CD36 adapts Treg cells to an acidic microenvironment through peroxisome proliferator-activated receptor (PPAR)-β signaling. Knocking out CD36 in Treg cells reduces Treg proliferation, increases antitumor activity, and inhibits tumor growth. Moreover, the effects of CD36 targeting can be augmented with anti-PD-1 therapy (Wang et al., 2020c).

Lymphocyte activation gene-3 (LAG-3) is an inhibitory receptor expressed in $CD4^+$ T cells. Blocking LAG-3 promotes the differentiation of naive T cells into Th1 cells, IL-7-mediated STAT5 activation, and inhibits of Tregs (Durham et al., 2014). Due to increased mitochondrial content, naive T cells lacking LAG-3 exhibit increased oxidation and glycolysis metabolism. These results indicate that targeting LAG-3 can regulate $CD4^+$ T-cell response (Previte et al., 2019).

Metformin is a drug used to treat hyperglycemia. Research has shown that metformin inhibits mTORC1 by activating

AMPK, thereby inhibiting glycolysis in tumor cells and promoting OXPHOS (Harun et al., 2008). The disease-free survival of type 2 diabetic patients treated with metformin is significantly increased compared with the control group, at least partially due to this metabolic conversion (Jiralerspong et al., 2009). Metformin is currently undergoing phase I and II clinical trials for cancer treatment. In immune cells, metformin has a controversial role; it is an activator of AMPK, which reprograms the metabolism of effector T cells and promotes antitumor immunity (Bahrambeigi and Shafiei-Irannejad, 2020). It can also inhibit the differentiation of naive $CD4^+$ T cells into inducible Tregs (Kunisada et al., 2017) and regulate the differentiation of Th17 and Tregs (Lee et al., 2015). However, some studies have shown that metformin reduced Th17 and increased Treg cell populations along with the levels of associated cytokines (Sun et al., 2016). Metformin can therefore both promote and suppress immunity. It is important to consider these multiple effects in an immunotherapy strategy.

Cytotoxic T lymphocyte antigen 4 (CTLA-4) and PD-1 act as molecular brakes, which prevent excessive and potentially harmful immune responses. However, studies have shown that CTLA-4 and PD-1 inhibit T-cell activation by inhibiting glycolysis (Patsoukis et al., 2015). Therefore, it is possible that blocking CTLA-4 and PD-1 will also partially relieve T-cell inactivation. In addition, the PD-1 ligand PD-L1, which exists on the surface of tumor cells, is very important for the activation of the Akt/mTOR signaling pathway, which promotes the expression of glycolysis enzymes. Blocking the expression of PD-L1 in tumor cells inhibits glycolysis in tumor cells, thereby reducing competition with TILs for nutrients (Chang et al., 2015). In addition, metformin increases CTL activity by reducing the protein stability and membrane localization of PD-L1. AMPK activated by metformin directly phosphorylates PD-L1 and induces abnormal PD-L1 glycosylation. Metformin-treated breast cancer tumor tissues showed reduced PD-L1 levels with AMPK activation. Blocking the inhibitory signal of PD-L1/CTLA4 with metformin can enhance the activity of CTLs against cancer cells (Cha et al., 2018).

Targeting lipid metabolism

Cholesterol synthesis is usually increased in tumors, leading to abnormal accumulation of lipid metabolites. Cholesterol in the microenvironment results in tumor-infiltrating T-cell exhaustion. However, drugs that target lipid metabolism and the effector function of T cells are controversial. Cholesterol-rich $CD8^+$ T cells were positively correlated with the upregulation of PD-1, 2B4, TIM-3, and LAG-3 expression. Adoptively transferred $CD8^+$ T cells take up cholesterol, induce immune checkpoint expression by increasing endoplasmic reticulum (ER) stress, and become exhausted after encountering tumor cells. Therefore, the ER pressure sensor X-box binding protein 1 (XBP1) can be activated and subsequently regulate PD-1 transcription. Inhibiting XBP1 or lowering cholesterol in $CD8^+$ T cells can effectively restore antitumor activity (Ma et al., 2019). ACAT1 is a key enzyme in cholesterol esterification. The inhibition of ACAT1 by avasimibe impairs T-cell cholesterol esterification, leading to potentiated effector function and $CD8^+$ T-cell proliferation. Avasimibe is more effective when combined with an anti-PD-1 antibody (Yang et al., 2016). In a glucose-deficient and hypoxic TME, $CD8^+$ TILs increase PPAR-α signaling and promote the catabolism of fatty acids. This metabolic shift preserves the effector function of $CD8^+$ TILs, and reverses immunosuppression. Measures to further promote FA catabolism may improve the effector function of $CD8^+$ TILs to a greater extent (Zhang et al., 2017).

Mevalonate kinase (MVK) is a rate-limiting enzyme in cholesterol synthesis. Blocking MVK activity inhibits downstream lipid synthesis. Some studies have shown that highly expressed MVK is important for T-cell activation in a mTOR signaling-dependent manner (Thurnher and Gruenbacher, 2015). Similarly, sphingosine 1-phosphate (S1P) is a biologically active lysophospholipid produced by sphingosine kinase 1 (SphK1), and SphK1-deficient T cells exhibit higher mitochondrial respiration and reduced Treg differentiation. PPARs are transcription factors that regulate lipolysis gene expression in T cells. There is a direct correlation between S1P and PPARγ activity, and the genetic and pharmacological inhibition of SphK1 can improve the metabolic adaptability and antitumor activity of T cells against melanoma. In addition, the joint inhibition of SphK1 and PD-1 improves the control of melanoma (Chakraborty et al., 2019).

Citrate and succinate have been linked to macrophage and DC activation. Increasing their levels using analogs can promote macrophage and DC effector functions (Williams and O'Neill, 2018). Citrate-derived lipid synthesis is related to membrane formation and cytokine release necessary for DC cell activation, while in macrophages, PGE2C production is related to citric acid metabolism.

Targeting amino acid metabolism

In the TME, tumor cells ingest a large amount of nutrients upon metabolic reprogramming to rapidly proliferate, which results in an inhibitory signal to T cells. L-arginine, tryptophan, and glutamine are important signaling mediators in the interplay of metabolism and immunity. Targeting these amino acids is expected to exert antitumor immunity by reversing energy reprogramming. Several clinical trials targeting amino acid metabolism are currently in progress.

The inhibition of arginine synthesis by the inhibitor ADI-PEG20 blocks the proliferation of tumor cells while also

inhibiting the accumulation of Tregs. This strategy is currently undergoing clinical trials with the combination of arginase inhibitor CB-1158 and immune checkpoint therapy. Imatinib activates effector T cells and inhibits Tregs via the IDO pathway. There is also a clinical trial underway for the combination of imatinib and anti-CTLA4 immunotherapy (Reilley et al., 2017; Tian et al., 2019).

Indoleamine-2,3-dioxygenase 1 (IDO1) catalyzes the oxidation of tryptophan, which is related to tumor cell immune tolerance. GDC-0919, an inhibitor of IDO1, has been shown to relieve the inhibition of $CD8^+$ T-cell function by degrading tryptophan in various tumor models of combination therapies (Nayak-Kapoor et al., 2018). Another recently developed IDO inhibitor, INCB024360, can promote the proliferation of T cells and the production of IFN-γ, thereby promoting antitumor immunity (Staron et al., 2014). Therefore, IDO inhibitors are novel means to activate T cells and promote their effector functions.

The antitumor activity of activated $CD8^+$ T cells in the TME may be limited by metabolic incompatibility. The poor metabolism in $CD8^+$ T cells may be similar to T-cell dysfunction in memory formation disorders; memory formation is vital to tumor adoptive immunotherapy (Hameed et al., 2018). The adoptive transfer of $CD8^+$ T cells treated with a

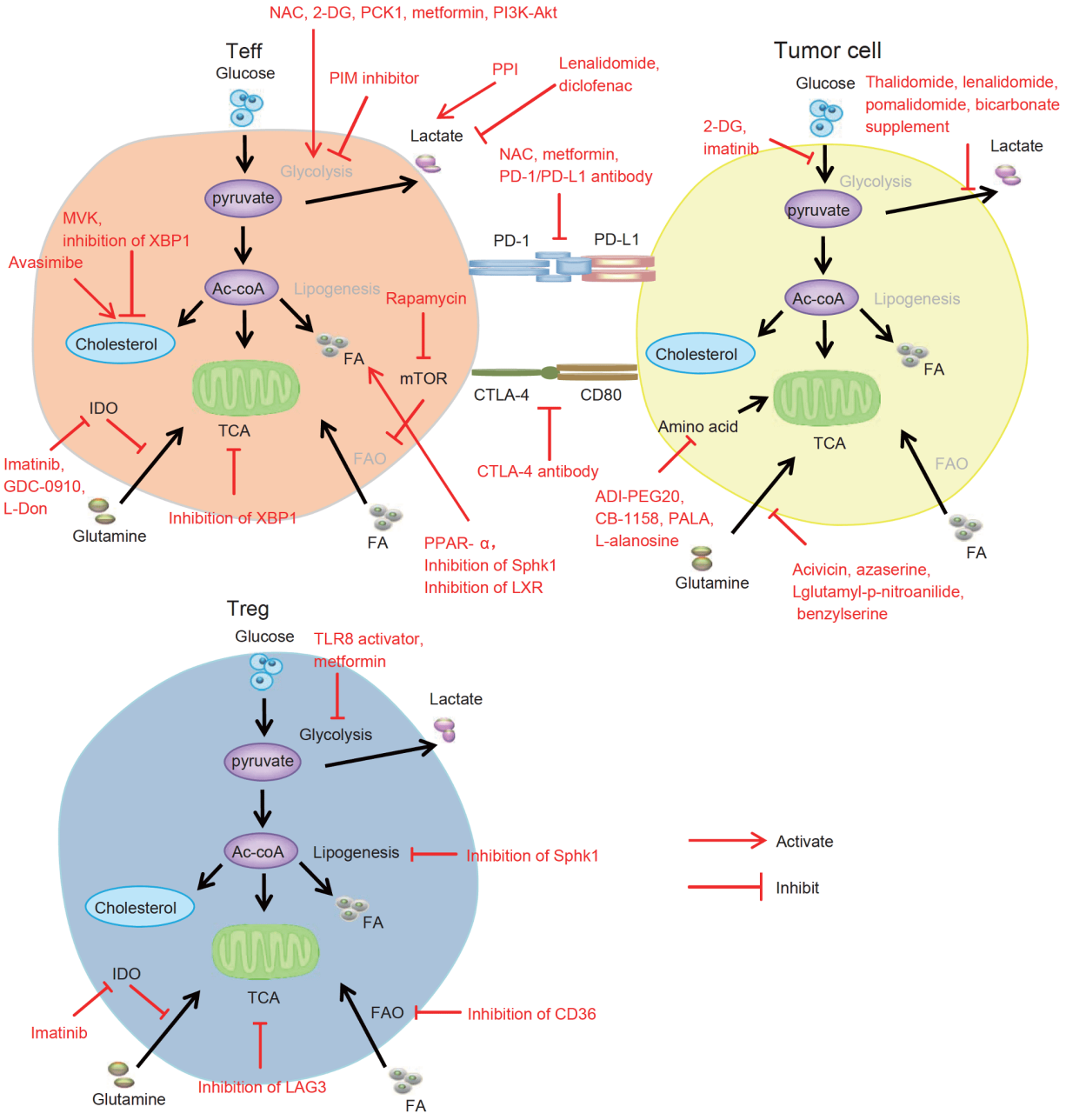

Figure 3 (Color online) Therapeutic targets of T-cell or tumor cell metabolism. T cells compete with tumor cells in the microenvironment for nutrients, further impairing T-cell function. Drugs that inhibit tumor metabolism or promote T-cell metabolism both represent favorable strategies.

Table 1 Metabolism-targeting immunotherapies of immune and tumor cells

	Items	Targets	Signaling pathway	Effects
Glucose	2-DG	HK	Glycolysis	Inhibit tumor cells glycolysis, promote $CD8^+$ memory cells and anti-tumor activity
	DCA	Glycolysis	Glycolysis	Inhibit tumor growth and induce Tregs
	Inhibition of PIM kinase	PIM kinase	Glycolysis	Inhibit T cells glycolysis, better anti-tumor activity when combined with anti-PD-1
	NAC	PDHK1	ROS signaling	Restore the formation of Th17 cells
	Overexpression of PCK1	Phosphoenolpyruvate	$Ca2^+$-NEAT signaling	Promote the effctor function of CD4 and CD8
	AZD3965	Lactate transporter MCT	Lactate transport	Inhibit the export of lactate from tumor cells
	Thalidomide, lenalidomide, pomalidomide	MCT	CD147-MCT1	Inhibit tumor cells, promote the secretion of IL-2 and IFN-γ in T cells
	diclofenae	MCT	Lactate transport	Inhibit the produce of lactate, counteract immunosuppression
	PPI	V-ATPase	Lactate transport	Increase T cells number
	Bicarbonate supplement	Acidic environment	Buffer acidic environment	Inhibit tumor cells, better anti-tumor activity combined with anti-PD-1
	Rapamycin	mTOR	PI3K-Akt-mTOR	Enhance the function of cytotoxic and memory T cells
	PI3K-Akt activator	PI3K-Akt	PI3K-Akt	Promote T cell glycolysis and activation
	TLR8 activitor	Glucose uptake	TLR8 signaling	Inhibit Tregs glycolysis, reversal suppression signal
	NAC	Foxo1	PI3K-Akt	Inhibit PD-1, Granzyme B
	Inhibition of CD36	Acidic environment	PPAR-β sigaling	Decrease Tregs, better anti-tumor activity combined with anti-PD-1
	Inhibition of LAG3	STAT5	IL-7 mediated STAT5	Promote naïve T cell differenciate into Th1, inhibit Tregs
	Metformin	AMPK	AMPK-mTORC1	Inhibit Tregs, Promote glycolysis and Teffs
	Anti-CTLA4 and PD-1	CTLA4 and PD-1	Akt/mTOR	Inhibit tumor cells glycolysis
	Metformin	AMPK	AMPK-PD-L1	AMPK phosphorylates PD-L1, enhance CTL
Lipid	Inhibition of XBP1	XBP1	Transcription of PD-1	Lower $CD8^+$ T cells cholesterol, restore the function of T cells
	Inhibition of XBP1	XBP1	IRE1-XBP1 signaling	Promote mitochondrial respiration and effector capacity
	Avasimibe	ACAT1	Cholesterol esterification	Promote effector function and proliferation of $CD8^+$ T cells
	PPAR-α activator	FA	PPAR-α signaling	Promote FA and effector function of $CD8^+$ T cells
	MVK activator	MVK	mTOR	Promote cholesterol synthesis and T cells activation
	Inhibition of Sphk1	Sphk1	Sphk1-PPAR	Improve the fitness of T cells, better anti-tumor effect combined with anti-PD-1
	Analog of citrate and succinate	Citrate and succinate	Cholesterol synthesis	Activate dentritic cells and macrophage
	Inhibition of LXR	LXR	Cholesterol synthesis	Promote cholesterol synthesis in Teffs
Amino acid synthesis	ADI-PEG20, CB-1158	L-arginine	Inhibit L-arginine	Inhibit tumor and Treg
	Imatinib	IDO	IDO signaling	Acivate T cells and inhibit Tregs, better anti-tumor effect combined with anti-PD-1
	GDC-0919	IDO1	Degradate tryptophan	Promote $CD8^+$ T cells
	INCB024360	IDO	Degradate tryptophan	Promote the proliferation and secretion of IFN-γ in T cells
	L-Don	Glutamine	Glutamine metabolism	Inhibit $CD8^+$ T cells exhaution
	Acivicin and azaserine	Glutamine	Glutamine metabolism	Inhibit nucleic acid formation in tumor cells
	PALA and L-alanosine	L-aspartic acid	L-aspartic acid metabolism	Inhibit nucleic acid formation in tumor cells
	Lglutamyl-p-nitroanilide and benzylserine	Glutamine transporter	Glutamine metabolism	Inhibit the uptake of glutamine of tumor
	Inhibotion of glutaminase	Glutaminase	IL-2 mediated mTORC1 signaling	Promote $CD4^+$ Th1 and $CD8^+$ CTL

specific inhibitor of glutamine metabolism (6-diazo-5-oxo-L-norleucine, L-Don) effectively eliminated tumors and reduced PD-1 expression, indicating that the inhibition of glutamine metabolism prevents the exhaustion of $CD8^+$ T cells. In addition, under glutamine-restricted conditions, the expression of survival and transcription factors associated with memory T cells increased (Nabe et al., 2018). L-glutamine analogs acivicin and azaserine and L-aspartic acid analogs PALA and L-alanosine all interrupt the synthesis of cellular nucleotides, thereby preventing the formation of DNA and/or RNA in tumor cells. Two other compounds, buthionine sulfoximine and difluoromethylornithine, inhibit glutathione and polyamine synthesis, respectively; these demonstrate limited antitumor activity on their own but are commonly used as chemotherapeutic agents or regulators (Ahluwalia et al., 1990). Moreover, inhibition of the glutamine transporter via gamma-l-glutamyl-p-nitroanilide or benzylserine leads to reduced glutamine uptake and tumor cell growth (Hassanein et al., 2015; van der Mijn et al., 2016).

Conclusion

The function of immune cells is inseparable from the metabolic reprogramming caused by the limited nutrients, enzymes, and metabolites in the TME. The plasticity of immune cells also makes modulation through metabolic checkpoints a potentially effective antitumor therapy. By summarizing the metabolic characteristics of glucose metabolism, lipid metabolism, and amino acid metabolism in tumor cells and various immune cells, we aim to improve the antitumor targeted therapy strategy and identify more valuable targets for adoptive immunotherapy (Figure 3 and Table 1). However, due to the different status of cell activation and the environment in which they are located, the simultaneous inhibition of tumor cells and the activation of T-cell function are still challenging. This challenge needs to be addressed with sound evaluation and experimental validation. Moreover, in addition to adapting to the environment, the interaction between tumor and immune cells may also affect the TME. In the future, research should focus on the effects of individual metabolic targets in different cell types on both killing tumor cells and augmenting the effector functions of immune cells, to promote the ideal outcome of antitumor immunity.

Compliance and ethics *The author(s) declare that they have no conflict of interest.*

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