Journal of Inflammation Research

Dovepress
open access to scientific and medical research

Open Access Full Text Article

REVIEW

Glutaminolysis of CD4$^+$ T Cells: A Potential Therapeutic Target in Viral Diseases

Yushan Xu, Miaomiao Li, Mengjiao Lin, Dawei Cui, Jue Xie

Department of Blood Transfusion, The First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, Zhejiang, 310003, People's Republic of China

Correspondence: Jue Xie; Dawei Cui, Tel +86571-87236391; +86571-87236390, Email zyyyxj2011@zju.edu.cn; daweicui@zju.edu.cn

Abstract: CD4$^+$ T cells play a critical role in the pathogenesis of viral diseases, which are activated by the internal metabolic pathways encountering with viral antigens. Glutaminolysis converts glutamine into tricarboxylic acid (TCA) circulating metabolites by α-ketoglutaric acid, which is essential for the proliferation and differentiation of CD4$^+$ T cells and plays a central role in providing the energy and structural components needed for viral replication after the virus hijacks the host cell. Changes in glutaminolysis in CD4$^+$ T cells are accompanied by changes in the viral status of the host cell due to competition for glutamine between immune cells and host cells. More recently, attempts have been made to treat tumours, autoimmune diseases, and viral diseases by altering the breakdown of glutamine in T cells. In this review, we will discuss the current knowledge of glutaminolysis in the CD4$^+$ T cell subsets from viral diseases, not only increasing our understanding of immunometabolism but also providing a new perspective for therapeutic target in viral diseases.

Keywords: CD4$^+$ T cells, viral diseases, glutamine, glutaminolysis, immune response

Introduction

In viral diseases, metabolic reprogramming of the host's cell occurs in response to viral infection. First, the virus hijacks the metabolic pathways and protein synthesis mechanisms of host cells to provide the energy and viral structural components required for viral replication. Subsequently, in the maintenance of immune homeostasis and response to antigenic challenges, CD4$^+$ T cells and other immune cells undergo metabolic reprogramming to address the needs of clonal expansion, as well as cytokine synthesis and secretion.[1–3] Glutaminolysis is one of the most important hallmarks of metabolic reprogramming.[4,5] Several studies, including those on various tumours and Mycobacterium tuberculosis infections,[6–9] have reported that the immunomodulatory effects of glutaminolysis are driven by their impact on T cells, and glutaminolysis mediates viral latency or reactivation and alters viral susceptibility to host cells.[10,11] However, the mechanisms by which metabolic-mediated CD4$^+$ T cells influence virulence development are still poorly understood. Infectious viruses such as HIV, herpes and hepatitis remain major global public health concerns due to their latent or carcinogenic nature. Therefore, a better understanding of the biological regulation of glutaminolysis in CD4$^+$ T cells would provide new options for the treatment of viral diseases.

In this study, we summarize the understanding of glutaminolysis in host CD4$^+$ T cell subsets after viral infection and discuss potential therapeutic approaches that target glutaminolysis for patients affected by viral diseases.

Glutamine Metabolism

Glutamine (Gln) is the most abundant amino acid in the human body and is a nonessential amino acid, but it becomes "conditionally" essential in extreme catabolic conditions, such as cancer and inflammation.[12] Glutaminolysis is the process by which cells convert Gln to TCA cycle metabolites to support biosynthesis and provide energy for T cell activation through the activity of multiple enzymes.[12,13] Two key transporters for Gln uptake into cells are solute carrier family 1 member 5 (SLC1A5) and solute carrier family 7 member 5 (SLC7A5). SLC1A5 mediates the influx of Gln and

Received: 7 October 2023
Accepted: 13 January 2024
Published: 1 February 2024

is considered to be the primary transporter for Gln in CD4+ T cells.[12,14] SLC7A5 covalent binding with the solute carrier family 3 member 2 (SLC3A2) heavy chain and mediates intracellular exchange of Gln and essential amino acids (EAAs).[15] Cytoplasmic Gln is transported into the mitochondria via the SLC1A5 variant (var), a mitochondrial glutamine transporter. Next, Gln is converted into glutamate (Glu) by mitochondrial glutaminase (GLS). Glu is converted to α-Ketoglutaric acid (α-KG) in mitochondria by glutamate dehydrogenase 1 (GLUD1), glutamate oxaloacetic acid amino-transferase 2 (GOT2) and glutamate pyruvate aminotransferase 2 (GPT2) to α-KG, which subsequently participates in the TCA cycle, supporting the oxidative phosphorylation (OXPHOS) pathway and Adenosine 5'-triphosphate (ATP) generation.[16] Cytosolic glutamate is involved in the biosynthesis of glutathione (GSH) and non-essential amino acids and transported out of the cell via SLC7A11 (Figure 1). Glutaminolysis generates fuel to maintain the primary energy electron transport chain (ETC) and provide carbon to support redox homeostasis, and also produces citrate to safeguard lipid biosynthesis processes.[17] Gln plays an important role both in the process of viral infection and in the antiviral process of immune cells (Figure 1).

Glutaminolysis Determines Cytokine Signalling and T Helper Cell Subset Differentiation

Naïve $CD4^+$ T cells subsequently differentiate into various subtypes under the influence of various cytokines. Different $CD4^+$ T cell subsets often do not share the same metabolic program. Only when activated T cells induce the appropriate metabolic pathways can effector function and the ability to induce inflammatory disease in vivo be fully realized[13] (Figure 2). Gln has been reported to be essential for the biological process of differentiation and survival of $CD4^+$ T cells,[3] and even moderate reductions within the normal physiological range could impair T-cell function; moreover, other amino acids, including direct biosynthetic precursors, cannot substitute for glutamine.[18] The metabolites α-KG from glutaminolysis also influence mTOR pathway signalling and play an important role in histone and DNA

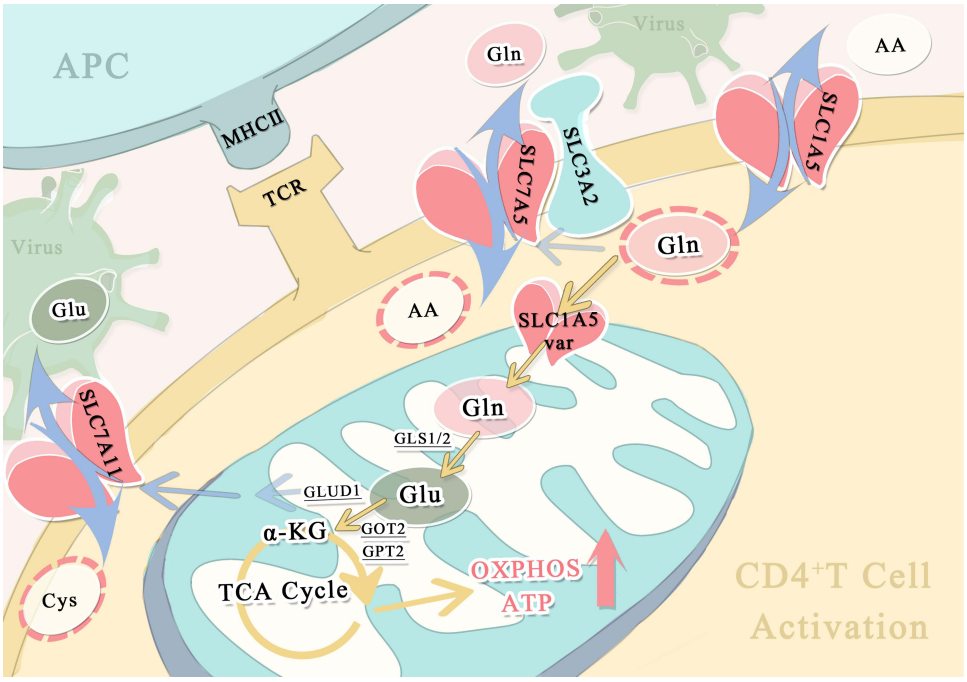

Figure 1 The biological process of glutamine metabolism in $CD4^+$ T cells. Glutamine enters the cytoplasm with the help of several membrane transport proteins. Intracellular glutamine is transported into the mitochondrial matrix via the SLC1A5 variant (var) and subsequently converted to glutamate with the help of GLS. Then, by catalysis of GLUD1 or several aminotransferases, Glu was converted to α-KG, then participates in the TCA cycle and supports the OXPHOS pathway, which provides energy for $CD4^+$ T cells activation and exerts antiviral functions.

Abbreviations: APC, antigen presenting cell; MHC-II, major histocompatibility complex-II; Gln, glutamine; GLS, glutaminases; Glu, glutamate; GLUD1, glutamate dehydrogenase 1; GOT2, glutamic-oxaloacetic transaminase 2; GPT2, glutamic-pyruvic transaminase 2; α-KG, alpha-ketoglutarate; Cys, cysteine; AA, Amino Acid; TCA cycle, tricarboxylic acid cycle; OXPHOS, oxidative phosphorylation; ATP, Adenosine 5'-triphosphate.

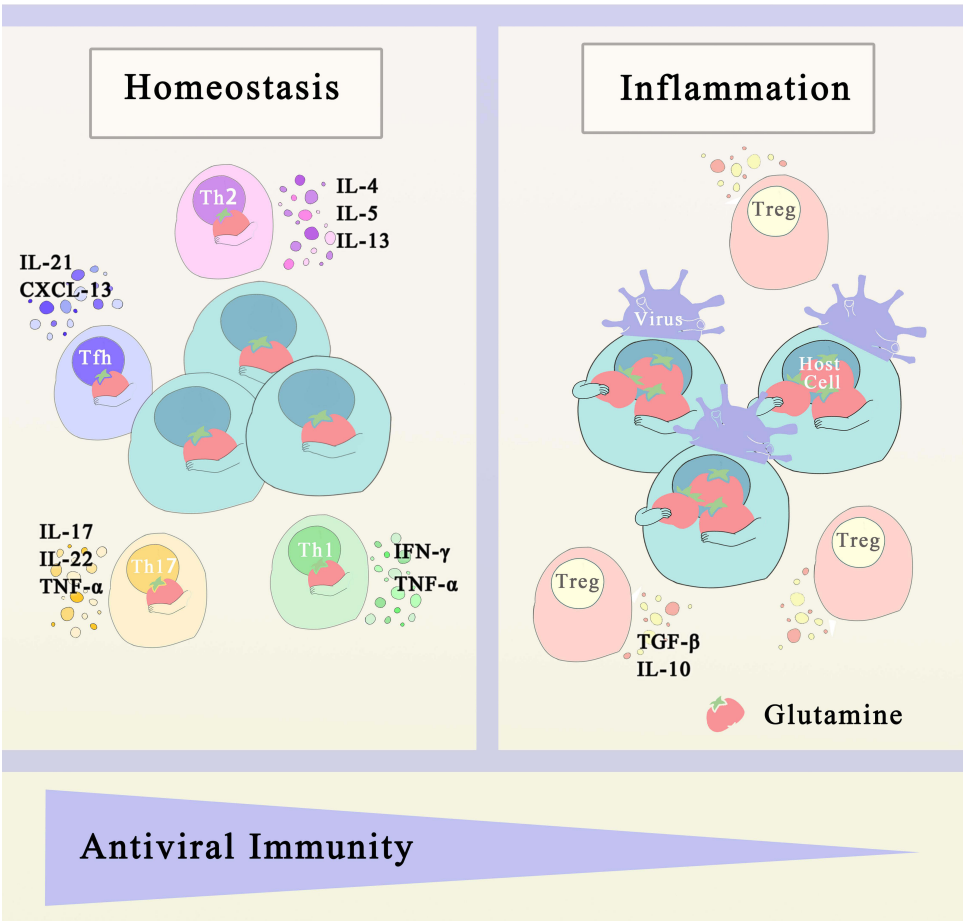

Figure 2 Glutaminolysis determines T helper cell subset differentiation and effects of viral infection on glutamine metabolism. The key cytokines are produced by $CD4^+$ T cells with different states. Following viral infection, the virus hijacks host cells for metabolic reprogramming, seizing more glutamine from the environment and forcing immune cells to convert to non-effector cells, resulting in reduced antiviral immunity.
Abbreviations: Th1, T helper 1; Th2, T helper 2; TFH, T follicular helper; Th17, T helper 17; Treg, regulatory T; CXCL-13, C-X-C motif ligand 13; TNF-α, Tumor necrosis factor-α; IFN-γ, Interferon -γ; TGF-β, Transforming growth factor-β.

methylation and affect chromatin status as a whole to determine gene expression and influence T-cell differentiation.[19] The importance of glutaminolysis for immune cell function has become apparent, we next summarize the current understanding of glutaminolysis in $CD4^+$ T cell subsets.

TFH Cells

$CD4^+$ T follicular helper (TFH) cells are a specialized subset of $CD4^+$ T cells that are localized in the germinal center region and stimulate B cells to produce long-lived and class-switched antibodies against pathogenic antigens. TFH cells are characterized by the expression of surface markers, such as programmed cell death protein 1 (PD-1), C-X-C Motif Chemokine Receptor 5 (CXCR5), inducible Co-Stimulator (ICOS), and the master transcriptional regulator BCL-6 (B-cell lymphoma 6 protein), and secrete effector cytokines, such as IL-21 (Interleukin 21) and CXCL-13 (C-X-C motif chemokine ligand 13) (Figure 2).

Glutamine is essential for TFH cells, especially those induced by exogenous antigens TFH.[12,20] Inhibition of glutaminolysis decreased the number of TFH cells in MRL/lpr mice (an autoimmune disease resembling systemic lupus erythematosus).[13] Positive correlation between SLC7A11 expression and TFH cells in liver hepatocellular carcinoma with poor survival.[17] However, glutaminolysis is utilised differently by TFH cells in the older adults. Sustained activation of the mechanistic target of mammalian target of rapamycin 1 (mTORC1), which depends on SLC7A5 as an amino acid source, leads to loss of cell differentiation, such as TFH and memory precursor cells, in the

$CD4^+$ T cell response of older adults.[21] Inhibition of SLC7A5 reduced mTORC1 activities in T cells from older individuals, which restored TFH generation in aged T cells.[18] SLC3A2 deficiency has been reported to reduce B-cell proliferation, plasma cells formation, and antibody production,[22] which may be related to TFH function.

Treg Cells

Regulatory T (Treg) cells, a subset of helper T cells, are pivotal in supporting immune tolerance and preventing autoimmunity.[23,24] Forkhead box protein P3 (Foxp3) is a master transcription factor for Tregs. Conventional $CD4^+$ T cells activated during immune responses may acquire Foxp3 expression under adequate conditions and become peripherally induced Treg (pTreg) cells, which can be further differentiated into peripherally induced Tregs (iTregs), IL-10-producing Tregs and TGF-β-producing Th3 cells[25,26] (Figure 2). And the level of self-reactivity is thought to support differentiation into thymus-derived Treg (tTreg) cells, which particularly important in the prevention of autoimmunity.[27] In tTreg cells, Foxp3 has been shown to be induced by strong TCR signals after the recognition of self-antigen–MHC complexes present on thymic antigen-presenting cells (APCs) with relatively high avidity. And glutamine deprivation, deletion of SLC1A5 or suppression of glutamate oxaloacetic acid aminotransferase 1 (GOT1) was shown to promote Foxp3 expression and Treg differentiation.[28–30] SlC3A2 is not involved in the Treg cell differentiation process but controls Treg cell functions, and the branched-chain amino acid (BCAA)/SLC3A2 axis might be useful for the treatment of autoimmune diseases with decreased numbers of Treg cells.[15,31] The Treg cell proliferative response was dependent on the induction of SLC7A11, whose expression was controlled by nuclear factor erythroid 2-related Factor 2 (NRF2).[32] Glutamine affects posttranslational modification after T cell receptor (TCR) activation by affecting substrate for the O-linked β-N-acetylglucosamine (O-GlcNAc)-mediated posttranslational modification levels, enhancing the stability and effector function of Treg lineages.[33] However, the increased level of glutamate in the tumour microenvironment (TME) promoted Treg infiltration and attenuated antitumour immunity.[34,35]

Th1 Cells

Th1 (T helper 1) cells are characterized by the release of interferon-γ (IFN-γ) and tumor necrosis factor-α(TNF-α), which stimulate innate immune cells, such as neutrophils and macrophages,[36,37] and intervene in cell-mediated immunity and delayed-type hypersensitivity reactions[38] (Figure 2).

Th1 cells are dependent on glutaminolysis for proliferation and survival. Glutaminolysis leads to the production of α-KG, which directs the expression of T-bet, which regulates Th1 cell differentiation.[29] IFN-γ production by Th1 T cells increases with the concentration of glutamine in a dose-dependent manner, indicating that Th1 differentiation is promoted by glutaminolysis at all glutamine concentrations. Inhibition of glutamine metabolism can decrease the proportion of Th1 cells in the spleen of B6 mice.[20] The absence of glutamine or deficiency of the glutamine transporter SLC1A5 prevented cytokine production and proliferation of both Th1 cells and instead promoted Treg generation.[28] SlC7A5-null $CD4^+$ T cells cannot respond to antigen receptor ligation and the appropriate polarizing cytokines to effectively produce Th1 or Th17 cells.[39] Slc3a2 deficiency in T cells impairs T-cell proliferation and Th1 and Th17 differentiation at the cell population level in mice.[40] The markers of Th1 cells, such as T-Box Transcription Factor 21 (TBX21), interleukin 12 receptor subunit beta 2 (IL12RB2), signal transducer and activator of transcription 1 (STAT1), and interferon gamma (IFNG), were strongly correlated with solute carrier family 7 member 11 (SLC7A11) expression.[41] In particular, glutaminase (GLS) deficiency selectively promotes Th1 cells while not affecting Tregs because Th1 cells can adapt to GLS inhibition and increase glucose uptake for anaplerotic reactions to maintain cell phenotypes.[16]

Th2 Cells

Th2 is mainly responsible for the host's defense against extracellular pathogens, producing IL-4, IL-5, and IL-13 that promote humoral immunity.[42] STAT6 activation by IL-4 results in the expression of the Th2 master transcription factor GATA3. And Th2 cells also play a crucial role in allergic responses, as they encourage B cell activation, differentiation, proliferation, and class switch recombination, leading to the production of allergen-specific IgE antibodies. Understanding the metabolic changes linked to Th2 differentiation and effector function may be beneficial in allergy treatment.[43,44]

In mice sensitized to Alternaria alternate extract, enhanced glutamine metabolism was observed in both Th2 and Th17 cells.[44] Inhibition of glutaminolysis reduces Th2 cytokine production and cell infiltration, enhances the conversion of naive $CD4^+$ T cells into regulatory T cells (Tregs). In breast cancer patients, according to The Cancer Genome Atlas (TCGA) plotter data, Th2 cells were strongly correlated with SLC7A family genes.[45] SLC7A5 inhibitor treatment suppressed allergen-induced skin inflammation in both ovalbumin (OVA)-immunized and OVA-specific Th2 cell-transferred mice and effectively suppressed allergen-induced airway and nasal hyperresponsiveness in immunized and/or Th2-transferred mice.[46–49]

It is noteworthy that in $CD4^+$ T cell differentiation models, glutamine restriction in the presence of all types of exogenous cytokine mixtures induces polarization toward Th2, whereas in the absence of Th2-induced cytokines, glutamine restriction promotes polarization toward Treg.[13] This model suggests that cytokine storm caused by viral infection may cause Th1 to tilt to Th2 phenotype when host cells ingest glutamine in large quantities.

Th17 Cells

T helper cell 17 (Th17) cells have been classified into pathogenic phenotypes associated with tissue inflammation and autoimmune disease and non-pathogenic phenotypes with immunomodulatory functions.[37,50,51] Pathogenic Th17 cells are characterized by the production of proinflammatory cytokines, including interleukin-17A (IL-17A), interleukin-17F (IL-17F), and interleukin 22 (IL-22)[52,53] (Figure 2). In contrast, nonpathogenic Th17 cells negatively regulate immune responses by secreting immunosuppressive factors, such as IL-10.[54] Metabolomic analysis showed that glutamine critically supports TCA cycling and bioenergetic activity in Oxidative phosphorylation (OXPHOS) TH17 cells.[55] Glutamine metabolism blockade inhibits the activation of mTOR signalling and suppresses the differentiation of Th1/Th17 cells,[56,57] and deficiency of the glutamine transporter Slc1a5 and inhibition of GOT1 both impair Th17 proliferation.[30] All these conditions simultaneously lead to enhanced Treg production. In contrast, deletion of GLS selectively impairs Th17 differentiation without affecting Tregs. SLC7A5 and SLC1A5 are positively (+) associated with the differentiation of Th17 cells,[58] the addition of excessive amounts of glutamine can rescue the defect of the SLC1A5 −/− T cells in differentiation into Th17 cells,[28] GLS promotes differentiation and immune function of Th17 cells,[16,59] and GLS inhibition may inhibit the activation of mTOR signalling and differentiation of T cells through suppressing the production of polyamines[60] or glutathione or downregulating Th17-promoting transcription factor, IL-2 release downstream of mTORC1 signal is reduced.[16] Increased reactive oxygen species (ROS) caused by GLS inhibition promote closed chromatin to prevent Th17 cell differentiation, which cannot be rescued by IL2, and its inhibition suppresses autoimmune disease in animals.[61,62]

$CD4^+$ T Cell Plasticity

Although cell plasticity has been found in almost all $CD4^+$ T cell subsets, Th17 cells are the most flexible in altering their phenotypes.[30,63,64] GLS deficiency impaired Th17 cells and promoted the transdifferentiation of Th17 cells into ex- Th17 TH1 cells, which is implicated in the pathogenicity of autoimmune diseases.[16,65,66] Manipulating the glutamate metabolic pathway could change Th17 cell fate by affecting methylation of the FOXP3 gene locus and ameliorate experimental autoimmune encephalomyelitis (EAE) in mice by regulating the Th17/iTreg balance.[30] Glutamine metabolism supports Th17 cell differentiation through the production of 2-hydroxyglutarate (2-HG), an intermediate of the TCA cycle.[67]

Overall, the metabolism of $CD4^+$ T cells and glutamine catabolism are interdependent and inseparable from each other. The discovery has made it possible to treat diseases by manipulating or targeting regulation of glutamine metabolism.

Glutaminolysis of $CD4^+$ T Cells as a Potential Antiviral Target

Metabolic reprogramming has proven to be critical in viral infections. Viruses impose metabolic reprogramming of the host cells to increase biomass to fuel viral genome replication and production of new virions.[14,68] Several studies have reported that viruses preferentially manipulate central carbon metabolism pathways in host cells to increase available energy by altering glycolysis and glutaminolysis.[69,70]

$CD4^+$ T cells participate in antiviral immunity mainly through the production of the cytokines IFN-γ and TNF and direct cytolytic effects.[71,72] On the one hand, competition for glutamine exists between immune cells and host cells,[73] and postinfection viral manipulation of host cells increases glutaminolysis, forcing immune cells to switch to noneffector

cells (Figure 2); at the same time, sustained activation of $CD4^+$ T cell checkpoint/suppressor receptor expression leads to effector cell exhaustion, weakening the immune response. On the other hand, uncontrolled immune cell homeostasis within the microenvironment after viral infection produces cytokine storms that adversely affect the organism. We selected three distinct diseases to understand the role of glutaminolysis in host cells and $CD4^+$ T cells under different viral infections that may provide better therapeutic targets for antiviral drugs (Table 1).[70]

Herpesvirus

Herpes viruses are double-stranded DNA viruses classified as alpha-, beta- and gamma-herpes viruses. Some herpes viruses have been directly linked to cancer. All herpes viruses contain two phases of the life cycle: latency and lytic replication.[74,75] Metabolic events during latency and lytic replication are certain to be different since latency involves minimal or even no synthesis of new viral proteins. Glutaminolysis can be a changing event, causing a latently infected cell to reenter the productive cycle.[76,77]

Herpesvirus infection increases glutaminolysis in host cells to supplement the TCA cycle, a hallmark of metabolic reprogramming. Increased glutamine anaplerosis and production of oxaloacetate by the TCA cycle were detected in herpes simplex virus-1 (HSV-1) infected cells;[78] at the same time, the decrease in viral replication associated with GLS inhibitors suggests that HSV-1 uses glutaminolysis in host cells to produce virions.[79,80] Similarly, Kaposi's Sarcoma-Associated Herpesvirus (KSHV) mediates host cell glutaminolysis to promote the proliferation of KSHV-transformed

Table 1 Effect of Glutamine Metabolism on Host Cells and CD4+ T Cells in Viral Infections

Virus	Effects on Host Cells	Effects on CD4+T Cell	Effects of Altering Glutamine Metabolism
Herpes viruses	Bringing latently infected cell to reenter the productive cycle; HSV-1 uses glutaminolysis in host cells to produce virions; Promote the proliferation of Kaposi's Sarcoma-Associated Herpesvirus (KSHV)-transformed cells	The response to latency-associated antigens becomes inhibitory to maintain latent viral carriage in vivo; TFH cells increase in number during the early phase of cytomegalovirus (CMV) infection; In severe herpes zoster patients, the proportion of CD4+ T cells were negatively correlated, while Tregs were positively correlated; In Epstein-Barr Virus (EBV) latent cells, inhibition of recognition and activation of EBV-specific CD4 cytotoxic T lymphocytes (CTLs) leads to EBV-associated malignancies	Increasing glutamine uptake by CD4+ T cells can alter CD4+ T cell subset differentiation and improve viral progression; Intraperitoneal administration of Gln and Leucine following mucosal infection with HSV-1 increased Th1-type CD4+ T cell activity and improved immune protection
HIV	Higher levels of metabolic activity are more susceptible to HIV infection; The early steps of HIV infection are supported by the entry of glutamine carbon into the TCA cycle; Upon entry into host cells, HIV replication further causes an increase in glutaminolysis, which promotes gene transcription and HIV replication, supporting completion of the HIV life cycle and facilitating latency	Proliferate poorly, low cytotoxicity and polyfunctionality; CD4+ T cell exhaustion	The use of mTOR inhibitors and related glutamine metabolic process inhibitors has been shown to inhibit the HIV-1 replication step of provirus establishment
Hepatitis virus	Cytokines and chemokines produced by hepatocytes after infection can affect the differentiation and function of lymphocytes; Glutamine anaplerosis are metabolic features of dysfunctional hepatocytes in patients with acute-on-chronic liver failure	The demand for glutamine by cells of the immune system and host cells, which together compete to cause glutamine deficiency; TGF-β secreted by HCV-infected hepatocytes recruits Treg to the inflamed liver, limiting the amplification of virus-specific T cell responses	Altering glutamine metabolism in hepatitis patients can alter the phenotype and function of CD4+ T cells, modulate cytokine differentiation and reverse T-cell exhaustion following hepatitis virus infection

cells, and profile analysis of high-throughput RNA sequencing has revealed that the expression levels of many enzymes (such as GLS2 and GOT2) in the glutamine pathway are upregulated by KSHV infection (Table 1).[81–84]

As there is competition for glutamine between immune and host cells, viral infection leads to an upregulation of glutamine catabolism in host cells, resulting in a downregulation of glutamine uptake by immune cells and causing changes in the distribution of $CD4^+$ T cell subtypes. The heterogeneity and potential functions of herpesvirus-reactivated $CD4^+$ T cell subsets isolated from human peripheral blood were analysed by single-cell RNA-seq and TCR sequencing. Th1 phenotype Tregs comprised the largest population of these reactivated cells, with expression of IFNG and TNF.[85] TFH cells increase in number during the early phase of cytomegalovirus (CMV) infection, resulting in a rise in neutralizing antibodies. Once the virus is cleared, TFH numbers decrease, but glycoprotein-specific TFH $CD4^+$ T cells are maintained over time.[86] In severe herpes zoster patients, the proportion of $CD4^+$ T cells from peripheral blood mononuclear cells (PBMCs) were negatively correlated, while Tregs were positively correlated.[87] Herpesvirus skews the $CD4^+$ T cell responses to latency-associated antigens following herpesvirus infection to one that is overall suppressive to sustain latent carriage in vivo (Table 1).[88,89]

However, when the subtype distribution of $CD4^+$ T cells changes, the latent or activated state of the virus also changes. Immune escape of CMV regulates IFN-γ by affecting the function of Th1.[90]

Interferon regulatory factor 1 (IRF-1) expressed by TFH cells controls chronic infection and reactivation of herpesviruses.[91] Half of the CMV-specific Th1, Th2, and Th17 cells are in a state of exhaustion that can be reverted by IL-7.[92] CMV reactivation drives posttransplant T-cell reconstitution, causes dramatic effector memory T-cell (Tem)-specific amplification and results in a linked contraction of all naive T cells.[93] Some of the above alterations in $CD4^+$ T cell subsets could account for pathogenesis changes, including contributing to neoplasia. In Epstein-Barr Virus (EBV) latent cells, inhibition of recognition and activation of EBV-specific CD4 cytotoxic T lymphocytes (CTLs) leads to EBV-associated malignancies, if induced to activate Th1 and/or Th2 cells that are cross-reactive to self-antigens, which would form an autoimmune disease.[94,95] Increasing glutamine uptake by $CD4^+$ T cells can alter $CD4^+$ T cell subset differentiation and improve viral progression. Intraperitoneal administration of Gln and Leucine following mucosal infection with HSV-1 increased Th1-type $CD4^+$ T cell activity and improved immune protection.[96] In another study in mice, glutamine acted through the T-cell-IFN-γ pathway to reduce HSV-1 reactivation (Table 1).[97]

HIV

Human immune deficiency virus (HIV) belongs to the retroviridae family and attacks the immune system by targeting $CD4^+$ T lymphocytes. Combination antiretroviral treatment (cART) blocks HIV replication but does not eliminate infected cells. Replication-competent HIV persists in cellular reservoirs that are the origin of rapid viral rebound when treatment is interrupted. The composition of $CD4^+$ T cells that remain infected is mainly determined by the susceptibility of $CD4^+$ T cell subsets to HIV infection, their resistance to HIV-induced apoptosis, and their lifespan and turnover potential.[98,99] $CD4^+$ T cells with higher levels of metabolic activity are more susceptible to HIV infection, independent of the type of $CD4^+$ T cell differentiation (Table 1).[98] Glutaminolysis is the major factor regulating human $CD4^+$ T cell proliferation and early steps in HIV infection.[10] The early steps of HIV infection are supported by the entry of glucose and glutamine carbon into the TCA cycle, respectively, glutamine catabolism is necessary for the induction of glucose transporter type 1 (GLUT1), and glutamine antagonists can reduce HIV infection without inducing cell death.[98,100] Upon entry into $CD4^+$ T cells, HIV replication further causes an increase in glutaminolysis, which promotes gene transcription and HIV replication, supporting completion of the HIV life cycle and facilitating latency.[101,102] With chronic antigen stimulation and the onset of T-cell exhaustion, the suppression of the glycolysis pathway ensues with reduced cellular glucose uptake and signs of dysregulated mitochondrial function.[103] T cells during untreated chronic infection proliferate poorly, have low cytotoxicity, and low polyfunctionality. Early initiation of cART results in rapid and near-complete normalization of T-cell subsets and preservation of T-cell function,[104,105] but epigenetic features of HIV-induced T-cell depletion persist.[106] T-cell function and exhaustion are intimately linked to metabolic changes within cells, and dysfunctional OXPHOS leads to increased ROS generation, which damages mitochondrial DNA, membrane lipids, and proteins. Furthermore, reduced levels of OXPHOS protein were associated with an increased frequency of $CD4^+$ T cell exhaustion.[107] The use of immune checkpoint inhibitors can rescue T cells from a state of failure, and partially mitigates the progression of cellular failure by enhancing OXPHOS, glycolysis, IL-2 signalling pathways and T-cell

effector functions. Combination therapy including metabolic and immune checkpoint inhibitors may be the solution to achieve HIV remission.[108,109] It is noteworthy that metabolic changes in T cells in HIV-infected individuals can influence HIV control. Elite HIV controllers represent <1% of people living with HIV/AIDS (PLWH) who can naturally suppress viral infection in the absence of cART, and also showed higher Th17 cell frequencies in the gut and peripheral blood.[110] In contrast to HIV progressors, elite HIV controllers showed intact mitochondrial function and greater metabolic plasticity of T cells, and the mTOR pathway was upregulated. mTOR signalling is regulated by glutaminolysis, the increased uptake of glutamine supplies key nucleotide precursors used by multiple mTOR-dependent rate-limiting nucleotide biosynthetic enzymes that facilitate the expansion of all deoxy-ribonucleoside triphosphate (dNTPs) necessary for reverse transcription.[111] The use of mTOR inhibitors and glutamine metabolism inhibitors has been shown to inhibit the HIV-1 replication step of provirus establishment,[112] and it also explores the administration of combination metabolic drugs during early-stage ART to help suppress residual HIV replication and "starving the HIV reservoir" in patients to potentially delay HIV rebound for more extended periods off ART (Table 1).[113]

Hepatitis Virus

The human liver is the target organ of five hepatotropic viruses, specifically hepatitis viruses A–E. Hepatitis B (HBV) or C (HCV) virus causes an acute-resolving infection in only a minority of patients, while the majority of those infected will develop a chronic infection.[114,115] Chronic viral hepatitis is a major global health problem because it can lead to progressive liver disease, including acute (including fulminant hepatic failure) to chronic hepatitis, cirrhosis, and hepatocellular carcinoma. Despite the availability of an effective prophylactic HBV vaccine, approximately 290 million people are chronically infected with HBV worldwide. Curative treatment for HBV does not exist.[116] In contrast, chronic HCV, which affects approximately 58 million people worldwide, is associated with advanced liver disease and can induce hepatocellular carcinoma, which causes many extrahepatic manifestations.[79,117,118]

In the hepatic microenvironment, hepatocytes interact with intrahepatic immune cells due to the open window structure of the hepatic sinusoids combined with the lack of basement membrane and low blood flow. Cytokines and chemokines produced by hepatocytes after infection can affect the differentiation and function of lymphocytes. In vitro hepatocyte cell lines are able to produce IL-7, IL-15, TGF-β, macrophage inflammatory protein-1 alpha (MIP-1α) and IL-8d following HCV infection.[119,120] Many of these cytokines and chemokines are important for the survival and differentiation of $CD4^+$ T cells; for example, TGF-β secreted by HCV-infected hepatocytes recruits Treg to the inflamed liver, antagonising effector $CD8^+$ T cells and thus limiting the amplification of virus-specific T cell responses (Table 1). On the other hand, the demand for glutamine by cells of the immune system and host cells, which together compete to cause glutamine deficiency in humans.[76] By analysing metabolomics data at different stages in patients with chronic hepatitis B (CHB), glutamine and glutamate metabolism and disorders of the tricarboxylic acid cycle were found to be influencing factors in the progression of patients with CHB.[77,121] Enhanced fatty acid oxidation (FAO) and glutamine anaplerosis are metabolic features of dysfunctional hepatocytes in patients with acute-on-chronic liver failure,[122] and high plasma levels of glutamine can be predictive of an unfavourable outcome in critically ill patients.[123] Unbalanced metabolism of amino acids plays an important role in the development and progression of hepatocellular carcinoma following hepatitis virus infection.[121] Glutamine metabolism in hepatocytes and/or intrahepatic immune cells may serve as a novel biomarker for diagnosis and prognosis, as well as a therapeutic target for screening viral hepatitis and different disease processes (Table 1).

Sustained expression of PD-1 on $CD4^+$ T cells in chronic HBV patients is accompanied by low expression of other inhibitory receptors, including cytotoxic T lymphocyte-associated antigen-4 (CTLA-4), TIM-3 and killer cell lectin-like receptor subfamily G member 1 (KLRG1).[124] PD-1 and CTLA-4 can regulate the expansion and restoration of HCV-specific $CD4^+$ T cells in patients with chronic HCV infection.[125] Neutralization of PD-L1/2 was able to improve the ability of $CD4^+$ T cells to produce Th1 cytokines, including IFN-γ, IL-2 and TNF-α, with enhanced T-cell proliferation in treated patients with successful viral control.[126] The glutamine metabolism inhibitor JHU083h was found to exhibit superior tumour growth inhibition in concert with PD-1 blockers. In an immune microenvironment where glutamine metabolism is blocked, cancer cell growth is inhibited, but $CD4^+$ T cell proliferation is enhanced.[117] This phenomenon is due to the presence of a flexible metabolic compensation mechanism in T cells, which is absent in tumour cells.[7] A sufficient number of immune cells is a prerequisite for the sustained action of PD-1 blockers. Thus, modulation of

glutamine metabolism may be a synergistic strategy for anti-hepatitis virus therapy because altering glutamine metabolism in hepatitis patients can alter the phenotype and function of $CD4^+$ T cells, modulate cytokine differentiation and reverse T-cell exhaustion following hepatitis virus infection (Table 1).

Here, we describe how glutaminolysis regulates the immune metabolism of CD4+T cell immune responses in different viral disease conditions (Figure 2). Metabolic pathways are complex and fine-grained networks, and the potential therapeutic effects of targeting this pathway are attracting increasing attention.

Development of Glutaminolysis-Related Drugs in Viral Diseases

The antiviral effect of glutamine catabolism against $CD4^+$ T cells is mainly in two aspects (Table 2). The first is to reduce the inflammatory response caused by the release of large amounts of cytokines in acute infections by downregulating glutamine catabolism. Glutamine blockade can be divided into glutamine uptake inhibitors, glutamine antagonists and glutaminase inhibitors. Extensive inhibition of glutamine metabolism by the drugs 6-diazo-5-oxo-L-leucine (DON), such as JHU083 and Sirpiglenastat (DRP-104), is heavily used in the treatment of solid tumours.[127,128] In viral diseases, treatment of nonfatal alphavirus encephalomyelitis infection in mice with DON reduced lymphocyte metabolism can reduce the inflammatory response caused by the release of large amounts of cytokines in acute infections by reducing $CD4^+$ Th1 and Th17 T cells, reducing the severity of acute stromal keratitis lesions and pathological angiogenesis in the corneas of HSV ocularly infected mice.[79] In another study, the novel glutamine inhibitor C19 was characterized by high-throughput screening. C19 inhibits GLS1 activity and reduces proliferation and cytokine secretion from activated $CD4^+$ T cells.[129] However, in the presence of latent infection, reduced levels of $CD4^+$ Th1 and Th17 T cells may mean that delayed reactivation of the virus may become more frequent.[130]

The second is to improve antiviral capacity in chronic infections by increasing glutamine metabolism in $CD4^+$ T cells (Table 2). On the one hand, glutamine supplementation may increase $CD4^+$ T cell proliferation and cytokine production following viral infection or vaccination.[131] Intraperitoneal injection of Gln showed enhanced protective immunity of Th1-type $CD4^+$ T cells against herpes simplex virus type 1 mucosal infection.[96] As previously shown, it may benefit the differentiation of proinflammatory $CD4^+$ T cell subtypes and modulate $CD4^+$ T cell plasticity. On the other hand, similar to the tumour environment, viruses replicate and proliferate heavily in host cells and, like tumour cells, reduce the anti-infective effects of glutamine-dependent $CD4^+$ T cells by competing for and depleting glutamine available to immune cells. It is known that a unique metabolic compensation mechanism exists in T cells and in a microenvironment where inhibition of glutamine metabolism leads to suppression of cancer cell growth without a compensatory mechanism,[117] and $CD4^+$ T cells maintain some proliferative efficiency through compensation.[7] T cells express very low levels of SLC7A11.[132] Furthermore, this transporter has been described to be nonfunctional in T cells.[133] In line with this, an approach to block SLC7A11 impairs glutamate/cystine exchange in tumour cells but has only a moderate influence on T-cell function.[134]

Table 2 Targets of Glutamine Metabolism in the Regulation of Viral Diseases

Process	Role	Category	Drugs	Target	Reference
Glutamine Blockade	Reduce the Inflammatory Response	Glutamine Uptake Inhibitors			
		Glutamine Antagonists	Drugs 6-diazo-5-oxo-L-leucine (DON)	Th1 ↓ Th17 ↓	1,19,120
		Glutaminase Inhibitors	C19	CD4+ T cells ↓	97
Glutamine Supplementation in CD4+ T cells	Improve Antiviral Capacity	Intraperitoneal injection of Gln		Th1 ↑	86
		Glutamine Supplementation		CD4+ T cells↑	122
Improving the Metabolic Competition of CD4+ T cells	Improve Anti-infective Effects of Glutamine-dependent CD4+ T cells		Block SLC7A11	CD4+ T cells↑	23,124

Notes: ↓ Reduced number. ↑ Increased number.

Therefore, using this mechanism to specifically inhibit glutamine catabolism in host cells would provide a new mechanism for $CD4^+$ T cells to provide new insights into the antiviral mechanisms of $CD4^+$ T cells.

Conclusions and Future Perspectives

Viral infections and transmission remain a major global health problem that can lead to chronic, latent and even fatal consequences, although the current development of antiviral drugs and vaccines has improved the survival rate of viral infections. The increased demand for glutamine by $CD4^+$ T cells to perform their immune functions coincides with the high utilization of glutamine by host cells in patients with viral infections (Figure 2), and this competitive relationship suggests that the use of glutaminolysis for the diagnosis and treatment of viral diseases is an area for future research (Table 2). However, the development of antiviral drugs that modulate glutamine metabolism must balance the various demands on glutamine metabolism by different components of the immune system, and the methods to precisely promote/inhibit glutamine catabolism in different cell types remain to be investigated.

Data Sharing Statement

Enquiries about data availability should be directed to the corresponding author.

Acknowledgments

Thanks for the reviewers for their helpful comments on this paper, and thank American Journal Experts (AJE) for English language editing.

Funding

This research was supported by Zhejiang Provincial Key Research and Development Program grant number 2020C03032, Zhejiang Provincial Natural Science Foundation of China grant number LQ20H080002, and the National Natural Science Foundation of China grant number 82172335, 81971994, 81871709 and 91846103.

Disclosure

The authors have no relevant financial or non-financial interests to disclose in this work.

References

1. Wik JA, Skålhegg BS. T cell metabolism in infection. *Front Immunol*. 2022;13:840610. doi:10.3389/fimmu.2022.840610
2. Yu W, Li C, Zhang D, et al. Advances in T cells based on inflammation in metabolic diseases. *Cells*. 2022;11(22):3554. doi:10.3390/cells11223554
3. Feng X, Li X, Liu N, Hou N, Sun X, Liu Y. Glutaminolysis and CD4(+) T-cell metabolism in autoimmunity: from pathogenesis to therapy prospects. *Front Immunol*. 2022;13:986847. doi:10.3389/fimmu.2022.986847
4. Kono M. New insights into the metabolism of Th17 cells. *Immunol Med*. 2023;46(1):15–24. doi:10.1080/25785826.2022.2140503
5. Yang X, Xia R, Yue C, et al. ATF4 regulates CD4(+) T cell immune responses through metabolic reprogramming. *Cell Rep*. 2018;23(6):1754–1766. doi:10.1016/j.celrep.2018.04.032
6. Parveen S, Shen J, Lun S, et al. Glutamine metabolism inhibition has dual immunomodulatory and antibacterial activities against Mycobacterium tuberculosis. *bioRxiv*. 2023. doi:10.1101/2023.02.23.529704
7. Leone RD, Zhao L, Englert JM, et al. Glutamine blockade induces divergent metabolic programs to overcome tumor immune evasion. *Science*. 2019;366(6468):1013–1021. doi:10.1126/science.aav2588
8. Oh MH, Sun IH, Zhao L, et al. Targeting glutamine metabolism enhances tumor-specific immunity by modulating suppressive myeloid cells. *J Clin Invest*. 2020;130(7):3865–3884. doi:10.1172/JCI131859
9. Parveen S, Shen J, Lun S, et al. Glutamine metabolism inhibition has dual immunomodulatory and antibacterial activities against Mycobacterium tuberculosis. *Nat Commun*. 2023;14(1):7427. doi:10.1038/s41467-023-43304-0
10. Clerc I, Moussa DA, Vahlas Z, et al. Entry of glucose- and glutamine-derived carbons into the citric acid cycle supports early steps of HIV-1 infection in CD4 T cells. *Nat Metab*. 2019;1(7):717–730. doi:10.1038/s42255-019-0084-1
11. Loucif H, Dagenais-Lussier X, Avizonis D, et al. Autophagy-dependent glutaminolysis drives superior IL21 production in HIV-1-specific CD4 T cells. *Autophagy*. 2022;18(6):1256–1273. doi:10.1080/15548627.2021.1972403
12. Chakraborty S, Khamaru P, Bhattacharyya A. Regulation of immune cell metabolism in health and disease: special focus on T and B cell subsets. *Cell Biol Int*. 2022;46(11):1729–1746. doi:10.1002/cbin.11867
13. Zhang X, Wang G, Bi Y, Jiang Z, Wang X. Inhibition of glutaminolysis ameliorates lupus by regulating T and B cell subsets and downregulating the mTOR/P70S6K/4EBP1 and NLRP3/caspase-1/IL-1β pathways in MRL/lpr mice. *Int Immunopharmacol*. 2022;112:109133. doi:10.1016/j.intimp.2022.109133

14. Zhao X, Petrashen AP, Sanders JA, Peterson AL, Sedivy JM. SLC1A5 glutamine transporter is a target of MYC and mediates reduced mTORC1 signaling and increased fatty acid oxidation in long-lived Myc hypomorphic mice. *Aging Cell*. 2019;18(3):e12947. doi:10.1111/acel.12947
15. Ikeda K, Kinoshita M, Kayama H, et al. Slc3a2 mediates branched-chain amino-acid-dependent maintenance of regulatory T cells. *Cell Rep*. 2017;21(7):1824–1838. doi:10.1016/j.celrep.2017.10.082
16. Johnson MO, Wolf MM, Madden MZ, et al. Distinct regulation of Th17 and Th1 cell differentiation by glutaminase-dependent metabolism. *Cell*. 2018;175(7):1780–95.e19. doi:10.1016/j.cell.2018.10.001
17. Liang Y, Su S, Lun Z, et al. Ferroptosis regulator SLC7A11 is a prognostic marker and correlated with PD-L1 and immune cell infiltration in liver hepatocellular carcinoma. *Front Mol Biosci*. 2022;9:1012505. doi:10.3389/fmolb.2022.1012505
18. Jin J, Kim C, Xia Q, et al. Activation of mTORC1 at late endosomes misdirects T cell fate decision in older individuals. *Sci Immunol*. 2021;6(60). doi:10.1126/sciimmunol.abg0791
19. Tajima M, Strober W. Evaluation of Glutaminolysis in T Cells. *Current Protocols*. 2022;2(9):e540. doi:10.1002/cpz1.540
20. Choi SC, Titov AA, Abboud G, et al. Inhibition of glucose metabolism selectively targets autoreactive follicular helper T cells. *Nat Commun*. 2018;9(1):4369. doi:10.1038/s41467-018-06686-0
21. Kim C, Hu B, Jadhav RR, et al. Activation of miR-21-regulated pathways in immune aging selects against signatures characteristic of memory T cells. *Cell Rep*. 2018;25(8):2148–62.e5. doi:10.1016/j.celrep.2018.10.074
22. Cantor J, Browne CD, Ruppert R, et al. CD98hc facilitates B cell proliferation and adaptive humoral immunity. *Nat Immunol*. 2009;10(4):412–419. doi:10.1038/ni.1712
23. Bednar KJ, Lee JH, Ort T. Tregs in autoimmunity: insights into intrinsic brake mechanism driving pathogenesis and immune homeostasis. *Front Immunol*. 2022;13:932485. doi:10.3389/fimmu.2022.932485
24. Sakaguchi S, Yamaguchi T, Nomura T, Ono M. Regulatory T cells and immune tolerance. *Cell*. 2008;133(5):775–787. doi:10.1016/j.cell.2008.05.009
25. Lee J, Kim D, Min B. Tissue Resident Foxp3(+) regulatory T cells: sentinels and saboteurs in health and disease. *Front Immunol*. 2022;13:865593. doi:10.3389/fimmu.2022.865593
26. Kanamori M, Nakatsukasa H, Okada M, Lu Q, Yoshimura A. Induced regulatory T cells: their development, stability, and applications. *Trends Immunol*. 2016;37(11):803–811. doi:10.1016/j.it.2016.08.012
27. Shevach EM, Thornton AM. tTregs, pTregs, and iTregs: similarities and differences. *Immunol Rev*. 2014;259(1):88–102. doi:10.1111/imr.12160
28. Nakaya M, Xiao Y, Zhou X, et al. Inflammatory T cell responses rely on amino acid transporter ASCT2 facilitation of glutamine uptake and mTORC1 kinase activation. *Immunity*. 2014;40(5):692–705. doi:10.1016/j.immuni.2014.04.007
29. Klysz D, Tai X, Robert PA, et al. Glutamine-dependent α-ketoglutarate production regulates the balance between T helper 1 cell and regulatory T cell generation. *Sci Signaling*. 2015;8(396):ra97. doi:10.1126/scisignal.aab2610
30. Xu T, Stewart KM, Wang X, et al. Metabolic control of T(H)17 and induced T(reg) cell balance by an epigenetic mechanism. *Nature*. 2017;548(7666):228–233. doi:10.1038/nature23475
31. Carbone F, De Rosa V, Carrieri PB, et al. Regulatory T cell proliferative potential is impaired in human autoimmune disease. *Nature Med*. 2014;20(1):69–74. doi:10.1038/nm.3411
32. Procaccini C, Garavelli S, Carbone F, et al. Signals of pseudo-starvation unveil the amino acid transporter SLC7A11 as key determinant in the control of Treg cell proliferative potential. *Immunity*. 2021;54(7):1543–60.e6. doi:10.1016/j.immuni.2021.04.014
33. Liu B, Salgado OC, Singh S, et al. The lineage stability and suppressive program of regulatory T cells require protein O-GlcNAcylation. *Nat Commun*. 2019;10(1):354. doi:10.1038/s41467-019-08300-3
34. Long Y, Tao H, Karachi A, et al. Dysregulation of glutamate transport enhances treg function that promotes VEGF blockade resistance in glioblastoma. *Cancer Res*. 2020;80(3):499–509. doi:10.1158/0008-5472.CAN-19-1577
35. Valvo V, Parietti E, Deans K, et al. High-throughput in situ perturbation of metabolite levels in the tumor micro-environment reveals favorable metabolic condition for increased fitness of infiltrated T-cells. *Front Cell Develop Biol*. 2022;10:1032360. doi:10.3389/fcell.2022.1032360
36. Raphael I, Nalawade S, Eagar TN, Forsthuber TG. T cell subsets and their signature cytokines in autoimmune and inflammatory diseases. *Cytokine*. 2015;74(1):5–17. doi:10.1016/j.cyto.2014.09.011
37. Gomez-Bris R, Saez A, Herrero-Fernandez B, Rius C, Sanchez-Martinez H, Gonzalez-Granado JM. CD4 T-cell subsets and the pathophysiology of inflammatory bowel disease. *Int J Mol Sci*. 2023;24(3):2696. doi:10.3390/ijms24032696
38. Wang P, Zhang Q, Tan L, Xu Y, Xie X, Zhao Y. The regulatory effects of mTOR complexes in the differentiation and function of CD4(+) T cell subsets. *J Immunol Res*. 2020;2020:3406032. doi:10.1155/2020/3406032
39. Sinclair LV, Rolf J, Emslie E, Shi YB, Taylor PM, Cantrell DA. Control of amino-acid transport by antigen receptors coordinates the metabolic reprogramming essential for T cell differentiation. *Nat Immunol*. 2013;14(5):500–508. doi:10.1038/ni.2556
40. Kurihara T, Arimochi H, Bhuyan ZA, et al. CD98 heavy chain is a potent positive regulator of CD4+ T cell proliferation and interferon-γ production in vivo. *PLoS One*. 2015;10(10):e0139692. doi:10.1371/journal.pone.0139692
41. Cheng X, Wang Y, Liu L, Lv C, Liu C, Xu J. SLC7A11, a potential therapeutic target through induced ferroptosis in colon adenocarcinoma. *Front Mol Biosci*. 2022;9:889688. doi:10.3389/fmolb.2022.889688
42. Yeh CL, Su LH, Wu JM, et al. Effects of the glutamine administration on T helper cell regulation and inflammatory response in obese mice complicated with polymicrobial sepsis. *Mediators Inflammation*. 2020;2020:8869017. doi:10.1155/2020/8869017
43. Goretzki A, Zimmermann J, Rainer H, Lin YJ, Schülke S. Immune metabolism in TH2 responses: new opportunities to improve allergy treatment - disease-specific findings (Part 1). *Curr Allergy Asthma Rep*. 2023;23(1):29–40. doi:10.1007/s11882-022-01057-8
44. Lin YJ, Goretzki A, Rainer H, Zimmermann J, Schülke S. Immune metabolism in TH2 responses: new opportunities to improve allergy treatment - cell type-specific findings (Part 2). *Curr Allergy Asthma Rep*. 2023;23(1):41–52. doi:10.1007/s11882-022-01058-7
45. Yan L, He J, Liao X, et al. A comprehensive analysis of the diagnostic and prognostic value associated with the SLC7A family members in breast cancer. *Gland Surg*. 2022;11(2):389–411. doi:10.21037/gs-21-909
46. Hayashi K, Kaminuma O, Nishimura T, et al. LAT1-specific inhibitor is effective against T cell-mediated allergic skin inflammation. *Allergy*. 2020;75(2):463–467. doi:10.1111/all.14019

47. Hayashi K, Kaminuma O. Therapeutic potential for intractable asthma by targeting L-type amino acid transporter 1. *Biomolecules*. 2022;12 (4):553. doi:10.3390/biom12040553
48. Kaminuma O, Nishimura T, Saeki M, et al. L-type amino acid transporter 1 (LAT1)-specific inhibitor is effective against T cell-mediated nasal hyperresponsiveness. *Allergol Int*. 2020;69(3):455–458. doi:10.1016/j.alit.2019.12.006
49. Ito D, Miura K, Saeki M, et al. L-type amino acid transporter 1 inhibitor suppresses murine Th2 cell-mediated bronchial hyperresponsiveness independently of eosinophil accumulation. *Asia Pac Allergy*. 2021;11(3):e33. doi:10.5415/apallergy.2021.11.e33
50. Omenetti S, Bussi C, Metidji A, et al. The intestine harbors functionally distinct homeostatic tissue-resident and inflammatory Th17 cells. *Immunity*. 2019;51(1):77–89.e6. doi:10.1016/j.immuni.2019.05.004
51. Wu X, Tian J, Wang S. Insight into non-pathogenic Th17 cells in autoimmune diseases. *Front Immunol*. 2018;9:1112. doi:10.3389/fimmu.2018.01112
52. Ghoreschi K, Laurence A, Yang XP, et al. Generation of pathogenic T(H)17 cells in the absence of TGF-β signalling. *Nature*. 2010;467 (7318):7318):967–71. doi:10.1038/nature09447
53. Lee Y, Awasthi A, Yosef N, et al. Induction and molecular signature of pathogenic TH17 cells. *Nat Immunol*. 2012;13(10):991–999. doi:10.1038/ni.2416
54. Esplugues E, Huber S, Gagliani N, et al. Control of TH17 cells occurs in the small intestine. *Nature*. 2011;475(7357):7357):514–8. doi:10.1038/nature10228
55. Hong HS, Mbah NE, Shan M, et al. OXPHOS promotes apoptotic resistance and cellular persistence in T(H)17 cells in the periphery and tumor microenvironment. *Sci Immunol*. 2022;7(77):eabm8182. doi:10.1126/sciimmunol.abm8182
56. Yu Q, Tu H, Yin X, et al. Targeting glutamine metabolism ameliorates autoimmune hepatitis via inhibiting T cell activation and differentiation. *Front Immunol*. 2022;13:880262. doi:10.3389/fimmu.2022.880262
57. Xia X, Cao G, Sun G, et al. GLS1-mediated glutaminolysis unbridled by MALT1 protease promotes psoriasis pathogenesis. *J Clin Invest*. 2020;130(10):5180–5196. doi:10.1172/JCI129269
58. Ren W, Liu G, Yin J, et al. Amino-acid transporters in T-cell activation and differentiation. *Cell Death Dis*. 2017;8(3):e2655.
59. Kono M, Yoshida N, Maeda K, Tsokos GC. Transcriptional factor ICER promotes glutaminolysis and the generation of Th17 cells. *Proc Natl Acad Sci USA*. 2018;115(10):2478–2483. doi:10.1073/pnas.1714717115
60. Zhang J, Zhao L, Wang J, et al. Targeting mechanistic target of rapamycin complex 1 restricts proinflammatory T cell differentiation and ameliorates takayasu arteritis. *Arthritis Rheumatol*. 2020;72(2):303–315. doi:10.1002/art.41084
61. Hisada R, Yoshida N, Orite SYK, et al. Role of glutaminase 2 in promoting CD4+ T cell production of interleukin-2 by supporting antioxidant defense in systemic lupus erythematosus. *Arthritis Rheumatol*. 2022;74(7):1204–1210. doi:10.1002/art.42112
62. Bystrom J, Taher TE, Henson SM, Gould DJ, Mageed RA. Metabolic requirements of Th17 cells and of B cells: regulation and defects in health and in inflammatory diseases. *Front Immunol*. 2022;13:990794. doi:10.3389/fimmu.2022.990794
63. Zhou Y, Hu L, Zhang H, et al. Guominkang formula alleviate inflammation in eosinophilic asthma by regulating immune balance of Th1/2 and Treg/Th17 cells. *Front Pharmacol*. 2022;13:978421. doi:10.3389/fphar.2022.978421
64. Zhu J, Paul WE. Heterogeneity and plasticity of T helper cells. *Cell Res*. 2010;20(1):4–12. doi:10.1038/cr.2009.138
65. Hirota K, Duarte JH, Veldhoen M, et al. Fate mapping of IL-17-producing T cells in inflammatory responses. *Nat Immunol*. 2011;12 (3):255–263. doi:10.1038/ni.1993
66. Schnell A, Huang L, Singer M, et al. Stem-like intestinal Th17 cells give rise to pathogenic effector T cells during autoimmunity. *Cell*. 2021;184 (26):6281–98.e23. doi:10.1016/j.cell.2021.11.018
67. Zhang X, Liu J, Cao X. Metabolic control of T-cell immunity via epigenetic mechanisms. *Cell Mol Immunol*. 2018;15(3):203–205. doi:10.1038/cmi.2017.115
68. Shikuma CM, Chew GM, Kohorn L, et al. Short communication: metformin reduces CD4 t cell exhaustion in HIV-infected adults on suppressive antiretroviral therapy. *AIDS Res Hum Retroviruses*. 2020;36(4):303–305.
69. Butterfield TR, Hanna DB, Kaplan RC, et al. Elevated CD4 + T-cell glucose metabolism in HIV+ women with diabetes mellitus. *AIDS*. 2022;36 (10):1327–1336. doi:10.1097/QAD.0000000000003272
70. Crater JM, Nixon DF, Furler O'Brien RL. HIV-1 replication and latency are balanced by mTOR-driven cell metabolism. *Front Cell Infect Microbiol*. 2022;12:1068436. doi:10.3389/fcimb.2022.1068436
71. Moyo D, Tanthuma G, Cary MS, et al. Cohort study of diabetes in HIV-infected adult patients: evaluating the effect of diabetes mellitus on immune reconstitution. *Diabetes Res Clin Pract*. 2014;103(3):e34–e36. doi:10.1016/j.diabres.2013.12.042
72. Tong X, Zhao F, Thompson CB. The molecular determinants of de novo nucleotide biosynthesis in cancer cells. *Curr Opin Genet Dev*. 2009;19 (1):32–37. doi:10.1016/j.gde.2009.01.002
73. Benito-Lopez JJ, Marroquin-Muciño M, Perez-Medina M, et al. Partners in crime: the feedback loop between metabolic reprogramming and immune checkpoints in the tumor microenvironment. *Front Oncol*. 2022;12:1101503. doi:10.3389/fonc.2022.1101503
74. Taylor HE, Calantone N, Lichon D, et al. mTOR overcomes multiple metabolic restrictions to enable HIV-1 reverse transcription and intracellular transport. *Cell Rep*. 2020;31(12):107810. doi:10.1016/j.celrep.2020.107810
75. Abrahams MR, Joseph SB, Garrett N, et al. The replication-competent HIV-1 latent reservoir is primarily established near the time of therapy initiation. *Sci Trans Med*. 2019;11(513). doi:10.1126/scitranslmed.aaw5589
76. Cruzat V, Macedo Rogero M, Noel Keane K, Curi R, Newsholme P. Glutamine: metabolism and immune function, supplementation and clinical translation. *Nutrients*. 2018;10(11):1564. doi:10.3390/nu10111564
77. Nguyen HTT, Wimmer R, Le VQ, Krarup HB. Metabolic fingerprint of progression of chronic hepatitis B: changes in the metabolome and novel diagnostic possibilities. *Metabolomics*. 2021;17(2):16. doi:10.1007/s11306-020-01767-y
78. Raniga K, Liang C. Interferons: reprogramming the metabolic network against viral infection. *Viruses*. 2018;10(1):36. doi:10.3390/v10010036
79. Sumbria D, Berber E, Miller L, Rouse BT. Modulating glutamine metabolism to control viral immuno-inflammatory lesions. *Cell Immunol*. 2021;370:104450. doi:10.1016/j.cellimm.2021.104450
80. Wang K, Hoshino Y, Dowdell K, et al. Glutamine supplementation suppresses herpes simplex virus reactivation. *J Clin Invest*. 2017;127 (7):2626–2630. doi:10.1172/JCI88990

81. Clark SA, Vazquez A, Furiya K, et al. Rewiring of the host cell metabolome and lipidome during lytic gammaherpesvirus infection is essential for infectious-virus production. *J Virol*. 2023;97(6):e0050623. doi:10.1128/jvi.00506-23
82. Li T, Zhu Y, Cheng F, Lu C, Jung JU, Gao SJ. Oncogenic Kaposi's sarcoma-associated herpesvirus upregulates argininosuccinate synthase 1, a rate-limiting enzyme of the citrulline-nitric oxide cycle, to activate the STAT3 pathway and promote growth transformation. *J Virol*. 2019;93 (4):10–128.
83. Sanchez EL, Carroll PA, Thalhofer AB, Lagunoff M, Dittmer DP. Latent KSHV infected endothelial cells are glutamine addicted and require glutaminolysis for survival. *PLoS Pathogens*. 2015;11(7):e1005052. doi:10.1371/journal.ppat.1005052
84. Zhu Y, Li T, Ramos da Silva S, et al. A critical role of glutamine and asparagine γ-nitrogen in nucleotide biosynthesis in cancer cells hijacked by an oncogenic virus. *mBio*. 2017;8(4). doi:10.1128/mBio.01179-17
85. Lyu M, Wang S, Gao K, et al. Dissecting the landscape of activated CMV-stimulated CD4+ T cells in humans by linking single-cell RNA-Seq with T-cell receptor sequencing. *Front Immunol*. 2021;12:779961. doi:10.3389/fimmu.2021.779961
86. Lim EY, Jackson SE, Wills MR. The CD4+ T cell response to human cytomegalovirus in healthy and immunocompromised people. *Front Cell Infect Microbiol*. 2020;10:202. doi:10.3389/fcimb.2020.00202
87. Jin W, Fang M, Sayin I, et al. Differential CD4+ T-cell cytokine and cytotoxic responses between reactivation and latent phases of herpes zoster infection. *Pathog Immun*. 2022;7(2):171–188. doi:10.20411/pai.v7i2.560
88. Freeman ML, Burkum CE, Cookenham T, et al. CD4 T cells specific for a latency-associated γ-herpesvirus epitope are polyfunctional and cytotoxic. *J Iimmunol*. 2014;193(12):5827–5834. doi:10.4049/jimmunol.1302060
89. White DW, Suzanne Beard R, Barton ES. Immune modulation during latent herpesvirus infection. *Immunol Rev*. 2012;245(1):189–208. doi:10.1111/j.1600-065X.2011.01074.x
90. Spekker-Bosker K, Ufermann CM, Maywald M, et al. hCMV-mediated immune escape mechanisms favor pathogen growth and disturb the immune privilege of the eye. *Int J Mol Sci*. 2019;20(4):858. doi:10.3390/ijms20040858
91. Schmalzl A, Leupold T, Kreiss L, et al. Interferon regulatory factor 1 (IRF-1) promotes intestinal group 3 innate lymphoid responses during Citrobacter rodentium infection. *Nat Commun*. 2022;13(1):5730. doi:10.1038/s41467-022-33326-5
92. Kamali AN, Noorbakhsh SM, Hamedifar H, et al. A role for Th1-like Th17 cells in the pathogenesis of inflammatory and autoimmune disorders. *Mol Immunol*. 2019;105:107–115. doi:10.1016/j.molimm.2018.11.015
93. Suessmuth Y, Mukherjee R, Watkins B, et al. CMV reactivation drives posttransplant T-cell reconstitution and results in defects in the underlying TCRβ repertoire. *Blood*. 2015;125(25):3835–3850. doi:10.1182/blood-2015-03-631853
94. Peng H-Y, Wang L, Das JK, et al. Control of CD4+ T cells to restrain inflammatory diseases via eukaryotic elongation factor 2 kinase. *Sig Transd Target Ther*. 2023;8(1):415. doi:10.1038/s41392-023-01648-5
95. Preglej T, Ellmeier W. CD4(+) cytotoxic T cells - phenotype, function and transcriptional networks controlling their differentiation pathways. *Immunol Lett*. 2022;247:27–42. doi:10.1016/j.imlet.2022.05.001
96. Uyangaa E, Lee HK, Eo SK. Glutamine and leucine provide enhanced protective immunity against mucosal infection with herpes simplex virus type 1. *Immun Net*. 2012;12(5):196–206. doi:10.4110/in.2012.12.5.196
97. Hu YM, Yeh CL, Pai MH, Lee WY, Yeh SL. Glutamine administration modulates lung γδ T lymphocyte expression in mice with polymicrobial sepsis. *Shock*. 2014;41(2):115–122. doi:10.1097/SHK.0000000000000086
98. Valle-Casuso JC, Angin M, Volant S, et al. Cellular metabolism is a major determinant of HIV-1 reservoir seeding in CD4(+) T cells and offers an opportunity to tackle infection. *Cell Metab*. 2019;29(3):611–26.e5. doi:10.1016/j.cmet.2018.11.015
99. Deeks SG, Lewin SR, Ross AL, et al. International AIDS Society global scientific strategy: towards an HIV cure 2016. *Nature Med*. 2016;22 (8):839–850. doi:10.1038/nm.4108
100. Taylor HE, Palmer CS. CD4 T cell metabolism is a major contributor of HIV infectivity and reservoir persistence. *Immunometabolism*. 2020;2 (1). doi:10.20900/immunometab20200005
101. Guo H, Wang Q, Ghneim K, et al. Multi-omics analyses reveal that HIV-1 alters CD4+ T cell immunometabolism to fuel virus replication. *Nat Immunol*. 2021;22(4):423–433. doi:10.1038/s41590-021-00898-1
102. Gubser C, Pitman MC, Lewin SR. CD4+ T cell signatures in HIV infection. *Nat Immunol*. 2019;20(8):948–950. doi:10.1038/s41590-019-0447-5
103. Fenwick C, Joo V, Jacquier P, et al. T-cell exhaustion in HIV infection. *Immunol Rev*. 2019;292(1):149–163. doi:10.1111/imr.12823
104. Chan YT, Cheong HC, Tang TF, et al. Immune checkpoint molecules and glucose metabolism in HIV-induced T cell exhaustion. *Biomedicines*. 2022;10(11):2809. doi:10.3390/biomedicines10112809
105. Plana M, García F, Gallart T, et al. Immunological benefits of antiretroviral therapy in very early stages of asymptomatic chronic HIV-1 infection. *AIDS*. 2000;14(13):1921–1933. doi:10.1097/00002030-200009080-00007
106. Martin GE, Sen DR, Pace M, et al. Epigenetic features of HIV-induced T-cell exhaustion persist despite early antiretroviral therapy. *Front Immunol*. 2021;12:647688. doi:10.3389/fimmu.2021.647688
107. Gangcuangco LMA, Mitchell BI, Siriwardhana C, et al. Mitochondrial oxidative phosphorylation in peripheral blood mononuclear cells is decreased in chronic HIV and correlates with immune dysregulation. *PLoS One*. 2020;15(4):e0231761. doi:10.1371/journal.pone.0231761
108. Vellas C, Nayrac M, Collercandy N, et al. Intact proviruses are enriched in the colon and associated with PD-1(+)TIGIT(-) mucosal CD4(+) T cells of people with HIV-1 on antiretroviral therapy. *EBioMedicine*. 2023;100:104954. doi:10.1016/j.ebiom.2023.104954
109. Benito JM, Restrepo C, García-Foncillas J, Rallón N. Immune checkpoint inhibitors as potential therapy for reverting T-cell exhaustion and reverting HIV latency in people living with HIV. *Front Immunol*. 2023;14:1270881. doi:10.3389/fimmu.2023.1270881
110. Caetano DG, De Paula HHS, Bello G, et al. HIV-1 elite controllers present a high frequency of activated regulatory T and Th17 cells. *PLoS One*. 2020;15(2):e0228745. doi:10.1371/journal.pone.0228745
111. Saxton RA, Sabatini DM. mTOR signaling in growth, metabolism, and disease. *Cell*. 2017;168(6):960–976. doi:10.1016/j.cell.2017.02.004
112. Ueda Y, Saegusa J, Okano T, et al. Additive effects of inhibiting both mTOR and glutamine metabolism on the arthritis in SKG mice. *Sci Rep*. 2019;9(1):6374. doi:10.1038/s41598-019-42932-1
113. Li JZ, Aga E, Bosch RJ, et al. Time to viral rebound after interruption of modern antiretroviral therapies. *Clinl Infect Dis*. 2022;74(5):865–870. doi:10.1093/cid/ciab541
114. Yuen MF, Chen DS, Dusheiko GM, et al. Hepatitis B virus infection. *Nat Rev Dis Primers*. 2018;4(1):18035. doi:10.1038/nrdp.2018.35
115. Manns MP, Maasoumy B. Breakthroughs in hepatitis C research: from discovery to cure. *Nat Rev Gastroenterol Hepatol*. 2022;19(8):533–550.

116. Lopez-Scarim J, Nambiar SM, Billerbeck E. Studying T cell responses to hepatotropic viruses in the liver microenvironment. *Vaccines*. 2023;11(3):681. doi:10.3390/vaccines11030681
117. Chen J, Wang R, Liu Z, et al. Unbalanced glutamine partitioning between CD8T cells and cancer cells accompanied by immune cell dysfunction in hepatocellular carcinoma. *Cells*. 2022;11(23):3924. doi:10.3390/cells11233924
118. Baxter VK, Glowinski R, Braxton AM, Potter MC, Slusher BS, Griffin DE. Glutamine antagonist-mediated immune suppression decreases pathology but delays virus clearance in mice during nonfatal alphavirus encephalomyelitis. *Virology*. 2017;508:134–149. doi:10.1016/j.virol.2017.05.013
119. Sun J, Tumurbaatar B, Jia J, et al. Parenchymal expression of CD86/B7.2 contributes to hepatitis C virus-related liver injury. *J Virol*. 2005;79(16):10730–10739. doi:10.1128/JVI.79.16.10730-10739.2005
120. Correia MP, Cardoso EM, Pereira CF, Neves R, Uhrberg M, Arosa FA. Hepatocytes and IL-15: a favorable microenvironment for T cell survival and CD8+ T cell differentiation. *J Iimmunol*. 2009;182(10):6149–6159. doi:10.4049/jimmunol.0802470
121. Huang BY, Tsai MR, Hsu JK, et al. Longitudinal change of metabolite profile and its relation to multiple risk factors for the risk of developing hepatitis B-related hepatocellular carcinoma. *Mol Carcinogen*. 2020;59(11):1269–1279. doi:10.1002/mc.23255
122. Yu Z, Li J, Ren Z, et al. Switching from fatty acid oxidation to glycolysis improves the outcome of acute-on-chronic liver failure. *Adv Sci*. 2020;7(7):1902996. doi:10.1002/advs.201902996
123. Helling G, Wahlin S, Smedberg M, et al. Plasma glutamine concentrations in liver failure. *PLoS One*. 2016;11(3):e0150440. doi:10.1371/journal.pone.0150440
124. Raziorrouh B, Heeg M, Kurktschiev P, et al. Inhibitory phenotype of HBV-specific CD4+ T-cells is characterized by high PD-1 expression but absent coregulation of multiple inhibitory molecules. *PLoS One*. 2014;9(8):e105703. doi:10.1371/journal.pone.0105703
125. Raziorrouh B, Ulsenheimer A, Schraut W, et al. Inhibitory molecules that regulate expansion and restoration of HCV-specific CD4+ T cells in patients with chronic infection. *Gastroenterology*. 2011;141(4):1422–31, 31.e1–6. doi:10.1053/j.gastro.2011.07.004
126. Ye B, Liu X, Li X, Kong H, Tian L, Chen Y. T-cell exhaustion in chronic hepatitis B infection: current knowledge and clinical significance. *Cell Death Dis*. 2015;6(3):e1694. doi:10.1038/cddis.2015.42
127. Kaushik AK, Tarangelo A, Boroughs LK, et al. In vivo characterization of glutamine metabolism identifies therapeutic targets in clear cell renal cell carcinoma. *Sci Adv*. 2022;8(50):eabp8293. doi:10.1126/sciadv.abp8293
128. Rais R, Lemberg KM, Tenora L, et al. Discovery of DRP-104, a tumor-targeted metabolic inhibitor prodrug. *Sci Adv*. 2022;8(46):eabq5925. doi:10.1126/sciadv.abq5925
129. Cederkvist H, Kolan SS, Wik JA, Sener Z, Skålhegg BS. Identification and characterization of a novel glutaminase inhibitor. *FEBS Open Bio*. 2022;12(1):163–174. doi:10.1002/2211-5463.13319
130. Al-Dujaili LJ, Clerkin PP, Clement C, et al. Ocular herpes simplex virus: how are latency, reactivation, recurrent disease and therapy interrelated? *Future Microbiol*. 2011;6(8):877–907. doi:10.2217/fmb.11.73
131. Monteiro FR, Roseira T, Amaral JB, et al. Combined exercise training and l-glutamine supplementation enhances both humoral and cellular immune responses after influenza virus vaccination in elderly subjects. *Vaccines*. 2020;8(4):685. doi:10.3390/vaccines8040685
132. Howden AJM, Hukelmann JL, Brenes A, et al. Quantitative analysis of T cell proteomes and environmental sensors during T cell differentiation. *Nat Immunol*. 2019;20(11):1542–1554. doi:10.1038/s41590-019-0495-x
133. Pacheco R, Oliva H, Martinez-Navío JM, et al. Glutamate released by dendritic cells as a novel modulator of T cell activation. *J Iimmunol*. 2006;177(10):6695–6704. doi:10.4049/jimmunol.177.10.6695
134. Arensman MD, Yang XS, Leahy DM, et al. Cystine-glutamate antiporter xCT deficiency suppresses tumor growth while preserving antitumor immunity. *Proc Natl Acad Sci USA*. 2019;116(19):9533–9542. doi:10.1073/pnas.1814932116