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Review

CD4$^+$ T cell metabolism, gut microbiota, and autoimmune diseases: implication in precision medicine of autoimmune diseases

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Abstract

CD4$^+$ T cells are critical to the development of autoimmune disorders. Glucose, fatty acids, and glutamine metabolisms are the primary metabolic pathways in immune cells, including CD4$^+$ T cells. The distinct metabolic programs in CD4$^+$ T cell subsets are recognized to reflect the bioenergetic requirements, which are compatible with their functional demands. Gut microbiota affects T cell responses by providing a series of antigens and metabolites. Accumulating data indicate that CD4$^+$ T cell metabolic pathways underlie aberrant T cell functions, thereby regulating the pathogenesis of autoimmune disorders, including inflammatory bowel diseases, systemic lupus erythematosus, and rheumatoid arthritis. Here, we summarize the current progress of CD4$^+$ T cell metabolic programs, gut microbiota regulation of T cell metabolism, and T cell metabolic adaptions to autoimmune disorders to shed light on potential metabolic therapeutics for autoimmune diseases.

Keywords: immunometabolism, gut microbiota, metabolic adaption, autoimmune disorders

Introduction

CD4$^+$ T cells play an essential role in the pathogenesis of autoimmune disorders. The aberrant CD4$^+$ T cell responses have been demonstrated in patients with autoimmune disorders, including inflammatory bowel diseases (IBD), [1] systemic lupus erythematosus (SLE),[2] and rheumatoid arthritis (RA).[3] Many studies have identified the importance of metabolic pathways in modulating T cell phenotypes and functions. For example, naïve CD4$^+$ T cells are maintained in a quiescent state, which requires a low amount of glucose and fatty acids for oxidative phosphorylation (OXPHOS), while aerobic glycolysis and glutaminolysis become the primary metabolic pathways in T cells once activated.[4] Gut microbiota, which emerges as an important regulator in human health and diseases, has a critical role in regulating T cell functions.[5] Gut microbiota modulates CD4$^+$ T cell metabolic profiles to regulate immune responses, especially through bacteria-derived metabolites.[6] T cell metabolic alteration has been linked with the pathogenesis of autoimmune disorders, and manipulation of metabolic pathways becomes the potential therapy for treating these diseases. In this review, we describe the distinct metabolic programs in different T cell subsets, provide evidence of T cell metabolism regulated by gut microbiota, explore the T cell metabolic abnormalities in autoimmune disorders, and discuss the rationale behind T cell metabolism-related approaches to treat autoimmune disorders.

CD4$^+$ T cell metabolism

Different nutrition, mainly glucose, lipids, and amino acids, provides energy for maintaining CD4$^+$ T cell survival and functions through distinct metabolic pathways (Fig. 1). Glycolysis is the process that breaks glucose into pyruvate by a series of enzymes in the cytoplasm. Subsequently, glucose-derived pyruvate can be either metabolized to lactate, which is excreted from the cell or converted to acetyl coenzyme A (acetyl-CoA), and enters the tricarboxylic acid (TCA) cycle to generate reducing equivalents (NADH and $FADH_2$) for OXPHOS by delivering electrons to the electron transport chain in mitochondria. Therefore, glucose provides energy to cells through both glycolysis and OXPHOS. Besides glucose, fatty acids and glutamine can also be metabolized to acetyl-CoA and α-ketoglutarate via fatty acid oxidation (β-oxidation) and glutaminolysis, respectively. These substrates are recruited to the TCA cycle and generate ATP through OXPHOS. In addition, β-oxidation also generates reducing equivalents, which can be oxidized by complex I of the electron transport chain. The intermediates of these metabolic pathways also serve as essential components for the biosynthesis of nucleotides, amino acids, and lipids, which support T cell proliferation and survival. However, the metabolic profiles in different CD4$^+$ T cell subsets are not identical, which are regulated by different factors (Fig. 2).

Naïve T cell metabolism

After development and maturation in the thymus, naïve CD4$^+$ T cells enter the circulation as quiescent cells.[7] Naïve T cells have low metabolic demands and use nutrition, primary glucose and fatty acids, to generate ATP through OXPHOS and β-oxidation.[8] The survival and homeostasis of naïve CD4$^+$ T cells are maintained by tonic T cell receptor (TCR) signaling,[9] IL-7,[10] and sphingosine 1-phosphate (S1P).[11] Tonic TCR signaling maintains T cell

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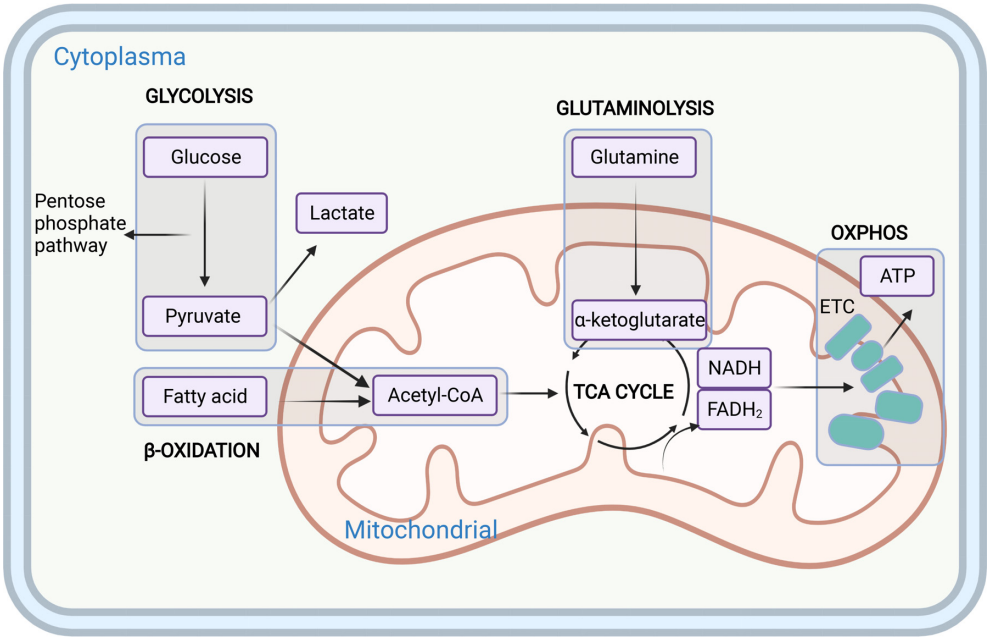

Figure 1. Key cellular metabolic pathways. Glucose, lipids, and amino acids provide major energy for maintaining CD4+ T cell survival and functions through distinct metabolic pathways. β-oxidation, fatty acid oxidation.

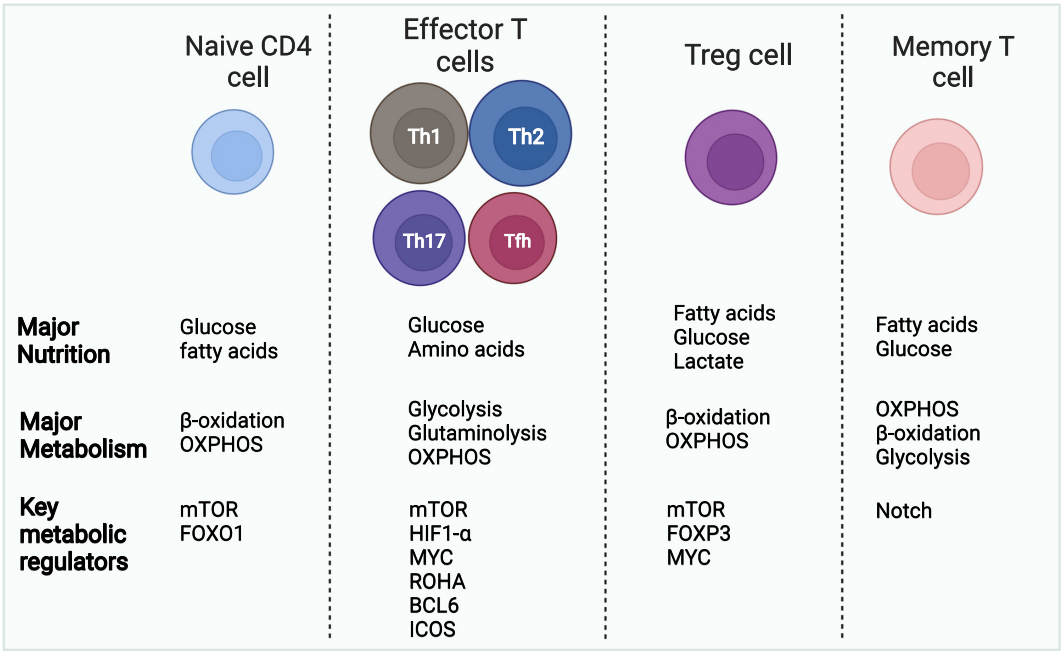

Figure 2. Distinct metabolic programs in CD4+ T cell subsets. Different CD4+ T cell subsets display different cellular metabolism, which is regulated by several key pathways. BCL6, B cell lymphoma 6; HIF1-α, Hypoxia-inducible factor 1 α; ICOS, inducible T cell costimulatory.

quiescence by controlling T cell metabolism,[12] and IL-7 signaling inhibits atrophy through upregulation of glucose metabolism.[13,14] S1P maintains mitochondrial function to suppress apoptosis in naïve T cells.[11]

The mechanistic target of rapamycin (mTOR), including mTOR complex 1 (mTORC1) and mTORC2, is critical in regulating T cell metabolism and responses.[15] mTORC1 is the central regulator of T cell quiescent homeostasis, which regulates glycolysis, lipid synthesis, and OXPHOS in T cells.[16] Loss of tuberous sclerosis complex 1 (TSC1), which negatively activates mTORC1, hyperactivates responses to the TCR pathway and decreases cell response to IL-7 signal, leading to abrogation of T cell quiescence.[17] Besides, forkhead box protein O1 (FOXO1), a transcription factor of naïve CD4+ T cells, is a downstream target of mTORC2 through activation of AKT, which is involved in regulating glycolysis through induction of glucose transporter 1 (GLUT1).[18] Therefore, suppressing the mTOR pathway is required for quiescence homeostasis in naïve CD4+ T cells.

Effector T cell metabolism

To obtain sufficient nutrition for the generation of building blocks required for the rapid proliferation and effector functions, CD4+ T cells undergo rapid metabolic reprogramming when activated by antigen-driven TCR stimulation and costimulatory signaling.[19,20] One of the most crucial pathways engaged in this process is phosphoinositide 3-kinase (PI3K)-AKT-mTOR signaling, which shifts the metabolic phenotype from OXPHOS and β-oxidation to anaerobic glycolysis and glutaminolysis for fueling the enhanced demands for biosynthesis.[21] Consistently, T cell activation increases the expression of nutrition transporters, e.g. glucose transporter GLUT1, glutamine transporters sodium-coupled neutral amino acid transporter (SNAT)1 and SNAT2, and alanine-, serine-, and cysteine-preferring transporter 2 (ASCT2), as well as the enzymes involved in glucose and glutamine metabolism.[22,23] In addition, activated T cells show increased mitochondrial mass and activity, facilitating the enhanced OXPHOS due to the elevated intermediates from glycolysis and glutaminolysis.[24–26]

CD4+ T cells differentiate into various effector T cells, mainly including helper T (Th)1, Th2, Th17, and follicular helper T (Tfh) cells.[27] The glycolytic activity is higher in effector T cells than in naïve T cells, promoting effector T cell expansion and functions.[28] In addition, glycolysis mediates effector T cell polarization. The rapid increase in GLUT1 induces effector T cell differentiation as evidenced by deficiency of GLUT1 leading to the decreased generation of Th1, Th2, and Th17 cells.[28] Although Tfh cells are less glycolytic than Th1 cells,[29] inhibition of glycolysis suppresses Tfh expression of IL-21, and GLUT1 promotes Tfh differentiation.[30] Deficiency in mTOR impairs Th1, Th2, and Th17 cell differentiation.[31] Specifically, mTOR1 regulates Th1 and Th17 differentiation, while Th2 generation is mTOR2 dependent.[32] Furthermore, the mTOR pathway promotes Tfh differentiation.[30] mTOR signaling serves as an indispensable factor in supporting glycolysis, thereby affecting effector T cell differentiation and functions.[33] However, the pathways for enhancing glycolysis are not identical among these effector T cell subsets. Hypoxia-inducible factor 1 α (HIF1-α), the downstream of mTOR, promotes glycolysis to induce and maintain Th17 cells,[34] but it negatively regulates Th1 function,[35] indicating other factors affect glycolysis in Th1 cells, such as MYC[19] and lactate dehydrogenase A.[36] The small GTPase RHOA couples glycolysis to Th2 differentiation.[37] B cell lymphoma 6 (BCL6), a key transcription factor for Tfh cells, has been found to suppress glycolysis.[29,38] However, Tfh cells highly express the costimulatory molecule, inducible T cell costimulatory (ICOS), which promotes glycolysis to enhance Tfh cell functions.[31]

The consumption of glutamine, a nonessential amino acid, is increased in activated CD4+ T cells, and MYC is indispensable for activation-induced glutaminolysis.[19] Glutamine regulates the balance of Th1 and regulatory T (Treg) cell differentiation, as evidenced by the depletion of glutamine, restricts Th1 cell differentiation, and promotes Treg development even under Th1 conditions through decreasing intracellular α-ketoglutarate.[39] Besides, glutamine deprivation does not affect GATA3 expression but increases T cell production of IL-4 under Th2 conditions.[39] The deficiency of glutamine also impairs Th17 development. Glutaminolysis induces Th17 differentiation by lowering N-glycan branching, which depends on the biosynthesis of UDP-GlcNAc via the hexosamine pathway.[40] The hexosamine pathway competes with glycolysis and glutaminolysis to use glucose and glutamine. In addition, inhibition of glutaminolysis reduces Tfh cells.[41] Interestingly, deficiency of glutaminase, which converts glutamine to glutamate, suppresses Th17 but promotes Th1 differentiation with no affecting Treg polarization,[42] indicating that modulation of glutaminolysis at different steps can result in different T cell phenotypes.

Regulatory T cell metabolism

Treg cells are critical in maintaining homeostasis by inhibiting excessive immune responses. As Treg functions are different from effector T cells, they have different metabolic features. Treg cells are less glycolytic and exhibit higher lipid oxidation rates than effector T cells.[43]

Foxp3, the key transcription factor for Treg cells, suppresses glycolysis through inhibition of PI3K-AKT-mTOR signaling[44,45] or suppression of MYC.[46] Glycolysis is required for Treg cell growth and proliferation, but it impairs Treg stability and suppressive functions.[47,48] However, the differentiation and suppressive functions of human Treg cells require glycolysis for regulating Foxp3 splicing variants containing exon 2 via the glycolytic enzyme enolase-1.[49] Besides, glycolysis supports Treg migration into inflammatory sites.[50] Therefore, glycolysis delicately controls Treg growth, proliferation, and functions. However, this regulation is not well understood. OXPHOS mediates Treg functions, whereas both pharmacological and genetic inhibition of OXPHOS impair Treg suppressive activity.[51,52] Treg cells mainly utilize fatty acids for generating energy through β-oxidation, TCA cycle, and OXPHOS, and β-oxidation inhibitor suppresses Treg functions.[43] In addition, acetyl-CoA converted from fatty acids via β-oxidation has been reported to enhance Treg stability.[53] mTOR regulates Treg metabolism, and inhibition of the mTOR pathway augments Treg population.[54,55] However, deficiency of mTORC1 signaling in Treg cells leads to a weaker suppressive activity through upregulation of cholesterol and lipid metabolism, while mTORC2 is dispensable for Treg suppressive function,[56] indicating that the roles of the mTOR pathway in Treg cells are complicated in different aspects.

According to the generation, function, and sites of Treg cells, Treg cells can be classified into different subsets, such as effector Treg cells and central Treg cells, which possess distinct metabolic features. Effector Treg cells take up more glucose and amino acids than central Treg cells, which are more metabolically quiescent.[57] Treg cells may have metabolic flexibility when they migrate to different tissue where the environmental nutrition is different. For example, in the tumor microenvironment, where lactic acid is enriched, Treg cells metabolize lactic acid instead of glucose to support their proliferation and function.[58]

CD4+ memory T cell metabolism

Memory (both CD4+ and CD8+) T (Tm) cells, integral to effective host immune responses, can rapidly transform from resting phenotypes to highly active effector T cells on antigen restimulation. There are a group of Tm cell subsets, mainly central Tm cells, effector Tm cells, and tissue-resident Tm cells. Tm cell growth and maintenance depend heavily on cellular metabolism. Various Tm cell subsets exhibit varying metabolic profiles.[59,60] Although CD8+ Tm cells mostly use fatty acids to generate energy via β-oxidation and OXPHOS, CD8+ effector Tm cells are less metabolically dependent on OXPHOS than CD8+ tissue-resident Tm cells and CD8+ central Tm cells.[61] However, metabolic features in CD4+ Tm cells are less investigated and need to be explored.

It has been reported that Notch signaling maintains CD4+ Tm cells through regulation of glucose uptake.[62] CD4+ effector memory T cells have higher OXPHOS than naïve T cells, which is

Table 1. Microbiota modulation of immunometabolism in CD4$^+$ T cells.

Microbiota/microbiota-derived metabolites	Changes in T cell metabolism	Effect on T cell function
Bifidobacterium	Mitochondrially mass ↑ Mitochondrial ROS ↑	Treg suppressive activity ↑
Pentanoate	Glucose oxidation ↑	IL-10 production in Th17 cells ↑
IsoalloLCA	OXPHOS ↑ Mitochondrial ROS ↑	Treg differentiation ↑

attributed to higher glycolytic capacity.[63] Increased spare respiratory capacity enables CD4$^+$ effector memory T cells to maintain survival and function under hypoxia conditions.[63] CD4$^+$ and CD8$^+$ Tm cells, predominantly tissue-resident Tm cells, are enriched in white adipose tissue where free fatty acids are released for substrates of β-oxidation.[60] The dependence of extracellular fatty acids is different in different tissues, indicating that the microenvironment affects the metabolic program in CD4$^+$ Tm cells.

Gut microbiota modulation of CD4$^+$ T cell responses and metabolism

Gut microbiota regulation of CD4$^+$ T cell responses

The role of intestinal microbiota in regulating host immunity, including CD4$^+$ T cell responses, has been extensively investigated.[64] The complex and dynamic interaction between gut microbiota and CD4$^+$ T cells shapes the immune responses during homeostasis and inflammation. Microbial antigens activate CD4$^+$ T cells, and diverse signals from the microbiome regulate CD4$^+$ T cell polarization and function differently. It has been reported that intestinal colonization of *Klebsiella aeromobilis* and *Klebsiella pneumoniae*, the human oral bacteria, drives colonic Th1 cell induction in mice.[65] The first known microorganism for producing Th17 cells in the mouse gut is segmented filamentous bacteria (SFB).[66] Later on, several microbes existing in the human gut have been found to trigger Th17 polarization, including *Bifidobacterium adolescentis*,[67] *Escherichia coli*,[68] and *Staphylococcus aureus*.[69] Besides, SFB has also been identified to promote Peyer's patch Tfh cells differentiation.[70] There are several Treg inducers found in the microbiota, in which *Clostridium* clusters IV and XIVa are the first described ones.[71] The surrounding microenvironment can also determine bacteria modulation of T cell fate. For example, mucosal-associated *Helicobacter* species increase Treg cells' frequency under homeostatic conditions and trigger effector T cells under intestinal inflammation.[72] In addition, commensal bacteria-specific memory CD4$^+$ T cells are present in both circulation and gut in healthy humans, which might support intestinal homeostasis.[73] Understanding individual microbiota regulation of T responses in different disease conditions is still in the early stages, which needs further investigation.

Besides providing Toll-like receptor ligands, microbiota affects CD4$^+$ T cells in many aspects via their metabolites[6]. One of the most investigated gut microbiota-derived metabolites, short chain fatty acids (SCFAs), mainly including acetate, propionate, and butyrate, are generated from undigested carbohydrates via gut microbiota, such as the *phylum* Bacteroidetes and *Firmicutes*. SCFAs induce Th1 cells[74] but suppress Th2 differentiation,[75] while SCFAs delicately regulate Th17 polarization in a context-dependent manner.[74,76] Besides, SCFAs also induce effector T cell production of IL-10 and IL-22,[77,78] key mediators in immune responses. Although no evidence demonstrates the direct roles of SCFAs in modulating Tfh cells, dietary fiber, which is the resource of SCFAs in the gut, has been reported to enhance Tfh cell responses.[79] Additionally, SCFAs promote peripheral and colonic Treg generation.[80–82] In addition to SCFAs, other microbiota-derived metabolites also mediate CD4$^+$ T cell responses, including secondary bile acids, bacterial tryptophan catabolites, and others.[6] Secondary bile acid lithocholic acid (LCA) derivatives, isoalloLCA and 3-oxoLCA induce Treg and suppress Th17 differentiation, respectively.[83] Besides, gut bile acid metabolites contribute to maintaining the colonic RORγt$^+$ Treg cells,[84] which mediate intestinal homeostasis. Indoles and indole derivatives, belonging to bacterial tryptophan catabolites, have been reported to induce Treg cells.[85,86] Readers can find a more detailed description and discussion on microbiota-derived metabolites regulation of T cell responses at different aspects in our previous review papers.[6,87,88]

Gut microbiota modulation of CD4$^+$ T cell metabolism

With the realization of the importance of immunometabolism, it is necessary to understand the role of microbiota in regulating CD4$^+$ T cell metabolism. A recent study demonstrated that colonization of *Bifidobacterium* in the intestine altered gut microbiota composition, which enhanced Treg suppressive function by promoting mitochondrial activity in Treg cells,[89] suggesting that gut microbiota contributes to T cell metabolic reprogramming. However, it is still unknown whether microbiota directly affects the CD4$^+$ T cell metabolic program (Table 1).

Most research exploring microbiota regulation of immunometabolism focuses on the importance of microbiota-derived metabolites.[90] For example, SCFAs increase mitochondrial mass and GLUT1 expression in CD8$^+$ T cells as SCFA serve as a substrate for β-oxidation.[91] In addition, SCFAs promote OXPHOS via β-oxidation and glutaminolysis instead of glycolysis in activated CD8$^+$ T cells, which is associated with differentiation into memory CD8$^+$ T cells.[92] However, the effect of dominant SCFAs, including acetate, propionate, and butyrate, on CD4$^+$ T cell metabolism has not been well investigated. Other groups and we have demonstrated that SCFAs induce CD4$^+$ T cell activation of mTOR to regulate T cell differentiation and cytokine production.[74,77,78] Besides, SCFAs promote CD4$^+$ T cell production of IL-22 through activation of HIF1-α.[78] Both mTOR and HIF1-α are key modulators in regulating T cell metabolic reprogramming, as we described and discussed above, suggesting that SCFAs affect CD4$^+$ T cell metabolism. A recent study revealed the direct effect of pentanoate, a subdominant type of SCFAs, on CD4$^+$ T cell metabolism.[93] Pentanoate enhances glycolysis in Th17 cells, and the suppression of glucose metabolism with 2-DG (2-deoxy-D-glucose) inhibits IL-10 production in Th17 cells, suggesting

Table 2. Manipulation of metabolic pathways in autoimmune diseases.

Drugs	Changes in metabolic pathways	Diseases	Human/mouse models	Effect
Oligomycin	OXPHOS ↓	IBD	TNBS	Colitis ↓
Rapamycin	mTORC1 ↓		TNBS	Colitis ↓
			$CD4^+$ T cell transfer model	Colitis ↓
			Refractory IBD patients	Colitis ↓
AZD8055	mTORC1/2 ↓		DSS	Colitis ↓
Metformin	Mitochondrial metabolism ↓	SLE	Lupus-prone B6.*Sle1.Sle2.Sle3* mice	Prevent disease development
2-DG	Glucose metabolism ↓		Lupus-prone B6.*Sle1.Sle2.Sle3* mice	Prevent disease development
Metformin and 2-DG	Mitochondrial metabolism ↓ Glucose metabolism ↓		Lupus-prone B6.*Sle1.Sle2.Sle3* mice	Reverse the disease symptoms
Bz-423	ATP synthase ↓		MRL-*lpr* mice	Disease ↓
BPTES	Glutaminolysis ↓		MRL-*lpr* mice	Disease ↓
Rapamycin	mTORC1 ↓		MRL-*lpr* mice	Disease ↓
			Clinical trial	Disease ↓
Menadione	ROS ↑	RA	Human synovium–NSG mice	Synovitis ↓
Buthionine sulfoximine	ROS ↑		Human synovium–NSG mice	Synovitis ↓
3-Bromopyruvate	Glycolysis ↓		K/BxN mice/SKG mice	Arthritis ↓
Rapamycin	mTORC1 ↓		Human synovium–NSG mice	Disease ↓

that glucose metabolism is involved in pentanoate induction of IL-10 production in Th17 cells.[93] Besides, pentanoate increases acetyl-CoA levels in Th17 cells. Treatment of dichloroacetate, which shifts glucose metabolism from glycolysis to pyruvate oxidation, leads to increased IL-10 production in Th17 cells,[93] indicating that glucose oxidation, instead of glycolysis, contributes to pentanoate induction of IL-10 in Th17 cells. In addition, trichostatin A (TSA), a pan-HDAC inhibitor, does not induce IL-10 production in Th17 cells,[93] further confirming that pentanoate regulates IL-10 expression through conversion into acetyl-CoA as the energy fuel but not by acting as an HDAC inhibitor. As the effects of different SCFAs on $CD4^+$ T cell functions are not identical, whether all the SCFAs regulate T cellular metabolism and whether such altered metabolism mediates T cell responses induced by SCFAs are still not completely understood.

Secondary bile acids also have been reported to regulate metabolic profiles in $CD4^+$ T cells. IsoalloLCA, a secondary bile acid, enhances OXPHOS in $CD4^+$ T cells, as evidenced by increased oxygen consumption, total mitochondrial mass, and mitochondrial membrane potential.[83] Furthermore, isoallaLCA promotes mitochondrial reactive oxygen species (ROS) but not cytoplasmic ROS.[83] Enhanced mitochondrial ROS mediates isolallaLCA induction of Treg cells.[83] However, other isomers of LCA have no impact on mitochondrial ROS in $CD4^+$ T cells,[83] indicating that different bile acids regulate immunometabolism in T cells differently.

Overall, further study is needed in $CD4^+$ T cell immunometabolism regulated by gut microbiota. Additionally, it is necessary to avoid generalizations and embrace the heterogeneity of microbiota in modulating T cell metabolism.

$CD4^+$ T cell metabolism in autoimmune diseases

Accumulating data have demonstrated that aberrant $CD4^+$ T cell responses contribute to the development of autoimmune diseases.[94] As described before, metabolic pathways are important in $CD4^+$ T cell functions. The microenvironment, including energy resources, is changed during inflammatory diseases, and, meanwhile, $CD4^+$ T cell metabolism is highly dynamic, and energy availability shapes the metabolic profiles.[95] Manipulation of metabolic pathways has been found to be beneficial or harmful for autoimmune diseases, including but not limited to IBD, SLE, and RA (Table 2).

Inflammatory bowel diseases

IBD is a chronic inflammatory intestinal disorder, which primarily includes Crohn's disease and ulcerative colitis. An imbalance between effector $CD4^+$ T cells and Treg cells contributes to the pathogenesis and development of IBD.

The link between cellular metabolic changes and IBD has been discovered in several studies. IBD patients display a higher level of plasma mitochondrial DNA, which is associated with the disease severity,[96] indicating that mitochondrial damage might mediate IBD development. Furthermore, genes related to OXPHOS are changed in paneth cells from pediatric patients with Crohn's disease, which is associated with gut microbiota.[97] However, the metabolic alteration in IBD $CD4^+$ T cells is not well-understood. Intestinal $CD3^+$ T cells from patients with ulcerative colitis exhibit a decreased expression of branched N-glycan, which shapes $CD4^+$ T cell responses.[98,99] N-glycan production depends on the hexosamine pathway, which competes with glycolysis and glutaminolysis for using glucose and glutamine,[40] so it is not hard to suppose that cellular metabolism is altered in $CD4^+$ T cells and plays a role in regulating the pathogenesis of IBD.

Increasing evidence suggests that controlling metabolism pathways that regulate $CD4^+$ T cell responses has a high potential for treating IBD patients. Deficiency of GLUT1, the major transporter of glucose, in $CD4^+$ T cells induces less severe colitis in *Rag1*$^{-/-}$ mice,[28] and GLUT1-overexpressed Treg cells fail to sufficiently reduce colitis in T cell transfer colitis model.[47]

High glucose diet has been reported to exacerbate colitis, in which gut microbiota plays critical roles.[100] Besides, mitochondrial ROS mediates high glucose induction of Th17 cells, which promotes intestinal inflammation.[101] Suppressing OXPHOS by oligomycin reduces colitis and intestinal Th17 cells in the 2,4,6-trinitrobenzenesulfonic acid (TNBS) model.[102] Blocking the mTOR pathway, the key regulator in cellular metabolism, has been reported to limit colitis. Rapamycin, specifically inhibiting mTORC1, decreases intestinal colitis in the TNBS model, which is related to the balance between Th17 and Treg cells in the intestine.[103] Rapamycin together with a synthetic peptide containing multiple flagellin T cell epitopes suppresses $CD4^+$ T cell-driven colitis.[104] Furthermore, the combination of T cell activation and metabolic checkpoint inhibition, targeting mTOR and AMPK by rapamycin and metformin, eliminates the circulating microbiota antigen-specific $CD4^+$ Tm cells.[105] It has been reported that rapamycin is potentially effective in treating refractory patients with Crohn's disease.[106,107] In addition, AZD8055, a dual mTORC1/2 inhibitor, also has benefits for treating colitis in the dextran sulfate sodium (DSS)-induced colitis model.[108]

Systemic lupus erythematosus

SLE, an autoimmune disorder, affects chronic inflammation in a variety of organs, including but not limited to skin, joints, kidneys, and blood vessels. The immune system in SLE patients mistakenly attacks its tissues, in which aberrant $CD4^+$ T cell responses are involved.[2]

Abnormalities in cellular metabolism have been found in both SLE patients[109–112] and experimental lupus models.[110,113,114] Splenocytes from NZB/W mice with lupus show enhanced glucose oxidation but a similar level of glycolysis compared with healthy control mice,[113] suggesting mitochondrial oxidative metabolism might mediate the immune responses in SLE. A more recent study further revealed that both glycolysis and mitochondrial oxidative metabolism are increased in $CD4^+$ T cells from lupus-prone B6.*Sle1*.*Sle2*.*Sle3* mice.[110] $CD4^+$ T cells from SLE patients exhibit enhanced glucose metabolism, including glycolysis and OXPHOS, which is associated with T cell activation status.[110] Besides, variants of ATP6 or F0F1-ATPase gene, the mitochondrial-related genes, are associated with human SLE.[112] Although the levels of β-oxidation and glutaminolysis in $CD4^+$ T cells from SLE are undetermined, altered lipid synthesis, specifically glycosphingolipids, has been found in $CD4^+$ T cells from SLE patients.[115] Overall, lupus $CD4^+$ T cells have unusually high oxidative stress, glycolysis, and lipid synthesis.

A number of studies have demonstrated that targeting $CD4^+$ T cell metabolism by several drugs is promising for SLE. The combination of metformin, a mitochondrial metabolism inhibitor, and 2-DG, a glucose metabolism inhibitor, normalizes T cell metabolism, and suppresses disease activity in lupus-prone B6.*Sle1*.*Sle2*.*Sle3* mice.[110,114] While either metformin or 2-DG can prevent disease development, combining these two drugs is necessary to reverse the disease symptoms in mice.[114] In addition, treatment of dichloroacetate, which favors pyruvate oxidation, does not affect the development of lupus in B6.*Sle1Sle2*.*Sle3* mice.[114] Bz-423, an ATP synthase inhibitor, ameliorates autoimmune symptoms, including glomerulonephritis and arthritis in MRL-*lpr* mice, which is associated with $CD4^+$ T cell responses.[116] Bis-2-(5-phenylacetamido-1,3,4-thiadiazol-2-yl)ethyl sulfide (BPTES), a selective inhibitor of Glutaminase 1, is involved in glutaminolysis. Treating T cells from SLE patients with BPTES suppresses Th17 polarization. Furthermore, treatment of BPTES decreases lupus-like disease in MRL-*lpr* mice.[117] Like cytotoxic T lymphocyte attenuator 4 (CTLA4) and programmed death 1 (PD1), B and T lymphocyte attenuator (BLTA) is an inhibitory receptor, which plays a critical role in dampening immune responses. It has been reported that deficiency of BLTA in MLP-*lpr* mice aggravates autoimmune disease,[118] and BLTA shows impaired capacity to inhibit the proliferation of $CD4^+$ T cells from SLE patients, which correlates with disease activity.[119] N-butyldeoxynojirimycin, which inhibits the synthesis of glycosphingolipids, can normalize lipid metabolism and restore BLTA functionality in $CD4^+$ T cells from SLE patients.[115,119] In addition, inhibiting mTOR signaling by rapamycin prevents the development of lupus in MLP-*lpr* mice.[120] Rapamycin normalizes mitochondrial hyperpolarization induced T cell hyperactivation in SLE patients and is useful for treating SLE patients, who are refractory to most traditional treatment, in a small group study.[121] In a recent clinical trial of 12 months of rapamycin in SLE patients, rapamycin is clinically efficacious in SLE patients.[122] The improvement in disease activity correlates with the correction of proinflammatory T cell subset specification.[122]

Rheumatoid arthritis

RA is an autoimmune disease that mostly affects the joints. The development of RA has been linked to immune cells, including innate and adaptive cells. Perpetual $CD4^+$ T cell responses activate macrophages and fibroblasts in the joint synovial tissues, which play a critical role in the pathogenesis of RA.[3]

Given the relationship between T cell function and metabolic program, it is no surprise that RA $CD4^+$ T cells have a different metabolic profile. A series of enzymes take participate in glucose use and determine the fate of glucose metabolism. $CD4^+$ T cells from RA patients are impaired in metabolizing glycose due to insufficient induction of 6-phosphofructo-2-kinase/fructose-2, 6-bis-phosphatase-3 (PFKFB3), a glycolytic rate-limiting enzyme[123]; meanwhile, glucose-6-phosphate dehydrogenase (G6PD), which shunts glucose and ATP production into the pentose phosphate pathway (PPP) pathway, is upregulated in RA $CD4^+$ T cells.[124] As a result, $CD4^+$ T cells from RA patients display a decreased glycolytic flux but produce more NADPH with the low cellular level of ROS and ATP.[123,124] RA $CD4^+$ T cells have age-impropriate erosion of telomeres, an indicator of cellular age, suggesting that RA $CD4^+$ T cells are prematurely old.[125] Growing evidence suggests that aging-related impaired T cell immunity may be attributed to mitochondrial disfunction.[126] $CD4^+$ T cells from RA patients have decreased expression of MRE11A, an exonuclease and endonuclease involved in nuclear and mitochondrial DNA repair, leading to leaked mitochondrial DNA into the cytoplasm and impaired mitochondrial oxidation.[127] Instead of using acetyl-CoA to generate ATP, mitochondrial malfunction results in an oversupply of intracellular acetyl-CoA, which promotes fatty acid synthesis.[128,129] The elevated PPP pathway also facilitates lipid synthesis and cytoplasmic lipid droplets by providing NADPH for biosynthesis in RA $CD4^+$ T cells.[129] Interestingly, not only fatty acid synthesis enzymes but also three of five genes related to β-oxidation are increased in RA T cells, indicating aberrant lipid metabolism in T cells from RA patients.[129] The glutaminolysis levels in RA T cells are not determined yet. In general, RA $CD4^+$ T cells switch from catabolic to the anabolic pattern, as demonstrated by decreased mitochondrial activity and glycolysis and enhanced lipid synthesis.

ROS regulates $CD4^+$ T cell differentiation, and a lower level of ROS in RA T cells leads to Th1 and Th17 polarization.[124]

Menadione, which increases ROS levels via redox cycling, inhibits RA T cells from differentiating Th1 cells *in vitro*.[124] In addition, the treatment of menadione suppresses synovitis in human synovium–NSG mice reconstituted with human RA T cells.[124] A similar effect has also been found when using buthionine sulfoximine, which raises ROS through the inhibition of glutathione.[124] Mirin, an MRE11A inhibitor, increases T cell recruitment in synovial tissue and upregulates proinflammatory cytokines in human synovium–NSG mice received healthy peripheral blood mononuclear cells (PBMCs). Besides, MRE11A-overexpressed RA PBMCs induce milder tissue inflammation in NSG mice compared with control RA PBMCs.[127] These indicate that drugs targeting mitochondrial DNA repair are promising for treating RA. Interestingly, although the glycolysis pathway is inhibited in RA $CD4^+$ T cells, several studies indicate that blocking glycolysis can reduce disease activity in animal arthritis models by impacting cells besides T cells. For example, inhibiting hexokinase-2 to reduce the first step in glycolysis by 3-bromopyruvate affects fibroblast-like synoviocytes[130] and T cell differentiation[131] and alleviates the development of arthritis in the K/BxN mice[130] and SKG mice.[131] In addition, mTORC1 is persistently activated in RA $CD4^+$ T cells, leading to proinflammatory Th1 and Th17 cells.[105] Blocking mTORC1 via rapamycin decreases T cell production of IFN-γ and reduces disease in human-synovium-NSG chimeras.[105]

Conclusion and future direction

The role of $CD4^+$ T cells in autoimmune diseases was highlighted a decade ago. Although the metabolism regulation of immune responses and diseases has been increasingly investigated recently, research on immunometabolism is still at an early stage. Here we described the key cellular metabolism in different $CD4^+$ T cell subsets and the key pathways involved in regulating T cell function (Figs. 1 and 2). Metabolic pathways are complicated and deliciated networks that are regulated in a context-dependent manner by a variety of factors, including cell status, locations, and disease conditions. Therefore, even the same $CD4^+$ T cell subsets show the different metabolic profiles under different conditions, for example, healthy control T cells versus RA T cells. Investigating the crucial factor(s) that control T cell metabolic fate is required.

Yet it is well-established that the mutual interaction between host and gut microbiota shapes the immune system; the studies on how the microbiota regulates cellular metabolism are scarce. This review summarized the progress related to microbiota and microbiota-derived metabolites regulation of $CD4^+$ T cell metabolism (Table 1). Of note, SCFAs and secondary bile acids modulate T cell responses by altering cellular metabolism; there remain several important questions. For example, whether all the SCFAs have the same effects on T cell metabolism? If not, which pathway(s) regulate the discrepancy? Why do other secondary acids not affect T cell ROS production? Besides SCFAs and secondary bile acids, whether and which microbiota-derived metabolites can affect the metabolism in $CD4^+$ T cells? Among these metabolites, which ones are the key regulators in regulating individual T cell subsets? Diet affects intestinal microbiota and human diseases,[132] and we recently found that GPR120, a receptor for long-chain fatty acids, promotes $CD4^+$ T cell IL-10 production partially through regulation of cellular metabolism.[133] Therefore, it is also essential to define the interplay among diet, microbiota, and T cell immunometabolism.

Manipulation of metabolic pathways by some drugs has been found to be beneficial in autoimmune diseases (Table 2). To better understand how these drugs work, it is needed to investigate the metabolic changes in immune cells from autoimmune disease patients, including but not limited to $CD4^+$ T cells. Although there are some same clinic features between SLE and RA, the metabolic profiles in T cells from SLE and RA patients are different. Therefore, the drugs are also not identical for potentially treating these diseases. Of note, inhibiting mTOR pathways is beneficial for all these three diseases. However, mTOR is also essential for cell functions. Therefore, it is important to investigate the optimized dose of mTOR inhibitors in treating different diseases at different stages. In addition, it is also necessary to find out the different mechanisms involved in the mTOR regulation of individual diseases, which helps discover new potential targets for diseases with fewer off-targets. The importance of microbiota in various autoimmune diseases has been well established; therefore, the next step is to understand the microbiota–immunemetabolism crosstalk in regulating autoimmune diseases.

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Author contributions

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Conflict of interest

None declared. In addition, as an Editorial Board Member of *Precision Clinical Medicine*, the corresponding author Yingzi Cong was blinded from reviewing or making decisions on this manuscript.

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