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REVIEW ARTICLE

Tumor-Induced Metabolism and T Cells Located in Tumor Environment

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Abstract: Several subtypes of T cells are located in a tumor environment, each of which supplies their energy using different metabolic mechanisms. Since the cancer cells require high levels of glucose, the conditions of food poverty in the tumor environment can cause inactivation of immune cells, especially the T-effector cells, due to the need for glucose in the early stages of these cells activity. Different signaling pathways, such as PI3K-AKt-mTOR, MAPK, HIF-1α, *etc.*, are activated or inactivated by the amount and type of energy source or oxygen levels that determine the fate of T cells in a cancerous environment. This review describes the metabolites in the tumor environment and their effects on the function of T cells. It also explains the signaling pathway of T cells in the tumor and normal conditions, due to the level of access to available metabolites and subtypes of T cells in the tumor environment.

Keywords: Cancer, t lymphocytes, metabolism, immunotherapy, immune evasion, cytokines.

1. INTRODUCTION

The cells present in the tumor environment are effective in determining the fate of the tumor. Both innate and acquired immune cells deploy in the tumor-like environment, so that cell recognition in the tumor environment can provide a clear picture of tumor status, the extent of tumor spread, and the effect of therapeutic agents in the tumor's environment, which can improve tumor immunotherapy. Of course, the purpose of these therapies is to repress regulatory T cells and activate the TCD4+, as well as TCD8+ cells, which act effectively against the tumor. In the tumor environment, due to cell proliferation, there is a certain nutrition restriction, which can cause a defect in immunity cell growth and interfere in cell signaling and transcription function. During the process of differentiating the primary T cells into effector cells or memories, a lot of energy isrequired for cellular functions, including cell proliferation, fecundity, and cytokines production. However, a lot of pathways controll cell differentiation and function [1].

The pathways controlling the differentiation and function of immune cells are related to cellular metabolism which plays a key role in immune cell maintenance and development [2, 3]. During the period of silence, resting T cells require a basic amount of energy and oxidize glucose-derived peptides, as well as lipids and amino acids. Once the stimulation of T cells, cell growth, cell division, and cellular functions are improved [4], then in this situation, the consumption of ATP and raw materials, such as lipids, proteins and especially nucleic acids, increases [4], through an exchange in the intracellular metabolism of cells from catabolism to anabolism. During the gradual progression of the tumor, the T-cells are exhausted, and their normal function is diminished. In this situation, tumor cells also undergo changes that result in the production of immunosuppressive agents in the tumor environment. Nevertheless, executable T cells also act against the progression of the tumor. Therefore, with regard to metabolic dependency and performance, T cells can affect the growth and progression of a tumor or suppressor of the tumor [5-7]. By manipulating the cells and the tumor environment, the progression of the T-eff cell metabolism and the increase in their function is induced, which contributes to the suppression of the tumor.

In the tumor, some CD28 receptors, such as PD1 and CTLA4, are expressed by T-exhausted cells, which interact with their ligand, B7, which is on the surface of the APCs (antigen-presenting cells), and inhibits immune responses [8]. Therefore, inhibitory receptors can lead to changes in metabolic models, and ultimately undermine the function of T cells [9]. Cancer cells require high levels of glucose and glutamine to produce energy (ATP), nucleotides, amino acids, and lipids, as the conditions of food poverty in the tumor can cause inactivation of immune cells, especially the T-eff cells, and lead to the anergic state of cells. The effect of Warburg is said to be one of the symptoms of cancer cells, which can be due to the inability of T cells to produce food supportive of metabolism [10-12].

Several factors have contributed to the effects of Warburg, the most important of which is BRAF V600E mutation [13], that during the activation of the EK_MAPK pathway leads to the proliferation of tumor cells, inhibition of OXP-

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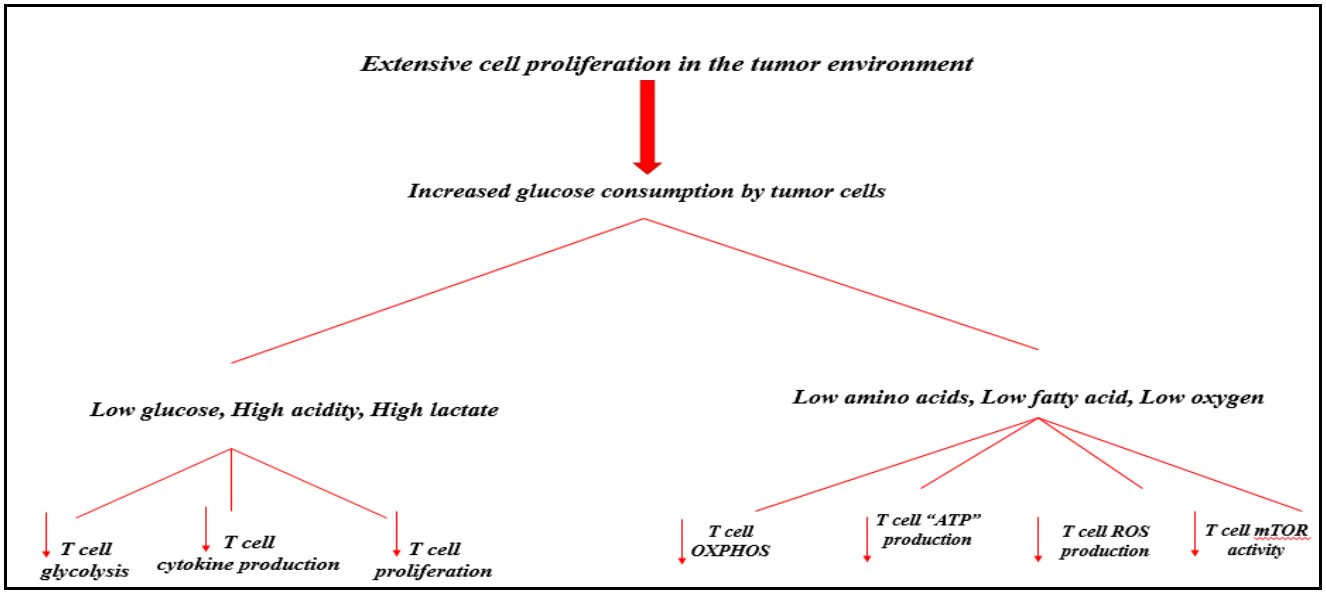

Fig. (1). HIF1a activates C-Myc under hypoxic conditions and subsequently increases glucose transfer to the cell through GLUT1. C-Myc also affects PFK3 and increases glycolysis, and pyruvate enters the pathway of anaerobic metabolism and is converted into lactate by LDH-a. The activation of c-Myc increases the intracellular glutamine through GLN-uptake, followed by increased glutaminase-1 activity. In general, increased glutamine and glucose absorption promote growth and cell proliferation. *(A higher resolution / colour version of this figure is available in the electronic copy of the article)*.

HOS, and increases glycolytic levels [14, 15]. Since glucose and glutamine are essential for differentiating the function of T cells and secretion of the IFNβ1 cytokines in cytotoxic T cells, mutations of BRAF V600E in melanoma, which is the most common driver oncogene in cutaneous melanoma [16], can lead to the proliferation of tumor cells and progression of the tumor, as well as the anti-tumor immune-suppressive activity [17].

2. METABOLITES IN THE TUMOR ENVIRONMENT: GLUCOSE, LIPIDS, AND PROTEINS

The high ability of cell proliferation in the tumor environment leads to high levels of glucose consumption by cancer cells, which subsequently encounters the tumor's environment by decreasing the extracellular glucose concentration (Fig. **1**), which is referred to as the "Warburg effect" [18]. Following the poor nutrition of the tumor, the ability of the cells to guide the aerobic glycolysis pathway is eliminated, resulting in a reduction in the production of PEP (phosphor enol pyruvate) metabolites, which are essential for activation of T cell receptor (TCR), and ultimately, inactivation of the TCR results in the loss of anti-tumor function of T cells [19].

3. T CELL AND MALIGNANCY CONDITIONS

The condition of acidosis in the tumor environment has a significant negative effect on the proliferation and production of T cell cytokines (Fig. **1**) [20] and ultimately inhibits the activity of TCD8+ cells [21], but does not affect Treg cells [22]. The immunosuppressive FoxP3+ T-cells that increase in the tolerogenic tumor microenvironment, and Th17 cells which formed in inflammatory conditions, are variably present in various cancers and both of them can regulate anti-tumor immune responses in positive and negative ways [23]. The excessive acidity of the tumor environment indicates the potential for metastasis of the tumor and is associated with undesirable prognosis in the tumor. The presence of glucose is essential in the early stages of the activity of TCD4+ cells. While TCD8+ naive cells are differentiated in the absence of glucose, but it is interesting to note that functional cells are lost in this condition [24]. The effects of glucose deficiency in different stages of differentiation of T cells are dissimilar and have negative effects on the function of TCD8+ TIL cells through various mechanisms [19, 24-28].

4. EFFECT OF GLUCOSE ON T CELL FUNCTION IN THE TUMOR ENVIRONMENT

Reduction in the glucose of blood (hypoglycemia) decreases the glycolysis pathway and causes more cell tendency for OXPHOS. T cells select glucose as their main source of metabolism, and glucose is involved in the growth, proliferation, and production of cytokines by T cells. Inducible glucose metabolism is dependent on PI3K signaling. Additionally, AKt, which is at the down-stream of PI3K, changes the glucose metabolism and its transporters expression [29]. AKt increases the incidence of GLUT1 expression on the surface of the membrane, thereby facilitating the absorption of glucose. Tregs are highly prone to PI3K inactivation using inhibitors compared with T-effs at the level of AKt and

NF-κB phosphorylation [30]. Glucose consumption causes changes in the inflammatory environment and affects the differentiation of TCD8+ cells by glucose utilization in the cells[27]. However, the final product of anaerobic glycolysis, lactate induces anti-inflammatory effects through IL17A but leads to inhibition of cytotoxic T-lymphocytes (CTL) cells. Unlike glucose, acetate restores IFN-γ in T cells, under prolonged glucose-restriction, by promoting histone acetylation and enhancing IFN-γ gene expression and rescuing effector function in glucose-restricted CD8+ T cells [31].

5. THE EFFECT OF FATS ON T CELL FUNCTION IN THE TUMOR ENVIRONMENT

Another source of energy in the tumor microenvironment is fat. Cancer cells increase the level of lipogenesis and lipolysis and secretion of fatty acids, leading fatty precursors to move towards the tumor's environment [32-34]. Besides, dying tumor cells also significantly release fatty acids into their surroundings; these fatty acids generate a lot of energy through the mitochondrial FAQ, which may be used by CD8+ TIL [35].

The production of energy from fatty acids requires more oxygen than the production of the same energy from glucose [36]. For example, oxidative phosphorylation of each glucose produces 36 molecules of ATP and consumes 6 oxygen molecules, while oxidative phosphorylation of palmitate produces 12 molecules of ATP and consumes 31 molecules of oxygen. Under the conditions of hypoxia and hypoglycemia, the neuron cells have been attempting to uptake the ketone bodies to provide energy [37]. In the tumor environment, in which cells experience a similar condition, the cell may exhibit the same metabolic pattern to the neurons and act directly through up taking the ketone bodies from the surrounding and their build-up [18, 38].

6. EFFECT OF AMINO ACIDS ON T CELL FUNCTION IN TUMOR ENVIRONMENT

The metabolism of amino acids is also an essential part of the progression of the tumor, as disturbances in the regulatory pathway of tryptophan and L-arginine catabolism are associated with malignant individuals [39, 40]. The metabolism of arginine is dependent on the activity of nitric oxide synthase and arginine, so that NOS oxidase converts arginine into citrulline and nitric oxide, while arginase in the urea cycle converts arginine into ornithine and urea [41]. Therefore, the expression of the iNOS (inducible NOS) and the activity of arginine can be considered as important diagnostic targets in some malignancies, as the increase in the ARG1 level is associated with the differentiation of macrophages towards M2 and TAM (tumor-associated macrophage) [42].

In the tumor environment, there are high levels of nitrotyrosine, and the function of T-cells is disturbed by the expression of nitrotyrosine-related RNS in the tumor, subsequently signal transduction and cytotoxicity are defective in tumor-induced lymphocytes. On the other hand, the presence of arginase and NOS inhibitors is sufficient to activate CTL cells and leads to the polarization of cytotoxic granules and the death of the target cells through various mechanisms. In addition, continuous contact with RNS changes the phosphorylation pattern of proteins, such as CD3ζ chain of the TCR complex, resulting in the release of Ca^{+2} from intracellular resources and decreased membrane receptors, such as CD4, CD8, and chemokine receptors [43]. Therefore, RNS can affect T cell recruitment and its function. Increasing arginase (I) in macrophages is dependent on the acidity and lactate rate, and thus, the level of immune response is reduced [44].

7. AMPK AND ANTI-TUMOR FUNCTIONS OF T CELLS

Interestingly, the ratio AMP: ATP induces the activation of the AMPK energy sensor, which affects the immunity of the T cells. Additionally, T cells increase their use of AMPK energy sensors to cope with the deficiency of glucose in the tumor and thus, try to survive, proliferate, and function in poor nutritional condition [45]. T cells expressing TGF-β and chemokines, such as CCL22, can easily withstand the nutritional poverty of the tumor, while the effector T-cells have very little tolerance [46] because Treg cells need only a small amount of glucose to survive and also express a little GLUT1 transporter [47]. Most Treg cells use the glycolysis and citric acid cycle pathways to supply their energy, but in poor conditions, the metabolic pathway of these cells is preferable to the beta-oxidation of lipids and the high level of AMPK sensors that use these two pathways to survive better [48, 49].

8. METABOLIC FEATURES OF SUPPRESSING IMMUNE CELLS IN THE TUMOR ENVIRONMENT

Another important factor in the progression of the tumor is AHR *(aryl hydrocarbon receptor)*, which allows Treg cells to be differentiated and proliferate despite the poor nutritional status of the tumor, which further contributes to the progression of the tumor through Treg cells suppressant effect. In the absence of glucose, other energy supply routes, such as FAO (fatty acid oxidation) are used by cells. Abrupt glucose excretion results in decreased ATP and an increase in AMP in activated cells, followed by the activation of AMPK, which maintains the energy in the cells through inhibition of cytokine production. Additionally, AMP contributes to the preservation and survival of cells through the effect on the PI3K-AKt-mTOR axis, which reduces glycosylation but increases the level of OXPHOs, and thus, prevents the apoptosis of T cells activated in conditions with glucose restriction [50]. (Fig. **2**)

Treg cells are dependent on glycolysis and mitochondrial oxidation, and the mitochondrial ROS level increases in these cells. Glycolytic metabolites, including PEP and mitochondrial ROS, affect the expression of FOXP3 through TCR signaling and activation of NFAT. FOXP3 acetylation is dependent on acetyl Co-A, which increases the stability of Treg cells during this process. Sirtuin 1 (SIRT1), also known as NAD-dependent deacetylase, deacetylates and poly ubiquities FOXP3, and is then exposed to destruction by a

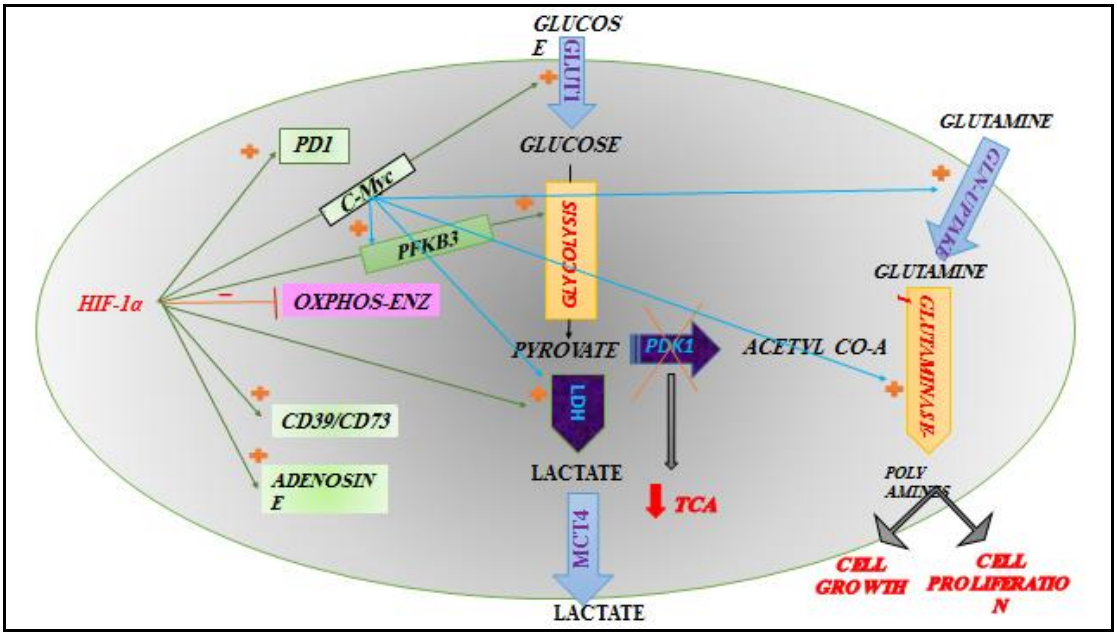

Fig. (2). Dendritic cells play a major role in increasing the survival and proliferation and metastasis of tumor cells *via* the production of IDO and the expression of inhibitors, such as CTLA-4. The IDO converts tryptophan into kynurenine, a toxic and deadly substance for effector T cells that express the L- kynurenine receptor. The decrease in L-Arg in the urea cycle results in the removal of the zeta CD3 chain in T cell, followed by a malfunction in T cell, and increases growth and proliferation of tumor cells. *(A higher resolution / colour version of this figure is available in the electronic copy of the article*).

protease. A strong correlation between the level of acetylation and the expression of FOXP3 is that fatty acid synthesis and FAO protect cell differentiation towards Th17 and iTreg responses, respectively [51-54]. Additionally, inhibiting the SIRT1 factor can also increase FOXP3 activity in human Treg cells. SIRT1 activity is dependent on NAD+, which is produced during the conversion of pyruvate to lactate by LDHA [54-56].

The regulation of intracellular metabolites, such as adenylate, which affects the activity of AMPK, may also affect FOXP3. It is noteworthy that phosphodiesterase "PDE3B" targets Treg cells and causes hydrolysis of cAMP and cGMP, and this is another way for reducing cAMP [57], which ultimately results in the proliferation of the Treg cells. Moreover, energy mediators such as ATP and NAD, are released in the surrounding during injury and inflammation, in which they activate a high level of P2X7 in Treg cell [58]. In contrast, Treg cells begin to metabolize extracellular ATP to adenosine to activate the pathways of CD39 ectonucleotidase and AMP nucleotidase, and the adenosine derived from the function of these two enzymatic markers of the adenosine receptor (*e.g.* A2AR) on the surface of activated T cell, ultimately inhibits the function of target cells, which have the A2AR receptor [59].

Contrary to T_h cells, Treg cells use beta-oxidation of fatty acids and mitochondrial respiration to provide their metabolic resources [60]. Inhibition of glycolysis following treatment with 2-DG and rapamycin leads to an increase in the production of T FOXP3+ and inhibition of the beta-oxidation of fatty acids with etomoxir, an irreversible inhibitor of palmitoyltransferase (I), which has the opposite effect [61]. In addition, PRARγ also facilitates the production of Treg, while HIF1 *(Hypoxia-inducible factor-1) opposes* Treg's evolutionary process. The selective deletion of either mTORC1 or mTORC2 alone does not result in the production of Treg, but the inhibition of both of these two complexes is required for Treg development [62]. Also, leucine is necessary for the expression of various nutrient transporters, such as GLUT1 and CD71, which is transmitted through the expression of the GLUT1 transporter of glycolysis in T effector cell, while Treg cells do not need GLUT *in vivo* and *in-vitro* condition [63]. All of this refers to the regulatory effect of the mTOR, which mainly affects T effector cells and has a lesser effect on Treg cells [64].

Additionally, enzymes degrade amino acids in Treg, such as IDO, as well as ARG (which increases in inflammation). One of the factors influencing the maintenance of FOXP3 activity in Treg cells and increasing the survival and function of these cells is the PTEN factor, which is a negative regulator of the activity of PI3K in T cells and restricts the activity of AKt [65, 66] (Fig. **3**). The PTEN affects the tumor through semaphorin (Sema4a) and neurophilin 1, and this pathway is an important therapeutic agent to interfere with the tumor-generated Treg cells [67]. On the other hand, the inducible activation of IDO and the function of the Treg cells depend on the activation of PTEN [67]. Teff cells with food deprivation, like Treg cells, have a high level of AMPK activity, but despite similarities, Treg cells are highly dependent on the oxidation of lipids and different in T--cell responses [49].

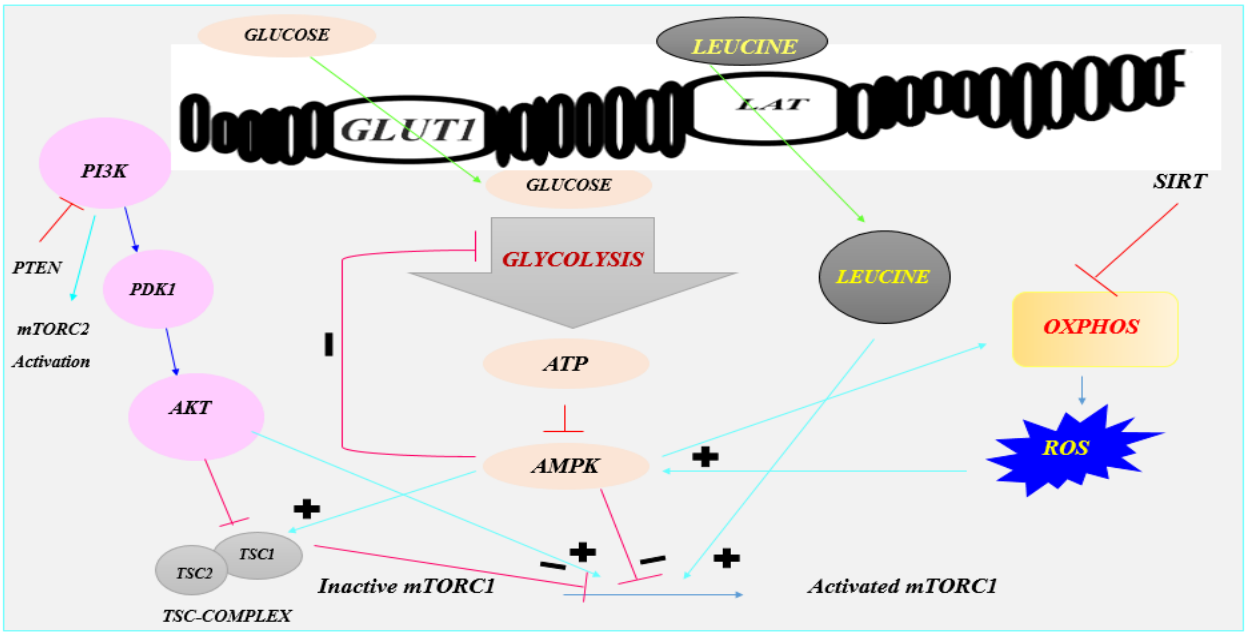

Fig. (3). Metabolism of different subsets of T cell: In a naive T cell, the activity of the Krebs cycle is high, but glutaminolysis is reduced. When a naive T cell is differentiated into TCD8+, cellular metabolism changes rapidly to aerobic glycolysis. In the differentiation of subgroups of T-cells, metabolic pathway changes, for example, TH1, TH2, and TH17 are mainly dependent on aerobic glycolysis and high activity of the glutaminolysis, while regulatory T and memory T increases the oxidation of fatty acids. *(A higher resolution / colour version of this figure is available in the electronic copy of the article).*

One of the characteristics of the Treg metabolic index is ERRα (Estrogen-related receptor alpha) that blocks glucose oxidation and promotes the synthesis of glucose-dependent lipids. These lipids make the Treg cells differentiate, while pyruvate has no role in the differentiation of Treg cells, as well as Th1, Th2, and Th17 [68]. It is noteworthy that in the absence of glutamine, mTORC1 activity is impaired in naive T cells and the distinction towards Treg, which is related to the decrease in the level of the glutamine-derived alpha-ketoglutarate metabolite, detects intracellular metabolites and controls the fate of cells through easier access to nutrients [69].

9. T CELL SIGNALING PATHWAYS IN NORMAL AND TUMOR CONDITIONS

9.1. HIF-1α

In the tumor environment, due to the strong proliferation of T cells and high oxygen consumption, the oxygen pressure is reduced and the expression of HIF-1α is increased, followed by expression of angiogenic factors, all of which affect the enzymes involved in the glycolysis pathway [70]. Additionally, mTOR located at the downstream of the PI3K-AKt can increase the expression of HIF-1α in the immune cells recruited into the tumor environment [71]. HIF-1α promotes the expression of several glycolysis-associated genes, including GLUT1 and PFKFB3 [72], as well as several enzymes involved in this pathway, including lactate dehydrogenase, pyruvate dehydrogenase kinase-1 (PDK1) [73], cause an increase in glucose and glycolysis, as well as reduction of the entry of pyruvate into the citric acid cycle, oxidative phosphorylation, and oxygen consumption [70]. Another important point in HIF-1α is the role of this factor in differentiating both Treg and Th17 cells [74]. When tumor cells are exposed to HIF-1α and c-MYC, glucose transporters are active, thereby helping to uptake more glucose by cells, and on the other hand, c-MYC oncogene promotes glycolysis by activating enzymes, such as PDK1and LDHA. Besides, the c-MYC oncogene, which is expressed by the high HIF-1α, activates the glutaminolysis through the upregulation of the expression of glutamine and glutamine-1 transporter [75], which further activates to produce polyamines, used for cell growth and differentiation (Fig. **2**) [43].

HIF-1α can increase the expression of PD1 ligand (PDL1) on the surface of the cancer cells, and as a result, it inhibits the activity of T cells [76]. TCD8+ cells are easily activated under the physiological pressure of oxygen, but under conditions of tumor formation and lowering of oxygen pressure, these cells gradually leave the adjacent region of the blood vessels, which activates HIF-1α. Furthermore, HIF-1α signaling results in the adoption of cell metabolism in hypoxic conditions [77, 78]. For example, HIF-1α increases the level of glycolysis in TCD8+ cells by activating lactate dehydrogenase induction (LDH-a) and increasing the expression of PDDK1 (similar to other executable cells) and also leads to OXPHOS inhibition. Subsequently, PDK1 prevents pyruvate oxidation to acetyl Co-A and ultimately leads to a reduction in the conductivity of the material in the citric

acid cycle [77, 78], while the pyruvate enters the anaerobic metabolism pathway and is converted into lactate by LDH-a, so that the presence of end product will help to acidify and deactivate the effector cells [77, 78]. At low oxygen pressure, TCD8+ cells use more glucose to trigger glycolysis, however, the proliferation and production of cytokines or enzymes effective in active cytotoxic T cells are decreased in hypoxia conditions. Increasing activity of HIF-1α can prevent the release of calcium from intracellular resources and inhibit the activation of T cells [79]. Moreover, HIF-1α is inhibited by an oxidative phosphorylation disorder that reduces the production of ATP, and therefore, inhibits the production of energy for activating cells, and following hypoxic condition, the level of ROS (active oxygen species) increases, whose excess production induces apoptosis of activated T cells [80, 81]. Expression of inhibitory receptors, such as CD244 and LAG-3, was increased in hypoxia, while T-bet was reduced, which is also one of the mechanisms used by HIF-1α to inhibit immune responses [82]. Paradoxically, HIF-1α can be involved in the production of lectin enzymes, such as granzyme B and perforin, and may promote the T effector activity [82, 83], as there is evidence of a genetic defect of HIF-1α, which has resulted in decreased TCD8+ function. Also, it has been shown that the excessive expression of HIF-1α improves the function of T cells through functional impairment of VHL. Hypoxia and excessive HIF-1α activity are usually associated with poor prognosis in patients with various malignancies [84, 85] because HIF-1α is trying to proliferate more cells and tumor progression [76].

Hypoxia increases the suppressive activity of tumor-associated macrophages (TAMs) as well as tumor-infiltration myeloid cells in the tumor, resulting in a defect in the activity of TIL CD8+ cells [86, 87]. Hypoxia provides energy through glycolysis and inhibits OXPHOS. HIF invokes the metabolism program of the cells involved in the tumor [88]. In Hypoxia, the complex of CD3 and TCR leads to an increase in the synthesis of HIF-1α protein, *via* the PI3K_mTOR pathway. In addition, active T cells also increase the HIF-1α mRNA by other mechanisms with PKC and Ca+2 synthesis. Furthermore, the presence of TGF-β and IL6 leads to the HIF-1α and STAT3 pathway (*via* STAT3 signaling), resulting in the accumulation of HIF-1α mRNA in T cells. In hypoxic conditions, the expression of several inhibitory receptors, including CTLA4, LAG-3, CD137, PD1, and OX40, increases T cells with VHL deficiency [82]. Among these inhibitors, CTLA4 and PD-1 are targets for direct transcription of HIF, which effectively suppresses immune responses by increasing the expression of two receptors. On the other hand, lack of oxygen causes increase in TCR activity, elevates the expression of FOXP3 in TGF-β+ CD4+ cells, and subsequently conducts immune-suppressive responses [89]. Furthermore, HIF-1α attempts to recruit Treg cells into the tumor by expressing cytokines and chemokines, such as TGF-β and CCL28 [90].

9.2. The Removal of VHL in CD8+ T Cells

The removal of VHL in CD8+ T cellsresults in the constant expression of HIF-1α and HIF-2, and with a delay in increased differentiation of CD8 T cells into effector cells, the cytotoxicity of these cells increases [82]. The lack of oxygen in the tumor can have reciprocal effects on cytokine secretion and cell survival. Hypoxia also affects TCD4+ cells and increases the cytokine secretion of TCD4+ effector cells, such as IFNα. In contrast, IL2 production decreases in T lymphocytes and this eventually leads to the detection of immune responses in this condition [91]. Similarly, hypoxia increases the amount of apoptosis in the number of activated T cells [91] but increased adrenomodulin mediates and leads to an increase in the survival of antigen-specific T cells [92]. Despite these two conditions, the HIF molecule involved in the tumor should be investigated in terms of an isoform.

9.3. mTOR

In the tumor environment, the survival and function of cancer cells are dependent on the activation of mTOR, as activating and increasing the expression of HIF-1α improves the glycolysis and the synthesis of protein and fatty acids [93, 94]. Additionally, mTOR controls the balance between the memory and the effector cell through the expression of T-bet [95]. The activity of T cells depends on the presence of two signals: (1) an antigen-specific signal that is included by T cells. (2) Stimulatory signals generated by CD28 activating the activity of the PI3K-dependent Akt [96]. In mammals, AKt controls the activity of mTOR [97], monitors the synthesis of a protein involved in growth and cellular performance [98]. The signaling of mTOR is essential for all stages of CD4+ and TCD8+ cellular differentiation and the recruitment of T cells into the inflammatory tissues, as well as the regulation of the migration pattern of these cells [99, 100]. Moreover, mTOR leads to the differentiation of Th17 through STAT3 activation [101]. In T cells, mTOR creates a link between the regulation of metabolism, function, and signaling. mTOR interacts with the metabolic and functional status of the cell as cellular traffic. In fact, mTOR uses specific mechanisms to differentiate a cell into a certain category and uses metabolic and translation of transcriptional programs in a coordinated manner in that particular category. For example, mTORC2 signaling will differentiate toward Th2 cells in both *in-vitro* and *in-vivo* conditions [102].

Activating the mTORC2 signaling activates the downstream factors, such as Akt, which results in the deactivation of FOXO and the reduction of KLF2. KLF2 is a cellular transducer controlling factor, including expression of CD62L and CCR7, which negatively correlates these two molecules involved in cellular hominization and mTOR and Akt activity [103, 104]. Moreover, continuous expression of CD62L was observed in active T cells lacking mTORC2 function (due to RICTOR deletion) [105]. As a result, a decrease in Akt weakens the regulation of T CD8+ controlled cellular traffic in the mTORC1-related path. This pathway involves activating mTORC1 through Akt, which takes place without the intervention of the FoxO signaling. Furthermore, CD62L, CCR7, CD127, and S1P1 are also regulated by KLF2. Interestingly, the increase in S1P1 results in an enhancement in mTOR, and their interaction promotes the differentiation of Th1 cell and inhibits differentiation of Treg cells [106, 107]. Similarly, the induced expression of the

transgenic S1P1 on T FOXP3+ results in a defect in the suppressive function of Treg [108]. Alternatively, Rapamycin inhibits mTOR signaling and,subsequently, S1P1. The inhibition of mTOR by rapamycin results in the elimination of activity of the TLR7 and TLR9 agonist to induce IFNα/IFNβ production. Therefore, the mTOR inhibition degrades the TLR9 and MyD88 complex and consequently leads to a reduction in the IRF7 [109]. Furthermore, 4EBP, an important molecule stimulant in the translation of IRF7, is also a selective target for mTORC1, which leads to the expression of mTORC1 and mTORC2 [110]. In T cells, mTORC1 activity is triggered by the signaling of TCR and the CD28 stimulator, as well as through a Nutrient transporter. For example, the ASCT2 and SLC7a5 transporter, which is preferable to leucine, plays a key role in expressing mTORC1-dependent expression and differentiating Th1and Th17 cells from naive T cell and even including iTreg cells [111, 112].

mTORC1 plays a very important role in inhibiting the mTORC2 signaling present in Treg cells and mTORC2 activity, which is essential for inhibiting FoxO molecule, enhances oxidative and glycolytic metabolism through its c-MYC antagonism and plays a role in the differentiation of TCD8+ cells and their function. The metabolism of memory T cells is also similar to Treg and the metabolism and FoxO signaling dependence may be related in these cells [113, 114]. The expression of HIF1α, due to reduced oxygen pressure, can lead to increased expression of PDL1 [115]. PDL1 prevents the final differentiation of effector TCD8+ cells, while the survival of these cells is dependent on fatty acid metabolism. The tumor environment increases the expression of inhibitory receptors, such as PD1 and CTLA4, in T-exhausted cells [116], where these inhibitory receptors inhibit glucose and glutamine metabolism, TCR activation, and stimulant receptors, and result in the tumor cells escape from the immune system [117, 118].

The expression of PDL1 by tumor cells is one of the most important checkpoints against NK and CTL, which is also effective in endothelial cell metabolism. Inactive T cell, PD1, uses glucose and glutamine and changes the metabolic pathway to FAs, which suggests that it may be one way to control PTEN mediated PT3 signaling, affecting the metabolism. If the PI3K signaling damages the differentiation, performance, and stability of Treg, it does not mean that Treg cells are completely independent of PI3K [116]. As the PI3K signaling through TCR and IL2 results in a balance between the effector and the suppressive activity [119], which is induced by the effect of mTORC1 on the metabolism of cholesterol and lipid, as well as the increase of CTLA4 expression [120].

With the general understanding of the metabolic pathways of the cells, it is possible to control the development of the process of differentiation of Treg cells. Some diseases, including malignancy, autoimmunity, allergies, and transplant rejection, can be controlled. For example, the blocking of glycolysis and glutamine in transplantation is done by the 2-DG and DON analogs, respectively [121]. Also, the increasing trend of the FAO with metformin prevents the rejection of the allograft of the skin and heart, which is likely to prevent the proliferation of lymphocytes. The use of carbonic acid inhibitors leads to an increase in the differentiation of Treg cells and, consequently, the blocking of the Th1 and Th17 pathways in asthma and EAE mice models [122]. Blocking glycolysis *via* 2-DG or inhibiting PDHK leads to a selective effector T failure and leads to the progression of Treg cells in laboratory models [19, 123]. In terms of blocking Treg cells, the PI3K-Akt signaling pathway is targeted at Treg cells, in which the inhibitors of the IDO and PTEN medications during the loss of FoxO3a (target Akt) cause the inhibitory function of Treg cells [124]. The use of carbonic acid inhibitors leads to an increase in the differentiation of Treg cells and, consequently, blocks the Th1 and Th17 cells in the Asthma and EAE mice models.

During the conversion of naive cells to the effector and memory T cells, the metabolism state changes from oxidative to anabolic. This new acquisition mode is suitable for performing cellular tasks of T-cells, including cell proliferation and cytotoxicity, as well as the production of cytokines. T cells are capable of starting an aerobic metabolism in order to get more glucose and glutamine from the surroundings [125], which, of course, consumes more oxygen [126, 127]. Paradoxically, the PD1 signaling pathway has a negative effect on the metabolic process, and consumes glucose and glutamine, but increases the amount of beta-oxidation (FAO) in these cells. Additionally, the activated T cells attempt to uptake most of their required materials by increasing the expression of the Nutrient receptors, including amino acid receptors, glucose transporters, as well as HIF1a, PI3K-Akt-mTOR, all of which play a fundamental role in the energy consistency of tumor and immune cells. During the activation of T cells, they uptake glucose through a high level of the GLUT1 transporter. Despite the decrease in glucose and glycolysis level, mitochondrial ATP plays a very important role in the function of T cells [128].

If there is a persistent nutrient deficiency, T cells will be anergy or cell death. Under poor glucose conditions, T cells will supply energy through the “glutaminolysis”. Recently, it has been shown that different subtypes of T do not have a specific metabolic program, and TCD4+ cells have more flexibility in metabolic pathways than TCD8+. One of the unique features of T effector cells is the limited availability of nutrient that promotes AMPK-dependent oxidative mitochondrial metabolism but suppresses the mTOR signaling and glycolysis. These cells, which have limited access to glucose, have limitations in cell growth, proliferation, and cytokine production, but maintain their cellular ATP and cellular survival levels while restoring the ability to produce cytokines in these cells during exposure to glucose. During glucose famine and the absence of AMPK, T cells use glutamine as a mediator for the entrance of the citric acid cycle (TCA), and the oxidative phosphorylation process is strengthened [127, 129] (Fig. **3**).

9.4. Under Malignant Conditions

TCD8+ cells increase their chemokine receptor and are directed to the tumor environment without the presence of a

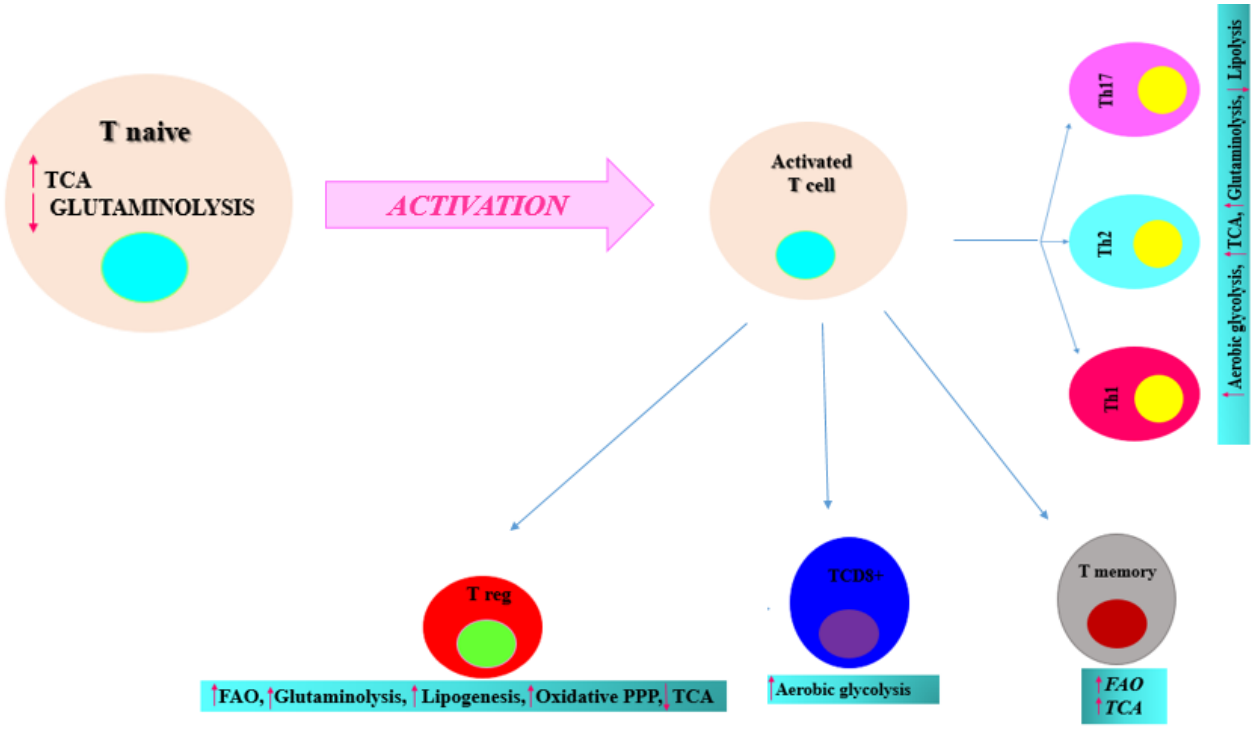

Fig. (4). Extensive cell proliferation in the tumor enhances glucose consumption by tumor cells and reduces metabolites, such as glucose, amino acids, and fatty acids. Reducing glucose, oxygen, and increasing lactate results in increasing the acidity of the tumor affecting the production of cytokines and cell proliferation and cause the deactivation of effector cells. *(A higher resolution / colour version of this figure is available in the electronic copy of the article).*

specific antigen [130]. In the tumor environment, these cells encounter nutrient constraints, such as glucose deficiency, and in response to this condition, TCD8+ cells express an increased level of transporter called GLUT1. However, *in-vitro* studies show that supplying sugar for TCD8+ cells fails because tumor cells do not allow glucose to be uptaken by these cells, and they must use simpler ways to access glucose [131].

On the other hand, the use of glucose in tumor cells leads to enormous amounts of lactate, which results in a reduction in the glycolysis pathway in TCD8+ cells located in the TME (tumor microenvironment), and the subsequent regression of lactate from these cells contribute to a sharp decrease in pH and inhibit glycolysis enzymes, such as PFK [132]. In addition, the conditions for the exclusion of glucose in active TCD8+ cells induces an increase in the expression of inhibitory receptors, such as PD1 [133], which has the effect of decreasing the glycolysis, while increasing the metabolism of FAs. Among T cells located in the tumor environment, the activated CD_8^+ T eff cells have the highest susceptibility to exogenous glucose, and the unstable compensatory pathway of intergranular glucose includes gluconeogenesis and glycogenolysis in these cells [134].

TILs (*Tumor*-infiltrating lymphocytes) have a dynamic state in the tumor environment. So that when T cells, adjacent to the blood vessels have access to oxygen; the FA enters the TCA cycle, and the acetyl COA derivative of the additional FA is packed in the form of ketone bodies in emergencies, such as T cell infiltration into the depth of the tumor, which is associated with severe oxygen depletion.

As antigen is identified by TCD_8^+ cells, mTOR is activated and the metabolism of the cell changes from catabolic to anabolic. Moreover, the pattern of the receptors involved in homing also changes: For example, the expression of CD62L (Sel-L) and CCR7 decreases, dueto which the new pattern of cellular receptors results in the activation of effector T cell efflux from the lymph nodes and recruitment of these cells to the peripheral tissues. In TCD8+ cells lacking PTEN inhibitor, PI3K continuous activation of mTOR leads to a sustained reduction of CCR7 and CD62L [106], which are involved in homing. Paradoxically, under conditions of recovery from infection, the metabolic status of TCD_8^+ cells change from anabolism to catabolism, while the expression state of mTOR is reduced. This change of state is accompanied by the expression of CD62L, CCR7, and the newly created memory cells allow to increase its surveillance during cellular traffic and outside of lymph nodes [135].

Among the different subtypes of Th cells, Th17 cells have the highest glycolysis tendency (Fig. **4**). HIF1a elevates glycolysis in Th17 cells, which increases the expression of PKM and GLUT1 [74]. Furthermore, the HIF1a can

differentiate Th17 cells through an effect on cell differentiation, an increase in the level of ROR-γT transcription factor, and expression of IL17 [136]. Besides, HIF1a results in the degradation of the FOXP3 of Treg cells [137] by proteases and then shifts the differentiation cell from Treg to Th17 [136].

Some reports also show the relationship between mTOR and STAT. It is clear that mTOR can regulate the STATs signaling, but the share of each mTOR1 or mTOR2 isoform has not been determined. In this context, there is a hypothesis that is T-RHEB-I cells decrease the phosphorylation due to increased activity of the SOCS3 inhibitor. Therefore, SOCS3 inhibits STAT6 signaling and reduces the differentiation to Th1/Th17. These findings suggest that SOCS3 levels in RHEB-/- T cells are effective in cell differentiation [138].

As the response to IL6 or IL12 decreases in T RHEB cells, T-bet/ RORGT transcription factors reduce in the Th1/ Th17. IL21 and IL6 induce activation of STAT3, an essential transcription factor in the development of Th17 cells. This is because IL6/ IL21 also induces the expression of SOCS3. It later became apparent that TGF-b inhibits the activation of the SOCS3 promoter in T cells, induced by IL6 [139]. The Th17 cell, just like Th1/ Th2, is mTOR-dependent and has a high glycolytic level. The inhibition of mTORC1 signaling by rapamycin and genetic deletion of RHEB from T cell leads to an impairment in differentiation towards Th17 [140].

10. THE METABOLIC PROGRAM OF T CELLS

The effect of TME (*tumor* microenvironment) on the metabolism of T cells has recently been evaluated, and research findings point to the regulatory role of the tumor environment on executable cells that may affect the function of T cells through metabolism [141]. Naive T cells mainly supply their energy through OXPHOS and fatty acid oxidation (FAO) [142]. The bioenergetics and biosynthetic index of T cells are related to their clonal proliferation and performance. The activated cells fallowed a new metabolic program: glycolysis and glutaminolysis, instead of OXPHOS and FAO representing the naive T-cell [142, 143]. *In vitro*, the absence of CD28 or the suppression of its signaling pathway results in defective GLUT1 and the aerobic glycolysis that is necessary for the functional T activity [144]. Co-stimulatory receptors, such as CD28, coordinate the enhancement of the expression and cellular traffic, and also increase the number of transporters at the cell surface including GLUT1 [28, 144, 145], the glutamine transducers; SNAT1, SNAT2 [146] and other amino acid transporters, such as SLG1a5 and SLC7a5 [111, 112]. To maintain aerobic glycolysis in effector T, the pyruvate produced from the TCA shunt progresses to lactate production, and this occurs in the tumor even under ideal oxygen conditions [142].

In the cell culture with glucose, inefficient proliferation and weakness in the production of IFNγ by T cells because of restriction to glucose availability in the early stages of activation was observed [145, 147]. The activation of the mTOR route promotes glycolysis from several different mechanisms: An increase in C-MYC and HIF1α. The use of rapamycin, an inhibitor of mTOR signaling, affects the mTORC1 Th1 more than Th2 because ECAR levels in Th1 cells decrease further compared to that of ECAR in Th2 cells. However, rapamycin may not have a significant effect on the metabolism of Th1 cells over a short period, as the mechanism of a long-term rapamycin effect is observed when extensive mTOR assemblies are available continually. Unlikely rapamycin, PP242, a kinase inhibitor of mTOR, effectively reduces the level of ECAR in both Th1 and Th2 cells, which ultimately suggests that both of these cells are dependent on mTOR to regulate their metabolic activity.

MYC and its subunits, AP4, increase the expression of glycolytic pathway enzymes [148], and T-eff cells with defects in MYC are impaired in terms of glycolysis enhancement that is sought after activation in the *in-vitro* conditions [143]. Increased activity of HIF1a induces aerobic glycolysis and decreases OXPHOS by increasing PDK1 and LDH-a [78] and effectively reduces the pyruvate from the TCA to lactate production [149]. The T cell distinction to its subgroups depends on mTOR activity so that an executor T cell, with an mTOR kinase defect, can only make Treg. The mTORC1 complex promotes the Th1 differentiation, while mTORC2 leads to the Th2 differentiation. Inversely, the loss of mTORC1 signaling prevented the formation of Th17, while Th2 was evolved without any obstructions [150]. MTORC1-dependent induction of HIF1a can lead to Th17 polarization and inhibition of Treg differentiation by increasing IL17 and RORγt, which degrades FOXP3 *in-vivo* and *in-vitro* [136].

11. EFFECTOR T CELLS

CD4+ T cells increase both OXPHOS and glycolysis pathways, while CD8+ T cells are only able to progress to the glycolysis pathway and do not affect OXPHOS. In addition, the functional differentiation of T cells requires biosynthetic pathways and distinct energy paths to support the cells. Thus, in the absence of glucose and other energy metabolites, the energy of T CD8+ cells is more sensitive, and gradual reduction of glucose will reduce the proliferation and function of these cells with a higher probability and prevent the production of cytokines by these cells. Recently, however, it has been determined that the activation of the T cell does not follow a particular metabolic program. Due to the metabolic difference between different subgroups in the presence of energy-rich substrates, TCD4+ cells exhibit greater metabolic flexibility than T CD8+.

In T-cells, the metabolic pathway of glycolysis occurs and this pathway is accompanied by the induction of mTOR signaling and HIF1a expression, all of which attempt to provide optimal performance in T-cells. Depending on the specific condition and the contents of the tumor, the metabolism of the cells is altered so that the cell shift is exhausted to the T cell and the T-cell anergic. Creating these cells in the tumor environment leads to changes in cancer cells that lead to tumor progression and immunosuppression.

12. TH1/ TH2

During the differentiation phase of Th1/ Th2, an increase in glucose transducers GLUT1 (SLC2a1), PFK1, G6PD, and glycolytic and pentose phosphates enzymes is observed. However, the expression of carnitine palmitoyltransferase I (CPT1a), which is the main enzyme of oxidation of fatty acid, decreases during the induction phase of Th1, Th2, which is respectively, the expression of T-bet and GATA3 at their highest levels [151]. However, after the induction phase, Th2 cells have a higher expression of CPT1 compared to Th1. However, Th1 cells have a higher oxygen consumption than Th2 cells. Therefore, after stimulating T helper, Th1 cells have a higher level of basal metabolism than Th2 cells, while the expression of the PFK1, G6PD, and GLUT1 genes is different in the resting and activating states of the cells [151].

Although Th1 cells express a higher level of proteins, especially G6PD, at the time of antigenic stimulation compared to their resting state, in the case of Th2, there is no significant change in the expression of the G6PD protein between the resting and stimulated cell. CPT1a expression in resting Th2 cells is also higher in resting Th1 and the expression of this gene in both Th1 and Th2 cells during antigenic stimulation can be reduced. While reducing this enzyme is more important during the activation of Th2 [151].

13. Th1

Th1 CD4+ cells have a high glycolytic profile and express a high level of the GLUT1 transporter. In the case of inhibition of glycolysis by competitive analogs, such as 2-deoxy- D- glucose (2DG1), a defect occurs in the secretion of IFNG, which is essential for this subtype [152]. As the evolution of the Th1 cell line is dependent on the signaling pathway of mTORC1, therefore the STAT3/ STAT4 signaling in RHEB-/- T cells decreases in response to IL6 and IL21, and thus, the differentiation of Th1 CD4+ cells decreases. In RHEB-/- T cell, the SOCS3 signaling, which inhibits STAT3 and STAT6, will be enhanced, likely reducing the phosphorylation of STAT [153].

14. Th2

Th2 cells have a high expression of GLUT1 and a high level of glycolysis. The subset of T cells contains cytokines, such as IL4, IL5, IL13, and the GLUT3 transcription factor. The differentiation of this subtype of the cell occurs through IL4 and due to the phosphorylation of STAT6, which is followed by the induction of GLUT3 [154]. Moreover, STAT5 activation is also essential for the differentiation of Th2. Th2 cells are dependent on the mTORC2 pathway during their evolutionary process. As in the RICTOR-/- T cells with the defective mTORC2 signaling, there is a potential for decreased activity of IL4 induced STAT6 activity [155, 156].

15. Th17

Although the deletion of mTORC2 does not affect the development of Th17, inhibiting the signaling of mTORC1 by rapamycin and the genetic deletion of RHEB from T cells results in loss of differentiation of Th17 cells. Since HIF1a is effective in expressing genes involved in the glycolytic pathway, the dependence on this pathway in Th17 cells is at a high level compared with other T subtypes of HIF1a expression in T helper cells [155]. Furthermore, the activation of SREBP1 refers to the deficiency of biosynthesis of fats and pentose phosphate during the Th17 evolutionary stages [155, 157].

16. TREG

Treg cells evolving *in-vivo* are similar to T-eff, and are dependent on glycolysis-derived lipogenesis for proliferation and function [158]. Studies on the B16 mouse model of the melanoma model showed that Treg in the tumor and spleen absorbed more glucose than non-Treg [159]. Besides, *in-vivo* blocking glycolysis and glutaminolysis, and increasing the oxidation of fatty acid reduces the proliferation of the Treg cells in an infectious model of smallpox and adoptable T cell transplantation (although less than the effect on the T-eff cell) [160]. It has been reported that glycolytic of the insulated human Treg is high in *in-vitro* and supply its energy through both glycolysis and FAO when cultivated *in-vitro*. Amino acids, especially glutamine and leucine, play an indispensable roll in the differentiation of T-eff, but it seems that iTreg is less dependent on amino acids for their energy supply. Therefore, TCD4+ deprivation of glutamine leads to differentiation towards the Treg phenotype [161]. Products of tryptophan catabolism, such as kynurenine, amplify iTreg by binding to the aryl hydrocarbon receptor [162, 163]. Also, T-memory cells depend on FAO, both exogenous glycerol and endogenous fats, to supply their energy [164]. These cells trigger exogenous glycerol by inducing IL-7 expression, the pore-forming membranes protein AQP9, as well as the *denovo* glucose-produced lipids [165].

Additionally, T-memory expresses the LAL enzyme (lysosomal acid lipase), which hydrolyzes endogenous cholesterol esters derived from glucose and triglycerides of the FAO route [166]. tTreg (thymus Treg) and pTreg (peripheral Treg) have some metabolic features similar to T-memory. pTreg may be dependent on FAO (unlike iTreg (induced in cell culture)) while tTreg uses the other pathways, including lipogenesis, glycolytic, and cholesterol biosynthesis for survival and suppressive function [49, 158]. Some features of the Treg metabolism are related to its anatomical location. For example, VAT Treg (visceral adipose tissue Treg) expresses the PPARγ receptor (peroxisome proliferator-activated receptors), which is a major regulator for the differentiation and function of adipocytes and high expression of CD36, a scavenger receptor to facilitate the entry of exogenous fatty acids [167, 168]. Also, the anatomical position of the colon, which provides a rich environment of short-chain fatty acids such as butyrate, acetate, and propionate, is closely related to the increase in the production of Treg cells [168-170]. One of the mechanisms that increase butyrate in the gut is through the inhibition of histone deacetylation, which increases H3 acetylation of Lys-27 in the locus of foxp3 and subsequently increases the expression of foxp3 [169, 170].

CONCLUSION

The function of T cells present in the TME depends on metabolism. Immunometabolic pathways affect T cells and control their differentiation and function, ultimately regulating anti-tumor immunity. The tumor is predominantly infiltrated with immunosuppressive factors that paralyze T cell responses against the tumor. These factors do not exist in normal tissues but are components of tumor regulatory pathways in response to inflammatory or infectious etiologies that tumor cells promote for the expansion of MDSCs through multiple inflammatory factors, and then these tumor-derived MDSCs decline T cell proliferation and induce tumor cell growth *via* oxidative metabolism. Finding new ways to provide the energy needed for T cells in the cancerous environment, as well as stimulating cellular signaling pathways that lead to the activation of TCD4+ and TCD8+ cells in the TME, can be effectives way to use self-immune cells against cancer cells. Identifying metabolic pathways that are shared between cancer and immune cells can lead to find new ways to the election of novel protocols of the metabolism-targeting treatment.

CONSENT FOR PUBLICATION

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CONFLICT OF INTEREST

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