Review Article

Immmunometabolism of systemic lupus erythematosus

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ABSTRACT

Systemic lupus erythematosus (SLE) is a potentially fatal chronic autoimmune disease which is underlain by complex dysfunction of the innate and adaptive immune systems. Although a series of well-defined genetic and environmental factors have been implicated in disease etiology, neither the development nor the persistence of SLE is well understood. Given that several disease susceptibility genes and environmental factors interact and influence inflammatory lineage specification through metabolism, the field of immunometabolism has become a forefront of cutting edge research. Along these lines, metabolic checkpoints of pathogenesis have been identified as targets of effective therapeutic interventions in mouse models and validated in clinical trials. Ongoing studies focus on mitochondrial oxidative stress, activation of the mechanistic target of rapamycin, calcium signaling, glucose utilization, tryptophan degradation, and metabolic cross-talk between gut microbiota and the host immune system.

1. Introduction

Metabolic pathways break down various compounds, carbohydrates, lipids, and amino acids that serve as biochemical source of energy, building blocks of DNA and RNA nucleotides, newly synthesize macromolecular complexes of proteins, lipids, and carbohydrates, regulate gene transcription, translation, and posttranslational modification of proteins, mediate intracellular and intercellular signaling, and sustain overall survival on the cellular and organismal levels. The field of immunometabolism has evolved to characterize the role of metabolic pathways that influence the development and function of the immune system under physiological and various pathological conditions. Cells of the innate and adaptive immune systems both require specific metabolites to support differentiation, clonal expansion, secretion of inflammatory mediators, phagocytosis, and tissue migration. The tricarboxylic acid (TCA) cycle, pentose phosphate pathway, fatty acid oxidation pathway, fatty acid synthesis and amino acid metabolism pathways have been studied in immune cells extensively [1].

Glucose catabolism via glycolysis is the fastest route of adenosine triphosphate (ATP) generation in the immune system [2]. While naïve cells and inflammatory T-cell lineages primarily rely of glycolysis, anti-inflammatory lineages, memory (T_m) and regulatory T cells (T_{reg}) depend on ATP synthesis via the mitochondrial TCA cycle (Fig. 1). The immune system consists of various cell subsets that have unique metabolic requirements in support of their functions. They undergo metabolic reprogramming to satisfy the changing demands for nutrients. For example, naïve/resting lymphocytes generate a substantial amount of energy mostly through glycolysis and fatty acid oxidation (FAO). On the other hand, highly differentiated lymphocytes shift to the mitochondrial oxidative phosphorylation (OXPHOS) which is far more efficient in terms of energy production (Fig. 1). Fatty acids can be divided by their length comprised of carbon (C) atoms into C3-C5 short chain fatty acids (SCFA) and C13-C21 long-chain fatty acids (LCFA), saturated or unsaturated. While SCFA are generated by commensal gut microbiota [3], LCFA originate from nutrition or membrane breakdown [4]. SCFA and LCFA integrate the metabolome of the host and gut microbiota and play
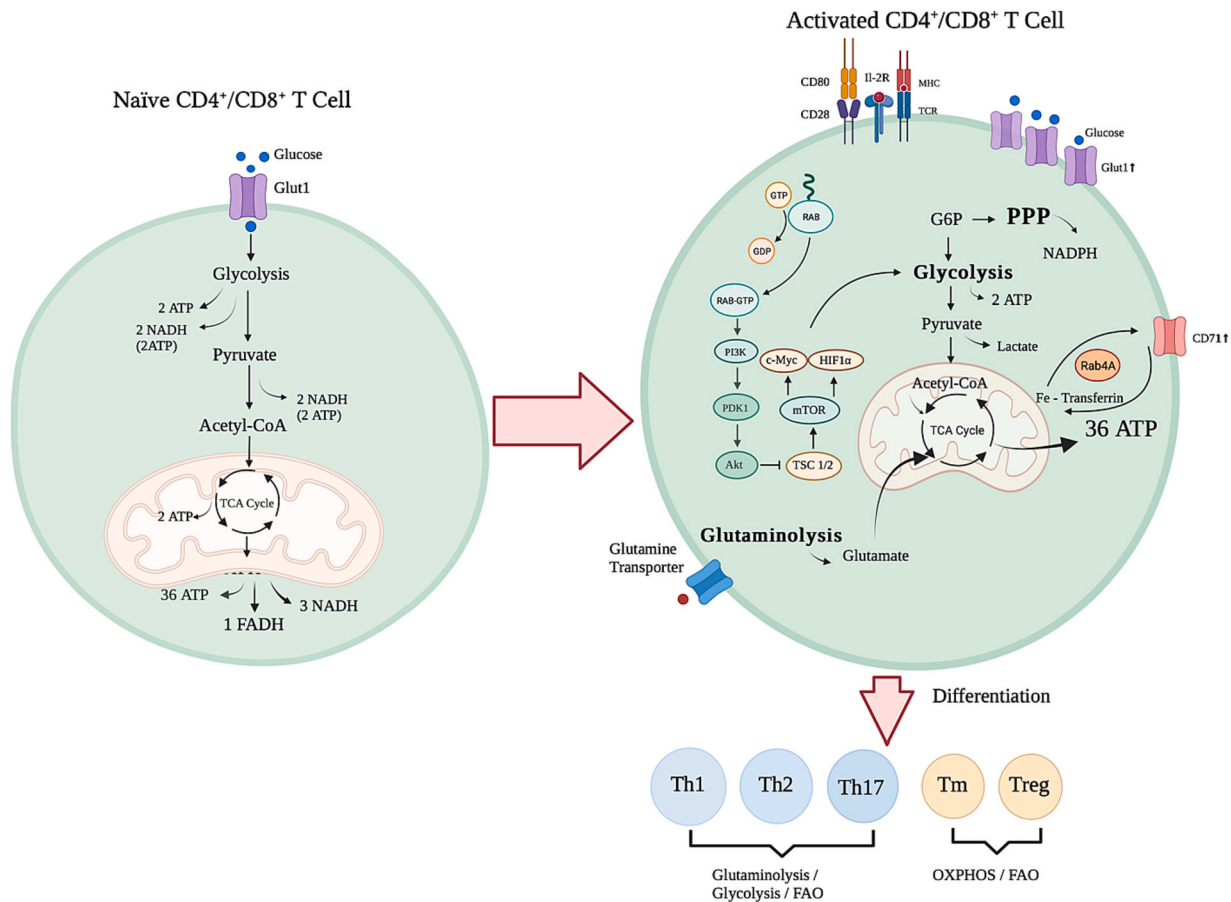

Fig. 1. Schematic diagrams of metabolic pathways preferentially utilized in naïve over activated T cells.

complex roles in signal transduction within the immune system [3,4]. Along these lines, gut microbiota also modulate inflammation by metabolizing other nutrients, in particular, tryptophan into kynurenine [5], which in turn activates the mechanistic target of rapamycin (mTOR) in human [6] and mouse T cells [7] (Fig. 2). Of note, mTOR is a sensor of metabolic stress and critical checkpoint of inflammatory lineage development in the immune system [8].

Importantly, mTOR blockade has shown preliminary evidence of therapeutic efficacy in patients with autoimmune diseases, such as systemic lupus erythematosus (SLE).

SLE is an autoimmune disease of unclear etiology which is characterized by T cell dysfunction and activation of autoantibody-producing B cells. Oxidative stress is known to contribute to its highly complex pathogenesis, including the oxidization of DNA and phospholipids, which thus triggers autoantigenicity of mitochondrial DNA (mtDNA) and mitochondrial phospholipids, such as cardiolipin, in mice and patients with SLE [9–12]. These processes are crucially dependent on the production of reactive oxygen intermediates (ROI) in mitochondria [13]. This review provides insights into metabolic control of inflammation by glucose within the adaptive and innate immune systems in SLE (Fig. 3).

2. T cells

Both resting and activated lymphocytes utilize glucose as substrate for their ATP synthesis.

Each molecule of glucose can rapidly generate to molecules of ATP via glycolysis or 36 molecular of ATP via oxphos. Routing glucose via these two alternative pathways depend on the expression of enzymes and availability of cofactors. As examples, expression of phosphofructokinase, the rate limiting enzyme of glycolysis, promotes inflammatory metabolism in lupus T cells [8] and macrophages [14].

In order to metabolize glucose, cells import it via Glut membrane transport proteins [15]. Glut1, is the major glucose transporter in T and B lymphocytes and it is significantly upregulated in response to T-cell Receptor (TCR), B-cell receptor (BCR) or cytokine stimulation [16–18]. It has been well established that long term survival of T cells requires receptor engagement through MHC to avoid death by neglect [19–22] and when there's loss of engagement, T cells downregulate Glut1 and decrease mitochondrial potential leading to cellular atrophy and eventual apoptosis [23].

Following the entry of glucose into the cells, the enzyme hexokinase catalyzes the phosphorylation of glucose into glucose 6-phosphate which can later enter either glycolysis or pentose phosphate pathway (PPP) [24]. Glycolysis generates 2 molecules of ATP and its end-product is pyruvate. Depending on the oxygen availability and subset of T cell, pyruvate then transforms into lactate in the cytoplasm or acetyl coenzyme A (acetyl-CoA) in the mitochondria (Fig. 3). When oxygen is available to naïve T cells, they use acetyl-CoA as the entry-level substrate for the mitochondrial tricarboxylic acid (TCA) cycle which at maximal capacity generates an additional 36 molecules of ATP via OXPHOS, 3 molecules of NADH and 1 molecule of FADH2 [25,26]. Generation of energy is also possible via glutaminolysis and β-oxidation of fatty acids via the TCA cycle. In fact, oxidation of LCFAs such as palmitate yields the highest amount of ATP, an estimated net of 129 ATP molecules [27].

As the main alternative pathway of glucose metabolism, the pentose phosphate pathway (PPP) converts glucose 6-phosphate to ribose 5-phosphate. This is a precursor for the synthesis of nucleic acids in proliferating cells [14]. The non-oxidative phase of the PPP produces
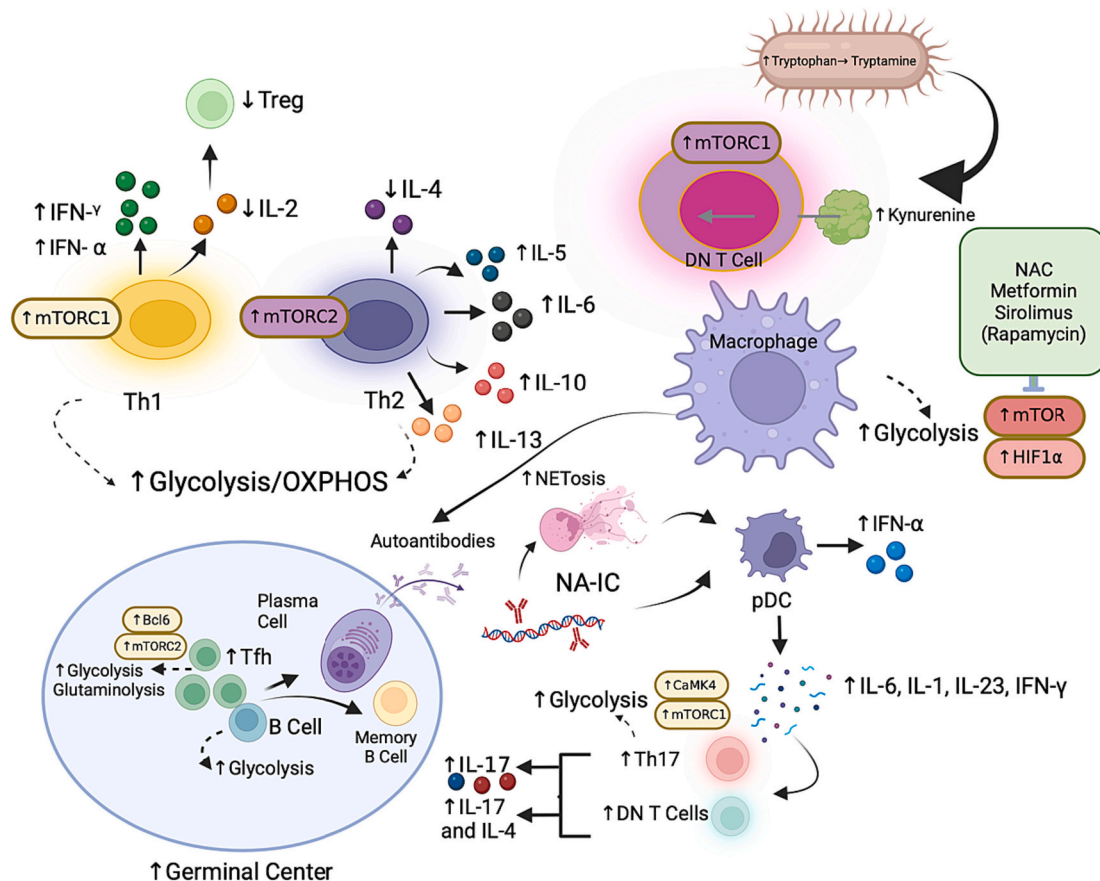
Fig. 2. Cell type-specific metabolic checkpoint during lupus pathogenesis. SLE patients have increased numbers of pro-inflammatory CD4+ T cells, Tfh, and CD3$^+$CD4$^-$CD8$^-$ double-negative (DN) T cells and memory B cells suggestive of increased formation of germinal centers [28]. Activated B cells have a preference for glycolysis for ATP production. Tfh utilize glycolysis and glutaminolysis dependent on increased Bcl6 transcription factor and mTORC2 [29]. B cells differentiate into memory B cells or plasma cells producing autoantibodies with aid of Tfh and DN T cells. Oxidized mitochondrial DNA from neutrophils for Nucleic Acid anti-DNA antibody immune complexes (NA-IC) that mediate NETosis and consequent IFN-α by plasmacytoid dendritic cells (pDCs). In turn, pDCs stimulate T-cell differentiation into Tfh, Th17 and DN T Cells which play a role in the increased production of IL-21, IL-17 and IL-4 underlying B-cell activation in SLE. Th17 utilize glycolysis as preferred metabolic pathway mediated by an increase in mTORC1 activity and CaMK4. Blockade of mTORC1 underlies therapeutic efficacy of NAC and rapamycin, also known as sirolimus, in SLE. Glucose metabolic pathway for double-negative T Cells has not been identified yet, but it is known that there's mitochondrial hyperpolarization, mTOR activation, overproduction of IL-4 and IL-17 and predisposition of these cells to pro-inflammatory cell death via necrosis [30]. Inhibition of mTORC1 with rapamycin decreased IL-4 production in these cells and was shown to promote expansion of Tregs in SLE patients [30].

erythrose-4-phosphate which is used for the synthesis of aromatic amino acids such as phenylalanine, tryptophan, histidine and tyrosine [31,32]. This pathway also generates reducing equivalents such as NADPH, known to protect against oxidative stress by neutralizing reactive oxygen intermediates and regenerating reduced glutathione (GSH) from its oxidized form GSSG [33]. Transaldolase (TAL) is the rate limiting enzyme of the non-oxidative branch of the PPP [34,35] which regulates the ability of mitochondria to generate an electrochemical gradient for ATP synthesis via cell type-specific production of NADPH in T cells [36] or hepatocytes [37]. Due to carbon trapping in the non-oxidative branch of the PPP, fructose 6-phosphate is depleted, which is essential for glycosylation of paraoxonase 1 (PON1), an antioxidant enzyme produced by the liver. Since glycosylation is required for secretion of PON1 into the plasma, circulating antigens become unprotected against oxidization, which increases their antigenicity, as evidenced by increased aPL production in TAL deficiency [38].

Metabolic reprogramming by cytokines, gene expression, and substrate availability all contribute to determining the fate of naïve cells upon differentiation into effector, regulatory or memory T cells. Naïve T cells are antigen inexperienced cells that become differentiated and released by the thymus. At rest, both CD4+ and CD8+ naïve T cells have low metabolic demand and utilize mostly OXPHOS pathway for glucose metabolism [39,40]. Similarly, Treg and memory CD4+ and CD8+ T

cells rely on OXPHOS and FAO for ATP generation [41–48]. Treg specifically, when activated, upregulate the transcription factor myocyte enhancer factor 2 (Mef2) which induces genes required to undergo oxidative phosphorylation (OXPHOS) [49]. Additionally, it has been demonstrated that CD4+ Treg engage in both glycolysis and FAO to proliferate [50]. In fact, glycolysis in Treg cells is essential to perform their suppressive function which is regulated via induction of the transcription factor Foxp3-E2 [51]. This Foxp3 splice variant was found to retain exon 2 of its coding sequence. Among all splicing variants of human Foxp3, Foxp3-E2 has been shown to serve a major role in conferring suppressive ability onto T$_{reg}$ cells. The glycolytic enzyme enolase (Eno)-1 has an inhibitory effect on the transcription of the Foxp3 containing the exon 2 sequence (Foxp3-E2) through the binding to the promoter or to the CNS2 region of Foxp3 [52].

Enolase-1 may translocate to the nucleus and suppress the expression of Foxp3-E2 after binding to FOXP2 regulatory regions, such as the promoter and conserved noncoding sequence 2 (CNS2).

Apparently, subjects with the autoimmune diseases relapsing-remitting multiple sclerosis (RRMS) or type 1 diabetes mellitus (T1DM) exhibit impaired glycolysis and Foxp3-E2 expression in iT$_{reg}$ cells. Foxp3 upregulates fatty acid oxidative phosphorylation in T$_{reg}$ cells by increasing the expression of electron transport chain (ETC) complexes [53]. Another mechanism to promote OXPHOS over
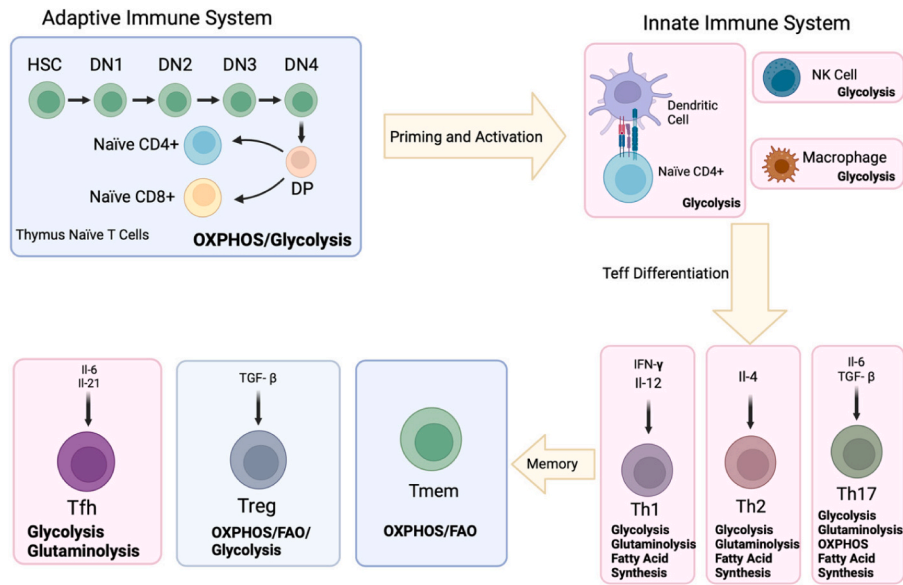
Fig. 3. Metabolic pathway utilized during physiological T cell developments.

glycolysis in T_{reg} cells involves the suppression of c-myc transcription factor and subsequent decreases in the expression of glycolytic enzymes including lactate dehydrogenase [54].

The development of Th17 cells starts with engagement of the TCR of an activated T helper Cell which in turn activates basic leucine zipper transcription factor TF-like (BATF) and interferon-regulatory factor 4 (IRF4) [55,56]. BATF and IRF4 promote chromatin accessibility for the Th17 transcription factors and along with STAT3 [56]. Interleukin-6 and TGF-β induce the transcription factor RAR-related orphan receptor (t (ROR(t) which in turn induces terminal differentiation of Th17 cells [57]. STAT3 activation via IL-6 along with TGF-β1 play essential roles in Th17 differentiation with simultaneous suppression of Treg development [58,59]. This balance of Th17 and Treg cells is critical for host immunity and preservation of tolerance [60]. IL-6 induces JAK1 and JAK 2-mediated STAT3 phosphorylation for Th17 development [61,62]. Phosphorylated STAT3 then translocates to the nucleus and dimerizes [62]. The STAT3 dimer then binds to the promoter region ROR(t, IL-21 and IL-23R [58,63]. The suppressor of cytokine signaling 3 (SOCS3) is a negative regulator of this IL-6 driven signaling pathway that provides a negative feed-back control of Th17 development [64]. Persistence of Th17 cells relies on mitochondrial OXPHOS for ATP production and STAT3 activation [65,66]. Th17 development may be aided by Stat3 via its mitochondrial localization and activation of complex II in the ETC. [67] Mitochondrial localization of Stat3 may be facilitated by oxidative stress that in turn facilitates fatty acid oxidation [68].

Engagement of TCR receptor on Th17 cells activates the stromal interaction molecule 1 (STIM1) and calcium influx through calcium release-activated channels (CRAC) [69]. This allows store-operated calcium entry which in turn activates calcium dependent enzymes and transcription factors such as the phosphatase calcineurin and the nuclear factor of activated T cells (NFAT) [69,70]. Calcineurin and NFAT regulate transcription of genes encoding inflammatory cytokines, IL-17A, IL-21, IL-22 and IFNγ [71,72]. Mice lacking STIM1 exhibit diminished STAT3-driven Th17 inflammation in the lung, skin and intestines [72]. Moreover, Th17 cells of STIM1-deficient mice show reduced expression of mitochondrial ETC genes, leading to impairment of OXPHOS and increased ROS production [72]. It has also been proven that IL-17A expression in pathogenic Th17 cells rely on mitochondrial respiration and OXPHOS blockade by oligomycin, and ATPase inhibitor, ameliorates colitis, lung and skin inflammation [72,73]. In fact,

OXPHOS inhibition with oligomycin has also been demonstrated to induce FOXP3-expressing cells and decrease the number of Th17 cells [66]. Moreover, inhibition of STAT3 phosphorylation enhances Treg generation by increasing FOXP3 expression, while impairment of STAT5 phosphorylation reduced the number of Treg cells [74,75]. Along these lines, STAT3-deprived Treg cells have upregulated suppressive function and it is associated with increased frequency of GARP$^+$ and PD-1$^+$ Tregs [75]. On the other hand, inhibition of STAT3 does not affect CTLA4, CD39 or LAG3, which have immunosuppressive functions [75]. STAT3 inhibition in Treg cells downregulates OXPHOS and stimulates a metabolic shift to glycolysis [75]. When electron deficiencies are replaced by directly stimulating complex II of the ETC with CoQ10 treatment, glycolysis was decreased and OXPHOS was restored [75]. Treatment with CoQ10 also enhanced the suppressive capacity of STAT3-deficient Treg cells, but this effect may not be attributed to increased OXPHOS. Other key players of suppressor function include PD-1 and GARP [75].

In a tumor microenvironment, there's decreased glucose availability and lactate accumulation instead. There's also an increased infiltration of Treg cells into tumor tissues that suppress the function of Teff cells contributing to the unchecked proliferation of tumor cells [65]. Treg cells use lactate as primary source of energy under these conditions. In fact, lactate promotes the differentiation of CD4+ T cells into Treg and mechanistically they do so by increasing the expression of the monocarboxylic acid transporter (MCT1) and lactate dehydrogenase leading to increased intracellular uptake and metabolism of lactate, respectively [76,77]. Lactate also promotes the transformation of α-ketoglutaric acid (α-KG) to 2-hydroxyglutaric acid (2HG) as well as NADH to NAD+ which in turn increases differentiation to Treg cells regulated by mTOR activation [77].

T_{reg} express high levels of the fuel-sensing enzyme AMP-activated protein kinase (AMPK) that enhances fatty acid uptake for oxidation as well as mitochondrial biogenesis [78]. Estrogen-related receptor γ (Esrrg) is a murine lupus susceptibility gene expressed in T_{reg} cells that has been recently proven to promote adequate mitochondrial metabolism and likely promoting OXPHOS [79]. Tregs mediate suppression of effector cells via the cytotoxic T lymphocyte-associated protein 4 (CTLA-4). CTLA-4 and programmed death 1 (PD-1) share ligands with the stimulatory receptor CD28 and are critical in T-cell response modulation as they act as antagonist to the CD28 co-stimulation. Ligation of both CTLA-4 and PD-1 interrupts glucose metabolism via inhibition of Akt [80].

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Th1 and Th2 also preferentially utilize glycolysis mediated by mTORC1 and mTORC2 respectively [81]. In SLE, Th1 cells exhibit decreased production of IL-2 which restrains Treg cell development, leading to uncontrolled autoimmunity. On the other hand, lupus Th2 cells demonstrate an increase in IL-5, IL-6, IL-10 and IL-13 but a decrease in IL-4. Lastly, defective phagocytosis by macrophages and/or aberrant activation also play a role in SLE pathogenesis. These macrophages exhibit an increase in glycolysis dependent on increase mTOR activity and HIF1α transcription factor [82]. Of note, mTOR-dependent IL-4 and IL-17 production by DN T cells is increased in patients with SLE [30]. While IL-4 may stimulate B cell development [83], IL-17 producing DN T cells cause nephritis in SLE [84,85].

mTORC1 and mTORC2 are activated in SLE Treg cells and blockade with rapamycin induces autophagy, restores the expression of GATA-3 and CTLA-4, therefore correcting Treg cell function in SLE [86]. In SLE patients given sirolimus, the generic version of rapamycin, there is expansion of CD4$^+$CD25$^+$FoxP3$^+$ regulatory T cells and CD8$^+$ memory T Cells, inhibition of IL-4 and IL-17 production by CD4$^+$ and CD4$^-$CD8$^-$ double negative T cells. SLEDAI and BILAG scores for disease activity were also reduced in this trial, highlighting the importance of defining a role of mTOR blockade as part of SLE treatment [87].

Pro-inflammatory CD4+ T Cells, Th1, Th2 and Th17 cells, rely on glutaminolysis, and glycolysis as metabolic sources of energy [41,44]. Th17 may also accumulate mitochondria and utilize OXPHOS due to limited mitophagy, enforced by OPA-1 expression. They also exhibit apoptosis resistance characterized by elevated Bcl-xL and decreased BIM transcription [65]. By contrast, Th17 cells, which preferentially depend on glycolysis, exhibit proapoptotic phenotype [65]. Here, it's important to note that increased expression of Rab4A limits mitophagy by targeting mitochondrial fission-initiating factor, dynamin-related protein 1 (Drp1) to lysosomal degradation in most T cells of patients and mice with SLE [88] and in hepatocytes of lupus-prone mice [89].

However, mitochondria are shrunken and dysfunctional in follicular helper T cells (Tfh) [90], which preferentially utilize glutaminolysis and glycolysis for energy production [91].

Glucose metabolism is essential for T cells of lupus patients to engage their function and proliferation (Table 1). Recently, it was demonstrated that Glut1 expression on the surface of the effector memory CD4+ T cells

was elevated in patients with SLE, which might contribute to the increased glycolysis observed in this disease [92]. Additionally, Glut1 overexpression, partly dependent on mTORC1 signaling, was found to correlate with increased number of Tfh and germinal center B cells and consequent increase in IL-21 and IgA [93]. Increased expression of Glut6 transporter by overexpression of the gene Slc2A6 was shown in Tfh in lupus mice [93]. Parting from this concept, a glucose transporter inhibitor (CG-5) was tested on lupus-prone mice and indeed showed that it improved autoimmune phenotypes as it reduced germinal centers with subsequent decrease in ANA and anti-dsDNA [94].

Calcium/calmodulin-dependent protein kinase 4 (CaMK4) balances the expression of IL-2 and IL-17 is increased in lupus T cells [97]. Inhibition of CaMK4 decreases the expression of Glut1 during Th17 cell differentiation phase, reducing the levels of IL-17 [107,108]. Along this lines, pharmacological inhibition or genetic silencing of CaMK4 significantly decreases glycolysis and improves disease activity in lupus-prone mice [97,108–111].

SLE patients are known to have hyperpolarized megamitochondria in their T cells [112], however they demonstrate decreased ATP production and leakage of reactive oxygen species (ROS), contributing to SLE pathogenesis [11,113]. The accumulation of ROS-producing mitochondria underlies mTOR activation in lupus T cells [114]. Rab4A-mediated accumulation of mitochondrial and mTOR activation are also detected in the liver of lupus-prone mice, which contribute to the antigenicity of β$_2$-glycoprotein I or apolipoprotein H and the production of anti-phospholipid antibodies [89]. Rapamycin block the production of β$_2$-glycoprotein I and anticardiolipin antibodies in lupus-prone mice [89].

A significant minority of SLE patients also have liver injury in correlation with higher SLE disease activity index (SLEDAI) as well as elevated markers of autoimmunity such as anti-DNA antibodies, hypocomplementemia, proteinuria, leukopenia, thrombocytopenia and antiphospholipid antibodies. Abnormal liver function tests are responsive to treatment with rapamycin [115]. Demethylation has been associated with the expression of the epigenetic regulator EZH2 in lupus CD4+ T cells which occurs with increased glycolysis in the setting enhanced T cell activation [116].

CD4+ T cells from murine samples and patients with SLE have elevated extracellular acidification rate and oxygen consumption rate

Table 1

Summary of preferred metabolic pathways and APT generation on healthy T cells and B cells compared to SLE T cells and B cells.

Healthy Cells	Preferred metabolic pathway	Reference	SLE cells	Preferred metabolic pathway	Defect	Reference
CD4+ Naïve T Cells	OXPHOS	[39]	CD4+ Naïve T Cells	Not determined		
CD4+ Tmem	FAO/OXPHOS	[46]	CD4+ Tmem	Not determined		
CD4+ Th1	Glycolysis Glutaminolysis Fatty Acid Synthesis	[41,44]	CD4+ Th1	↑Glycolysis/ OXPHOS	↑mTORC1	[95] [96]
CD4+ Th2	Glycolysis Glutaminolysis Fatty Acid Synthesis	[41,44]	CD4+ Th2	↑Glycolysis/ OXPHOS	↑mTORC1	[95] [96]
CD4+ Th17	Glycolysis Glutaminolysis Fatty Acid Synthesis OXPHOS	[41,44,65]	CD4+ Th17	↑Glycolysis/ OXPHOS	↑mTORC1 ↑CaMK4	[97,95,96]
CD4+ Tfh	Glycolysis/Glutaminolysis	[91]	CD4+ Tfh	Glycolysis Glutaminolysis	↑mTORC1, ↑Bcl6	[93]
CD4+ Treg	Glycolysis/FAO	[41,50]	CD4+ Treg	Not determined	↑mTORC1	[30,98]
CD8+ Naïve T Cells	OXPHOS	[39]	CD8+ Naïve T Cells	Not determined		
CD8+ Tmem	FAO/OXPHOS	[45,48]	CD8+ Tmem	Not determined	↑mTORC1	[87]
CD8+ Treg	FAO/OXPHOS	[47]	CD8+ Treg	Not determined		
CD4/CD8 Double Negative T Cells	Not determined	N/A	CD4/CD8 Double Negative T Cells	Not determined	↑mTORC1	[30,98]
B Cells	Glycolysis	[99]	B Cells	Glycolysis	Not defined	[100]
Plasma Cells	Glycolysis	[101]	Plasma Cells	Not determined	↑mTORC1	[102]
Plasmacytoid Dendritic Cells	Glycolysis	[103]	Plasmacytoid Dendritic Cells	Not determined		
Monocytes/Macrophages	Glycolysis/FAO	[104,105]	Monocytes/Macrophages	Glycolysis	↑mTOR ↑Hif1a	[82]
NK Cells	Glycolysis	[106]	NK Cells	Not determined		

consistent with upregulated glycolysis and OXPHOS. Upon treating these cells in vitro, metformin inhibited mitochondrial ETC complex I and normalized the generation of IFN-γ. Similar results were obtained when the glucose-metabolism inhibitor 2-deoxy-ᴅ-glucose (2DG) was used in vitro. When metformin and 2DG were combined, it reversed lupus phenotypes in the lupus-prone mice in vivo [95,117]. Moreover, the use of metformin in this study increased IL-2 production which is decreased in lupus T cells and is known to help maintain function in regulatory T cells [95,118,119]. Interestingly, pharmacologic inhibition of glycolysis suppressed the expansion of germinal-center B cells and autoreactive T_FH cells leading to decreased production of autoantibodies in lupus prone mice. Conversely, antibody production to protein immunization or viral infection was not impaired, suggesting that autoreactive CD4+ T cells and B cells have a glucose-dependent mechanism and activation by a foreign antigen is glucose-independent [29,120].

Few studies have explored the benefits of metformin in SLE patients with conflictive results, highlighting the necessity of larger clinical trials that could potentially help elucidate clinical benefits in SLE patients [121,122].

Additionally, PPP metabolites were found to be accumulated in peripheral blood lymphocytes in patients with SLE, supporting the notion that this pathway is glucose metabolism is also upregulated in SLE [123]. Given that glucose metabolism is increased in SLE activated T cells, measurement of glucose uptake by positron emission tomography with fluorine-18 fluorodeoxyglucose ([^{18}F] FDG PET/CT) has been explored. It has been found particularly useful in helping diagnose neuropsychiatric manifestations of lupus particularly when conventional imaging was unrevealing [124–126].

Peroxisome-proliferator activated receptor gamma (PPARγ) is a transcription factor with anti-inflammatory properties that plays a central role in glucose homeostasis. PPARγ mRNA in real-time PCR has been shown to be elevated in patients with active SLE where the CD40/CD40L pathway is activated. This pathway favors production of inflammatory cytokines and PPARγ acts as its negative modulator [127]. *Pioglitazone, a* PPAR-γ agonist, has been shown to restrain the activation of effector CD4+ T cells, while it expanded Tregs in patients with SLE [128].

Metabolic dysfunction in lupus T cells has been associated with the overexpression of the endosomal traffic regulator small GTPase, Rab4A [88,114]. Rab4A is overexpressed in T cells of SLE patients as well as T cells and hepatocytes of all lupus-prone mouse strains so far examined [88,115]. Rab4A promotes endocytic recycling of surface receptors CD4 [129] and CD3 [114] and the mitochondrial fission initiator Drp1 to lysosomal degradation [88,130]. Although Rab4A also regulates the traffic of CD71 [130], it is recycled rather than targeted to degradation [129]. Lupus-associated polymorphic alleles of Rab4 regulate its expression and activation of mTORC1 in lupus T cells [131].Enhanced CD71 expression has recently been associated with enhanced endocytic recycling, mTORC1 activation, and mitochondrial ROS production by CD4+ lupus T cells [132]. Given that CD71 mediates iron uptake, one can presume that lupus T cells might also exhibit enhanced ferroptosis and mitochondrial ROS production in SLE, as recently been documented in HIV-infected CD4+ T cells [133].

3. Dendritic cells

Dendritic cells (DC) are antigen presenting cells that migrate to lymph nodes to prime naïve T cells when immune response is activated. They develop from hematopoietic progenitors into two different subsets: conventional DCs (cDCs), previously known as myeloid dendritic cells, and plasmacytoid DCs (pDCs). cDCs are subdivided into cDC1 and cDC2 and they give rise to macrophages and DC progenitors. cDC1s activate CD8+ T cells through antigen presentation via MHCI and cDC2s present antigens via MHCII to CD4+ T cells [134]. pDCs on the other hand, largely produce type I interferon during inflammatory responses [134]. Quiescent DCs that have not been stimulated by toll-like receptors

(TLR), TLR-2, TLR-4, and TLR-9, rely on OXPHOS for ATP production [103]. When they are activated by engagement of TLR to become mature DCs, they exhibit increase in aerobic glycolysis and they do so by signaling via kinases TBK1, IKKε and PI3K/Akt and the transcription factor HIF-1α. Simultaneously, they have a decrease in OXPHOS metabolism due to suppression by nitric oxide (NO) [103,135,136].

Upon TLR engagement they mature and differentiate into various subsets, and this is controlled by Fms-related tyrosine kinase 3 ligand (Flt3L), which activates the PI3K-mTOR pathway. In fact, in mice who are Flt3L deficient there's a paucity of DCs [137–141]. However, mTORC1 activation in mice lacking its negative regulator tuberous sclerosis 1 (Tsc1), theirs is also an impairment of DC development [142]. Tsc1-deficient DCs exhibit enhanced glycolysis, mitochondrial respiration and lipid synthesis [142]. Hematopoietic progenitor cells that are induced with Flt3L to differentiate into cDC and pDC show increased expression of Glut-1 and increased aerobic glycolysis [143]. Fatty acid oxidation modulates cDC differentiation, as its inhibition favors cDC2 over cDC1 proliferation [143]. cDC1 have enhanced mitochondrial content and membrane potential as compared to cDC2 and have a much stronger predilection for oxidative metabolism [143,144]. Notably, treatment with *N*-acetylcysteine (NAC) promoted cDC1 differentiation over cDC2 [143]. Overall, differentiation of cDC1 relies on LKB1/AMPK/FAO axis while cDC2 differentiation relies more on ROS production [143,145]. Tolerogenic dendritic cells moderate balance in the immune response by inducing tolerance by deleting self-reactive T cells [146]. NAC also blocked mTORC1 activation in DN T cells which was accompanied by clinical improvement in SLE patients in a double-blind placebo-controlled randomized clinical trial [98]. Interestingly, Vitamin D3 promotes tolerogenic DCs and mediate the increase seen in oxidative and glycolytic pathways in these cells [147].

4. Natural killer (NK) cells

Activated dendritic cells induce Natural Killer cell (NK) proliferation, activation and subsequent release of cytokines such as IFN-(γ) during physiological immune response [148]. These activated NK cells undergo metabolic reprogramming and rely on mTORC1-dependent aerobic glycolysis for their effector functions as well as OXPHOS [106,149,150]. The transcription factor SREBP is required to carry this reprogramming and promotes utilization of glucose via the cytosolic citrate-malate shuttle [150]. Interestingly, INF-γ production by NK cells is independent of glycolysis or OXPHOS when these are activated by IL-12 and IL-18 simultaneously, but if activated through NK receptors it requires glucose-mediated OXPHOS [151]. On the other hand and very similarly to naïve T cells, quiescent NK cells preferentially utilize glucose-fueled OXPHOS for ATP production, with very low levels of simultaneous glycolysis [151].

Natural Killer T cells (NKT) are a subset of T cells that express NK receptors such as NK1.1 and CD1d. They recognize glycolipid antigens via the MHC class I-like CD1d receptor [152]. When activated, they produce IFN-γ, IL-4 and IL-17 [153,154]. These mature NKT cells rely on aerobic glycolysis with enhanced Glut1 expression but are less efficient than activated CD4+ T cells and utilize more OXPHOS for their survival and effector functions. Mice lacking the essential autophagy gene Atg7 in the T-cell compartment, fail to develop iNKT cells. This is attributed to the dependence of iNKT cells on autophagy and maintenance of mitochondrial homeostasis through mitophagy. Autophagy defects result in the intracellular accumulation of mitochondrial superoxide species and subsequent apoptotic cell death of iNKT cells [155]. Thus, mTOR activation and deficient autophagy may thus underlie a long-established paucity of NK cells is SLE [156].

5. B cells

Most of the research on metabolism in lupus has been done in T Cells, but B cells also play a significant role in the pathogenesis of the disease

by secreting autoantibodies. When glycolysis was inhibited in vitro, differentiation of quiescent B cells into activated B cells was impaired [100]. Additionally, activated B cells switch from glycolysis to OXPHOS as they differentiate into plasmablasts [157].

Naïve B cells appear to rely heavily on fatty acid oxidation to generate ATP and are very minimally glycolytic [158]. When they become activated following interaction between antigen and B cell receptor (BCR), CD40 or interleukin-4 (IL-4) they undergo metabolic reprogramming to upregulate the energy production required to supply the new demand. They switch to and enhance aerobic glycolysis [99,101,159,160]. In fact, induction of this pathway is critical for antibody production [161]. One of the mechanisms is increased glucose uptake via augmented Glut1 expression [99].

B cell activating factor (BAFF), also known as B lymphocyte stimulator (BLyS), is essential for B cells' survival, growth, and eventual maturation. BAFF/BLyS utilizes the phosphatidyl inositol 3'OH kinase (PI3K) pathway and CD19 to accomplish its function [162–164]. BAFF/BLyS stimulation has been shown to increase glucose metabolism in B cells via PCKβ and Akt kinase activation [159,165]. B cells rely on the induction of HIF-1α and c-Myc transcription factors to upregulate glycolysis in a similar way to T cells [166,167]. Glycogen Synthase Kinase 3 (Gsk3), a metabolic checkpoint regulator, was also demonstrated to play a role in regulating glycolysis in B cells [168]. Similar to CD4 T cells, lupus plasmablasts [169] and B cells in general overexpress CD71 which is associated with nephritis and overall disease activity in SLE [170]. Along this line, mTOR activation also promotes the development and persistence of autoantibody-producing plasma cells in SLE [102].

6. Macrophages

Macrophages are also key players in the innate immune system and are remarkable phagocytic cells. They clear cellular debris, immune complexes, apoptotic cells and engulf bacteria, but they also have a role in wound healing and immune regulation [171]. Activated macrophages are sub-classified into M1 and M2 with distinct functions in an immune response. M1 are considered mostly pro-inflammatory and produce cytokines such as IL-6, IL-12, IFN-γ, TNF-α, and NO. [172,173] On the other hand, M2 carry anti-inflammatory functions and play a role in regenerating connective tissue during wound healing by producing vascular endothelial growth factor (VEGF), transforming growth factor (TGF)-β1 and IL-10 [173]. Activated M1 macrophages exhibit an enhanced glycolytic metabolism with increased Glut1 expression with simultaneous mitochondrial dysfunction and reduced OXPHOS [174–176]. These cells express a highly active isoform of phophofructokinase-2 (uPFK2) that enhances glycolysis [104]. TCA cycle in these activated macrophages is inhibited at isocitrate dehydrogenase (IDH2) with compensated increase in the aspartate-arginosuccinate shunt [177]. Accumulating citric acid from this break is then redirected to itaconic acid synthesis via IRG1, which has antimicrobial effects [178].TCA cycle is also fragmented at succinate dehydrogenase (SDH) leading to succinate accumulation [177].Accumulated succinate then stabilizes HIF-1α which in turn increases IL-1β production during an inflammatory response [179].

M1 macrophages upregulate the pentose phosphate pathway which provides NADPH for the neutralization of ROS and de novo synthesis of nitric oxide by downregulating the carbohydrate kinase-like protein (CARKL) [177,180]. The *car*bohydrate *k*inase-*l*ike protein CARKL, is rapidly downregulated in vitro and in vivo upon LPS stimulation in both mice and humans. Interestingly, CARKL catalyzes the phosphorylation of sedoheptulose to sedoheptulose 7-phosphate (S7P), a unique metabolite of the non-oxidative branch of the PPP. CARKL overexpression resulted in a severely blunted "proinflammatory" response. Specifically, IL-6, IL-1α, IL-1β, TNFα, TNFsf15, MIP1α (Ccl3), MCP1 (Ccl2), CxCL2, and the IL-13 receptor were repressed upon CARKL overexpression. In contrast, the "anti-inflammatory" associated constituents IL-10, macrophage migration inhibitory factor (MIF), and C—C motif cytokine 7

(Ccl7, MCP3), and IL-4R all showed exaggerated responses in the pCARKL cells after LPS. CARKL blocked M1 and promoted M2 polarization in RAW264.7 macrophage-like cells. The effect of CARKL on de novo NADPH production by the PPP was not conclusively determined.

Activated M2 macrophages exhibit decreased glycolytic activity and are more dependent on mitochondrial OXPHOS [177]. The decrease in aerobic glycolysis is due to expression of a less active isoform of phosphofructokinase-2 (PFKFB1) which has a higher bisphosphate activity than uPFK2 therefore it enhances break down of F-2,6-BP into fructose 6-monophoshate, decreasing glycolytic activity [104]. Glycolysis, however is required for M2 activation [181,182].

7. Neutrophils in SLE

Neutrophils has been implicated informing neutrophil extracellular traps or "netosis" during lupus pathogenesis [183]. Netosis has also been identified as a major source of circulating oxidized mtDNA that drives anti-DNA production and type I interferon production by pDCs [184]. In vivo treatment with the antioxidant mitoquinone has reduced netosis, anti-DNA production and nephritis in lupus-prone mice [185]. Patients that carry interferon regulatory factor 5 risk alleles also exhibit increased netosis, implying a bi-directional crosstalk between these two pro-inflammatory pathways in SLE [186]. The endoplasmic reticulum stress sensor inositol-requiring enzyme 1 α (IRE1α) has been implicated in mitochondrial oxidative stress and enhanced netosis by neutrophils in SLE [187]. Enhanced ferroptosis underlies neutropenia without affecting netosis in patients with SLE [188].

8. Mitochondrial dysfunction in end-organs

NAC has shown preliminary evidence of clinical efficacy in patient with SLE primarily reducing rash, arthritis and fatigue [98]. NAC also reduced anti-DNA antibody production, a major driver of nephritis in SLE [98]. Of note, NAC has shown efficacy in reducing anti-DNA autoantibody production and lupus nephritis in mice [189]. Clinical efficacy has occurred by reversing mitochondrial dysfunction via blocking ROS production [190] and mTOR activation in T cells [98]. Since mTOR is also activated in renal parenchymal and vascular endothelial cells, mTOR blockade may also exert therapeutic benefit by reducing end-organ damage [191].NAC alleviative ferroptosis via maintaining mitochondrial redox homeostasis through activating SIRT3-SOD2/Gpx4 pathway in diabetic nephropathy [192]. Reduction of ferroptosis may also be involved in reversing mitochondrial dysfunction in renal cells in SLE [193]. Genetic studies in lupus identified chromosomal loci affecting susceptibility to renal end-organ damage in SLE [194]. In particular, NLRP3 [195] and RIP3 genes have been so implicated in mitochondrial dysfunction [196] and renal injury in SLE [197,198].

The largest parenchymal organ, the liver also exhibits mitochondrial dysfunction within hepatocytes, which is responsive to mTOR blockade in patients [199] and mice with SLE [115]. Although the liver is also the largest metabolic organ, its involvement in immunopathogenesis of SLE in poorly understood. Given that the liver is the original source of both β2GP1, the initial target of anti-phospholipid antibody production, and paraoxonase 1 (PON1), the enzyme that prevents oxidization and autoantigenicity of β2GP1 [200] which PON1 is deficient in SLE patients which may play a central role in cardiovascular disease, liver injury, and aPL production in SLE [201]. As recently, uncovered diminished glycosylation and secretion of PON1 underlie aPL production and cirrhosis in TAL deficiency [38].

Neuroimaging has recently identified a loss of the mitochondrial translocator TSPO protein in SLE patients with cognitive impairment [202]. The accumulation of kynurenine has been associated with neurobehavioral abnormalities in mice [203] and in patients with SLE [204]. Kynurenine has been found the most potent metabolite capable of discriminating lupus from control metabolome [123,205]. Moreover, the accumulation of kynurenine in lupus lymphocytes was also found

more responsive to treatment with NAC over placebo [123]. Remarkably, NAC has improved cognitive dysfunction in patients with SLE in the context of a placebo-controlled clinical trial [98].

Lastly, but perhaps most importantly, non-lesional keratinocytes have been found to serve as sensors of ultraviolet light [206] and activators of IFN production, primarily IFN-kappa, in patients with SLE [207,208].

9. Conclusions

Metabolic pathways have been increasingly recognized as controllers of the development, lineage specification, and operation of the immune system on the molecular, cellular, and organismal levels, giving rise to a newly exploding field of immunometabolism. Elevation of the mitochondrial transmembrane potential or mitochondrial hyperpolarization (MHP) is a reversible checkpoint of physiological cellular activation that drives efficient ATP synthesis via oxidative phosphorylation. By contrast, lupus T cells exhibit persistent MHP which underlies diminished production of ATP, enhanced ROS production, and depletion of reduced glutathione (GSH) that characterize oxidative stress in SLE. These metabolic defects lead to the generation of highly reactive lipid hydroperoxides that spread oxidative stress through the bloodstream. The ensuing oxidization of DNA, proteins, and phospholipids generates neoepitopes that elicit autoantigenicity and trigger the production of antinuclear, antiphospholipid, and other autoantibodies. Increased ROS production also underlies the activation of the mechanistic target of rapamycin (mTOR), a sensor of metabolic stress and key checkpoint of proinflammatory lineage development in SLE. Along these lines, mTOR activation promotes glycolysis and metabolic flux through the pentose phosphate pathway in support of DNA synthesis and generation of the antioxidant pyridine nucleotide, NADPH. Importantly, MHP, GSH depletion, activation of mTOR and CAMK4, and enhanced glutamine, tryptophan, and glucose utilization have been identified as metabolic checkpoints of pathogenesis and promising targets of therapeutic intervention in SLE.

CRediT authorship contribution statement

Marlene Marte Furment: Data curation, Investigation, Writing – original draft. **Andras Perl:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

Data availability

No data was used for the research described in the article.

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