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Clinical Science (2023) **137** 807–821
https://doi.org/10.1042/CS20220869

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Review Article

Essential metabolism required for T and B lymphocyte functions: an update

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Lymphocytes act as regulatory and effector cells in inflammation and infection situations. A metabolic switch towards glycolytic metabolism predominance occurs during T lymphocyte differentiation to inflammatory phenotypes (Th1 and Th17 cells). Maturation of T regulatory cells, however, may require activation of oxidative pathways. Metabolic transitions also occur in different maturation stages and activation of B lymphocytes. Under activation, B lymphocytes undergo cell growth and proliferation, associated with increased macromolecule synthesis. The B lymphocyte response to an antigen challenge requires an increased adenosine triphosphate (ATP) supply derived mainly through glycolytic metabolism. After stimulation, B lymphocytes increase glucose uptake, but they do not accumulate glycolytic intermediates, probably due to an increase in various metabolic pathway 'end product' formation. Activated B lymphocytes are associated with increased utilization of pyrimidines and purines for RNA synthesis and fatty acid oxidation. The generation of plasmablasts and plasma cells from B lymphocytes is crucial for antibody production. Antibody production and secretion require increased glucose consumption since 90% of consumed glucose is needed for antibody glycosylation. This review describes critical aspects of lymphocyte metabolism and functional interplay during activation. We discuss the primary fuels for the metabolism of lymphocytes and the particularities of T and B cell metabolism, including the differentiation of lymphocytes, stages of development of B cells, and the production of antibodies.

Introduction

Lymphocytes are produced in bone marrow with maturation in the thymus for T (thymus-derived) cells or in the bone marrow itself in the case of B cells (*b*ursal or *b*one marrow-derived). Each of these populations can be subdivided into cells with different characteristics, leading to the generation of cells with different abilities to proliferate, exhibit toxic properties, produce cytokines and antibodies, and pro- or anti-inflammatory features. Lymphocytes require specific metabolic pathways for cell function. Energy generation, synthesis of macromolecules, supply of precursors for the synthesis of structural lipids (phospholipids and cholesterol), immune system regulators (such as arachidonic acid derivatives), deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) synthesis [1] all rely on cell metabolism.

Lymphocytes can act as regulatory or effector cells, and these cells can respond to infection but also act as essential players in cancer and autoimmune diseases. There is substantial knowledge on the metabolic characteristics of different T lymphocyte subsets regarding their energy demands at rest and activation.

Received: 19 December 2022
Revised: 04 May 2023
Accepted: 05 May 2023

Version of Record published:
23 May 2023

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https://doi.org/10.1042/CS20220869

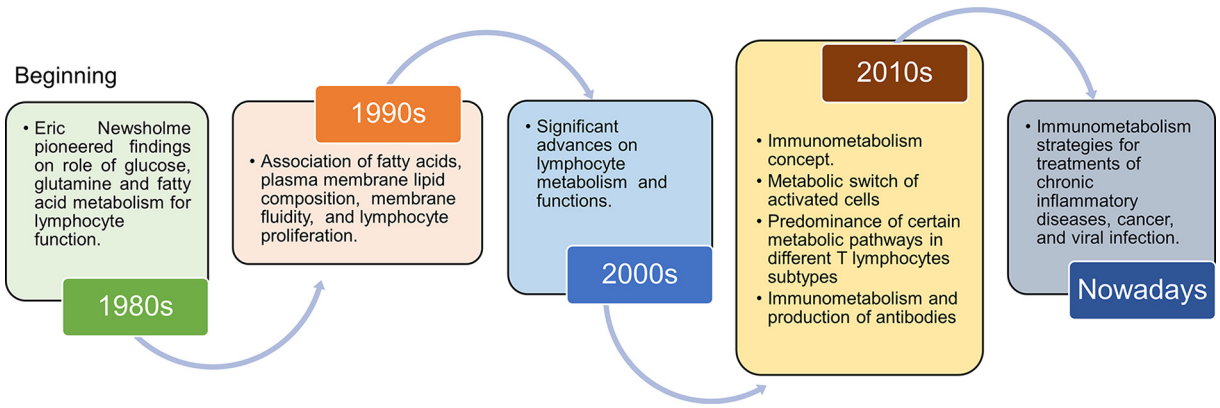


Figure 1. Milestones of lymphocyte metabolism discoveries

Here we demonstrate the historical and contemporary facts related to the key fuels (glucose, glutamine, and FAs) for lymphocyte metabolism. In the 1980s, Professor Eric Newsholme's laboratory at the University of Oxford pioneered the studies on glucose, glutamine, and fatty acid metabolism as fuels for the essential functions of lymphocytes and macrophages. The knowledge acquired in recent decades about the relationship between metabolic diseases and the immune system, as well as the development of techniques for metabolite analysis, have boosted the recent advancement of this research area and enabled the development of new strategies for treatments of chronic inflammatory diseases, cancer and viral infection.

In B lymphocytes, studies have focused on the metabolic switch related to the generation of plasmablasts and plasma cells. Various studies have recently reported essential metabolic changes during clonal expansion of B lymphocytes.

Lymphocyte metabolism, history, and milestones

In the 1980s, Professor Eric Newsholme's laboratory at the University of Oxford pioneered the studies on glucose, glutamine, and fatty acid metabolism as fuels for the essential functions of lymphocytes and macrophages (Figure 1).

Ardawi and Newsholme, in 1982 and 1983 [2,3], reported that rat lymphocytes, obtained from mesenteric lymph nodes incubated for one hour, at 37°C, have higher than expected rates of glucose and glutamine utilization. Glucose is converted mainly to lactate whereas glutamine produces glutamate, aspartate, and lactate [4,5]. Although glucose and glutamine are the essential substrates used by lymphocytes, the rate of complete oxidation is low [6] (Figure 1).

Lymphocyte activation on local immunological challenges increases the activities of hexokinase, 6-phosphofructokinase, pyruvate kinase, and lactate dehydrogenase, confirming the importance of the glycolytic pathway for cell division [2]. Ardawi and Newsholme [2] also noted that ketone bodies do not serve as an alternative fuel for glucose. This was confirmed by the lower activities of the enzymes related to the formation of ketone bodies 3-oxo acid CoA-transferase, acetoacetyl-CoA thiolase, and 3-hydroxybutyrate dehydrogenase when compared with glycolytic enzymes, hexokinase or 6-phosphofructokinase. Activation of glutamine metabolism and TCA cycle activity is required for lymphocyte proliferation, as confirmed by increased glutaminase and citrate synthase activities [2]. Glutamine consumption increases (by 50%) in concanavalin A (a T lymphocyte mitogen) treated lymphocytes [3] compared with non-stimulated lymphocytes. Glutamine also participates in the maintenance of the redox state in proliferating lymphocytes [7]. Curi et al. [8] described that lymphocytes from lymph nodes stimulated with concanavalin A have a low rate of pyruvate oxidation through the TCA cycle. The authors reported that pyruvate derived from either glucose or glutamine is a precursor for acetate synthesis and contributes to the synthesis of lipid molecules such as fatty acids (FAs) and cholesterol.

The pioneering studies on the role of fatty acid metabolism for lymphocyte function took place in the 1990s (Figure 1). Anel et al. [9,10] reported that, in mitogen-stimulated lymphocytes, specific changes in fatty acid composition and membrane fluidity occur, and different FAs in the culture medium lead to an increase of fatty acid incorporation into the cell membrane. Calder et al. [11] reported that the inhibition of lymphocyte proliferation by FAs is independent of the production of eicosanoids. The authors suggested that changes in proliferation are associated with alterations in membrane fatty acid composition, leading to modification of membrane fluidity, as also observed by Anel et al. [10,11]. Later, Calder et al. [12] demonstrated that supplementation with FAs altered the function of lymphocytes. Curi et al. [13] reported that propionate, at 2 and 5 mmol/L, promoted inhibition of lymphocyte proliferation and this effect is related to a reduction in lipogenesis.

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In the 2000s, Jeff Rathmell's group studied the use of metabolites as energetic substrates required for the function of active and non-active immune cells (Figure 1) [1,14]. Following the loss of receptor engagement, lymphocytes negatively regulate glucose transporter 1 (GLUT-1), and reduce mitochondrial membrane potential and cellular ATP, suggesting depletion of glucose-associated derivatives [14]. The Rathmell group also reported the importance of glycolysis and GLUT1 in B cells. If glycolysis is inhibited, there is a decrease in the proliferation and secretion of antibodies. B cell-specific deletion of GLUT1 led to reduced B cell numbers and impaired antibody production *in vivo* [15]. A recognition of the importance of metabolism for immune cell function was the wide spread acceptance of the term 'immunometabolism'. For example, Mathis and Shoelson [16] popularized the use of 'immunometabolism' for an emerging field of investigation involving the importance of metabolism to immune function.

The increase in knowledge about the relationship between metabolic diseases and the immune system and the development of techniques for metabolite analysis have boosted the recent advancement of this research area [17,18]. Among the numerous reports over the past two decades on lymphocyte metabolism, some highlights are: (a) the metabolic switch in effector and memory cells [19–21]; (b) the predominance of certain metabolic pathways in different subtypes of T lymphocytes (Th1, Th2, Th17, Treg) [22–24]; (c) the similarity between metabolism of activated inflammatory cells (Th1 and Th17 lymphocyte, M1 Macrophage and Neutrophils) and tumor cells [25–28]; (d) the changes involved with the production of antibodies [29,30]; and (e) specific pathways of metabolism as targets for the treatment of autoimmune diseases [31], viral infections[32,33], cancer [34]and other chronic diseases [33,35].

Importance of cell metabolism for T lymphocyte function

Glucose uptake by T and B lymphocytes occurs through GLUT1, GLUT3, and GLUT4 transporters [36,37]. When activated, there is an increase in the expression of all these glucose transporters in lymphocytes [37]. The expression of GLUT4 and GLUT3 isoforms in the plasma membrane of monocytes and B lymphocytes is increased by insulin, both in basal and stimulated conditions (Phorbol 12-myristate 13-acetate and ionomycin) [37]. GLUT1 in leukocytes does not respond to physiological or supraphysiological levels of insulin [36,37]. However, glucose uptake in T and B lymphocytes in activated conditions occurs mainly through GLUT1 [20,38,39].

GLUT1 is an important metabolic signal for lymphocyte activation, as it migrates rapidly to the cell surface after stimulation and is not detectable in non-activated lymphocytes [15,20,40]. In addition, co-stimulation is necessary for glucose uptake [41]. It is worth mentioning that non-effector cells (regulatory T cells) can develop independently of the expression of GLUT1 and glucose uptake [24,42]. Phosphatidylinositol 3-kinase (PI3K)/ protein kinase B (Akt) pathway is vital to increasing expression and maintaining GLUT1 levels on the cell surface [43]. Aerobic glycolysis and over-expression of GLUT1 can modulate IL-2 and IFN-γ production [41,44].

After transport by GLUT1, glucose can be a primary substrate for ATP generation. It can be used in the pentose phosphate pathway (PPP) as a carbon source for synthesizing macromolecules, such as nucleic acids and phospholipids; it can also be metabolized to generate reduced form nicotinamide-adenine dinucleotide phosphate (NADPH) and regulate the cell redox balance [5,19,45].

Quiescent lymphocytes have low metabolic demand; however, when stimulated by a specific antigen or mitogen, lymphocytes begin cell proliferation and require a large amount of energy [20,46]. About 90% of the glucose obtained in CD3/CD28 stimulated T cells in activated T lymphocytes is converted into lactate [47]. The glucose to lactate conversion does not result in CO_2 release and, at the same time, it results in relatively low energy production; for each mole of glucose consumed, only 2 ATP are formed. This process has been shown to be beneficial in tumor cells mainly through the provision of elevated levels of metabolic intermediates [19,48].

The rate of pyruvate consumption in lymphocytes obtained from the mesenteric lymph node of adult rats, incubated at 37°C for 1 h, increases by 40% when concanavalin A (100 μg/ml) is added to the culture medium [49]. This response does not occur with the cells obtained from aged rats (15 months old). Thus, aging, which is accompanied by immunodeficiency [50], causes marked changes in the metabolism of pyruvate in lymphocytes, and this seems to be linked to defective cell proliferation, as shown by Butler et al. [51] in the intestinal epithelium.

Increased glycolysis in proliferating cells is linked to increased glucose uptake and activity of glycolytic enzymes, while the use of glucose in the oxidative phosphorylation pathway (OXPHOS) is reduced. This metabolic feature meets the highest energy requirements, generates the necessary metabolic intermediates for the biosynthesis of macromolecules, and decreases the OXPHOS of resting cells (Figure 2). On the other hand, inadequate nutrient supply or specific metabolic inhibition prevents T cell activation and proliferation since the inability to use glucose inhibits T cell differentiation *in vitro* and *in vivo* [52,53].

Effector T cells (Th1 and Th17) mainly use the glycolytic pathway to supply their energy demand and perform their pro-inflammatory functions. This characteristic may be associated with the requirement to produce cytokines

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Clinical Science (2023) **137** 807–821
https://doi.org/10.1042/CS20220869

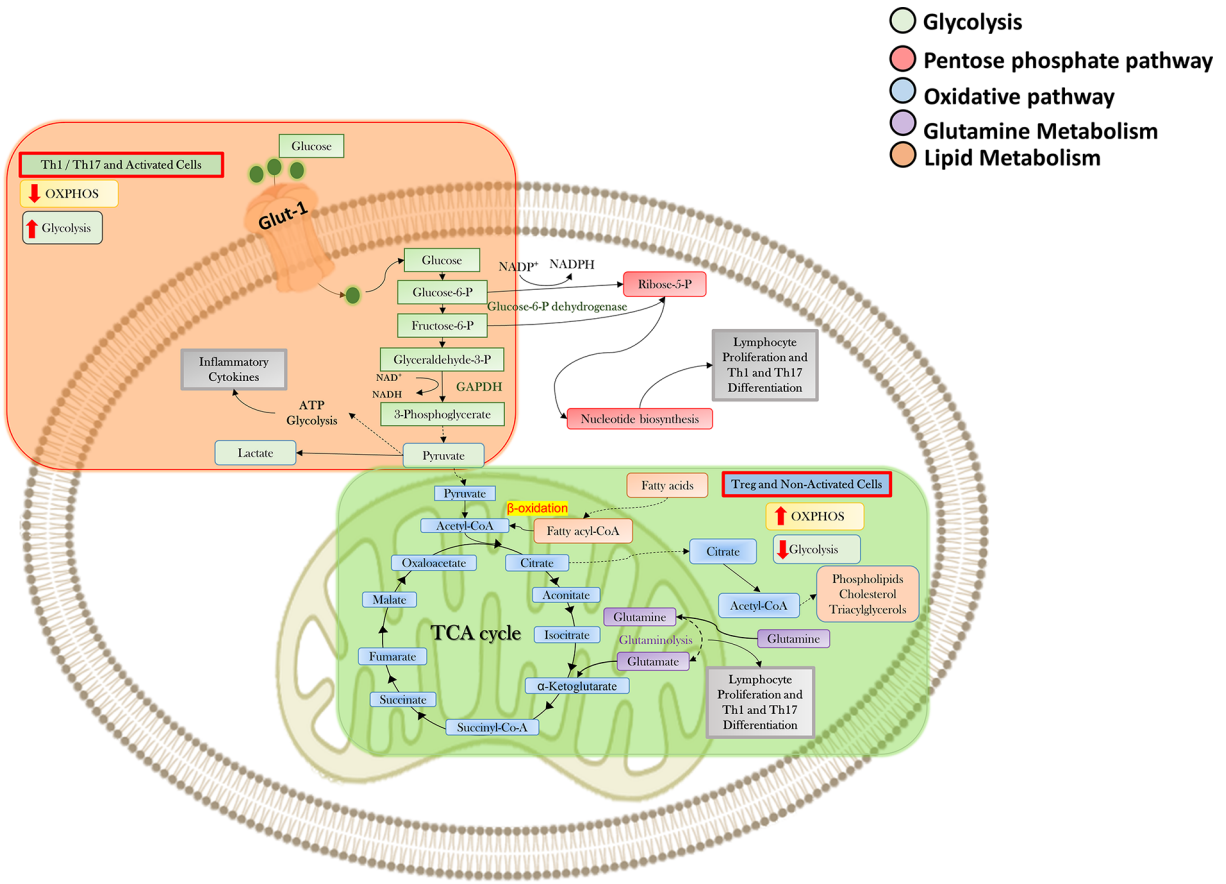


Figure 2. Main lymphocyte metabolism pathways

In T lymphocytes, activation and differentiation are dependent on glucose and glutamine. In Th1 and Th17 cells, glucose is mainly converted into lactate to supply their metabolic demand, generates the necessary metabolic intermediates for the biosynthesis of macromolecules and perform their pro-inflammatory functions. Orange box indicates predominance of this metabolic pathway in activated Th1 and Th17 cells. Treg cells use exogenous FAs and mitochondrial metabolism during differentiation. Green box indicates predominance of this metabolic pathway in T regulatory (Treg) and resting cells. Grey boxes indicate the importance of this pathway for lymphocyte function. Abbreviations: ATP, adenosine triphosphate; GLUT-1, glucose transporter 1; NAD, nicotinamide-adenine dinucleotide; NADH, nicotinamide-adenine dinucleotide (reduced form); NADP, nicotinamide-adenine dinucleotide phosphate; NADPH, nicotinamide adenine dinucleotide phosphate (reduced form); P, phosphate; OXPHOS, oxidative phosphorylation; TCA, tricarboxylic acid cycle; Th, T helper cell.

and to proliferate, in different types of immune responses, such as combating antigens and processes related to autoimmune diseases [22,24,54] (Figure 2). Glycolysis is an important pathway for effector T cell function to produce inflammatory cytokines, mainly IFN-γ and IL-2 [44]. Chang et al. [44] observed that removing functional messenger RNA (mRNA) of glyceraldehyde 3-phosphate dehydrogenase (GAPDH) by using siRNA (small interfering RNA) in lymphocytes also reduces IFN-γ, indicating that the production of this cytokine can be influenced by GAPDH activity. The predominance of the glycolytic pathway can then promote the differentiation of Th0 cells into Th1 [24]. Inhibition of the glycolytic pathway blocks this process while promoting differentiation for regulatory T cells (Treg). Treg cells use exogenous FAs and mitochondrial metabolism during differentiation [24] (Figure 2).

Glucose is also metabolized in the pentose phosphate pathway by lymphocytes. The pentose phosphate pathway is the main catabolic pathway that generates ribose, which is necessary for the synthesis of nucleotides and for the proliferation of lymphocytes, as it provides equivalent substrates for the metabolic process of glucose through the synthesis of FAs and cholesterol. In addition, the role of regulating redox homeostasis is related to the modulation of glutathione production, caused by maintaining the reducing environment (high ratio of NADPH to $NADP^+$ concentration). This is important to preventing or recovering oxidative damage in lipids, proteins, and other molecules, becoming important to the differentiation process (Th1, Th2 and Th17 lymphocytes) and proliferative capacity of T

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lymphocytes [55]. The use of the PPP is generally high in cancer cells and T lymphocytes with increased proliferative capacity. Pike et al. [56] and Wahl et al. [57] reported that T lymphocytes pass through successive phases of clonal division and expansion, changing their degree of differentiation and, in parallel, its phenotype and functional capacity in response to viral antigens. The metabolic changes result in a more oxidative phenotype, unequivocally associated with increased production of ROS (reactive oxygen species) in the mitochondrial matrix. On the other hand, the inhibition of fatty acid oxidation decreases the levels of NADPH and glutathione. However, when ROS production increases, controlling fatty acid oxidation and the PPP helps regulate NADPH levels. This is essential to regenerate glutathione levels, which in turn prevents the exacerbated increase in oxidative damage of lipids, proteins, and other essential molecules in the metabolic changes during the differentiation and proliferation of T lymphocytes [56,57]. A recent study also demonstrated that blockage of 6-phosphogluconate dehydrogenase (6PGD) promotes the reduction of the suppressive function of Tregs, leading to higher polarization to Th1, Th2, and Th17 phenotypes. This fact is associated with the development of foetal inflammatory disorder in mice model. Tregs with blocked 6PGD demonstrated elevated levels of glycolysis and increased non-oxidative PPP activity to contribute to nucleotide biosynthesis [54].

Glutamine acts by modulating lymphocyte energy and biosynthetic metabolism, being one of the primary energetic substrates of these cells. Glutamine is an essential substrate for lymphocyte functions and is used at a rate of about 2.7 μmol/min per gram dry weight when these cells are submitted to incubation in aerobic conditions [3]. When stimulated with concanavalin A, there is a 51% increase in glutamine utilization [3]. Studies have already reported that glucose deprivation can decrease cell proliferation, increase the expression of genes related to glutamine metabolism, reduce the consumption of oxygen and the amount of ATP, and to induce an increase in glutamine transporters (such as SNAT1 and SNAT2) in activated T lymphocytes. Therefore, there is an increase in glutamate and pyruvate derived from glutamine metabolism to furnish the activity of the TCA cycle in these cells when other substrates are limiting [58,59]. In lymphocytes, glutaminase activity is restricted to mitochondria, enabling the production of the substrates required for TCA cycle maintenance, such as succinate, fumarate, and citrate, which can regulate the activation of these cells, as well other leukocytes [59,60].

In general, when glutamine is hydrolyzed, releasing glutamate, the next metabolic step is catalyzed by glutamate dehydrogenase 2 (GLUD2) to produce α-ketoglutarate (α-KG) in the cytosol or, within the mitochondria, contributing to the formation of aspartate. When submitted to the action of aspartate aminotransferase (AST) or glutamate dehydrogenase 1 (GLUD1), it results in the formation of α-KG that is used in the TCA cycle [20]. In fact, there is evidence that the activation of different leukocytes can be regulated by mitochondrial function through the availability and action of other substrates, such as fumarate, succinate, and citrate, obtained through α-KG in the TCA cycle. Therefore, regulation of immune response and the inflammatory response is involved with the metabolism of glucose and glutamine since both are fundamental in producing the mentioned metabolites [58,59].

In T lymphocytes, activation and differentiation depend on glucose and glutamine (Figure 2). Carr et al. [61] demonstrated that T cells, when stimulated via CD3 and CD28, can increase glutamine uptake by 5 to 10 times. The authors demonstrated that extracellular signal regulated kinase (ERK) could influence the activity of SNAT proteins, which, as mentioned before, are related to glutamine transport and changes in glucose metabolism when stimulated by CD28 [61,62]. Sena et al. [63] also reported that, in the absence of glucose, there is an increase in the consumption of mitochondrial oxygen in $CD4^+$ T lymphocytes stimulated with anti-CD3/CD28 and that this consumption may be related to the action of α-KG. The authors also described that the production of reactive mitochondrial oxygen species (mROS) is crucial for activating specific antigens of T CD4+ and T CD8+ lymphocytes. Indeed, Nakaya et al. [64] demonstrated that glutamine is vital in differentiating CD4+ T lymphocytes into inflammatory cell types, such as Th1 and Th17. Still, it does not significantly affect differentiation to anti-inflammatory profiles in lymphocytes whose glutamine uptake was stimulated through T cell receptor (TCR) and CD28 (Figure 2).

Glutamine is a critical amino acid for several cellular functions. Glutamine restriction, although minimal, can impair the function of lymphocytes, inhibiting the production of cytokines and cell proliferation. Regardless of the lymphocyte profile, the abundant bioavailability of glutamine is crucial for the maintenance of immune function, and there is no way to replace it with any other amino acid [61].

ATP generation is essential for lymphocyte development, proliferation, and survival; macronutrient metabolism should be regulated to supply metabolic demands [47,65]. Lymphocyte proliferation also occurs with the energy of β-oxidation [19,66,67]. Lymphocytes require energy to support their function and development, which in case of metabolic dysfunction, leads to a reduced membrane-bound IL-2 receptor expression [68]. It is clear, therefore, that energy generation and macronutrient metabolism are essential for the function and development of the lymphocytes (Figure 2).

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Clinical Science (2023) **137** 807–821
https://doi.org/10.1042/CS20220869

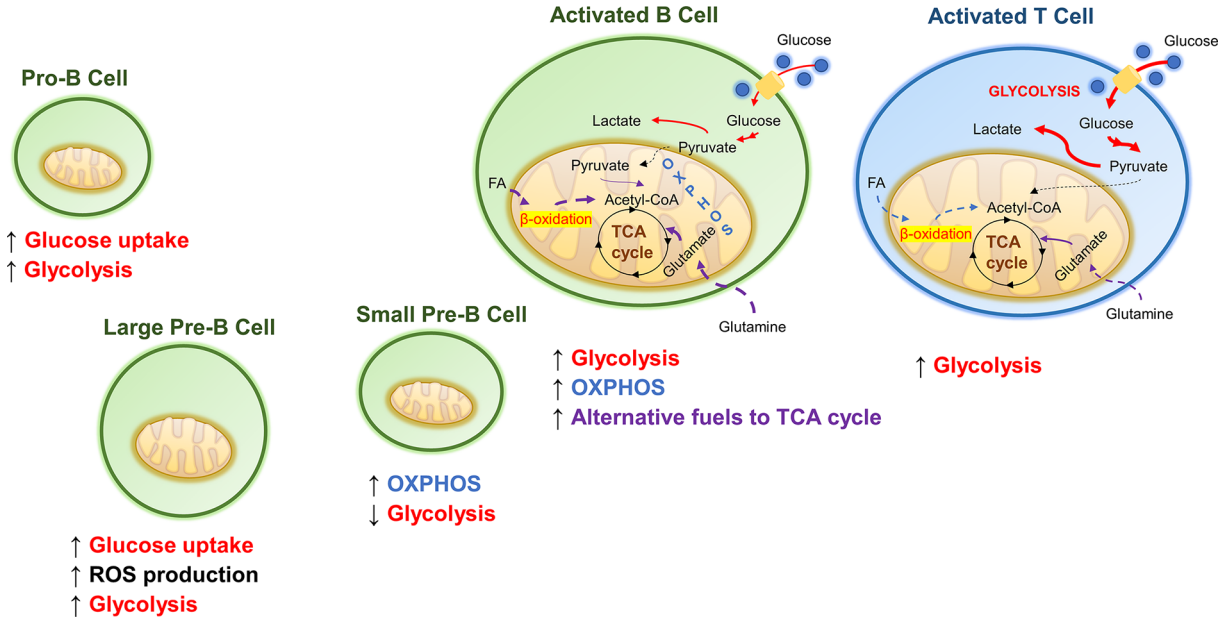


Figure 3. Metabolic differences between T and B lymphocytes

B lymphocytes have several stages of development. Each stage have different characteristics in their proliferation rate, protein synthesis, longevity, and ability to respond to metabolic stress, thus having very different metabolic needs. Here we describe the main metabolic characteristics of B cells in each stage. Abbreviations: FA, fatty acid; OXPHOS, oxidative phosphorylation; ROS, Reactive oxygen species; TCA, tricarboxylic acid cycle.

Fatty acid β-oxidation is necessary for the generation of $CD8^+$ tissue-resident memory. The generation of central memory of $CD8^+$ T cells requires endogenous FA biosynthesis, supplying substrate for β-oxidation, which is required for cell survival [69,70]. Some authors have been shown that the up-regulation of genes involved in the biosynthesis of FA is followed by activation of the T cell receptor, suggesting that the biosynthesis of FA is essential to sustain their energy demands. Moreover, the lack of sterol regulatory element-binding protein (SREBP) inhibits the anabolic program of FA biosynthesis, leading to impaired T cells undergoing clonal expansion after activation [71].

FAs are considered critical T cell regulators due to their capacity to modulate cellular differentiation, function, and activation. These cells require ATP generation to support their specific functional requirements and biosynthetic pathways [42,69,72]. In addition, when activated, T cells use FA as the substrate to support their energy demand; however, resting cells are considered inert and present low energy requirements, depending mainly on FA β-oxidation, TCA cycle, and oxidative phosphorylation [73]. Berod et al. [74] demonstrated that *de novo* FA biosynthesis performs an essential role in $CD4^+$ T cell differentiation to Treg $Foxp3^+$ or T effector Th17 (Figure 2).

It is important to highlight that the conditions associated with the *in vitro* experiments do not reflect the physiological concentrations of glucose, glutamine and fatty acids. Therefore, *in vitro* findings must be interpreted carefully and further studies targeting metabolite flux of T cells in vivo by using isotope labeling techniques may contribute to the understanding the impact of metabolism in lymphocyte function [46].

B lymphocyte metabolism feature

B lymphocyte metabolism is very similar to T cells in several aspects. However, B cells have different stages of development with distinct functions, and this cell has some peculiarities in its metabolism. Different subsets of B cells vary in their proliferation rate, protein synthesis, longevity, and ability to respond to metabolic stress, thus having very different metabolic needs. These metabolic differences can be related to developing alternative fuels to supply the TCA cycle and production of antibodies (Figure 3).

B lymphocytes exhibit several stages of development, with each stage having different characteristics in cell metabolism, as evidenced by several authors [53,75,76]. The microenvironment [77] and the type of activation [75] also influence the metabolism of this cell. Transcription factors related to the definition of B lineage, such as Pax5, are involved with glucose uptake. However, naive B cell activation with bacterial lipopolysaccharide (LPS) promotes increased glucose transporter expression, glucose uptake, glycolysis, and oxidative phosphorylation. Germinal center

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B cells also depend on glycolysis [15,78]. However, recent studies have demonstrated that Germinal center B cells promote oxidative metabolism rather than significant increases in glycolytic metabolism [77], indicating that further studies are needed to clarify this point. After activation, glucose-derived carbons can be found in glycolytic and TCA cycle intermediates and in cataplerotic biosynthetic pathways to generate lipid molecules. FAs synthesized by the *de novo* pathway are fundamental for initial expansion of the endoplasmic reticulum, characteristic of plasma cell differentiation [79]. This endoplasmic reticulum expansion is associated with increased production of antibodies [78].

Small pre-B cells exhibit lower oxygen consumption and extracellular acidification rate than pro/large-pre-B cells [53,76]. Pro-B cells demonstrate higher levels of glucose uptake when compared to the pre-B cells stage [75]. Large pre-B cells have increased glucose uptake and reactive oxygen species (ROS) production when compared with small pre-B cells; this result may be associated with demands connected to changes in cell size and proliferation [76,80]. Oxygen consumption increases when pre-B cells develop to naive B cells [75]. After inhibiting the glycolytic pathway with iodoacetate, pro-B cells were the most affected and had a high level of death. In contrast, the naive-B cells were the least affected. Together, these data demonstrate that the early stages of development are more dependent on increased activity of the glycolytic pathway compared to oxidative metabolism. In contrast, mature lymphocytes (Naive-B) are more dependent on oxidative metabolism [75] (Figure 3).

In response to an antigen, B cell receptor (BCR) signaling initiates B cell activation [81]. Thus, cell growth occurs when B lymphocytes are activated, which is associated with increased synthesis of new macromolecules. Therefore, the fundamental aspects of the cellular response of the B lymphocytes to the antigen challenge are to provide metabolic substrates and intermediates associated with the PPP [40,82].

Doughty et al. [40] suggested that after activation of B cells via the BCR pathway, lymphocytes leave the G0 phase of the cell cycle and pass to the S phase, where the glucose catabolism changes from the glycolytic pathway to the PPP. The high activity in this pathway may reflect the demand for ribose-5-phosphate and, consequently, nucleic acid synthesis that are critical for subsequent proliferation.

After stimulation, B lymphocytes increase glucose uptake, but they do not accumulate glycolytic metabolites, except for 3-phosphoglycerate [83]. After stimulation with LPS, B lymphocytes increase the extracellular acidification rate (ECAR) when measured using extracellular flux analysis due to raised lactate production (glycolytic). There is also an increase in oxygen consumption rate (OCR), maximum respiratory capacity, and glucose oxidation when measured through extracellular flux analysis. B cells thus increase glycolytic and mitochondrial metabolic activity in a balanced manner after stimulation with LPS [15,24]. Activated B cells also have increased mitochondrial mass, membrane potential, and ROS production when oxidative phosphorylation increases [84,85]. However, Waters et al. [83] demonstrated that glucose restriction does not affect some B cell functions. On the other hand, the inhibition of OXPHOS or glutamine restriction impairs B cell growth and differentiation.

Activated B lymphocytes exhibit increased levels of fumarate, malate and α-ketoglutarate, and OCR, which indicates an increase in TCA cycle flux. Waters et al. [83] demonstrated that glucose and pyruvate do not donate carbon atoms to these intermediates. The authors suggested that activated B cells use alternative metabolites to feed the TCA cycle, such as FAs, ketones, lactate, and glutamine (Figure 3).

B lymphocytes also make use of glutamine during different functional processes, such as clonal expansion [86]. Interestingly, Waters et al. [83] found that B lymphocytes do not necessarily need glucose for their initial activation and function. The authors described that glucose restriction stimulates OXPHOS and the TCA cycle and does not affect cell function. In contrast, OXPHOS inhibition and glutamine restriction can affect B lymphocyte differentiation and growth. These data suggest that, in the absence of glucose, there is increased uptake of glutamine, which would be sufficient for the activation and function of these cells. Le et al. [87] found that, in the absence of glucose and under hypoxia, there was an increase in glutamine uptake evidenced by the significant increase in products, such as fumarate, malate, and citrate derived from the TCA cycle in B lymphocytes. In this case, glutamine can maintain cell function and proliferation even under specific forms of metabolic stress. In addition, the authors found that glutamine metabolism is predominant under hypoxia, even with the abundant presence of glucose.

Activation of B lymphocytes is also associated with increased metabolism of pyrimidines and purines and also elevated lipid metabolism, where an increase in transcription is observed for 3-hydroxy-3-methylglutaryl-CoA reductase (HMGCR), the rate-limiting enzyme in cholesterol biosynthesis and elongation of very long chain fatty acids protein 6 (Elovl6), an enzyme involved in the extension of FAs [83]. The omega-3 polyunsaturated FAs (n-3 PUFAs) lead to a modified lipid composition and FA synthesis stimulation in activated B cells. Dufort et al. [79] reported that ATP citrate lyase, which catalyzes the conversion of coenzyme A and citrate (which itself has been formed in the mitochondria before being transported to the cytosol), forming acetyl-CoA and oxaloacetate, has a critical role

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Clinical Science (2023) **137** 807–821
https://doi.org/10.1042/CS20220869

in *de novo* lipogenesis and the inhibition of ATP Citrate Lyase activity impairs FA synthesis and free FA, leading to suppression in B cell proliferation.

Stimulating B cell antigen receptors through the activation of PI3K and Akt increases glucose uptake and cell proliferation. However, other signals could also activate B cells, including the PI3K-independent pathway [40,88]. In addition, the proliferation and differentiation of B cells could be induced by FA synthesis through the endogenous ATP citrate lyase, which produces acetyl-CoA from mitochondria-derived citrate; on the other hand, the proliferation and function of B cells are also regulated by mitochondrial OXPHOS, as a result from ROS production, indicating an important role of mitochondrial activity [79,85]. Thus, in the beginning, B cell activation requires glycolysis for proliferation; however, FA metabolism and mitochondrial function are essential to later cellular events [89].

Once plasma cells are formed, one necessary change is mediated by the transcription factor Prdm1 described at the beginning of this topic. Prdm promotes the expression of amino acid transporters. In addition, amino acids such as leucine and arginine activate the mechanistic target of rapamycin complex 1 (mTORC1) in these cells, which then enhances protein synthesis capacity [90]. In completely differentiated plasma cells, mTORC1 is largely used to increase antibody production.

Metabolic machinery required for antibody production

The generation of antibodies (Ab) involves complex mechanisms related to significant metabolic changes to maintain the high secretory capacity of plasma cells. These cells must critically expand the endoplasmic reticulum and Golgi interaction to accomplish their function. The process involved with the generation of plasmablasts and plasma cells is the crucial step for antibody production. Many control mechanisms trigger the regulation of this fundamental immune response process. The first metabolic adaption of cellular antibody secretion related to their Ab secretory capacity is the increased glucose consumption, 90% of which is used for Ab glycosylation [30,91] (Figure 4). One initial step to this increased demand is the higher GLUT1 expression in cell surface observed in plasma cells than in plasmablasts, resulting in increased glucose uptake [92]. Another vital characteristic involved with these different mechanisms is that, in plasma cells, there is a predomination of pyruvate-dependent respiration. The inhibition of mitochondrial pyruvate import decreases plasma cell function [30]. However, a fascinating fact is that the metabolic pathway has a different profile depending on the plasma cell compartment. For example, lamina propria IgA+ antibody-secreting cells have elevated glycolytic activity compared to splenic cells [78]. Long-lived plasma cells that import high glucose levels and express amino acid transporter CD98 (leucine transporter) secrete more antibodies than their short-lived counterparts. As described before, glucose is used to glycosylate antibodies, but the generation of pyruvate for spare respiratory capacity is related to cell survival [78]. CD98 is expressed in plasma cells at a high level, and its deficiency impairs antibody production [93].

As described in the previous session, mTORC1 has an important effect on plasma cell secretion capacity. Nutrient and mitogenic stimuli may activate mTORC1, which regulates protein, nucleic acid, and fatty acid synthesis, in addition to glycolysis and organelle biosynthesis. This control is fundamental to allowing antibody-secreting cells to adapt their metabolism. mTORC1 activity is positively regulated by Blimp-1 through the transcriptional control of the CD98 and two members of the Sestrin family, which are inhibitors of adenosine monophosphate-activated protein kinase (AMPK). The latter is an inhibitor of mTORC1. The depletion of mTORC1 activity by reduction of Raptor inhibits antibody-secretory cells differentiation but does not disturb their survival [90,92].

Glycosylation arrangements can influence the interaction of antibodies with Fc receptors, thus conferring different effector functions. Glycosylation predominantly occurs at Asn297 in a constant region of the heavy chain, but some antibodies also have a secondary site in a variable region [94]. Inhibition of glycosylation using tunicamycin results in plasma cell death, altering IgA and IgE antibody production [95].

Amino acid and glucose consumption are involved with cell ability to produce antibodies, and this process is related to N-glycosylation patterns. IgG production correlates with amino acids with the highest consumption rates (Figure 4). Leucine and arginine are the most critical amino acids related to increased IgG productivity. Fan et al. [29] demonstrated that extracellular glucose and glutamine concentrations and uptake rates are positively correlated with intracellular UDP-Gal availability [29].

Afroz et al. [96] reported that simulating amino acid starvation response with halofuginone (HF) increased the level and affinity of neutralizing, antigen-specific IgG antibody responses in mice immunized with dengue virus envelope domain III protein, a vaccine tested against the four serotypes of dengue virus. Amino acid starvation also enhanced the production of IL-10 and expression of a gene involved in antigen-specific memory B cell formation and proliferation in the lymph nodes. These data demonstrate that compounds that promote amino acid starvation simulation are important agonists of vaccine responses by B cells.

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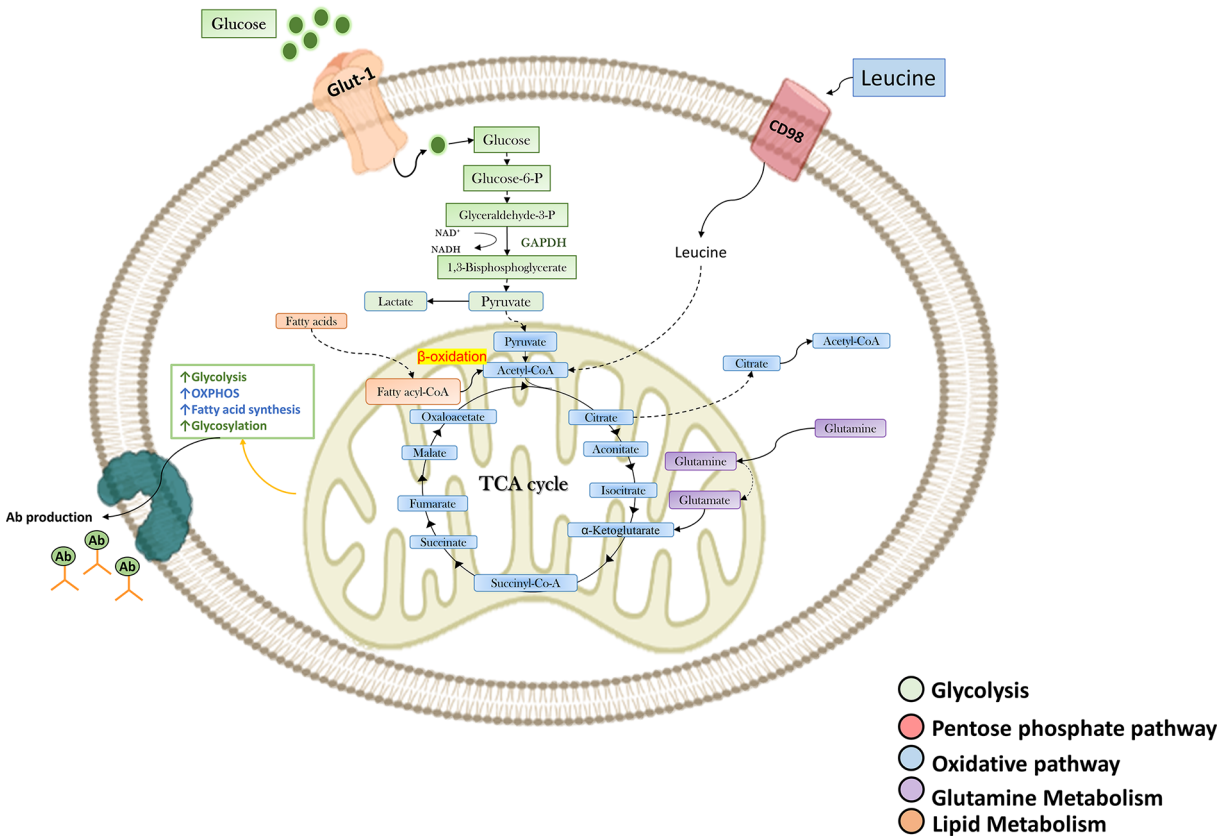


Figure 4. The metabolic machinery required for antibody production

The Machinery for Antibody Production involves important changes in the metabolism of B lymphocyte. B Lymphocyte increases glucose uptake and glycolysis, CD98 expression, oxidative phosphorylation, mainly to antibody glycosylation. Short-chain Fatty acids are used to acetyl-CoA generation. Fatty acid synthesis also is increased leading to supporting mechanisms for antibody production by B lymphocytes. Abbreviations: Ab, antibody; CD98, cluster of differentiation 98; NAD, nicotinamide-adenine dinucleotide; NADH, nicotinamide adenine dinucleotide (reduced form); NADP, nicotinamide-adenine dinucleotide phosphate; NADPH, nicotinamide adenine dinucleotide phosphate (reduced form); GAPDH, Glyceraldehyde-3-phosphate dehydrogenase; GLUT-1, glucose transporter 1; OXPHOS, oxidative phosphorylation; TCA cycle, tricarboxylic acid cycle.

Short-chain FAs (SCFAs), generated by gut microbiota, modulate host antibody responses [97]. SCFAs increase acetyl-CoA generation, glycolysis, oxidative phosphorylation, and fatty acid synthesis in B lymphocyte, leading to supporting mechanisms for antibody production (Figure 4). These FAs also control gene expression to express molecules necessary for plasma B cell differentiation. It is interesting that mice, submitted to reduced dietary fiber consumption and consequently low SCFA production, have decreased pathogen-specific antibody responses. However, SCFA or dietary fiber intake can restore this immune deficiency [97,98].

Future perspectives

In recent years, the number of articles addressing the use of immunometabolic strategies has increased considerably. Immunometabolism and associated changes in metabolic pathway activity have been used for the treatment of some autoimmune diseases [31], viral infections [32,33], cancer [34] and other chronic diseases [33,35].

Among the main strategies that use metabolism for treatment of diseases, AMPK activators [31,99] and inhibitors of mTORC1 signaling [100,101], inhibitors of lactate [102,103], pyruvate production [104], OXPHOS [34] and consumption of glutamine [32] have generated promising results.

TH17 cells polarized under standardized culture conditions are predominately glycolytic. Hong et al. [34] developed a modified standardized culture media to induce OXPHOS dependence in Th17 cells. The adoptive cell transfer (ACT) of OXPHOS Th17 cells in a murine model of melanoma, resulted in survival advantage of OXPHOS Th17 cells in vivo due the increased resistance to apoptotic cell death and the enhanced persistence in the periphery and tumor

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https://doi.org/10.1042/CS20220869

microenvironment [34]. This resistance to apoptosis may be related to higher levels of the anti-apoptotic regulators BCL-XL and MCL-1, and lower levels of the pro-apoptotic activator BIM expressed in OXPHOS Th17 cells [34]. The adoptive transfer of OXPHOS Th17 cells decreased the tumor progression in mice [34]. The authors also demonstrated that glutamine supports TCA cycling and bioenergetic activity in OXPHOS Th17 cells. Together, these results could improve the development of potential therapies targeting OXPHOS and glutamine in cancer treatment [34]. In patients with cancer, Metformin, a mitochondrial inhibitor, has been reported to provide modest clinical benefit in some trials [102]. New treatments combining lactate inhibitors with metformin have been proposed for cancer [102,103].

Interventions in pyruvate metabolism demonstrated some potential positive results in tumors. Wenes et al. [104] evaluated the effect of inhibition of mitochondrial pyruvate Carrier (MPC) on T cell differentiation and antitumor function. Deletion of MPC drives CD8+ T cell differentiation due the facilitated acetyl-coenzyme-Glutamine and fatty acid oxidation can contribute to enhanced histone acetylation and chromatin accessibility on pro-memory genes [104]. The authors found that mitochondrial pyruvate is essential to an antitumor effector function of tumor-infiltrating lymphocyte. They demonstrated a decreased tumor growth of wild type mice after ACT but MPC1 KO mice was not able to control tumor growth after ACT [104]. In immunocompetent mouse solid tumor model and a xenograft human leukemia model they demonstrated that conditioning chimeric antigen receptor (CAR) T cells with a mitochondrial pyruvate carrier inhibitor (MPCi) improved antitumor effects [104].

Lymphocytes from patients with systemic lupus erythematosus (SLE) exhibit some metabolic alterations including mitochondrial hyperpolarization, GLUT1 expression, increased oxidative stress and glycolysis,and the mammalian target of rapamycin complex 1 (mTORC1) activity is increased, as reviewed by Sharabi and Tsokos [31]. Some metabolic intervention such as blockade of glucose utilization, inhibition of glutaminase, mTOR or purine and pyrimidine metabolism using various approaches improved the T cell function and reduced disease activity in patients with SLE [31]. It is important to highlight that some of these results obtained are already in clinical phase studies and have provided interesting results [101,105]. Lai et al. [101] demonstrated that 12 months of treatment with mTOR inhibitor (Sirolimus) reduced disease activity and restored the balance of T cells in patients with SLE. The positive effects of sirolimus on SLE disease activity were lately confirmed [100].

Virus-infected host cells exhibit increased glutamine and glucose and metabolism [32]. The inhibition of glutamine, glucose and OXPHOS demonstrated positive results in antiviral treatments. Glutamine inhibition decreases the susceptibility of T cells to HIV-1 infection [106]. The inhibition of glutaminase, an important enzyme for optimal adenovirus replication, decreases the replication of herpes simplex virus 1 and influenza *in vitro* [107]. The inhibition of HIF- α, in Monocytes, inhibits SARS-CoV-2 replication in vitro [108]. Inhibition of OXPHOS by Metformin reduces HIV replication in human CD4+ T cells *in vitro*, and in humanized mice reconstituted with human CD4+ T cells [109]. A chemically synthesized, cell-permeable derivative of Itaconate, 4-octyl-itaconate (4-OI) and a derivative of fumarate, dimethyl fumarate (DMF), suppress the pro-inflammatory response and inhibit replication of SARS CoV2 [110]. 4-OI and DMF causes viral inhibition of Zika virus, Herpes Simplex Virus-1 (HSV1), Herpes Simplex Virus-2 (HSV2), and Vaccinia virus (VACV) [111].

In summary, the advancement of research immunometabolism area has contributed to the treatment of some diseases. Although most studies are only in the initial phase, using in vitro culture conditions or in animal models, but some studies are already in the clinical phase. The main strategy used in the clinical phase studies was to use widely available drugs such as Metformin and Sirolimus, previously used for the treatment of diseases. There is a lot of further work to be done, starting with the development of new drugs and translating from in vitro studies to clinical applications.

Concluding remarks

We have described herein historical and more recent findings concerning lymphocyte metabolism. In recent years, the number of articles on immunometabolism has increased dramatically due to the development of techniques for metabolite analysis and the increase in knowledge of the relationship between metabolic diseases and the immune system. Here we describe the primary fuels (glucose, glutamine, and FAs) and their role in lymphocyte function, in addition to the main differences between T and B lymphocytes. Activated T lymphocyte to Th1 and Th17 profile recruits mainly glycolytic pathways. Glycolytic pathway inhibitions block this process while favoring differentiation for Treg cells. In the early stages of development of B lymphocytes, Pro-B cells, and Large Pre-B cells, there is an increase in glucose uptake and glycolytic metabolic flux due to differences in cell size and proliferation activity. In the last stages of development (Small Pre-B cell), OXPHOS and a decrease in glycolytic pathway activity occur. In activated B cells, there is an increase in the activities of the glycolytic pathway, OXPHOS, and alternative fuels to

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supply the TCA cycle. The Machinery for Antibody Production involves essential changes in the metabolism of the B lymphocyte. The main features are: increased glucose uptake and glycolysis; oxidative phosphorylation, glucose diverted to antibody glycosylation; altered amino acid metabolism, mainly by increased amino acid transporter CD98 expression; increased utilization of short-chain FAs to acetyl-CoA generation. Fatty acid synthesis also often increased leading to support mechanisms for antibody production by B lymphocytes. These characteristics demonstrate the plasticity of B lymphocyte metabolism during stages of development and production of antibodies, but further studies are needed to describe how changes in the availability of essential metabolites, especially during illness, can influence the development and function of immune cells, both in health and in disease.

Data Availability

NA. Review Article

Competing Interests

The authors declare that there are no competing interests associated with the manuscript.

Funding

This work was supported by grants from the São Paulo State Research Foundation [grant numbers FAPESP 2021/13119-2, 2018/09868-7, 2018/07283-1, and 2017/07818-0]; the Coordination for the Improvement of Higher-Level Personnel, the National Council for Scientific and Technological Development (CNPq), the Pro-Rectory of Post-Graduate and Research of the Cruzeiro do Sul and Cidade de São Paulo Universities. This review was completed while V.L.S.D. was involved in PhD training at the Curtin Medical School and CHIRI, Curtin University, Perth, Western Australia.

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Abbreviations

α-KG, alpha-ketoglutarate; 4-OI, 4-octyl-itaconate; 6PGD, 6-phosphogluconate dehydrogenase; Ab, antibody; ACT, adoptive cell transfer; AKT, protein kinase B; AMPK, adenosine monophosphate-activated protein kinase; AST, aspartate aminotransferase; B cell, B lymphocyte; BCR, B cell receptor; Blimp-1, B lymphocyte-induced maturation protein 1; CAR, chimeric antigen receptor; CD28, cluster of differentiation 28; CD3, cluster of differentiation 3; CD98, cluster of differentiation 98; DMF, dimethyl fumarate; ECAR, extracellular acidification rate; ELOVL6, elongation of very long chain fatty acids protein 6; ERK, extracellular signal-regulated kinase; FA, fatty acid; Foxp3, forkhead box P3; GAPDH, glyceraldehyde-3-phosphate dehydrogenase; GLUD1, glutamate dehydrogenase 1; GLUD2, glutamate dehydrogenase 2; GLUT1, glucose transporter 1; GLUT3, glucose transporter 3; GLUT4, glucose transporter 4; HF, halofuginone; HMGCR, 3-hydroxy-3-methylglutaryl-CoA reductase; HSV1, herpes simplex virus-1; HSV2, herpes simplex virus-2; ICOS, inducible T cell co-stimulator; IFN-γ, interferon-γ; IgA, immunoglobulin A; IgE, immunoglobulin E; IgG, immunoglobulin G; IL-10, interleukin 10; IL-2, interleukin 2; IL-21, interleukin 21; LPS, lipopolysaccharide; MPC, mitochondrial pyruvate carrier; MPCi, mitochondrial pyruvate carrier inhibitor; mROS, mitochondrial reactive oxygen species; mTORC1, mechanistic target of rapamycin complex 1; n-3 PUFA, omega-3 polyunsaturated fatty acid; NADP, nicotinamide-adenine dinucleotide phosphate; NADPH, nicotinamide adenine dinucleotide phosphate (reduced form); OCR, oxygen consumption rate; OXPHOS, oxidative phosphorylation; PI3K, phosphoinositide 3-kinase; ROS, reactive oxygen species; SCFAs, short-chain fatty acids; siRNA, small interfering RNA; SLE, systemic lupus erythematosus; SREBP, sterol regulatory element-binding protein; T CD4+, CD4 T lymphocytes; T CD8+, CD8 T lymphocytes; TCA cycle, tricarboxylic acid cycle; TCR, T cell receptor; TD, T cell-dependent; Th0, naive T cell; Th1, T helper type 1; Th17, T helper type 17; Th2, T helper type 2; TI, T cell-independent; Treg, regulatory T cells; VACV, vaccinia virus.

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