REVIEW

Immune cell metabolism and metabolic reprogramming

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Abstract

Energy metabolism maintains the activation of intracellular and intercellular signal transduction, and plays a crucial role in immune response. Under environmental stimulation, immune cells change from resting to activation and trigger metabolic reprogramming. The immune system cells exhibit different metabolic characteristics when performing functions. The study of immune metabolism provides new insights into the function of immune cells, including how they differentiate, migrate and exert immune responses. Studies of immune cell energy metabolism are beginning to shed light on the metabolic mechanism of disease progression and reveal new ways to target inflammatory diseases such as autoimmune diseases, chronic viral infections, and cancer. Here, we discussed the relationship between immune cells and metabolism, and proposed the possibility of targeted metabolic process for disease treatment.

Keywords Immune cells · Immune metabolism · Metabolic reprogramming · Targeted therapy

Abbreviations

1,3-DPG	1,3-Diphosphoglyceric acid
3-PG	3-Phosphoglycerate
α-KG	α-Ketoglutarate
Acetyl-CoA	Acetyl-coenzyme A
ACLY	ATP-citrate lyase
ADP	Adenosine diphosphate
AMPK	AMP-activated protein kinase
ATP	Adenosine-triphosphate
BCR	B cell antigen receptor
BMDCs	Bone marrow-derived dendritic cells
CCR7	C–C motif chemokine receptor 7
CD	Cluster of differentiation
CoQ	Coenzyme Q
Cyt c	Cytochrome c
EIF2AK2	Eukaryotic translation initiation factor 2-alpha kinase 2
ETC	Electron transport chain
F-1,6-BP	Fructose 1,6-bisphosphate
F-6-P	Fructose-6-phosphate
FAD	Flavin adenine dinucleotide
FAO	Fatty acid oxidation
FAS	Fatty acid synthesis
FOXP3	Forkhead box P3
GCs	Germinal centers
GLS	Glutaminase
Glut-1	Glucose transportase-1
GSK3	Glycogen synthase kinase 3
G-3-P	Glyceraldehyde-3-phosphate
G-6-P	Glucose-6-phosphate
HIF1α	Hypoxia-inducible factor 1α
HK	Hexokinase
IFN	Interferon
IL	Interleukin
LDHA	Lactate dehydrogenase A
LPS	Lipopolysaccharide
M-CSF	Macrophage colony-stimulating factor
MDSCs	Myeloid-derived suppressor cells
MHC	Major histocompatibility complex
mTOR	Mammalian targets of the rapamycin
NAD	Nicotinamide adenine dinucleotide
NADH	Nicotinamide adenine dinucleotide

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NADPH	Nicotinamide adenine dinucleotide phosphate
NF-κB	Nuclear factor-k-gene binding
OAA	Oxaloacetate
OXPHOS	Oxidative phosphorylation
PAMPs	Pathogen-associated molecules
PBMC	Peripheral blood mononuclear cells
PEP	Phosphoenolpyruvate
PFKFB3	Phosphofructokinase-2/fructose-2,6-bisphosphatase
PGC	Peroxisome-proliferator-activated receptorγcoactivator
PI3K	Phosphoinositol 3-kinase
PKM	Pyruvate kinase
PPARγ	Receptor peroxisome proliferator-activated receptor γ
PPP	Pentose phosphate pathway
PRRs	Pattern-recognition receptors
ROS	Reactive oxygen species
SLOs	Secondary lymphoid organs
STAT	Signal transducers and activators of transcription
T1D	Type I diabetes
T-ALL	T cell acute lymphoblastic leukemia
TAPP	Tandem PH domain containing protein
TCA cycle	Tricarboxylic acid cycle
TCR	T cell receptor
TLR	Toll-like receptor
TME	Tumor microenvironment
TRAF3	TNF receptor-associated factor 3

Introduction

Immune cells refer to all the cells and their precursors related to the immune response, which can be divided into innate immune cells and adaptive immune cells. The former include dendritic cells (DCs), macrophages, and natural killer (NK) cells; the latter refer to T lymphocytes and B lymphocytes that play a major role in the immune response. In most normal cases, immune cells are in a relatively static state [1]. When the body is confronted with abnormal interference such as infection, trauma and inflammation, it will rapidly activate to exert immune function, eliminate target substances, and maintain homeostasis [2]. In immune cells, metabolic changes may occur in response to indicative signals received from other cells or from environmental changes, such as the presence of danger signals or antigens [3]. The transformation of cells from resting to excited state involves a series of metabolic changes, especially the transformation of intracellular energy materials and metabolic pathways [4]. Previous studies have shown that the participation of immune receptors such as TLR and

IL-2 receptors, metabolic transformation and immune cell function are highly correlated [5]. For example, the activation of immune receptors promotes glycolysis, which is the energy source of regulatory T cells (Tregs) migration and determines the polarization direction of macrophages [6].

With the development of immunology and metabolism, more and more studies have found that metabolism can affect the differentiation and function of immune cells [7]. Immune metabolism refers to the interaction between metabolism and immune response, which has been proved to be related to immune activation in many diseases [8]. The activation, differentiation and function of immune cells are dependent on energy supply and metabolic transformation (Fig. 1A). Assessing the response of immune cells to metabolic processes in health and disease states, may provide new therapeutic approaches for clinic.

In this review, we summarize several common metabolic reprogramming of immune cells, focusing on the metabolic pathways (Figure S1 and reviewed in [9, 10]) of cell resting and activation. In addition, we will discuss metabolism in health and disease, as well as current treatment strategies for targeted metabolism, and aim to apply metabolic reprogramming to disease treatment.

Innate immune cells

Dendritic cells

Dendritic cells (DCs), as the most functional professional antigen-presenting cells, are the bridge between innate immunity and adaptive immunity [11]. DCs can produce antigen-carrying MHC molecules and rapidly deploy them to the cell surface, which is crucial for their ability to initiate naive T (Tn) cells [12].

DCs undergo metabolic reprogramming during activation, which is driven by PI3K/Akt pathway and antagonized by the AMPK pathway, similar to the Warburg effect in tumor cells [13]. This metabolic transformation is marked by the transition of mitochondrial OXPHOS from lipid oxidation to aerobic glycolysis [11] (Fig. 1B). Recent evidence suggests that the early glycolytic burst in BMDCs can partly bypass the requirement for glucose during activation [14]. The development of DCs from progenitor cells is associated with mitochondrial biogenesis, which is driven by PGC-1α and promoted by PPARγ, mTOR and MYC [15] (Table S1). Activated DCs provide energy through glycolysis and lactic acid fermentation and convert glycolysis intermediates into the PPP [16]. TLR signal is the main pathway for DCs activation. It leads to increased glycolysis metabolism and triggers the necessary metabolic reprogramming for DCs maturation [7, 11]. CCR7 stimulates the activation of HIF1α transcription factor pathway in DCs, leading to the
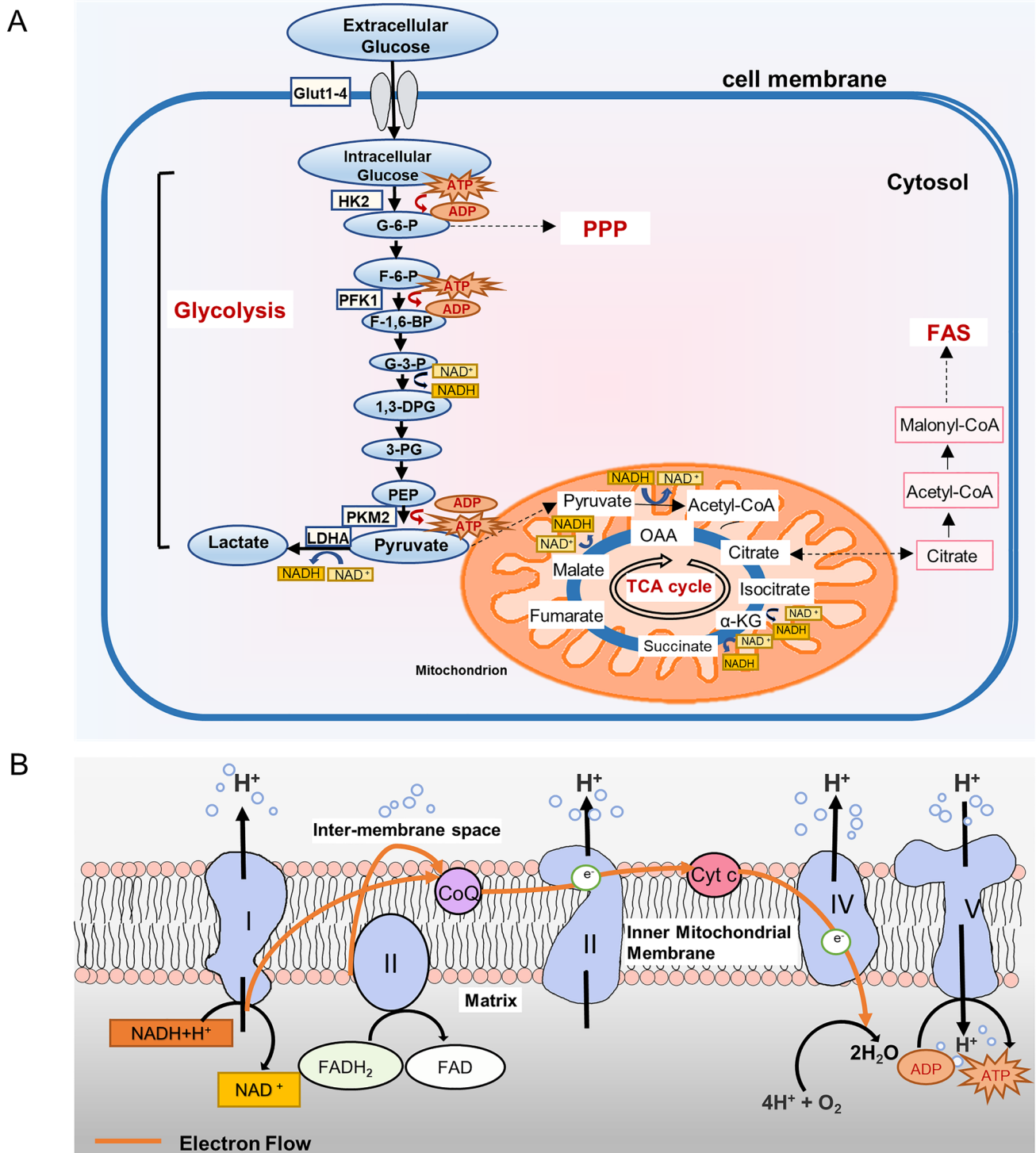
Fig. 1 Simplified representation of glucose metabolic pathways. **A** Glycolysis occurs in the cytoplasm, converting glucose into pyruvate and then into lactic acid in the mitochondria. Under aerobic conditions, pyruvic acid is oxidized and decarboxylated to form acetyl CoA, which can be completely oxidized into TCA. Intermediates in glucose metabolism can flow to other metabolic pathways, such as PPP and FAS. **B** ETC refers to the structure of NADH or FADH2 transferring electrons to oxygen. OXPHOS causes the gain and loss of electrons on the electron carrier, which is transferred between redox substrates to form ETC

conversion of metabolic reprogramming to glycolysis for DCs migration [17]. Regardless of the stimulation and activation phenotypes of PRRs, inducing the glycolysis of DCs in vivo is necessary for supporting the movement of DCs and CCR7 oligomerization [18].

In addition, it has recently been found that fatty acid metabolism is related to different functions of DCs [19]. When the synthesis of fatty acids was blocked, the number of DCs from PBMC precursors decreased [20]. Blocking of FAS also inhibits the DCs development of human PBMC and induces the apoptosis of DCs precursors [19].

Delivery antigen DCs play a pro-inflammatory role, enhance and prolong T cell response [21]. Thus, DCs vaccine work better than other anticancer vaccines because they integrate other immune-related signals to effectively induce antigen-directed T cell responses on a cellular platform [22]. The "second generation" DCs vaccine strategy is more effective in clinical practice, so it becomes the preferred choice of cancer immunologists [23].

Macrophage

Macrophages exist in all mammalian tissues. They can not only resist infection, but also are key members of homeostasis and tissue repair. Macrophages are considered to be the most plastic cells in innate immune system and the first line of defense against external infection [24].

In resting state, macrophages use TCA cycle to breathe normally. The expression of PRRs on cell surface allows resting macrophages to quickly recognize PAMPs, thereby inducing inflammation [25]. Macrophages activated by the bacterial product LPS are known as M1 or classically activated macrophages, and have very different metabolic characteristics compared with IL-4 activated macrophages, namely M2 or alternately activated macrophages [26]. The former has pro-inflammatory properties, while the latter has anti-inflammatory and parasitic effects [27]. In LPS-induced macrophages, TCA cycle is broken and results in elevated levels of intermediates such as succinate and malate [26, 28]. Glycolysis can play a role in M1 and M2, but the way is different. In the former, glycolysis is associated with the activation of the PPP for biosynthesis of biomolecules and ATP production, while in the latter, glycolysis is used to support OXPHOS [29, 30]. In M1, glucose uptake is enhanced and switches to glycolysis, while in M2, the main metabolic feature is enhanced FAO and OXPHOS [31].

Changes in metabolic processes are inseparable from enzymes involved in glycolysis. PKM is a rate-limiting enzyme in glycolysis, converting PEP to pyruvate. PKM2 exists in the proliferation of a few normal cells, while it is present at high levels in activated immune cells [32]. Palsson-McDermott indicated that PKM2 is a key determinant of macrophage glycolytic reprogramming, and that

PKM2 is activated in macrophages to inhibit lipopolysaccharide-induced glycolysis and HIF1α expression related genes [33]. A previous study showed that PKM2 selectively promotes the activation of macrophages inflammasome by activating EIF2AK2 phosphorylation [32]. Glycolytic activator PFKFB3 promotes macrophages to clear infected cells and enhance their antiviral ability [34]. A recent study shows that macrophages mobilize glycogen metabolism, which governs macrophage-mediated inflammatory response [35].

The nuclear receptor PPARγ is known to regulate lipid metabolism in many tissues, including macrophages. PPARγ controls macrophage glutamine metabolism, providing a link between transcription and metabolism [36]. As reports, endogenous oxidized lipids promote simultaneous OXPHOS, aerobic glycolysis, and the hyperproduction of IL-1β in LPS-stimulated macrophages [37]. Fatty acid metabolism pathways can be categorized into FAS and FAO, which are highly activated in M1 and M2 [38]. It has been suggested that the activation of inflammatory macrophages is dependent on glycolysis, while IL-4-induced macrophages are driven by FAO [27]. Citrate will be withdrawn for fatty acid biosynthesis, one hallmark of the M1 [39]. However, M2 has a fully functional respiratory redox chain that allows FAO without producing ROS [29] (Fig. 2).

Van den Bossche et al. show that the activation of inflammatory M1 inhibited mitochondrial function, thereby preventing the repolarization of anti-inflammatory M2 phenotype [26]. Blocking oxidative metabolism not only blocks M2 phenotype, but also makes macrophages enter M1 state [27]. Therefore, intervening in the metabolic pathway of macrophages and regulating the phenotypic transformation of M1/M2 may help to resist autoimmune diseases, tumors and other immune-related diseases [40].

Natural killer cell

Human NK cells are lymphocytes that connect innate immunity and adaptive immunity. They have excellent antiviral and anti-tumor properties, produce cytokines IFN, and directly kill target cells through cytotoxic mechanisms [41].

Glucose is the key fuel of NK cells, which directly affects the rate of glycolysis and OXPHOS [42]. At rest, NK cells preferentially use OXPHOS [43]. The levels of glycolysis and OXPHOS in stationary NK cells of mice were low but sufficient to sustain a rapid initial immune response [42]. Using cytokines to stimulate NK cells to activate, the incidence of glycolysis and OXPHOS is greatly increased. OXPHOS is required for the secretion of IFN-γ by receptor-stimulated NK cells [43]. ^{13}C-glucose-tracing metabolomics have shown that NK cells use glucose to promote the biosynthesis of amino acids and fatty acids 18 h after cytokine stimulation [44]. Activating mouse NK cells with IL-2 and
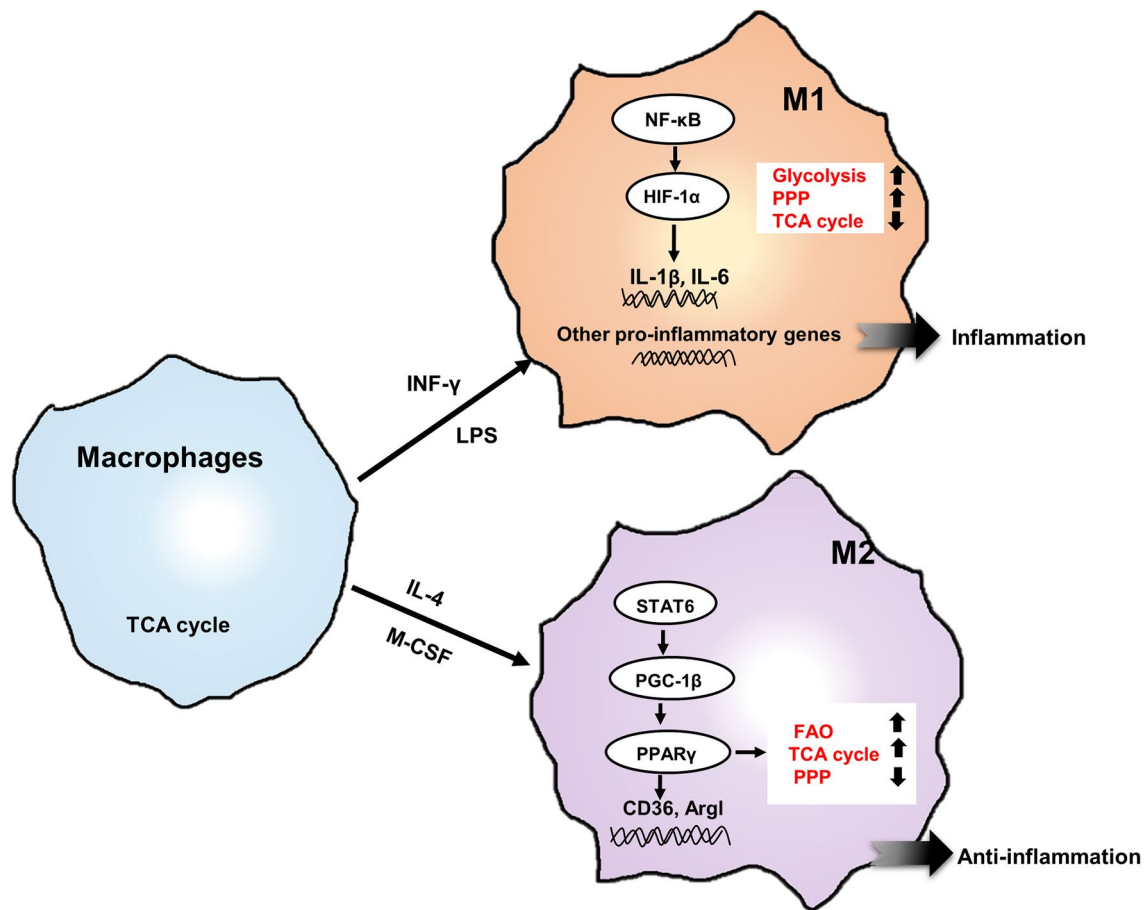
Fig. 2 Major metabolic patterns in macrophages. The metabolic modes of M1 and M2 are different. In M1, the increase of glucose uptake is used for glycolysis and PPP. While in M2, the main metabolic characteristics are the increase of FAO and OXPHOS. M1 induced by LPS/INF-γ are regulated by HIF1α. In LPS (+IFN-γ)-activated inflammatory macrophages, HIF1α not only promotes glycolysis, but also induces the expression of genes encoding inflammatory cytokines, especially IL-1β and IL-6. In IL-4-induced macrophages, PPARγ as the main regulator can use the transported glucose for TCA cycle. FAO can promote the development and activity of anti-inflammatory macrophages. Moreover, FAO has been proved to support mitochondrial oxidation and metabolism of M2, and ATP is continuously through OXPHOS. In M2, the anti-inflammatory effect was exerted by activating the expression of anti-inflammatory genes such as CD36 and ArgI

IL-12 breaks down glucose into pyruvate, which then produces lactic acid through aerobic glycolysis [42].

Transcription factors play an important role in the activation and metabolism of NK cells. The activity of transcription factor SREBP is necessary for the increase of glycolysis and OXPHOS. The glycolysis is increased by regulating the expression of citric acid and malic acid reverse transporter SLC25A1 and ACLY15 [44]. MYC controls the activation of metabolic pathways in NK cells, supporting glycolysis and mitosis by increasing the expression of glucose transporters and glycolytic enzymes to improve mitochondrial quality to support high levels of OXPHOS [45]. In NK cells stimulated by cytokines, elevated glycolysis requires mTORC1 signal transduction [46, 47].

In recent years, the research on the metabolic characteristics of NK cells in tumor microenvironment has become a new direction for cancer treatment. NK cell activity is negatively correlated with the incidence of cancer. New evidence suggests that NK cell infiltration into squamous cell lung is associated with better prognosis [48]. Brand et al. found that LDHA increased the production of lactic acid in cancer cells. The accumulation of lactic acid will destroy the production of IFN-γ in tumor-infiltrating T cells and NK cells, thereby inhibiting tumor immune surveillance and promoting tumor growth [49]. A high concentration of lactic acid in tumor microenvironment can damage the function of NK cells [48, 50]. Changes in NK cell metabolism may be an important factor in NK cell dysfunction (Table 1). Therefore, if we want to further explore the anti-tumor effect of NK cells, it will be a good choice from the perspective of metabolism.

Table 1 Major metabolic pathways in innate cells

Cell type	Energy sources in quiescent state	Energy sources in activation state	Related pathway changes	References
DCs	TCA cycle, OXPHOS	Glycolysis, lactic fermentation	TBK1-IKKε/AKT/HK-II pathway,PI3K/AKT/mTOR pathway,mTOR/HIF1α/iNOS pathway	[13, 15, 17, 18]
Macrophage	TCA cycle, OXPHOS	M1: aerobic glycolysis, FAO M2: FAO, gluconeogenesis	HIF-1a/PDK1 pathway, Akt/mTORC1 pathway, JAK/STAT6 Pathway, PPARγ/LXR/ABCA1 pathway	[32, 33, 36, 38]
NK cells	TCA cycle, OXPHOS, glutaminolysis	OXPHOS, aerobic glycolysis	PI3K/Akt/mTORC1 pathway, JAK/STAT pathways,NF-kB pathways	[44, 46–48]

Adaptive immune cells

T lymphocytes

T lymphocytes are a highly heterogeneous group, containing a large number of subsets, which play a central role in the immune response of foreign antigens [51, 52]. The latest research progress shows that metabolic changes have taken place in various biological processes of T cells, such as TCR-mediated activation and auxiliary T cell differentiation [53], suggesting that metabolic pathways can seriously affect T cell function. In the activation process of TCR-dependent T cells, glucose, glutamine, and other biological molecules as nutrients determine whether T cells can be activated and play a role [52]. T cell subsets perform different functions in the immune response and have different metabolic patterns.

NAIVE T cell

T lymphocytes develop and mature in the thymus, named Tn cells, which are recirculated through the paracortical regions of SLOs to recognize antigens [51].

The function of Tn cells maintained by TCR engagement by self-peptide-MHC molecules and the cytokine IL-7. Tn cells are mostly in static state, lack of mTOR expression, priority use OXPHOS as fuel [53, 54]. The absence of negative regulatory factors activated by TCR or the uninhibition of AKT activity will lead to the loss of resting state of Tn cells and increase the proliferation of homeostasis [55]. After T cells were activated, mTORC1 up-regulated C-MYC expression, indirectly accelerating glycolysis and glutamine metabolism [54, 55].

Memory T cell

Memory T(Tm) cells are named for making the immune system remember. Tm cells can persist in the body for decades. Tm cells circulate in the blood and exist in lymphatic organs, which is an important part of long-standing T cell immunity. When the antigen first stimulates the human body, it forms a Tm cells subset that enhances human immunity [56]. As the most important T cell subsets, memory CD8 + T cells and memory CD4 + T cells have attracted the attention of many studies.

Like Tn cells, memory CD8 + T cells are metabolically quiescent cells that use OXPHOS for energy conversion [54]. After infection, memory CD8 + T cells can remain in the tissue, rather than through the blood circulation of Tm cells in the tissue [56]. Owning to they are stationary in tissues, their glycolysis is at a low level, mainly using exogenous fatty acids as fuel. In the study of memory CD8 + T cells in the skin, it is found that the oxidation of fatty acids is necessary for cell growth. When the oxidation of free fatty acids in mitochondria is inhibited, memory persistence is reduced [57, 58]. CD4 + memory T cells preferentially adhere to mucosal tissues, and the number of CD4 + T cells is more than that of CD8 + T cells [59]. At present, there are few studies on CD4 + memory T cells, and no special metabolic pathways have been found.

Regulatory T cell

Tregs are a kind of T cell subsets that control the autoimmunity in the body. They inhibit the activation and proliferation of potential autoreactive T cells in the normal body through active regulation, thereby regulating the immunity of the body [60].

Tregs are more likely to use FAO and OXPHOS for energy, suggesting that T cells can function through lipid oxidation without glucose [61]. Valerie A et al. reported that Tregs not only oxidize lipids at high rates but also produce pyruvate by glycolysis [62]. The expression of Foxp3 leads to the up-regulation of mitochondrial protein-coding genes, thereby promoting the respiratory capacity of Tregs and enhancing their ability to utilize fatty acids to provide energy for OXPHOS. Foxp3 maintains regulatory function by inhibiting the expression of MYC and the glycolysis of Tregs, thereby giving Tregs metabolic advantages in low

lactate environments [63, 64]. After inhibition of mTORC1 in mice, Tregs could not effectively synthesize lipids from glucose, and the cholesterol content was also reduced [65]. Deborah Cluxton et al. showed that Tregs oxidizes exogenous fatty acids as metabolic fuel instead of glucose [66].

Effector T cells

During the transition from Tn cells to effector T cells(Teffs), glucose uptake is upregulated and most glucose-derived pyruvate is excreted to lactic acid, which is similar to tumor cells' Warburg physiology [53]. CD4 + T cells proliferate and differentiate into Teffs or Tregs that mediate or regulate immunity after activation [67]. Teffs use large amounts of glucose and high-speed glycolysis to meet energy needs [62]. mTOR signaling pathway has a profound impact on the fate of CD4 + T cells by regulating metabolic reprogramming [56]. A recent study showed that inhibition of mTORC1 activity attenuates glycolysis

and reduces effector function, while absence of mTORC2 enhances glycolysis and increases effector function [68]. In addition, mTOR activation induced the expression of glucose transporter Glut1, which enhanced the proliferation of T cells and the production of cytokines [69]. Glut1 is the main transporter in glucose uptake and maintains a high level of expression in effector T cells. Glut1 mediates a sharp increase in glucose intake, which is necessary to promote cell growth, effector function and Teffs proliferation [70] (Fig. 3). In the absence of Glut1, CD4 + and CD8 + effector T cells can only maintain limited proliferation [67].

T lymphocytes, as the effector cells of cellular immunity, maintain homeostasis and play an immunoregulatory role. T cells use different metabolic energy at different stages. Since metabolism controls the function and fate of T cells, it is necessary to study the changes made by different types of T cells in the state of disease.
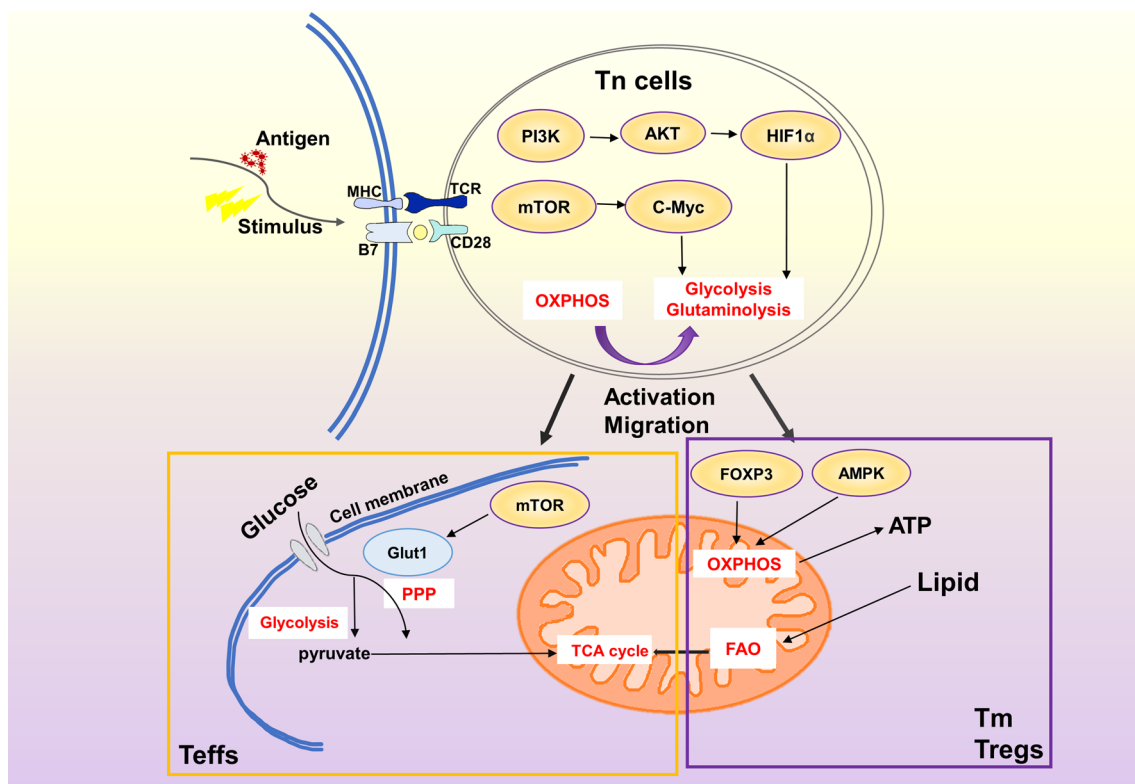

Fig. 3 The metabolic differences of Teffs, Tm, Tregs. When Tn cells were stimulated to recognize antigens, the resting state of energy supply by OHPHOS was broken. With the assistance of HIF1α and C-Myc, glutamine decomposition was enhanced, and a large amount of energy was provided by glycolysis. It will undergo a development process characterized by rapid growth, proliferation and acquisition of special effects, and then differentiate into Teffs, Tregs and Tm cells. FAO plays an important role in regulating T cell response. So far, FAO has been observed to regulate the balance between inflammatory Teffs and inhibitory Tregs, and maintain the function of long-lived Tm cells. Compared with Teffs, Tregs and Tm cells showed more FAO and OXPHOS, and FAO promoted the generation of Tregs. Interestingly, the down-regulation of FAO by Teffs depends more on glycolysis and TCA cycle energy supply. FOXP3 and AMPK promote the OXPHOS and increase ATP production to meet the energy supply in Tm cells and Tregs. mTOR increases glucose uptake by targeting Glut1, making Teffs play an effective role in the body

B lymphocytes

B lymphocytes perform a variety of functions in adaptive immunity, the most critical of which are the secretion of disease-specific antibodies, antibody class switching, and affinity maturation [71]. During the immune response, B cells diversify their immunoglobulin genes in GCs, thus producing high-affinity, transformation-like antibodies that mediate humoral immunity [72].

Similar to other cells in the body, B cells mainly source of energy and carbon from glucose. Recently, it has been found that constitutively active GSK3 is a metabolic checkpoint regulator of resting B cells. Without antigen or growth factor stimulation, it assists cell survival by limiting protein synthesis and mitochondrial function [73]. Compared with the naïve B cells, the activated B cells absorb glucose, consume oxygen and secrete lactic acid more [74], suggesting that OXPHOS and glycolysis play a role simultaneously. Glucose is necessary to support cell activation, and to a certain extent supports the generation of new fats through ACLY activity, providing sufficient phospholipids for activated B cells to maintain morphological changes [75, 76]. Amino acids also contribute significantly to their metabolism. Amino acid consumption, alanine and glutamate production increased during B cell activation [76]. The increased absorption of amino acids such as leucine and lysine help to make the signal flow through in the downstream pathway of PI3K, and enhance the ability of solute transporters to absorb amino acid synthesis [77].

The metabolic process of B cells changes from static state to active state, and the role of molecular signals cannot be underestimated. Molecules such as TAPP [78], mTORC1 [79] and c-MYC [80] can control the activation of B cells. When TAPP expression is decreased, OXPHOS and glycolysis are increased, and the proliferation and autoimmunity of B cells in the germ center also increased [78]. Transcription factors c-MYC, HIF1α and STAT6 promote glycolysis gene expression, while Bcl6 inhibits transcription of certain target genes and glycolytic pathway [77].

GC B cells that react in GC will differentiate into long-lived memory B cells or plasma cells that produce antibodies [74]. GC B cells showed that mTORC1 activation and c-MYC accumulation were increased, and genes related to glycolysis were also up-regulated [81]. Due to the increased protein expression of glycolysis, TCA cycle and ETC in these cells, the number of mitochondria and the expression of HIF1α also increased [82]. Compared with the naive B cells, plasma cells have a higher protein synthesis rate, absorb more amino acids and glucose, and produce a large number of ROS [83]. In activated B cells, the decrease of oxygen concentration reduces mTORC1 signal transduction and inhibits the conversion of immunoglobulins isoforms [77]. However, hypoxia promotes plasma cell survival and supports regulatory B cell function. Hypoxia promotes the expression of HIF1α [77, 83], triggers steady transcription and regulates the expression of glucose transporters and glycolytic enzymes when oxygen concentration is limited [77]. With the participation of BCR or IL-4 stimulation, activated B cells became larger, total protein and CD138 expression increased [84]. In addition, BCR signaling pathway increases Glut1 expression and glucose uptake in PI3K-dependent mechanisms [85] (Table 2).

B cells transit from static state and recycling to activation, proliferate rapidly, and produce a large number of antibodies. Only when metabolism, extracellular stimulation and intracellular signal transduction work together, the humoral response dominated by B cells can be successfully carried out. Breaking this balance will lead to malignant transformation of B cells. Therefore, the discovery of metabolic differences between B cell activation and malignant tumors is very important for the treatment and prevention of B cell lymphoma.

Table 2 Major metabolic pathways in adopted cells

Cell type	Energy sources in quiescent state	Energy sources in activition state	Related molecular changes	References
Tn cells	OXPHOS	Glycolysis	IL-7, mTORC1,MYC	[53, 54, 63]
Tm cell	FAO, mitochondrial metabolism	OXPHOS, TCA cycle	Akt, mTORC2, aquaporin 9	[54, 56]
Tregs	FAO, OXPHOS	Glycolysis	AMPK, HIF1α Foxp3	[62, 65, 98]
Teffs	FAO	Glycolysis, glutaminolysis, TCA cycle	mTOR, HIF1α	[68, 69]
B lymphocytes	OXPHOS	Glycolysis, glutaminolysis, TCA cycle	TAPP, mTORC1, C-MYC	[78–80]

Conclusion

Nowadays, studies on immune cells and metabolism have received extensive attention. Immune cells are involved in the progression of many human diseases, such as cancer [86–88], autoimmune diseases [89], and heart disease [90].

The metabolic pathways of sugar, fat and amino acids interact with each other, which are closely related to the survival and activation of immune cells. Studies have shown that immune cell subsets in disease state show different metabolic pathways to promote cell survival, lineage generation and function. Enhanced glycolysis enables immune cells to produce sufficient ATP and biosynthetic intermediates to perform their specific effector functions [89]. In acute lymphoblastic leukemia, carcinogenic signaling induces metabolic stress, increases glucose uptake and aerobic glycolysis of activated T cells [91]. After COVID-19 infection, monocytes and macrophages trigger mitochondrial ROS production, stabilize HIF1α expression, and promote glycolysis to maintain high viral replication level [92]. T cells in rheumatoid arthritis divert intracellular glucose to PPP and produce NADPH, which uses lactic acid from the external environment to meet their energy needs [93]. In normal kidney, the level of OXPHOS of Tregs and DCs was higher than that of glycolysis, and the two metabolic patterns were exchanged during acute kidney injury [94]. In addition, the accumulation of lactic acid in tumor promotes DCs OXPHOS and induces Tregs response [95]. Therefore, glycolysis enhancement is considered to be a marker metabolic change for the rapid activation of most immune cells.

It has therapeutic potential to change the state or function of immune cells by regulating immune cell metabolism in diseases. For example, In multiple sclerosis, targeted glycolysis enhances the inhibitory ability of Tregs and affects the differentiation of proinflammatory cells [96]. Glycolysis and TCA cycle have significant changes in autoimmune diseases (such as systemic lupus erythematosus). And there have been studies in animal models and preliminary human trials confirmed the efficacy of intervention in metabolic pathways. Besides, studies have shown that targeting key processes to reduce gluconeogenesis or increase glucose excretion can improve the prognosis of patients with type 1 diabetes [97].

In this review, we discuss the metabolic patterns of immune cells in different states. With the development of metabolomics, research in this field advances rapidly. However, due to the dynamic changes of the body and the complex and diverse metabolic pathways, there are still many problems to be solved in the treatment of diseases by reprogramming immune cell metabolism. Further elucidating the mechanism of metabolism mediated by immune cells, especially in the state of disease, is expected to realize the prospect of immunotherapy in this field.

Declarations

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