T cell metabolism in chronic viral infection

Laura J Pallett[1]*; Nathalie Schmidt[1]; Anna Schurich[2]*

[1] Division of Infection & Immunity, University College London, London, UK

[2] Department of Infectious Diseases, King's College London, London, UK

*Joint corresponding author

Address: L. Pallett (laura.pallett@ucl.ac.uk), Division of Infection and Immunity, Rayne Building, 5 University Street, London, WC1E 6JF, UK; A. Schurich (anna.schurich@kcl.ac.uk), Department of Infectious Diseases, Guy's Hospital, Great Maze Pond, London, SE1 9RT, UK

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Abbreviations: fatty acid oxidation (FAO); oxidative phosphorylation (OXPHOS); effector T cell (T_{EFF}); memory T cell (T_{MEM}); tissue-resident memory T cell (T_{RM}); spare respiratory capacity (SRC); oxygen consumption rate (OCR); mammalian target of rapamycin (mTOR); AMP-activated protein kinase (AMPK); antigen presenting cell (APC); human immunodeficiency virus-1 (HIV-1); human T lymphotropic virus-1 (HTLV-1); hepatitis B virus (HBV); hepatitis C virus (HCV); cytomegalovirus (CMV); lymphocytic choriomeningitis virus (LCMV); myeloid-derived suppressor cell (MDSC); T cell receptor (TCR); sterol regulatory element-binding protein (SREBP); liver X receptor (LXR); programmed-death 1 (PD-1).

Keywords: T cell; immunometabolism; metabolic exhaustion; tissue residency; viral infection, immunotherapy

Abstract

T cells are a fundamental component of the adaptive immune response in the context of both acute and chronic viral infection. Tight control over the metabolic processes within T cells provides an additional level of immune regulation that is interlinked with nutrient sensing and the continued balancing of co-stimulatory and co-inhibitory signals. Underpinning T cell responsiveness for viral control are a number of phenotypic and functional adaptations ensuring adequate nutrient uptake and their utilisation. T cells responding to persistent viral infections often exhibit a profile associated with immune cell exhaustion and a dysregulated metabolic profile, driven by a combination of chronic antigenic stimulation and signals from the local microenvironment. Understanding alterations in these metabolic processes provides an important basis for immunotherapeutic strategies to treat persistent infections.

Viral infections present a constant challenge to the host's immune system; at any given moment, an individual is on average infected with 8-12 chronic viruses [1], in addition to any acute ones contracted. It is therefore essential that the adaptive immune response, that aims to eradicate or at least control infection, is tightly regulated. The intricacies of the success or failure of the antiviral response are entrenched in cellular metabolism, and with advancing technologies providing novel insights into lymphocyte biology, it is now hard to deny that antiviral T cells excel in 'bioenergy management'. T cells constantly process numerous signals to orchestrate the six key metabolic pathways (glycolysis, tricarboxylic acid cycle, pentose phosphate, fatty acid oxidation (FAO), fatty acid synthesis and amino acid metabolism) for their expansion and effector function [2]. In this minireview we will explore how CD8+ T cells - the key effectors of the antiviral immune response - process cell-intrinsic and cell-extrinsic signals to fine-tune the immune response.

Predictably, the metabolic demands placed on a T cell following activation shift from an energy-orientated quiescent profile, providing host immunosurveillance, to an anabolic, biosynthetic profile, capable of supporting cell division [3]. Metabolically inactive naïve CD8+ T cells use glucose catabolism and oxidative phosphorylation (OXPHOS) driven by fatty acid oxidation (FAO) to fuel their homeostatic cell turnover. Upon antigen recognition, naïve CD8+ T cells undergo profound reprogramming whereby they increase glucose and amino acid uptake, reducing their reliance on OXPHOS and lipid oxidation, and differentiate into an effector CD8+ T cell (T_{EFF}) [4]. These adaptations allow T_{EFF} to meet the increased biosynthetic demands for clonal expansion, and to facilitate transcription (and translation) of key cytolytic mediators and non-cytolytic chemokines and cytokines. After antigenic clearance, T_{EFF} contract, leaving behind a long-lived memory CD8+ T cell (T_{MEM}) pool that is adept at secondary recall when re-challenged. T_{MEM} revert to a state that is largely dependent on endogenously synthesised fatty acids and OXPHOS, increased mitochondrial mass and an enhanced spare respiratory capacity (SRC) [5].

In order to translate environmental cues into metabolic changes, lymphocytes are reliant on a number of critical transcriptional mediators, including c-Myc, mammalian target of rapamycin (mTOR) and AMP-activated protein kinase (AMPK). c-Myc is a transcriptional regulator required

by T cells for glycolytic reprogramming upon antigenic stimulation, and binds a number of genes involved in glycolysis and nutrient uptake [6]. Additional rheostats for control of T cell function include mTOR, which has two distinct complexes - mTOR complex 1 (mTORC1) and (mTORC2) - that sense nutrients and growth factor availability, and promote mRNA translation and lipid synthesis [2]. Finally, the kinase AMPK is a critical sensor and regulator of the cellular ATP pool. Upon nutrient deprivation, AMPK is activated and promotes catabolism, for example of fatty acids, whilst simultaneously inhibiting mTOR activity and limiting immune cell activation [7].

Effector cell function and nutrient sensing

Viruses can modulate the metabolism of both their host cell and neighbouring cells [8], leading to functional and phenotypic changes that impact the antiviral T cell response. Varying the bioavailability of nutrients (whether exogenous or endogenous glucose, amino acids, fatty acids or cholesterol/oxysterols) has profound effects on the metabolic fitness and structural integrity of the cell. When nutrient availability is restricted, T cells are forced to undergo adaptations and/or compensatory changes in phenotype or fuel source in order to retain functionality and survive. Thus, the local milieu provides an additional dimension of immune cell regulation that can interact with transcriptional programs to support differential cell fate.

Modulation of mTORC1 activity can drive asymmetric division of CD8+ T cells during the first round of division following interaction with cognate peptide presented by antigen presenting cells (APC). The emerging daughter cells have differential metabolic profiles: the daughter cell proximal to the APC differentiates into an effector-like CD8+ T cell that is more glycolytic. In comparison, distal daughter cells phenotypically and functionally resemble CD8+ T_{MEM}, with an increased propensity for lipid metabolism, greater SRC and upregulated expression of anti-apoptotic molecules. These features underpin their long-term maintenance and survival [9, 10].

Glucose metabolism and its role in infection

T_{EFF} make increased use of glycolysis, converting glucose to pyruvate and lactate. Despite the significantly lower yield of ATP produced per glucose molecule in glycolysis compared to

OXPHOS, the reaction has three key advantages: 1. a high rate of ATP production per unit time, as glycolysis is faster than mitochondrial energy production and not easily saturated [11]; 2. its independence of oxygen availability, enabling T cells to adapt better to hypoxic environments; and 3. the rapid generation of biological building blocks needed for clonal expansion [12] [13].

Consequently, a hallmark of T cell activation is the *de novo* production and increased surface expression of glucose transporters to fuel the glycolytic pathway. In humans, this transporter family has 14 members, referred to as Glut1-14 (or Slc2a1-Slc2a14) [14]. T cells primarily use Glut1 and Glut3 for the uptake of exogenous glucose [15]; however, many persistent viruses interfere with the regulation of glucose uptake and down-stream metabolism to suit their own needs and to enhance the production of viral progeny. For example, infection of primary CD4+ T cells with human immunodeficiency virus 1 (HIV-1) leads to increased glycolysis (**Table 1**), which directly supports viral production [16]. In line with this, Glut1 is upregulated on the surface of CD4+ T cells isolated from patients with HIV-1 infection irrespective of treatment status, with transporter expression directly correlating with disease progression [17] (**Fig.1b**). *In vitro*, metabolically active CD4+ T cells expressing Glut1 preferentially harbour HIV-1 [18]. Other viruses such as human T lymphotropic virus (HTLV) directly interact with Glut1 and use it as an entry receptor [19]. Upon infection, HTLV stimulates further upregulation of Glut1 for its own advantage (**Fig.1b and Table 1**). A number of latent viruses also respond to metabolic cues [20]; hypoxia and glucose deprivation can cause reactivation of HTLV within T cells [20] and Epstein-Barr virus in B cells [21]. These findings demonstrate the intimate relationship and dependence of viral infection and propagation on the host cell metabolism. While the majority of viruses do not directly infect T cells, many can interfere with T cell function by indirect modulation of metabolic pathways, as discussed below.

T cell control of amino acid bioavailability

Although glucose is a critical substrate, essential amino acids provide the building blocks for protein and nucleotide biosynthesis. Their uptake and utilisation are critical for T cell development, homeostasis, activation, differentiation and induction of a long-lasting memory response. The

dependence on amino acids necessitates tight regulation of transporter expression and flux of nutrients in and out of the cell, exemplified by the fact mTORC1 activity is acutely sensitive to the availability of certain amino acids (including leucine and arginine) [22, 23].

Glutamine availability is also essential for mTORC1 activity; activated T cells upregulate members of the glutamine transporter family, including Slc38a1 and Slc1a5 consistent with active uptake of exogenous glutamine **(Fig. 1a)** [22, 24]. Deprivation of glutamine from the microenvironment impairs both T cell proliferation and effector function [25, 26] (**Fig.1c)**. More specifically, Slc1a5 deficiency on activated CD4+ T cells was recently shown to decrease glutamine uptake upon T cell receptor (TCR)-engagement, and an impaired ability to utilise OXPHOS appropriately, resulting in impaired differentiation *in vitro* and *in vivo*. Intriguingly, the authors suggested Slc1a5 deficiency was dispensable for T cell proliferation and IL-2 production [24]. Glutamine availability is also an essential amino acid for T cell function as it is required for the efficient uptake of other amino acids. For example, the neutral amino acid transporter Slc7a5, functions as an obligate antiporter, efluxing glutamine to allow import of large neutral amino acids [27].

Further evidence for T cell reliance on amino acid uptake comes from an elegant study by Sinclair *et al.,* which details the role for Slc7a5 and CD98 (Slc3a2) as a critical checkpoint governing the metabolic response of T cells to antigenic stimulation. In line with this, an Slc7a5 deficiency, and an associated abrogation of leucine uptake, restricts re-programming and clonal expansion of T cells [23, 28]. Slc7a5-deficient T cells also fail to adequately increase glucose and glutamine uptake on demand and have impaired mTORC1 activity. Notably, glutamine and glucose are nutrients consumed the quickest by proliferating T cells [29]. However, T cells also require methionine to provide methyl donors for protein and nucleotide methylation; tryptophan for cellular proliferation; arginine as a precursor for polyamines and protein biosynthesis; and leucine which functions as an mTORC1 activator [23, 30-32]. As a result, reduced availability of any one of these amino acids can negatively impact the magnitude of the antiviral response.

Virus-specific T cells regulate differential expression of nutrient transporters *in vivo* as an additional rheostat to directly modulate the intracellular concentrations of amino acids. Studies in patients with either chronic hepatitis B virus (HBV) or HIV-1 infection, have both revealed enzymatic depletion of arginine and tryptophan by myeloid-derived suppressor cells (MDSC), which potently inhibits the antiviral T cell response [33, 34]. An accumulation of granulocytic MDSC, and the consequent elevated concentrations of the enzyme arginase-I, result in a local deprivation of arginine [33, 35, 36]. Complete absence of arginine from the microenvironment prevents T cell proliferation and aerobic glycolysis *in vitro* [37, 38], and is sensed by the cell through Slc38a9, leading to inhibition of mTORC1 activity [39] (**Fig.1c)**. Cytomegalovirus (CMV)-reactive T cells also have increased expression of the nutrient transporters Glut1 and CD98, compared to global T cells, consistent with prior antigen experience [33, 40]. A further study revealed a secondary modulation of arginine within the T cell itself whereby elevation of intracellular arginine concentrations, via modulation of mitochondrial arginase-II, skewed T cell metabolism from glycolysis towards OXPHOS, enhancing memory formation, function, and survival *in vivo* [41].

Fatty acid and lipid metabolism

Fatty acids and lipids represent an important energy source for cellular metabolism, but also constitute an essential component of the T cell plasma membrane and lipid rafts. Lipid rafts are highly organised cell surface micro-domains that consist largely of cholesterol, glycosphingolipids and sphingomyelin, and facilitate the formation of the immunological synapse between T cells and APC. Upon T cell activation, the TCR and associated signalling molecules localise within lipid rafts, enabling TCR clustering to enhance downstream signalling [42].

The regulation of cholesterol and fatty acid availability is crucial for T cell function. A decrease in cholesterol availability limits proliferation, membrane lipid raft formation and the strength of TCR signalling [43]. In opposition, an excess of cholesterol promotes CD8+ and CD4+ T cell expansion [44]. Thus, cholesterol and fatty acid homeostasis is tightly regulated by two key transcription factors: the sterol regulatory element-binding proteins (SREBP) and liver X receptors (LXR;

Fig1a). Upon activation, T cells switch to a programme, dependent on increased cholesterol and fatty acid synthesis, enhanced SREBP signalling, and suppression of the LXR pathway [45, 46]. An absence of SREBP signalling in CD8+ T cells leads to a reduced frequency of virus-specific T_{EFF} in the context of lymphocytic choriomeningitis virus (LCMV) infection [46]. Accordingly, a lack of the negative regulatory pathway LXRβ enhances the functionality of adenovirus-specific CD8+ T cell responses [45].

T_{MEM} have an increased SRC compared to T_{EFF} that is largely associated with increased mitochondrial biogenesis and expression of CPT1α - a rate-limiting enzyme of mitochondrial FAO [47]. However, by using a mouse model with CPT1α deletion, Raud *et al*. recently demonstrated that CPT1α is not required for the formation of T_{EFF} or T_{MEM}, and suggest that the previously described effect of the CPT1α inhibitor etomoxir on T cell differentiation and function is likely due to off-target effects of etomoxir on mitochondrial respiration [48]. T_{MEM} engage FAO to a greater extent than T_{EFF}, yet CD8+ T_{MEM} take up less long chain fatty acids compared to CD8+ T_{EFF} since they preferentially use exogenous glucose to support FAO and OXPHOS [5]. Besides FAO, fatty acid synthesis itself is important for T cells. Modulation of fatty acid synthesis in the effector phase through deletion of acetyl-CoA carboxylase 1 (the rate-limiting enzyme in *de novo* synthesis of long chain fatty acids) impairs T cell persistence and proliferation. Importantly, supplementation with exogenous fatty acids can rescue T cell proliferation *in vitro [49, 50]*.

Finally, local concentrations of cholesterol not only impact the magnitude of antiviral T cell responses but can also have a direct effect on viruses themselves (**Table 1**). Several viruses are known to directly alter the lipid and fatty acid metabolism within the host cell for their own benefit, including HIV-1 [51, 52], hepatitis C virus (HCV) [53], and CMV [54] (**Table 1**). Certain viruses, including HIV-1, utilise the organised lipid raft structure at the T cell plasma membrane for entry and assembly, with both processes requiring the presence of cholesterol [55]. In support of this, the cholesterol content of the plasma membrane of dendritic cells, B cells and macrophages in HIV-1 non-progressors is reduced compared to rapid progressors, with the cholesterol content of the cell correlating with the capacity of HIV-1 to undergo cell to cell spread [56, 57].

Tissue residency

In light of mounting evidence showing that a subset of memory T cells persist and patrol within lymphoid and non-lymphoid tissues [58], it is important to consider the immuno-metabolic requirements of lymphocytes found locally at the site of disease. Tissue-resident memory T cells (T_{RM}) are compartmentalised away from the circulating pool via the expression of the tissue-retention signals CD69 and/or CD103 [58]. This is particularly pertinent as many persistent viruses exhibit tissue-specific tropism. CD8+ T_{RM} provide rapid antigen-specific recall responses *in situ* and therefore act as highly-functional defence specialists, with adaptations imposed by their local niche. They can be directed against viruses that invade these sites: for example, HBV-specific CD8+ T_{RM} have been found in the human liver [59], murine herpes simplex virus 1-specific T_{RM} in the lamina propria of the vagina [60] and human influenza A-specific T cells in the lung [61]. Consequently, virus-specific T_{RM} are forced to function within the confines of the specific metabolic environment of the niche, which can often be hypoxic or nutrient-restricted. Liver-resident CD8+ T_{RM}, have for example been shown to exhibit increased expression of CD98 [59] and upregulate glycolysis, likely in response to local arginine deprivation [33] and the hypoxic hepatic environment [40], respectively. Further evidence for metabolic control over CD8+ T_{RM} emanates from studies of murine CD8+ T_{RM} generated by skin vaccinia virus, where increased expression of fatty acid binding protein 4 and 5 (FABP-4 and -5), along with CD36, enable CD8+ T_{RM} to increase uptake of exogenous free fatty acids to fuel oxidative metabolism to promote long-term survival in the tissue [62]. Interestingly, the uptake of exogenous free fatty acids is not only vital for CD8+ T_{RM} survival but also immunosurveillance. Antigen-specific CD8+ T_{RM} cells lacking expression of FABP-4 and FABP-5, or when FAO is impaired by the addition of the pharmacological agent etomoxir, no longer provide T cell mediated protection within a tissue, against viruses such as vaccinia virus (54).

Metabolic alterations in T cell exhaustion

Growing evidence suggests that metabolic changes are not only a response to cellular activation, but can drive T cell function, as well as regulate the progression of T cell dysfunction and

exhaustion [63, 64]. T cell exhaustion is characterised by a step-wise reduction in proliferation and effector function, culminating in the deletion of the most severely exhausted cells [65]. Exhaustion is associated with chronic TCR-signalling, as is characteristic of persistent viral infection [65], the tumour microenvironment and autoimmunity [64]. Indeed, in the setting of chronic infection, HBV appears to drive lymphocyte exhaustion by producing high amounts of non-infectious subviral particles at 1000-100,000 fold excess over infectious virus [66].

Recently, it has been suggested that even low levels of antigenic stimulation (as could be found in some cancers) can lead to T cell exhaustion where cells are simultaneously exposed to prolonged metabolic stress [12] - a process described as 'metabolic exhaustion' [64, 67]. The most prominent metabolic deficiency described in exhausted T cells is mitochondrial dysfunction (**Fig.1c**), which may result directly from environmental stresses such as hypoxia and nutrient deprivation and/or an excess of coinhibitory signalling [68]. Changes to mitochondrial function can already be observed early during the establishment of chronic infection in LCMV [63] and are maintained in long-term chronic viral infection [40, 69] - a situation that is also observed in cancer [67]. Interestingly, mitochondria in exhausted T cells have an increased mass but are typically depolarised and with a lower oxygen consumption rate (OCR) and SRC (**Fig.1c**) [40, 63] while reactive oxygen species production is increased [64].

Low mitochondrial function can be promoted by signalling through the coinhibitory receptor programmed death-1 (PD-1) in early chronic LCMV infection [63]. As such, PD-1^{hi} peripheral human T cells have a lower SRC than PD-1^{lo} cells [40]. The level of PD-1 expression correlates with the degree of exhaustion, with high expression associated with exhausted T cells in HBV, HCV and HIV-1 [65]. In CD4+ T cells the expression of PD-1 is associated with a downregulation of glycolysis and an upregulation of FAO and lipolysis [70]. In HIV-1, T cells expressing lower levels of PD-1 are more polyfunctional (i.e. capable of producing more than one cytokine) and are found in long term non-progressors [71]. Interestingly, whilst genetic deletion of PD-1 in human TCR-redirected transgenic T cells have an increased capacity for virus-specific killing, the

complete genetic absence of PD-1 is correlated with reduced survival of the T cell pool in the context of chronic infection [72] [73].

In addition to promoting T cell exhaustion the presence of a chronic viral infection also leads to the accumulation of terminally differentiated, senescent T cells. T cell senescence is characterised by critical telomere shortening due to the loss of telomerase expression, which in turn terminates cellular proliferation [74]. In contrast to exhaustion, senescent T cells are capable of producing significant quantities of cytokine, are often present in large numbers and do not necessarily express increased coinhibitory receptors. Instead, they are phenotypically distinguished by the expression of CD57 and KLRG1. Recently, senescent T cells have been shown to harbour dysfunctional mitochondria and become more dependent on glycolysis [75]. During the normal process of immune cell aging for example, mitochondrial function is generally reduced and likely impacts the antiviral T cell response [76]. Two characteristic viruses known to drive T cell senescence are CMV and HIV-1. CMV-specific CD8+ T cells accumulate in large numbers over time and single clones can often dominate the T cell pool in the blood. This inflated CMV response is thought to contribute to the reduced immune response towards new pathogens in the elderly [77]. Telomere shortening was documented in CD4+ and CD8+ T cells in HIV-1 patients, with accumulation of these cells demonstrated in progressors compared to non-progressors [78]. Interestingly patients on anti-retroviral therapy also accumulated senescent T cells, suggesting that long term low level antigenic stimulation was a driving force [74].

Future perspectives for immunotherapy

The development of new, effective therapies for chronic viral infections is of major clinical importance to improve patient care. The success of immunotherapy has been demonstrated in recent cancer treatment trials, and offers a novel therapeutic approach to enhance the functionality of present but exhausted antiviral T cells, or to induce *de novo* T_{EFF}. Several strategies have focussed on the blockade of inhibitory immune checkpoints, such as PD-1 or cytotoxic T-lymphocyte associated protein 4 (CTLA-4), and have shown clinical benefit in boosting anti-tumour responses [79]. However, immunotherapy targeting chronic viral infections is still in

its infancy; since the mechanisms behind T cell exhaustion and dysfunction in tumours and persistent viral infection share many similarities, developments in anti-tumour immunotherapies also hold promise for the treatment of chronic viral infections. Due to the multifaceted immune dysfunction in the context of chronic antigenic stimulation, early trials have suggested that targeting more than one pathway may be necessary to achieve long-lasting clinical results. Further exploration will be required to understand what determines treatment responsiveness.

Interestingly, several studies have demonstrated the influence of the gut microbiome and their metabolites on the outcome of anti-PD-1 therapy in cancer patients, for example certain bacterial species skew CD4+ T cell responses towards proinflammatory cytokine production [80-82]. Furthermore, potential complementary effects of modulating T cell metabolism have been highlighted by observed metabolic changes following checkpoint blockade. The addition of an inhibitor to Acyl-CoA cholesterol acyltransferase - an enzyme involved in cholesterol esterification – demonstrated reduced tumour growth and increased survival when combined with anti-PD-1 therapy [83]. Experimentally, enhancing FAO through treatment with rapamycin results in a higher frequency and improved functionality of virus-specific CD8+ T cells in acute LCMV infection [84]. Rapamycin also enhances T_{MEM} responses after vaccinia virus vaccination in non-human primates [85]. Addressing the mitochondrial dysfunction of exhausted CD8+ T cells in patients with chronic HBV infection, mitochondria-targeted anti-oxidants [69] as well as stimulation with inflammatory cytokines [40, 86] and modulation of amino acid availability [33] to restore HBV-specific T cell functionality *in vitro* have been successfully tested.

Additionally, metabolic modulators can directly influence viral replication and release, and thus may have the potential to control viral infection. Statins that inhibit cholesterol synthesis have an inhibitory effect on the replication of several different viruses *in vitro* including HCV [87] and CMV [88], while blockade of CD36 on macrophages inhibits the release, and therefore transmission, of HIV-1 particles [89]. Another potential approach is to enhance T cell metabolism *in vitro* prior to T cell therapy. The supplementation of amino acids (e.g. arginine [41]) or cytokines (e.g. IL-7, IL-12 [40, 90]), or the modulation of mitochondrial biogenesis (e.g. via an enhanced expression of

PPARγ coactivator1α [67]) with or without checkpoint inhibition, are all promising targets to improve *in vivo* survival and effector function of transferred antiviral T cells.

In summary, immunometabolism is a new and fast-moving field with a constant development of novel analytic approaches, from large-scale studies including metabolomics, proteomics and lipidomics, to in-depth single cell analysis of nutrient uptake. These will provide new insights with the potential to progress promising novel immunotherapeutic approaches for the treatment of chronic viral infections and tumours in the future.

Table 1:

Virus	Host cells	Metabolic modulation	Reference
HCV	Hepatocytes	Increases CD98 & mTORC1 signalling, CD98 acts as cofactor for HCV entry, & needed for viral propagation. Drives alteration in cholesterol synthesis.	[91] [53]
HBV	Hepatocytes	Induces Ca^{2+} release from mitochondria, supporting viral replication.	[92, 93]
HIV-1	T cells	T cells - increased glycolysis, & Glut1 expression. $Glut1^{hi}$ CD4+ T cells harbor HIV-1, with viral transcription linked to cholesterol metabolism via SREBP2 and enhanced FAS.	[16-18] [51, 52]
HIV-1	Monocytes	Increased glucose metabolism and surface Glut1 and Glut 3 expression	[94]
HTLV	T cells	T cell upregulation of Glut1. Glut1 acts as HTLV entry receptor	[95, 96]
EBV	B cells	Activation of the PI3K/Akt pathway & enhanced HIF1α expression increasing glucose uptake and glycolytic flux.	[97, 98]
CMV	HF cells	Glut4 upregulation increasing lipid biosynthesis. With increased mitochondrial ATP production by Ca^{2+} modulation accelerating viral replication	[99] [54]
KSHV	Endothelial cells	Increased glycolysis via induction of HIF1α	[100]
HPV	Cutaneous epithelial cells	Disruption of p53 signalling and stabilisation of HIF1α enhancing glycolysis and glucose uptake	[101] [102]

Table 1: Metabolic modulation of host cells by the infecting virus.

Hepatitis C virus (HCV); Hepatitis B virus (HBV); Human immunodeficiency virus-1 (HIV-1); Human T lymphotropic virus (HTLV); Epstein-Barr virus (EBV); Cytomegalovirus (CMV); Kaposi's sarcoma-associated herpesvirus (KSHV); Human papillomavirus (HPV).

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Figure Legend: Schematic overview demonstrating characteristic metabolic features of: A a fully functional activated T_{EFF}; **B** a T cell infected by HIV-1 or HTLV; and **C** an exhausted CD8+ T cell in the context of chronic viral infection.

HTLV: Human T lymphotropic virus; HIV-1: Human immunodeficiency virus-1; PD-1: Programmed cell death protein 1; FAO: fatty acid oxidation; SREBP: Sterol regulatory element-binding protein; LXR: Liver X receptor; OXPHOS: oxidative phosphorylation; TCR: T cell receptor; MHC1: Major histocompatibility antigen class I; mTORC1: mammalian target of rapamycin complex 1; ATP: Adenosine triphosphate