

Metabolic Regulation of T cell Activity: Implications for Metabolic-Based T-cell Therapies for Cancer

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ABSTRACT

Immunometabolism is an emerging field in tumor immunotherapy. Understanding the metabolic competition for access to the limited nutrients between tumor cells and immune cells can reveal the complexity of the tumor microenvironment and help develop new therapeutic approaches for cancer. Recent studies have focused on modifying the function of immune cells by manipulating their metabolic pathways. Besides, identifying metabolic events, which affect the function of immune cells leads to new therapeutic opportunities for treatment of inflammatory diseases and immune-related conditions. According to the literature, metabolic pathway such as glycolysis, TCA cycle, and fatty acid metabolism, significantly influence the survival, proliferation, activation, and function of immune cells and thus regulate immune responses. In this paper, we reviewed the role of metabolic processes and major signaling pathways involving in T-cell regulation and T-cell responses against tumor cells. Moreover, we summarized the new therapeutics suggested to enhance anti-tumor activity of T cells through manipulating metabolic pathways. **DOI: 10.52547/ibj.3811**

Keywords: Cancer, metabolic pathways, metabolism, T-cell

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INTRODUCTION

Immunometabolism, a term first used in 2011, is a new field of research that seeks to improve our understanding of the multifaceted relationship between the metabolic and the immune system, from metabolic features of the immune cells to metabolic disorders by these immune cells^[1,2]. Over the past decade, immunologists have focused on altering metabolic pathways within immune cells to enhance their optimal function^[3]. Also, identifying metabolic

events affecting the function of immune cells provides new therapeutic opportunities for treatment of the immune-related and inflammatory diseases^[4]. Metabolic processes, such as glycolysis, TCA cycle, and fatty acid metabolism, notably influence the function of immune cells and are now considered as the main factors regulating the immune responses^[4]. This review aims to understand the role of metabolic pathways in T-cell responses, especially against tumor cells; we also provide the present knowledge on how the antitumor activity of T cells

List of Abbreviations:

ACC1, acetyl-CoA carboxylase 1; **ATP**, adenosine triphosphate; **CFH**, complement factor H; **CPT1**, carnitine palmitoyltransferase 1; **DC**, dendritic cell; **FAO**, fatty acid oxidation; **FAS**, fatty acid synthesis; **FHL-1**, factor H like protein 1; **FOXP**, forkhead box protein P; **GAPDH**, glyceraldehyde-3-phosphate dehydrogenase; **HIF-1 α** , hypoxia-inducible factor 1-alpha; **IDO**, indoleamine 2,3-dioxygenase; **IRF4**, regulatory factor interferon 4; **LAG-3**, lymphocyte activating gene-3; **LDHA**, lactate dehydrogenase A; **LKB1-AMPK**, liver kinase B1 and AMP-activated protein kinase; **MDSC**, myeloid-derived suppressor cell; **mTOR**, mechanistic target of rapamycin; **mTORC2**, mTOR complex 2; **MVK**, mevalonate kinase; **Myc**, myelocytomatosis; **NAC**, N-acetylcysteine; **OXPHOS**, oxidative phosphorylation; **PD-L1**, protein 1 ligand; **PIM**, proviral integration site for moloney murine leukemia virus; **PI3K**, phosphoinositide-3-kinase; **PIP2**, phosphatidylinositol 4,5-bisphosphate; **PIP3**, phosphatidylinositol (3,4,5)-trisphosphate; **PTEN**, phosphatase and tensin homolog; **TCA**, tricarboxylic acid; **TNBC**, triple-negative breast cancer; **Treg**, regulatory T

can be enhanced through manipulating the metabolic events.

Six major metabolic pathways

The major metabolic pathways involved in the survival, proliferation, and activation of the immune cells contain glycolysis, pentose phosphate pathway, TCA cycle, fatty acid oxidation, fatty acid synthesis, and amino acid synthesis, particularly tryptophan, arginine, and glutamine^[5] (Fig. 1).

Glycolytic metabolic pathway

In glycolytic metabolism, two molecules of pyruvate are produced from each molecule of glucose, resulting in only two molecules of ATP. It is considered a relatively inefficient pathway for the production of cellular ATP. However, the glycolytic pathway does not require oxygen and can occur in both aerobic and anaerobic conditions^[6,7]. Furthermore, it provides other imperative factors for cell survival by promoting the production of NADH, a cofactor of various enzymes,

and shifting some byproducts to other biosynthetic pathways to support anabolic growth, including glucose-6-phosphate for the synthesis of ribose during the pentose phosphate pathway, 3-phosphoglycerate for the production of amino acids during the biosynthesis of serine, and pyruvate for the synthesis of citrate in the Krebs cycle^[6].

Pentose phosphate pathway

The pentose phosphate pathway shifts the mediators of the glycolytic pathway to the production of nucleotide and amino acid precursors that are necessary for cell growth and proliferation^[8]. This pathway involves the oxidation of glucose but is an anabolic rather than a catabolic pathway, generating NADPH, pentose, and ribose-5-phosphate^[5]. Pentose is produced in the non-oxidative phase, while NADPH is generated in the oxidative phase and used to produce reactive oxygen species during respiratory explosion as well as glutathione and other antioxidants^[5].

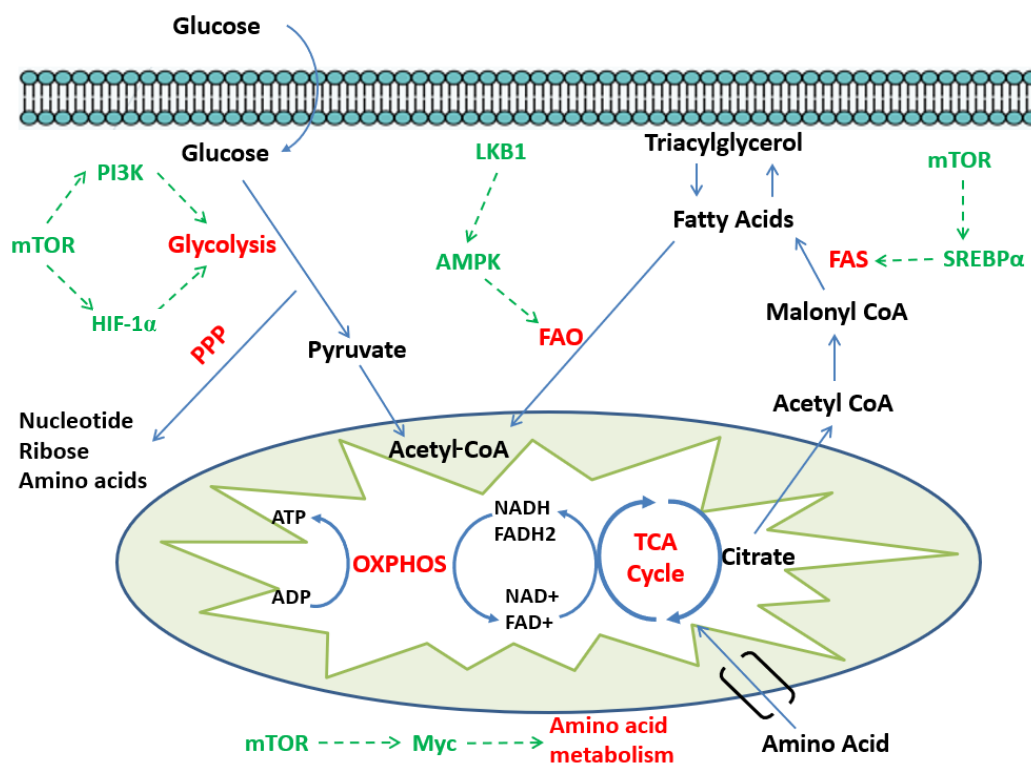


Fig. 1. Major metabolic and signaling pathways in immunometabolism. During the glycolysis pathway, glucose is converted to pyruvate, which can trigger the TCA cycle. NADH and FADH₂ produced in this cycle deliver their electrons to the electron transport chain, which finally leads to ATP production. The pentose phosphate pathway (PPP) converts glycolytic pathway intermediates to compounds such as ribose to produce nucleotides, amino acids, and NADPH. Citrate removed from the TCA cycle is used together with NADPH for fatty acid synthesis. Fatty acids can also be oxidized to produce NADH and FADH₂, which again leads to the production of ATP from the electron transport chain. Finally, amino acid metabolism provides energy for cell growth and protein biosynthesis through the TCA cycle. Under nutrient deficiency conditions, LKB1-AMPK pathway signaling inhibits glycolysis and FAS pathways as well as increases fatty acid oxidation. During the activation or in nutrient-rich conditions, PI3K-Akt and mTORC1 signaling increases glycolysis, fatty acid synthesis, and amino acid metabolism. SREBP- α , sterol regulatory element-binding protein- α ; ADP, adenosine diphosphate

Tricarboxylic acid cycle pathway

The TCA cycle (citric acid cycle or Krebs cycle) is a metabolic pathway appropriate for supplying cellular ATP and CO₂ through oxidation of acetyl-CoA, derived from carbohydrates, fatty acids, and proteins^[9]. The TCA cycle and OXPHOS are the principal sources for ATP production in cells and need more energy and longevity^[6]. Other byproducts of the TCA cycle, including NADH and FADH₂, support OXPHOS and highly efficient for ATP production by transferring electrons to oxygen during cellular respiration; moreover, citrate generates N-acetylglucosamine uridine diphosphate and succinate, two essential substances for the physiological function of immune cells^[9].

Fatty acid oxidation pathway

The FAO pathway converts fatty acids into several products, including acetyl-CoA, NADH, and FADH₂, that are needed to produce cellular energy^[6]. Acetyl-CoA then enters the TCA cycle, while NADH and FADH₂ transfer electron to the coenzyme Q of the electron transport chain, which eventually produces ATP^[10].

Fatty acid synthesis pathway

The FAS pathway leads to production of needful lipids for cell growth and proliferation^[6]. This pathway uses the products of other metabolic pathways such as glycolysis, TCA cycle, and pentose phosphate pathway^[6]. The major substrate for synthesis of fatty acids is cytoplasmic acetyl-CoA that is converted to malonyl-CoA. Seven molecules of malonyl-CoA are then combined with an acetyl-CoA via the fatty acid synthase enzyme to form palmitate, which finally produces other types of fatty acids^[11].

Metabolic pathways of amino acids

Amino acid metabolism plays an important role in different aspects of cell biology^[6]. Glutamine, arginine, and tryptophan are the key amino acids studied in the immune system. For instance, glutamine and aspartate are required for the synthesis of purine and pyrimidine. Glutamine may also be utilized by active proliferating cells as an alternative to entering the TCA cycle, where it involves in ATP production or fatty acid synthesis. Other amino acids, including arginine and tryptophan, are metabolized through several other pathways to support cell proliferation and anabolic processes^[6,12]. Taken together, all the mentioned metabolic pathways possess unique purposes within the cell and are regulated by specific signaling pathways, depending on the cell requirements.

Major signaling pathways in immunometabolism

Major signaling pathways involve in immunometabolism are PI3K/AKT, mTOR, and LKB1-AMPK^[13].

PI3K-Akt signaling in T-cell activation

Following T-cell activation, signaling mediated by TCR, CD28, and IL-2R leads to the phosphorylation and activation of PI3K, as well as inactivation of PI3K suppressor molecules such as PTEN and phosphoinositide-3-kinase interacting protein^[13]. PI3K converts PIP₂ to PIP₃, a factor that facilitates the activation of downstream molecules, including Akt. Finally, the activation of Akt increases the metabolism and the activation of T cells^[13,14].

mTOR signaling in T-cell activation

mTOR is a member of the phosphatidylinositol 3-kinase family of kinases, and the main component of two distinct protein complexes, including mTORC1 and mTORC2. These complexes regulate diverse cellular processes such as growth, proliferation, stimulation, survival, autophagy, and transcription^[13]. mTORC1 is sensitive to nutrients such as amino acids, and upon activation, it promotes cell growth, protein transport, lipid synthesis, and autophagy inhibition. On the other hand, mTORC2 acts as a protein tyrosine kinase that activates insulin receptors and insulin-like growth factor receptors. It is also involved in the organization of the cytoskeleton^[15].

LKB1-AMPK signaling pathway in T cell activation

LKB1 is a serine/threonine kinase that acts as a tumor suppressor and inhibits the proliferation and metabolism of cancer cells through phosphorylating and activating AMPK^[16]. The LKB1-AMPK signaling pathway plays a substantial role in regulating cellular metabolism, proliferation, and survival in response to nutrients^[17]. The signaling of AMPK inhibits metabolic pathways such as glycolysis^[18], glutaminolysis^[13], and lipogenesis^[19] while enhances catabolic processes like mitophagy and autophagy^[13].

Cross-regulation of signaling pathways

The signaling pathways can regulate each other; for instance, in nutrient-rich conditions, activating the PI3K-Akt and mTORC1 signaling pathways increases glycolysis, mitochondrial development, and fatty acid synthesis, but suppresses autophagy. Akt activation leads to the phosphorylation of LKB1 and suppression of its function. This regulation has not yet been reported in T cells^[20]. Under a nutrient-deficient condition, LKB1-AMPK signaling inhibits glycolysis

and fatty acid synthesis while elevates mitochondrial homeostasis and autophagy. However, the modulation of these mechanisms in T cells needs further investigation^[13]. Understanding the signaling pathways regulating immunometabolism may help discover therapeutic strategies to target metabolic mediators and enhance the T-cells responses in human diseases, including cancer (Fig. 1).

Metabolic regulation during T cell evolution

During the development of T lymphocytes in the thymus, the proliferation of double-negative thymocytes, along with the activation of the PI3K-AKT signaling transduction, increases the expression of glucose transporter, Glut1, which promotes glycolysis pathway. Therefore, double-negative thymocytes transit to double-positive thymocytes^[21,22]. At this stage, the expression of Glut1, and

subsequently the proliferation rate and metabolic activity of double-positive thymocytes decreases^[23]. Finally, during the transition to the single positive T cells, glycolysis reduces, and shifts to FAO and OXPHOS pathways^[23,24].

Metabolic regulation of naive T cells

The primary function of naive T cells is antigen monitoring, which requires a relatively small amount of ATP to support processes such as ion homeostasis, membrane adhesion, and actin cytoskeleton rearrangement. Thus, naive T cells bear a rather catabolic profile and tend to produce energy through OXPHOS^[25]. In addition to glucose, glutamine and fatty acids are considered the main sources of fuel for naive T cells. Under glucose deficiency, glutamine could be a source of ATP to facilitate naive T-cell proliferation^[26] (Fig. 2).

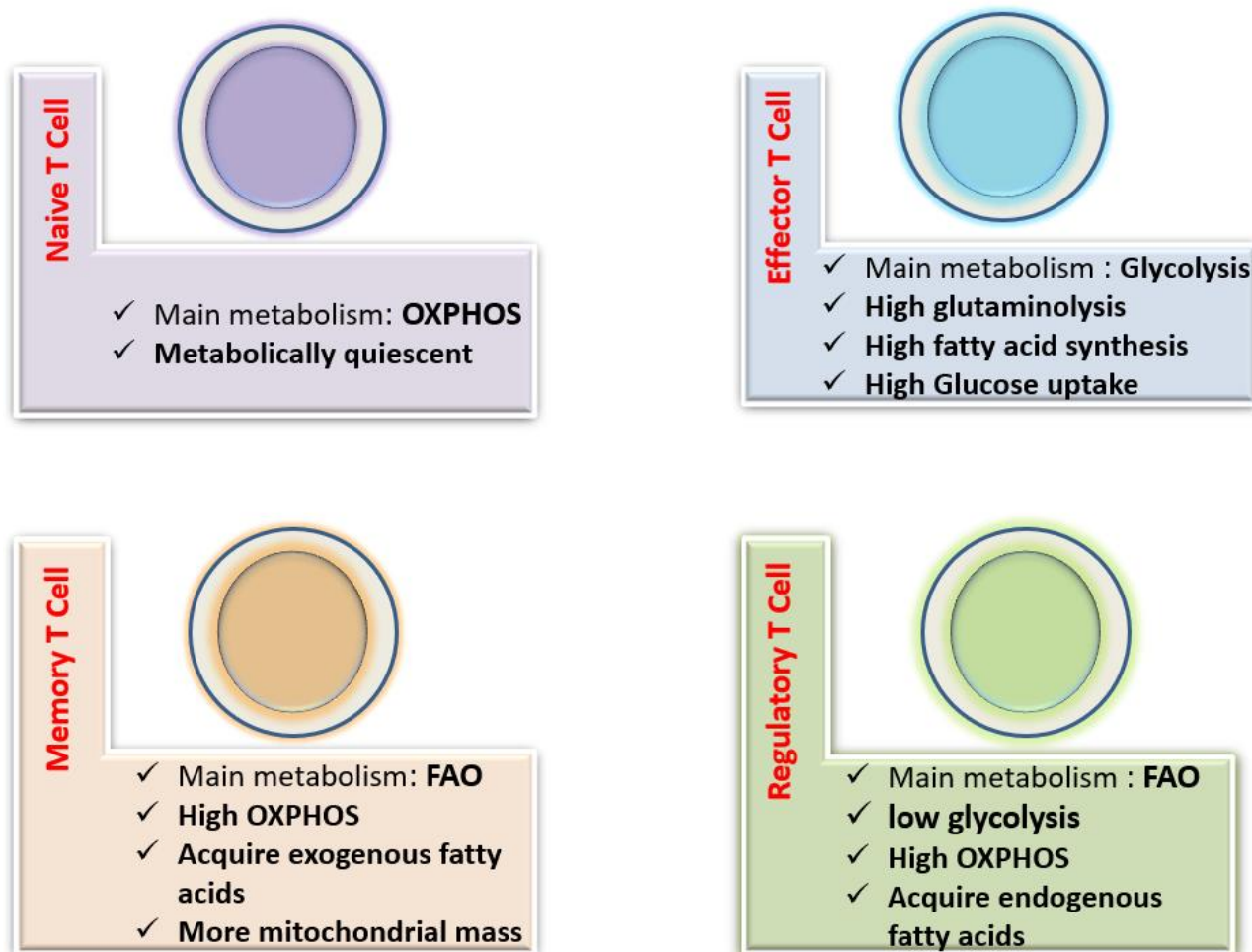


Fig. 2. Metabolic pathways of T cell subtypes. Different T cell subsets rely on distinct metabolic pathways to promote cell survival, lineage generation, and function. Naïve T cells mainly use the OXPHOS metabolic pathway. Effector T cells use glycolysis, fatty acid synthesis, and glutaminase to proliferate and produce cytokine. Treg cells utilize OXPHOS and fatty acid oxidation. Similarly, memory T cells also require OXPHOS and FAO to increase cell lifespan.

Metabolic regulation of effector T cells

Effector T cells prefer glycolysis and OXPHOS metabolism, indicating higher metabolic needs than naive T cells^[25]. Unlike naive T cells, high expression of Glut1 is of special importance in the survival of effector T cells. However, evidence has shown that these cells are not completely dependent on glucose to produce ATP. A study in mice has reported that effector T cells use glutamine to maintain intracellular ATP levels in glucose-deficient conditions^[27], but another study has highlighted the role of Glut1 expression and glycolysis in the differentiation of effector T cells^[28]. While both CD8⁺ T and CD4⁺ T subsets augment glycolysis and glucose transporter Glut1 expression, CD8⁺ T cells perform less glycolytic activities than CD4⁺ T cells and, thus, rely more on the OXPHOS for their effector function^[29] (Fig. 2).

Glucose metabolism in effector T cells

The mTOR is considered as the major regulator of effector T cell metabolism by modulating glycolysis. When T cell is activated, triggering the PI3K/Akt signaling pathway can augment mTOR signaling and rises the expression of HIF-1 α , the key player in response of cells to hypoxic conditions. HIF-1 α impresses different downstream targets including nutrient receptors (such as GLUT-1, SLC1a5, and Solute Carrier Family 1 Member 5) to enable cells to uptake and utilize glucose during glycolysis^[30]. According to the available data, this pathway predominantly induces the differentiation to Th17 cells through direct interaction with the IL-17 promoter^[31]; indeed, mTORC1 predominantly regulates the differentiation into Th1 and Th17, and mTORC2 is involved in differentiation into Th2 subset^[15]. Other factors activated by mTOR is Myc transcription factors, present in the downstream of TCR signaling to regulate glycolysis and glutaminolysis in T cells^[32]. In addition to mTOR, the IRF4 controls the glycolytic pathway of effector T cells, as in the absence of IRF4, glucose uptake and glycolysis are impaired in the activated CD4⁺ T cells^[33]. Glycolysis can control the production of IFN- γ from T cells by the glycolytic enzyme GAPDH. This enzyme inhibits the translation of IFN- γ by binding to the 3'UTR region in the related mRNA^[27]. Also, LDHA regulates the production of IFN- γ in a 3'UTR-independent mechanism. Increased conversion of pyruvate to lactate leads to less dependence of the cell on OXPHOS and the TCA cycle for energy production. Afterwards, transferring of the citrate from mitochondria to the cytosol and its conversion to acetyl-CoA in the cytosol results in histone acetylation and transcription of the IFN- γ gene^[34]. Overall, these studies highlight the vital role of metabolic features in determining the phenotype of the cell.

Amino acid metabolism in effector T cells

Amino acid metabolism can affect the activity and the differentiation of T cells. For example, the high levels of glutamine and its metabolite, alpha-ketoglutarate, stimulate the mTORC1 signaling pathway to differentiate into Th1 and Th17 subsets^[35,36]. In contrast, diminished glutamine and leucine metabolism leads to a decrease in mTORC1 activity and cellular Myc expression, thereby, blocking T-cell activation and differentiation into Th1 and Th17, while maintaining Treg cells^[37,38]. According to the literature, effector CD4⁺ T cells, including Th1, Th2, and Th17, rely mainly on glycolysis and glutaminolysis, while Treg cells use lipid oxidation pathway^[39]. Together, these studies suggest that the uptake and utilization of amino acids are required for proliferation and optimal performance of the effector T cells.

Fatty acid metabolism in effector T cells

Effector T cells use several anabolic pathways to achieve appropriate cellular responses. For instance, high glucose catabolism leads to the production of short chains of carbon molecules that can be transferred to the TCA cycle and increases FAS. In this context, Berod *et al.*^[40] have observed that blocking FAS rate-limiting enzyme ACC1, disrupts Th17 differentiation in both mouse and human T cells; in addition, knock-out of the ACC1 gene in murine T cells, protects animals against Th17-mediated autoimmune encephalomyelitis

Metabolic regulation of memory T cells

During an inflammatory response, effector T cells need high metabolic activity for their proliferation and function. At the peak of a response, a metabolic shift from anaerobic glycolysis in effector T cells to FAO is required to generate a memory T cell population^[21,41]. Memory T cells primarily use FAO oxidation as their main energy source, which is regulated by tumor necrosis factor 6 receptor and IL-15. TRAF6 increases FAO by activation of adenosine monophosphate-activated kinase^[21,42], while IL-15 does the same by up-regulating the FAO rate-limiting enzyme, CPT1, and inducing mitochondrial biogenesis^[43]. Finally, we can conclude that changes in metabolism and mitochondrial dynamics are critical for the development, longevity, and secondary response in memory T cells (Fig. 2).

Metabolic regulation of regulatory T cells

The differentiation into Treg cells is highly dependent on the mitochondrial FAO metabolism, and a high rate of glycolysis prevents their generation. Treg cells also rely on OXPHOS for their survival and bear

more mitochondrial mass and reactive oxygen species production than effector T cells^[28,44]. In comparison with memory T cells, Treg cells primarily prefer exogenous fatty acids for FAO and need lower FAS metabolism^[40]. Indeed, both Treg and memory T cells perform FAO as a basal metabolism, but Treg cells also require some aerobic glycolysis to boost their suppressive function^[45]. Activation of AMPK results in more Treg differentiation both *in vivo* and *in vitro* by increasing FAO levels^[28]. FOXP3 is the main transcription factor of Treg cells that limits glycolysis by blocking the signaling of mTOR, expression of Glut1, and glycolytic enzymes, but promotes FAO by rising the expression of the CPT1 enzyme^[46]. PTEN is an intracellular phosphatase that supports Treg function and prevents autoimmunity by stabilizing FOXP3 expression and inhibiting mTOR signaling, and as a result, hindering glycolysis. Deletion of PTEN gene from Treg cells of mice leads to dysfunction of Tregs and consequently, systemic autoimmunity, and lymphoproliferative disorders^[47]. Similarly, protein phosphatase 2 is another intracellular phosphatase that enhances Treg function by inhibiting mTOR and glycolysis^[48] (Fig. 2).

Effects of tumor metabolism on T cells

Tumor metabolism refers to changes in the metabolism pathways of tumor cells compared to most normal cells. Tumor cells mainly use glycolysis to produce energy, which causes acidification and lacking the oxygen in the tumor microenvironment^[30,49]. These highly proliferating cells compete with T cells to uptake extra amounts of urgent nutrients, including glucose, amino acids, and fatty acids, which leads to food deprivation, hypoxia, and toxic metabolites deposited in the environment^[50]. These conditions, together with the expression of PD-L1 in tumor cells, impede T-cell metabolism and instead rise tumor metabolic activity^[51]. There are also subsets of suppressive cells in the tumor microenvironment including MDSCs, which can also halt the antitumor response of T cells by reducing key amino acids such as arginine and tryptophan^[52]. Moreover, different types of myeloid cells such as MDSCs, DCs, and tumor-associated macrophages release IDO into the tumor microenvironment; this enzyme converts tryptophan to its metabolites, especially kynurenine, and prevents the anti-tumor activity of T cells^[53]. In addition, IDO can increase the expression of CFH and FHL-1^[54,55]. FHL-1 levels is related to the increased recruitment of MDSCs and Treg cells, both of which cause immuno-suppression^[54]. The hypoxic condition has been shown to induce the expression of CD39 and CD73 enzymes in various cell types in the tumor

microenvironment. These ectonucleotidases break down the ATP molecules into adenosine, a ligand for purine receptors A2A and A2B that express on a diverse range of immune cells and enable the cells to suppress the antitumor immunity in T cells^[56,57]. The Treg cells in most cancer tissues display a high expression level of CD36 in comparison to other tissues^[58]. Also, a study on a mouse model with a genetic knockout of CD36 has shown as decrease in the infiltration of Treg cells into the tumor site, but the levels of infiltrated antitumor T cells increased^[58]. Therefore, concentrated CD36 in Treg cells probably inhibits the metabolic fitness of Tregs in the tumor microenvironment and improves tumor prognosis^[59]. *In vitro* studies have revealed that the increased levels of extracellular lactate and H⁺ in the tumor microenvironment can hamper proliferation, survival, cytotoxicity, and cytokine production in mouse and human CD8⁺ T cells, the fundamental players in eradicating tumor cells through triggering the signals from V-domain immunoglobulin suppressor of T-cell activation, an acidic pH-selective ligand for P-selectin glycoprotein ligand-1^[60]. Another mechanism reported for tumor cells to interfere with T-cell activity is releasing oncometabolite, (R)-2-hydroxyglutarate, which disrupts T-cell receptor signaling, nuclear factor of the activated T cells, and polyamine biosynthesis in CD4⁺ and CD8⁺ T cells. This metabolite also increases methylation and modifies transcription profile by inhibiting dioxygenase enzymes such as histone demethylase^[61]. A high rate of tumor cell necrosis causes an increment in potassium levels in the tumor microenvironment, which reduces the cytoplasmic levels of acetyl-CoA in T cells and limits T-cell function^[62]. Most tumor cells express the enzyme iNOS, which causes the elimination of arginine within the tumor microenvironment^[63]. In addition, M2 macrophages can also hydrolyze arginine by arginase expression and eventually cause arginine depletion^[64]. Arginine plays a critical role in the function of T and natural killer cells, and decreasing arginine levels in TIME suppresses the function of effector killer T cells^[65]. Mitochondrial metabolism is also crucial for T cells. Anoxia within the tumor microenvironment promotes mitochondrial fragmentation, decreases ATP manufacturing, and induces exhausted T cells^[66]. High mitochondrial mass shows advanced respiratory capacity necessary to produce long-lived memory CD8⁺ T cells^[43]. Consistent with this phenomenon, the ability of T effectors to generate memory T cells is impaired when the mitochondrial membrane fusion protein optical atrophy 1 is deleted in mice^[67]. Consequently, mitochondrial fusion can enhance the survival of CD8⁺ T cells and convert the surface

markers and bioenergetic profile of these cells to memory T cells^[67]. Current evidence has confirmed that tumor cells use nanotubes to hijack the mitochondria of immune cells^[68], which results in the immune cell suppression, but the empowerment of tumor cells.

Targeting T cell metabolism for cancer treatment

Regarding the key role of T cells in defense against tumor cells, recent studies have focused on targeting metabolic pathways in order to fortify T-cell function and longevity. It is clear that the modulation of mTOR signaling in the tumor microenvironment has significant effects on T-cell metabolism and function; thus, the accurate understanding of how targeting tumor cells alter T-cell immunity may be helpful^[69]. Research has also examined the effects of other molecular targets on metabolic pathways involving in T cell activation^[70,71]. Factor 4-1BB is a co-stimulatory molecule detectable in most immune cells and is highly inducible in DCs and Treg cells^[72]. Interaction of 4-1BB with its ligand induces strong NF- κ B activation to enhance CTL function^[73]. This molecule also increases fatty acid and glucose consumption and boosts mitochondrial biogenesis. In fact, 4-1BB supports antitumor immunity by enhancing T-cell mitochondrial function^[74,75]. Immunotherapy with 4-1BB agonist antibodies has long been used in several clinical trials^[76]. As mentioned earlier, high lactate levels and low pH are associated with a decrease in the effectiveness of immunotherapy. Hence, inhibiting lactate production may raise immunotherapy effectiveness by restoring T-cell function while repressing Treg activity^[77,78]. The gut microbiota can turn non-absorbable polysaccharide into short-chain fatty acids, such as acetate, butyrate, and propionate^[79]. He *et al.*^[80] confirmed that butyrate, the microbial metabolite of the intestine, stimulates the IL-12 signaling pathway to promote CD8⁺ cell-mediated antitumor response, leading to the improved efficacy of oxaliplatin treatment. Accordingly, the oxaliplatin-sensitive sufferers display higher ranges of serum butyrate in comparison to sufferers with tumors resistant to oxaliplatin. Altogether, exploring new strategies to inhibit tumor cell metabolism and improve the ability of T cells to obtain nutrients might be a challenge for future studies (Table 1 and Fig. 3).

Targeting glucose metabolism in T cells

Expression of the programmed cell death, PD-L1 on tumor cells activates the Akt/mTOR pathway to boost glycolytic metabolism in tumor cells. In contrast, the interaction between PD-L1 and its receptor PD-1 on T cells makes these cells unable to utilize glucose and

branched-chain amino acids, but instead, the levels of FAO increase. Monoclonal antibodies that block the PD-1/PD-L1 checkpoint may restore glucose levels in the tumor microenvironment, leading to an increase in T-cell glycolysis and IFN- γ production^[30,81]. Therefore, inhibitors of PD-1/PD-L1 interaction can help T cells eliminate tumor cells by modulating their metabolism^[81,82]. Similar to PD-1, LAG-3 is another inhibitory molecule on T cells. Previte *et al.*^[83] reported that naive T cells with LAG-3 deficiency showed increased oxidation and glycolytic metabolism due to an increase in the mitochondrial mass. Therefore, targeting LAG-3 may provide a new strategy for antitumor therapy. Cytotoxic T lymphocyte antigen 4 is expressed on the surface of chronically activated T cells. This inhibitory molecule suppresses the PI3K/Akt/mTOR signaling pathway and prevents glucose uptake in T cells^[84,85]. Imatinib, a BCR-ABL kinase inhibitor, has been indicated to have different effects on T-cell metabolism. According to Beckermann *et al.*^[86], this medication activates CD8⁺ T cells, while induces Treg cell apoptosis by reducing IDO expression. Moreover, metformin as a classic regulator of glucose metabolism, has a direct anti-tumor activity and an indirect effect on strengthening CTL function. This drug blocks the mTOR pathway and interferes with tumor glycolysis and thus tumor growth^[87]. Also, metformin downregulates the PD-L1 expression on the tumor cells and increases the cytotoxic function of CTL^[87]. The proviral integration site for moloney murine leukemia virus PIM is a serine/threonine kinase involved in regulating T-cell glucose metabolism. Inhibiting the PIM kinase, increases mTORC1 activity and leads to higher uptake of glucose by T cells and enhances the antitumor immunity^[88].

Targeting lipid metabolism in T cells

Some studies have noted the role of lipid metabolism, including intracellular cholesterol levels, in regulating tumor cell as well as T-cell activity. The effect of some lipid-metabolizing drugs, such as statins, on T cells is still controversial. According to the literature, statins can negatively affect tumor cells by inhibiting lipid metabolism and also affect T cells by reducing the cholesterol levels^[89]. One of the metabolic pathways for cholesterol synthesis is the MVK pathway. Some studies have reported that tumor cells using this pathway can activate the immune responses, introducing a new antitumor target for immunotherapy. MVK is also important for T-cell activation in an Akt/mTOR signaling-dependent manner^[90]. Avasimibe, as an acyl-CoA acyltransferase inhibitor, prevents cholesterol esterification and

Table 1. Therapeutic approaches for targeting T cell and tumor metabolism

Treat	Target	Signaling pathway	Effect
PD-1/PD-L1 antibodies	PD-1/PD-L1	PI3K/Akt/mTOR	Teffs: increase FAO Tumor: inhibit glycolysis
CTLA-4 antibodies	CTLA-4	PI3K/Akt/mTOR	Teffs: inhibit glucose uptake
Imatinib	BCR-ABL kinase/IDO	BCR/ABL IDO	Teffs: activation Treg: apoptosis Tumor: switch from glycolysis to OXPHOS
CTLA-4 antibodies	CTLA-4	PI3K/Akt/mTOR	Teffs: inhibit glucose uptake
Imatinib	BCR-ABL kinase/IDO	BCR/ABL IDO	Teffs: activation Treg: apoptosis Tumor: switch from glycolysis to OXPHOS
Metformin	PD-L1	LKB1-AMPK system mTOR	Tumor: down-regulate PD-L1 expression
PIM kinase inhibitor	PIM kinase	mTORC1	Teffs: increase glucose uptake
MVK inhibitor	MVK	PI3K/Akt/mTOR	Teffs: activation Tumor: inhibition
Avasimibe	ACAT-1	Cholesterol esterification	Teffs: activation Tumor: inhibit the proliferation and Metastasis
GDC-0919	IDO1	Tryptophan	Teffs: relieve CD8 ⁺ T-cell inhibition
INCB024360	IDO	Tryptophan	Teffs: increase proliferation and IFN- γ production
N-acetylcysteine	FOXO1	PI3K/Akt/mTOR	Teffs: affect granzyme B secretion and PD-1 expression
V-9302	Glutamine transporter	Glutamine	Teffs: no affect Tumor: inhibit the proliferation

Teff, effector T cell

enhances the level of intracellular free cholesterol tumor cells, thus inhibiting the proliferation and metastasis in tumor cells and increasing the activity of CD8⁺ T cells. Avasimibe has also been used to treat cancer in murine models of tumors and shown considerable antitumor effects. A combination of avasimibe with PD-1 antibodies has shown a better efficacy in regressing tumor progression rather than monotherapy^[30,91]. Fenofibrate is an activator of peroxisome proliferator-activated receptor alpha, involved in regulating lipid metabolism^[92], thereby increasing FAO in T cells and reversing the suppression of T cells in the tumor microenvironment^[93]. Liu et al.^[94] discovered that both Treg cells and tumor cells in the tumor microenvironment could modify the lipid metabolism in T cells by increasing the expression of group IVA phospholipase A, a change that eventually results in T cell senescence. Senescent T cells have little capacity to kill tumor cells. Inhibiting group IVA phospholipase A in T cells from breast cancer and melanoma models

showed that the lipid metabolism reprogrammed in T cells and the antitumor ability increased^[94]. Therefore, targeting lipid metabolism in T cells might synergistically enhance the therapeutic impact of most cancer treatments.

Targeting T cell amino acid metabolism

IDO1 catalyzes oxidation of tryptophan to kynurenine and is partly responsible for the acquired immune tolerance to cancer. A research performed on patients with colon cancer highlighted a reverse association between IDO expression and T-cell infiltration into the tumor microenvironment. This study also observed a lower rate of survival in the patients with higher IDO levels^[95]. Navoximod (GDC0919) is a new IDO inhibitor tested in several tumor models with potential immunomodulatory properties. This drug can improve CD8⁺ T cell cytotoxicity by reducing the amount of kynurenine^[96]. In addition, the combination treatment of Navoximod with chemotherapy, radiotherapy, or vaccine leads to

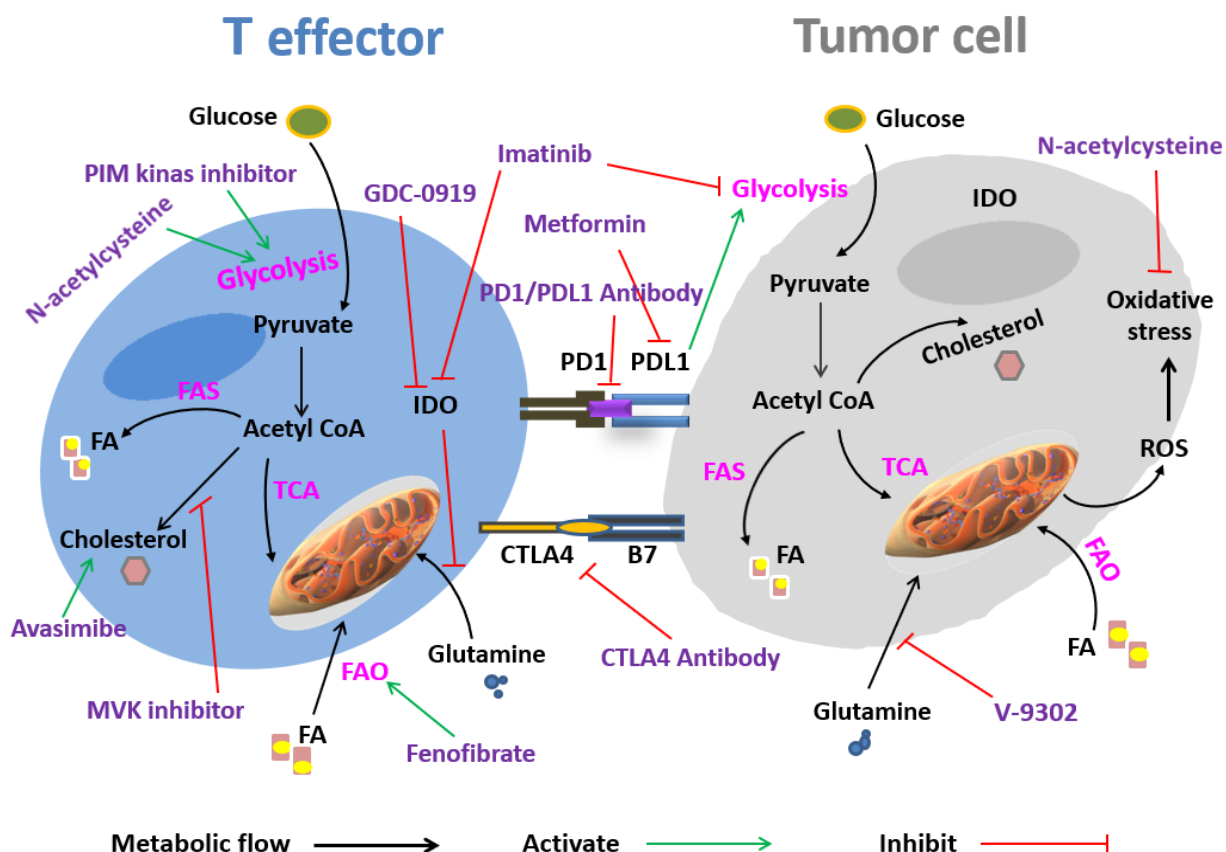


Fig. 3. Therapeutic approaches for targeting T cell and tumor metabolism. Tumor cells compete with T cells for the uptake of essential nutrients including glucose, amino acids, and fatty acids, leading to food deprivation, hypoxia, and the production of toxic metabolites in the tumor microenvironment to further inhibit T cell function. Some drugs targeting the metabolic processes of T cells and tumor cells contribute to the antitumor effect, such as PD-1/PD-L1 antibodies, CTLA4 antibodies, metformin, fenofibrate, V-9302, Avasimibe, MVK inhibitor, GDC-0919, and imatinib. PD1, death protein 1; FA, fatty acid; ROS, reactive oxygen species; CTLA-4, cytotoxic lymphocyte antigen 4

the progressed antitumor response^[96]. Another IDO inhibitor named INCB024360, results in the increased T-cell proliferation and IFN- γ production in mouse models^[97]. Administration of IDO inhibitors can substantially increase the production of cytokines including IL-2, TNF- α , and IFN- γ in CD8⁺ T cells and enhance their functions^[98]. Therefore, using IDO inhibitors is one of the strategies currently under investigation for activating T cells in tumor conditions. Studies have shown that PD-1 expression reduces when CD8⁺ T cells are cultivated under glutamine-restricted conditions^[99]. Decreased expression of PD-1 results in boosting the activity of CD8⁺ T cells, suggesting a helpful strategy to improve immunotherapy^[100]. Similarly, NAC can inhibit the expression of FOXO1 by activating the PI3K/Akt signaling pathway in CD8⁺ T cells and increase secretion of granzyme-B and, consequently, the anti-tumor capacity of these cells^[101]. NAC is an analogue of cysteine, which is required for glutathione

synthesis. Glutathione possesses antioxidant properties and counteracts the oxidative stress observed in the tumor microenvironment^[102]. Glutamine is also a target metabolite in cancer therapy. In a study on mouse TNBC model, T effectors and tumor cells compete for glutamine from the microenvironment; deletion of glutaminase in tumor cells, an enzyme crucial for glutamine metabolism, activates T cells and enhances antitumor immune responses^[103]. In addition, V-9302, an inhibitor of the glutamine transporter, can specifically inhibit glutamine uptake in TNBC cells, but not in antitumor T cells, representing a promising therapeutic strategy against TNBC^[103].

Metabolic changes in the tumor microenvironment can intensively affect T cells, from activation to their differentiation and function. Therefore, a better understanding of immunometabolic events is of utmost importance to achieve new anticancer therapeutics. Based on the preclinical and clinical studies, the longevity and stability of T cells used in

immunotherapy is the main factor determining the effectiveness of therapy. Further studies are needed to develop techniques for manipulation of the metabolic pathways in order to enhance T cell responses against cancer progression.

Conclusion

To sum up, studies on immunometabolism in T lymphocytes can not only facilitate basic research but also provide potential targets in drug discovery against immune-related disorders, including cancer.

DECLARATIONS

Ethical statement

Not applicable.

Data availability

The raw data supporting the conclusions of this article are available from the authors upon reasonable request.

Author contributions

JA: performed the literature search and data analysis and drafted the manuscript; FS: had the idea for the article and critically revised the work; MM: critically revised the work; HF: critically revised the work; MR: performed the literature search and data analysis.

Conflict of interest

None declared.

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REFERENCES

- Thiele K, Diao L, Arck PC, editors. Immunometabolism, pregnancy, and nutrition. *Seminars in immunopathology* 2018; **40**(2): 157-174.
- Wang Q, Wu H. T cells in adipose tissue: critical players in immunometabolism. *Frontiers in immunology* 2018; **9**: 2509.
- Man K, Kutuyavin VI, Chawla A. Tissue immunometabolism: development, physiology, and pathobiology. *Cell metabolism* 2017; **25**(1): 11-26.
- Ryan DG, O'Neill LA. Krebs cycle reborn in macrophage immunometabolism. *Annual review of immunology* 2020; **38**: 289-313.
- Ramalho R, Rao M, Zhang C, Agrati C, Ippolito G, Wang FS, editors. Immunometabolism: new insights and lessons from antigen-directed cellular immune responses. *Seminars in immunopathology* 2020; **42**(3): 279-313.
- O'Neill LA, Kishton RJ, Rathmell J. A guide to immunometabolism for immunologists. *Nature reviews immunology* 2016; **16**(9): 553-565.
- Cheng SC, Quintin J, Cramer RA, Shepardon KM, Saeed S, Kumar V, Giamarellos-Bourboulis EJ, Martens JHA, Appukudige Rao N, Aghajani-refah A, Manjeri GR, Li Y, Ifrim DC, Arts RJW, van der Veer BMJW, Deen PMT, Logie C, O'Neill LA, Willems P, Ng A, Joosten LAB, Wijmenga C, Stunnenberg HG, Xavier RJ, Netea MG. mTOR-and HIF-1 α -mediated aerobic glycolysis as metabolic basis for trained immunity. *Science* 2014; **345**(6204): 1250684.
- McGuire PJ. Chemical individuality in T cells: a Garrodian view of immunometabolism. *Immunological reviews* 2020; **295**(1): 82-100.
- Akram M. Citric acid cycle and role of its intermediates in metabolism. *Cell biochemistry and biophysics* 2014; **68**(3): 475-478.
- Watmough NJ, Frerman FE. The electron transfer flavoprotein: ubiquinone oxidoreductases. *Biochimica et biophysica acta* 2010; **1797**(12): 1910-1916.
- Röhrig F, Schulze A. The multifaceted roles of fatty acid synthesis in cancer. *Nature reviews cancer* 2016; **16**(11): 732-749.
- Holecek M, Vodenicarovova M, Siman P. Acute effects of phenylbutyrate on glutamine, branched-chain amino acid and protein metabolism in skeletal muscles of rats. *International journal of experimental pathology* 2017; **98**(3): 127-133.
- Saravia J, Raynor JL, Chapman NM, Lim SA, Chi H. Signaling networks in immunometabolism. *Cell research* 2020; **30**(4): 328-342.
- Chapman NM, Boothby MR, Chi H. Metabolic coordination of T cell quiescence and activation. *Nature reviews immunology* 2020; **20**(1): 55-70.
- Lee K, Gudapati P, Dragovic S, Spencer C, Joyce S, Killeen N, Magnuson MA, Boothby M. Mammalian target of rapamycin protein complex 2 regulates differentiation of Th1 and Th2 cell subsets via distinct signaling pathways. *Immunity* 2010; **32**(6): 743-753.
- Li N, Huang D, Lu N, Luo L. Role of the LKB1/AMPK pathway in tumor invasion and metastasis of cancer cells. *Oncology reports* 2015; **34**(6): 2821-2816.
- Shahouzehi B, Fallah H, Masoumi-Ardakani Y. L-carnitine administration effects on AMPK, APPL1 and PPAR γ genes expression in the liver and serum adiponectin levels and HOMA-IR in type 2 diabetes rat model induced by STZ and nicotinamide. *Ukrainian biochemical journal* 2020; **95**(5): 33-40.
- Zhang CS, Hawley SA, Zong Y, Li M, Wang Z, Gray A, Ma T, Cui J, Feng J-W, Zhu M, Wu YQ, Yang Li T, Ye Z, Lin SY, Yin H, Piao HL, Grahame Hardie D, Lin SC. Fructose-1, 6-bisphosphate and aldolase mediate glucose sensing by AMPK. *Nature* 2017; **548**(7665): 112-116.
- Mohammadi A, Fallah H, Shahouzehi B, Najafipour H. Effect of LXR agonist T0901317 and miR-33inhibitor on SIRT1-AMPK and circulating HDL-C levels. *Bulg chem commun* 2018; **50**(1): 111-118.
- Timilshina M, You Z, Lacher SM, Acharya S, Jiang L,

- Kang Y, Kim J, Wook Chang H, Kim KJ, Park B, Song JH, Ko HJ, Park YY, Ma MJ, Nepal MR, Cheon Jeong T, Chung Y, Waisman A, Chang JH. Activation of mevalonate pathway via LKB1 is essential for stability of Treg cells. *Cell reports* 2019; **27**(10): 2948-2961.
21. Poznanski SM, Barra NG, Ashkar AA, Schertzer JD. Immunometabolism of T cells and NK cells: metabolic control of effector and regulatory function. *Inflammation research* 2018; **67**(10): 813-828.
 22. Ciofani M, Zuniga-Pflucker JC. Notch promotes survival of pre-T cells at the β -selection checkpoint by regulating cellular metabolism. *Nature immunology* 2005; **6**(9): 881-888.
 23. Swainson L, Kinet S, Manel N, Battini JL, Sitbon M, Taylor N. Glucose transporter 1 expression identifies a population of cycling CD4⁺ CD8⁺ human thymocytes with high CXCR4-induced chemotaxis. *Proceedings of the national academy of sciences* 2005; **102**(36):12867-12872.
 24. Vigano MA, Ivanek R, Balwierz P, Berninger P, van Nimwegen E, Karjalainen K, Rolink V. An epigenetic profile of early T-cell development from multipotent progenitors to committed T-cell descendants. *European journal of immunology* 2014; **44**(4): 1181-1193.
 25. Peng M, Yin N, Chhangawala S, Xu K, Leslie CS, Li MO. Aerobic glycolysis promotes T helper 1 cell differentiation through an epigenetic mechanism. *Science* 2016; **354**(6311): 481-484.
 26. Ron Harel N, Sharpe AH, Haigis MC. Mitochondrial metabolism in T cell activation and senescence: a mini-review. *Gerontology* 2015; **61**(2): 131-138.
 27. Chang CH, Curtis JD, Maggi Jr LB, Faubert B, Villarino AV, O'Sullivan D, Ching Cheng Huang S, van der Windt GJV, Blagih J, Qiu J, Weber JD, Pearce EJ, Jones RG, Pearce EL. Posttranscriptional control of T cell effector function by aerobic glycolysis. *Cell* 2013; **153**(6): 1239-12351.
 28. Michalek RD, Gerriets VA, Jacobs SR, Macintyre AN, MacIver NJ, Mason EF, Sullivan SA, Nichols AG, Rathmell JC. Cutting edge: distinct glycolytic and lipid oxidative metabolic programs are essential for effector and regulatory CD4⁺ T cell subsets. *The Journal of immunology* 2011; **186**(6): 3299-3303.
 29. Jones N, Cronin JG, Dolton G, Panetti S, Schauenburg AJ, Galloway SA, Sewell AK, Cole DK, Thornton CA, Francis NJ. Metabolic adaptation of human CD4⁺ and CD8⁺ T-cells to T-cell receptor-mediated stimulation. *Frontiers in immunology* 2017; **8**: 1516.
 30. Yin Z, Bai L, Li W, Zeng T, Tian H, Cui J. Targeting T cell metabolism in the tumor microenvironment: an anti-cancer therapeutic strategy. *Journal of experimental and clinical cancer research* 2019; **38**(1): 1-10.
 31. Shi LZ, Wang R, Huang G, Vogel P, Neale G, Green DR, Chi H. HIF1 α -dependent glycolytic pathway orchestrates a metabolic checkpoint for the differentiation of TH17 and Treg cells. *Journal of experimental medicine* 2011; **208**(7): 1367-1376.
 32. Wang R, Dillon CP, Shi LZ, Milasta S, Carter R, Finkelstein D, McCormick L, Fitzgerald P, Chi H, Munger J, Green DR. The transcription factor Myc controls metabolic reprogramming upon T lymphocyte activation. *Immunity* 2011; **35**(6): 871-882.
 33. Mahnke J, Schumacher V, Ahrens S, Käding N, Feldhoff LM, Huber M, Rupp J, Raczkowski F, Mittrücker HW. Interferon regulatory factor 4 controls TH1 cell effector function and metabolism. *Scientific reports* 2016; **6**(1): 1-12.
 34. Ho PC, Bihuniak JD, Macintyre AN, Staron M, Liu X, Amezquita R, Tsui YC, Cui G, Micevic G, Perales JC, Kleinstein SH, Abel ED, Insogna KL, Feske S, Locasale JW, Bosenberg MW, Rathmell JC, Kaech SM. Phosphoenolpyruvate is a metabolic checkpoint of anti-tumor T cell responses. *Cell* 2015; **162**(6): 1217-1228.
 35. Klysz D, Tai X, Robert PA, Craveiro M, Cretenet G, Oburoglu L, Mongellaz C, Floess S, Fritz V, Matias MI, Yong C, Surh N, Marie JC, Huehn J, Zimmermann V, Kinet S, Dardalhon V, Taylor N. Glutamine-dependent α -ketoglutarate production regulates the balance between T helper 1 cell and regulatory T cell generation. *Science signaling*. 2015; **8**(396): ra97.
 36. Allocco JB, Alegre ML. Exploiting immunometabolism and T cell function for solid organ transplantation. *Cellular immunology* 2020; **351**: 104068.
 37. Nakaya M, Xiao Y, Zhou X, Chang JH, Chang M, Cheng X, Blonska M, Lin X, Sun SC. Inflammatory T cell responses rely on amino acid transporter ASCT2 facilitation of glutamine uptake and mTORC1 kinase activation. *Immunity* 2014; **40**(5): 692-705.
 38. Johnson MO, Wolf MM, Madden MZ, Andrejeva G, Sugiura A, Contreras DC, Maseda D, Liberti MV, Paz K, Kishton RJ, Johnson ME, de Cubas AA, Wu R, Li G, Zhang Y, Newcomb DC, Wells AD, Restifo NP, Rathmell WK, Locasale JW, Davila ML, Blazar BR, Rathmell JC. Distinct regulation of Th17 and Th1 cell differentiation by glutaminase-dependent metabolism. *Cell* 2018; **175**(7): 1780-1795.
 39. Macintyre AN, Gerriets VA, Nichols AG, Michalek RD, Rudolph MC, Deoliveira D, Anderson SM, Abel ED, Chen BJ, Hale LP, Rathmell JC. The glucose transporter Glut1 is selectively essential for CD4 T cell activation and effector function. *Cell metabolism* 2014; **20**(1): 61-72.
 40. Berod L, Friedrich C, Nandan A, Freitag J, Hagemann S, Harmrolfs K, Sandouk A, Hesse C, Castro CN, Bähre H, Tschirner SK, Gorinski N, Gohmert M, Mayer CT, Huehn J, Ponimaskin E, Abraham WR, Müller R, Lochner M, Sparwasser T. De novo fatty acid synthesis controls the fate between regulatory T and T helper 17 cells. *Nature medicine* 2014; **20**(11): 1327-1333.
 41. Prlic M, Williams MA, Bevan MJ. Requirements for CD8 T-cell priming, memory generation and maintenance. *Current opinion in immunology* 2007; **19**(3): 315-319.
 42. King CG, Kobayashi T, Cejas PJ, Kim T, Yoon K, Kim GK, Chiffolleau E, Hickman SP, Walsh PT, Turka LA, Choi Y. TRAF6 is a T cell-intrinsic negative regulator required for the maintenance of immune homeostasis. *Nature medicine* 2006; **12**(9): 1088-1092.
 43. van der Windt GJ, Everts B, Chang C-H, Curtis JD, Freitas TC, Amiel E, Pearce EJ, Pearce EL.

- Mitochondrial respiratory capacity is a critical regulator of CD8⁺ T cell memory development. *Immunity* 2012; **36**(1): 68-78.
44. Beier UH, Angelin A, Akimova T, Wang L, Liu Y, Xiao H, Koike MA, Hancock SA, Bhatti TR, Han R, Jiao J, Veasey SC, Sims CA, Baur JA, Wallace DC, Hancock WW. Essential role of mitochondrial energy metabolism in Foxp3⁺ T-regulatory cell function and allograft survival. *The FASEB journal* 2015; **29**(6): 2315-2326.
 45. Fan MY, Turka LA. Immunometabolism and PI (3) K signaling as a link between IL-2, Foxp3 expression, and suppressor function in regulatory T cells. *Frontiers in immunology* 2018; **9**: 69.
 46. Fontenot JD, Gavin MA, Rudensky AY. Foxp3 programs the development and function of CD4⁺ CD25⁺ regulatory T cells. *Nature immunology* 2003; **4**(4): 330-336.
 47. Shrestha S, Yang K, Guy C, Vogel P, Neale G, Chi H. Treg cells require the phosphatase PTEN to restrain TH1 and TFH cell responses. *Nature immunology* 2015; **16**(2): 178-187.
 48. Apostolidis SA, Rodríguez-Rodríguez N, Suárez-Fueyo A, Dioufa N, Ozcan E, Crispín JC, Tsokos MG, Tsokos GC. Phosphatase PP2A is requisite for the function of regulatory T cells. *Nature immunology* 2016; **17**(5): 556-564.
 49. Kishton RJ, Sukumar M, Restifo NP. Metabolic regulation of T cell longevity and function in tumor immunotherapy. *Cell metabolism* 2017; **26**(1): 94-109.
 50. Leone RD, Powell JD. Metabolism of immune cells in cancer. *Nature reviews cancer* 2020; **20**(9): 516-531.
 51. Chang CH, Qiu J, O'Sullivan D, Buck MD, Noguchi T, Curtis JD, Chen Q, Gindin M, Gubin MM, van der Windt GJW, Tonc E, Schreiber RD, Pearce EJ, Pear EL. Metabolic competition in the tumor microenvironment is a driver of cancer progression. *Cell* 2015; **162**(6): 1229-1241.
 52. Yu J, Du W, Yan F, Wang Y, Li H, Cao S, Yu W, Shen C, Liu J, Ren X. Myeloid-derived suppressor cells suppress antitumor immune responses through IDO expression and correlate with lymph node metastasis in patients with breast cancer. *The Journal of immunology* 2013; **190**(7): 3783-3797.
 53. Munn DH, Mellor AL. IDO in the tumor microenvironment: inflammation, counter-regulation, and tolerance. *Trends in immunology* 2016; **37**(3): 193-207.
 54. Zhai L, Bell A, Ladomersky E, Lauing KL, Bollu L, Nguyen B, Genet M, Kim M, Chen P, Mi X, Wu JD, Schipma MJ, Wray B, Griffiths J, Unwin RD, Clark SJ, Acharya R, Bao R, Horbinski C, Lukas RV, Schiltz G, Wainwright DA. Tumor cell IDO enhances immune suppression and decreases survival independent of tryptophan metabolism in glioblastoma. *Clinical cancer research* 2021; **27**(23): 6514-6528.
 55. Schramme F, Crosignani S, Frederix K, Hoffmann D, Pilotte L, Stroobant V, Preillon J, Driessens G, Van den Eynde BJ. Inhibition of Tryptophan-Dioxygenase Activity Increases the Antitumor Efficacy of Immune Checkpoint Inhibitors. *Antitumor Synergy Between TDO and Checkpoint Inhibitors. Cancer immunology research* 2020; **8**(1): 32-45.
 56. Leone RD, Sun IM, Oh M-H, Sun IH, Wen J, Englert J, Powell JD. Inhibition of the adenosine A2a receptor modulates expression of T cell coinhibitory receptors and improves effector function for enhanced checkpoint blockade and ACT in murine cancer models. *Cancer immunology, immunotherapy* 2018; **67**(8): 1271-1284.
 57. Ferrante CJ, Pinhal Enfield G, Elson G, Cronstein BN, Hasko G, Outram S, SJ. The adenosine-dependent angiogenic switch of macrophages to an M2-like phenotype is independent of interleukin-4 receptor alpha (IL-4R α) signaling. *Inflammation* 2013; **36**(4): 921-931.
 58. Wang H, Franco F, Tsui YC, Xie X, Trefny MP, Zappasodi R, Mohmood SR, Fernández-García J, Tsai CH, Schulze I, Picard F, Meylan E, Silverstein R, Goldberg I, Fendt SM, Wolchok JD, Merghoub T, Jandus C, Zippelius A, Ho PC. CD36-mediated metabolic adaptation supports regulatory T cell survival and function in tumors. *Nature immunology* 2020; **21**(3): 298-308.
 59. Xu S, Chaudhary O, Rodríguez Morales P, Sun X, Chen D, Zappasodi R, Xu Z, PintoAFM, Williams A, Schulze I, Farsakoglu Y, Karthik Varanasi S, Siong Low J, Tang W, Wang H, McDonald B, Trippl V, Downes M, Evans RM, Abumrad NA, Merghoub T, Wolchok JD, Shokhirev MN, Ho PC, Witztum JL, Emu B, Cui G, Kaech SM. Uptake of oxidized lipids by the scavenger receptor CD36 promotes lipid peroxidation and dysfunction in CD8⁺ T cells in tumors. *Immunity* 2021; **54**(7): 1561-1577.
 60. Johnston RJ, Su LJ, Pinckney J, Critton D, Boyer E, Krishnakumar A, Corbett M, Rankin AL, Dibella R, Campbell L, Martin GH, Lemar H, Cayton T, Y-C Huang R, Deng X, Nayeem A, Chen H, Ergel B, Rizzo JM, Yamniuk AP, Dutta S, Ngo J, Olga Shorts A, Ramakrishnan R, Kozhich A, Holloway J, Fang H, Wang YK, Yang Z, Thiam K, Rakestraw G, Rajpal A, Sheppard P, Quigley M, Bahjat KS, Korman AJ. VISTA is an acidic pH-selective ligand for PSGL-1. *Nature* 2019; **574**(7779): 565-570.
 61. Bunse L, Pusch S, Bunse T, Sahm F, Sanghvi K, Friedrich M, Alansary D, Sonner JK, Green E, Deumelandt K, Kilian M, Neftel C, Uhlig S, Kessler T, von Landenberg A, Berghoff AS, Marsh K, Steadman M, Zhu D, Nicolay B, Wiestler B, Breckwoldt MO, Al Ali R, Karcher-Bausch S. Suppression of antitumor T cell immunity by the oncometabolite (R)-2-hydroxyglutarate. *Nature medicine* 2018; **24**(8): 1192-1203.
 62. Eil R, Vodnala SK, Clever D, Klebanoff CA, Sukumar M, Pan JH, Palmer DC, Gros A, Yamamoto TN, Patel SJ, Guittard GC, Yu Z, Carbonaro V, Okkenhaug K, Schrumph DS, Marston Linehan W, Roychoudhuri R, Restifo NP. Ionic immune suppression within the tumour microenvironment limits T cell effector function. *Nature* 2016; **537**(7621): 539-543.
 63. Kostourou V, Cartwright J, Johnstone A, Boulton J, Cullis E, Whitley G, Robinson SP. The role of tumour-derived iNOS in tumour progression and angiogenesis. *British*

- journal of cancer* 2011; **104**(1): 83-90.
64. Grzywa TM, Sosnowska A, Matryba P, Rydzynska Z, Jasinski M, Nowis D, Golab J. Myeloid cell-derived arginase in cancer immune response. *Frontiers in immunology* 2020; **11**: 938.
 65. Fletcher M, Ramirez ME, Sierra RA, Raber P, Thevenot P, Al-Khami AA, Sanchez-Pino D, Hernandez C, Wyczechowska DD, Ochoa AC, Rodriguez PC. L-Arginine depletion blunts antitumor T-cell responses by inducing myeloid-derived suppressor cells suppression of T-cell responses by L-arginine depletion. *Cancer research* 2015; **75**(2): 275-283.
 66. Liu YN, Yang JF, Huang DJ, Ni HH, Zhang CX, Zhang L, Gao S, Li J. Hypoxia induces mitochondrial defect that promotes T cell exhaustion in tumor microenvironment through MYC-regulated pathways. *Frontiers in immunology* 2020; **11**: 1906.
 67. Buck MD, O'Sullivan D, Geltink RIK, Curtis JD, Chang CH, Sanin DE, Qiu J, Kretz O, Braas D, van der Windt GJ, Chen Q, Ching Cheng Huang S, O'Neill CM, Edelson BT, Pearce EJ, Sesaki H, Huber TB, Rambold AS, Pearce EL. Mitochondrial dynamics controls T cell fate through metabolic programming. *Cell* 2016; **166**(1): 63-76.
 68. Saha T, Dash C, Jayabalan R, Khiste S, Kulkarni A, Kurmi K, Mondal J, Majumder PK, Bardia A, Lin Jang H, Sengupta S. Intercellular nanotubes mediate mitochondrial trafficking between cancer and immune cells. *Nature nanotechnology* 2022; **17**(1): 98-106.
 69. Gomez Pinillos A, Ferrari AC. mTOR signaling pathway and mTOR inhibitors in cancer therapy. *Hematology/oncology clinics* 2012; **26**(3): 483-505.
 70. Yue W, Yang CS, DiPaola RS, Tan XL. Repurposing of metformin and aspirin by targeting AMPK-mTOR and inflammation for pancreatic cancer prevention and treatment. *Cancer prevention research* 2014; **7**(4): 388-397.
 71. Zaytseva YY, Valentino JD, Gulhati P, Evers BM. mTOR inhibitors in cancer therapy. *Cancer letters* 2012; **319**(1): 1-7.
 72. Vinay DS, Kwon BS. 4-1BB (CD137), an inducible costimulatory receptor, as a specific target for cancer therapy. *BMB reports* 2014; **47**(3): 122.
 73. Sanchez Paulete AR, Labiano S, Rodriguez Ruiz ME, Azpilikueta A, Etxeberria I, Bolaños E, Lang V, Rodriguez M, Angela Aznar M, Jure-Kunkel M, Melero I. Deciphering CD137 (4-1BB) signaling in T-cell costimulation for translation into successful cancer immunotherapy. *European journal of immunology* 2016; **46**(3): 513-522.
 74. Choi BK, Lee DY, Lee DG, Kim YH, Kim S-H, Oh HS, Han C, Kwon BS. 4-1BB signaling activates glucose and fatty acid metabolism to enhance CD8⁺ T cell proliferation. *Cellular and molecular immunology* 2017; **14**(9): 748-757.
 75. Menk AV, Scharping NE, Rivadeneira DB, Calderon MJ, Watson MJ, Dunstane D, Watkins Sc, Delgoffe GM. 4-1BB costimulation induces T cell mitochondrial function and biogenesis enabling cancer immunotherapeutic responses. *Journal of experimental medicine* 2018; **215**(4): 1091-1100.
 76. Chester C, Ambulkar S, Kohrt HE. 4-1BB agonism: adding the accelerator to cancer immunotherapy. *Cancer immunology, immunotherapy* 2016; **65**(10): 1243-1248.
 77. Ohashi T, Akazawa T, Aoki M, Kuze B, Mizuta K, Ito Y, Inoue N. Dichloroacetate improves immune dysfunction caused by tumor-secreted lactic acid and increases antitumor immunoreactivity. *International journal of cancer* 2013; **133**(5): 1107-1118.
 78. Pilon Thomas S, Kodumudi KN, El Kenawi AE, Russell S, Weber AM, Luddy K, Damaghi M, Wojtkowiak JW, Mulé JJ, Ibrahim Hashim A, Gillies RJ. Neutralization of tumor acidity improves antitumor responses to immunotherapy. *Cancer research* 2016; **76**(6): 1381-1390.
 79. Riley LW, Raphael E, Faerstein E. Obesity in the United States—dysbiosis from exposure to low-dose antibiotics? *Frontiers in public health* 2013; **1**: 69.
 80. He Y, Fu L, Li Y, Wang W, Gong M, Zhang J, Dong X, Huang J, Wang Q, Mackay CR, Fu YX, Chen Y, Guo X. Gut microbial metabolites facilitate anticancer therapy efficacy by modulating cytotoxic CD8⁺ T cell immunity. *Cell metabolism* 2021; **33**(5): 988-1000.
 81. Staron MM, Gray SM, Marshall HD, Parish IA, Chen JH, Perry CJ, Cui G, Li MO, Kaech SM. The transcription factor FoxO1 sustains expression of the inhibitory receptor PD-1 and survival of antiviral CD8⁺ T cells during chronic infection. *Immunity* 2014; **41**(5): 802-814.
 82. Patsoukis N, Bardhan K, Chatterjee P, Sari D, Liu B, Bell LN, Karoly ED, Freeman GJ, Petkova V, Seth P, Li L, Boussiotis VA. PD-1 alters T-cell metabolic reprogramming by inhibiting glycolysis and promoting lipolysis and fatty acid oxidation. *Nature communications* 2015; **6**(1): 1-13.
 83. Previte DM, Martins CP, O'Connor EC, Marre ML, Coudriet GM, Beck NW, Menk AV, Wright RH, Tse HM, Delgoffe GM, Piganelli JD. Lymphocyte activation gene-3 maintains mitochondrial and metabolic quiescence in naive CD4⁺ T cells. *Cell reports* 2019; **27**(1): 129-141.
 84. Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. *Nature reviews cancer* 2012; **12**(4): 252-264.
 85. Ho PC, Liu PS. Metabolic communication in tumors: a new layer of immunoregulation for immune evasion. *Journal for immunotherapy of cancer* 2016; **4**(1): 1-9.
 86. Beckermann KE, Dudzinski SO, Rathmell JC. Dysfunctional T cell metabolism in the tumor microenvironment. *Cytokine and growth factor reviews* 2017; **35**: 7-14.
 87. Cha JH, Yang WH, Xia W, Wei Y, Chan LC, Lim SO, Li CW, Kim T, Chang SS, Lee HH, Hsu GL, Wang HL, Kuo CW, Chang WC, Hadad S, Purdie CA, McCoy AM, Cai S, Tu Y, Litton JK, Mittendorf EA, Moulder SL, Symmans WF, Thompson AM, Pitwnica-Worms H, Chen CH, Khoo KH, Hung MC. Metformin promotes antitumor immunity via endoplasmic-reticulum-associated degradation of PD-L1. *Molecular cell* 2018;

- 71(4): 606-620.
88. Chatterjee S, Chakraborty P, Daenthanasanmak A, Iamsawat S, Andrejeva G, LA L, Wolf M, Baliga U, Krieg C, Beeson CC, Mehrotra M, Hill EG, Rathmell JC, Yu XZ, Kraft AS, Mehrotra S. Targeting PIM kinase with PD1 inhibition improves immunotherapeutic antitumor T-cell response. PIM-K inhibition potentiates ACT. *Clinical cancer research* 2019; **25**(3): 1036-1049.
 89. Frostegård J, Zhang Y, Sun J, Yan K, Liu A. Oxidized low-density lipoprotein (Ox LDL)-treated dendritic cells promote activation of T cells in human atherosclerotic plaque and blood, which is repressed by statins: micro RNA let-7c is integral to the effect. *Journal of the American Heart Association* 2016; **5**(9): e003976.
 90. Gruenbacher G, Thurnher M. Mevalonate metabolism governs cancer immune surveillance. *Oncoimmunology* 2017; **6**(10): e1342917.
 91. Yang W, Bai Y, Xiong Y, Zhang J, Chen S, Zheng X, Meng X, Li L, Wang J, Xu C, Yan C, Wang L, Chang CCY, Chang TY, Zhang T, Zhou P, Song BL, Liu W, Sun SC, Liu X, Li BL, Xu C. Potentiating the antitumor response of CD8+ T cells by modulating cholesterol metabolism. *Nature* 2016; **531**(7596): 651-655.
 92. Mohammadi A, Gholamhosseinian A, Fallah H. *Trigonella foenum-graecum* water extract improves insulin sensitivity and stimulates PPAR and γ gene expression in high fructose-fed insulin-resistant rats. *Advanced biomedical research* 2016; **5**: 54.
 93. Zhang Y, Kurupati R, Liu L, Zhou XY, Zhang G, Hudaihed A, Filisio F, Giles-Davis W, Xu X, Karakousis GC, Schuchter LM, Xu W, Amaravadi R, Xiao M, Sadek N, Krepler C, Herlyn M, Freeman GJ, Rabinowitz JD, Ertl HCJ. Enhancing CD8⁺ T cell fatty acid catabolism within a metabolically challenging tumor microenvironment increases the efficacy of melanoma immunotherapy. *Cancer cell* 2017; **32**(3): 377-391.
 94. Liu X, Hartman CL, Li L, Albert CJ, Si F, Gao A, Huang L, Zhao Y, Lin W, Hsueh EC, Shen L, Shao Q, Hoft DF, Ford DA, Peng G. Reprogramming lipid metabolism prevents effector T cell senescence and enhances tumor immunotherapy. *Science translational medicine* 2021; **13**(587): eaaz6314.
 95. Muller AJ, Manfredi MG, Zakharia Y, Prendergast GC, editors. Inhibiting IDO pathways to treat cancer: lessons from the ECHO-301 trial and beyond. *Seminars in immunopathology* 2019; **41**(1): 41-48.
 96. Nayak Kapoor A, Hao Z, Sadek R, Dobbins R, Marshall L, Vahanian NN, Ramsey WJ, Kennedy E, Mautino MR, Link CJ, Lin RS, Royer-Joo S, Liang X, Salphati L, Ari M, Morrissey K, Mahrus S, McCall B, Pirzkall A, Munn DH, Janik JE, Khleif SN. Phase Ia study of the indoleamine 2, 3-dioxygenase 1 (IDO1) inhibitor navoximod (GDC-0919) in patients with recurrent advanced solid tumors. *Journal for immunotherapy of cancer* 2018; **6**(1): 1-12.
 97. Beatty GL, O'Dwyer PJ, Clark J, Shi JG, Bowman KJ, Scherle PA, Newton RC, Schaub R, Maleski J, Leopold L, Gajewski TF. First in human phase I study of the oral inhibitor of indoleamine 2,3-Dioxygenase-1 epacadostat (INCB024360) in patients with advanced solid malignancies. *Clinical cancer research : an official journal of the American association for cancer research* 2017; **23**(13): 3269-3276.
 98. Spranger S, Koblish HK, Horton B, Scherle PA, Newton R, Gajewski TF. Mechanism of tumor rejection with doublets of CTLA-4, PD-1/PD-L1, or IDO blockade involves restored IL-2 production and proliferation of CD8+ T cells directly within the tumor microenvironment. *Journal for immunotherapy of cancer* 2014; **2**(1): 1-14.
 99. Nabe S, Yamada T, Suzuki J, Toriyama K, Yasuoka T, Kuwahara M, Shiraishi A, Takenaka K, Yasukawa M, Yamashita M. Reinforce the antitumor activity of CD8+ T cells via glutamine restriction. *Cancer science* 2018; **109**(12): 3737-3750.
 100. Sung JY, Cheong JH. New immunometabolic strategy based on cell type-specific metabolic reprogramming in the Tumor Immune Microenvironment. *Cells* 2022; **11**(5): 768.
 101. Scheffel MJ, Scurti G, Wyatt MM, Garrett Mayer E, Paulos CM, Nishimura MI, Voelkel Johnson C. N-acetyl cysteine protects anti-melanoma cytotoxic T cells from exhaustion induced by rapid expansion via the downmodulation of Foxo1 in an Akt-dependent manner. *Cancer immunology, immunotherapy* 2018; **67**(4): 691-702.
 102. Perl A, Hanczko R, Lai ZW, Oaks Z, Kelly R, Borsuk R, Asara JM, Phillips PE. Comprehensive metabolome analyses reveal N-acetylcysteine-responsive accumulation of kynurenine in systemic lupus erythematosus: implications for activation of the mechanistic target of rapamycin. *Metabolomics* 2015; **11**(5): 1157-1174.
 103. Edwards DN, Ngwa VM, Raybuck AL, Wang S, Hwang Y, Kim LC, Hoon Cho S, Paik Y, Wang Q, Zhang S, Charles Manning H, Rathmell JC, Cook RS, Boothby MR, Chen J. Selective glutamine metabolism inhibition in tumor cells improves antitumor T lymphocyte activity in triple-negative breast cancer. *The Journal of clinical investigation* 2021; **131**(4): e140100.