IMMUNOMETABOLISM

The metabolic tug of war between HIV and T cells

The loss of T cell immune function as a result of human immunodeficiency virus (HIV) infection leads to opportunistic infections and certain HIV-associated cancers. Two recent studies shed light on the complex immunometabolic changes during HIV infection and open the door to metabolic treatment options that could ultimately cure HIV.

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More than 35 million people worldwide live with HIV infection (https://www.who.int/gho/hiv/en/). As a result of the development of effective anti-retroviral therapy (ART), HIV infection is now considered a chronic disease. However, ART does not eliminate HIV from the body, and acquired therapeutic resistance has been observed[1]. Additionally, the life-long need for therapy imposes a financial burden associated with controlling viral load and complications of viral infection. Therefore, the development of immune-mediated therapies resulting in the generation of immunological memory and long-lived protection is needed. This development would require a better understanding of both the immune cells affected by HIV and the immune cells providing protection against HIV. Of particular relevance is a subset of HIV-infected individuals with spontaneous immune control of their HIV infection.

HIV infects human cells by binding the CD4 cell-surface receptor expressed on a subset of immune cells found within the T cell compartment (Fig. 1b). $CD4^+$ T cells, also known as helper T cells, influence immune responses by modulating the activity of other immune cells. HIV infection leads to a progressive loss of $CD4^+$ T cell number and function, thereby compromising the immune response to a variety of pathogens. Besides being the target of HIV infection, T cells also play a role in the antiviral response to HIV. $CD8^+$ cytotoxic T cells provide immune protection by killing cells that contain anything foreign to the body, such as viruses (Fig. 1c).

The regulation of T cell function after activation is intimately linked to metabolic reprogramming that facilitates the generation of biomass and bioenergetic capacity, thereby enabling rapid expansion of antigen-specific T cells[2]. During T cell activation, the upregulation of nutrient transporters drives the import of biomolecules such as glucose, amino acids and nucleosides, all of which can contribute to the generation of biomass and energy[3]. Depending on the activation context, naive $CD4^+$ T cells can differentiate into distinct helper T cell subsets, each associated with different metabolic requirements, and subsequently exert immune modulation[3]. $CD8^+$ T cell responses generate rapidly proliferating effector T (T_E) cells, which are important for the immediate control of infection but also give rise to long-lived memory T (T_M) cells, which protect against future infections with the same pathogen. As in the $CD4^+$ T cell subsets, the engagement of specific metabolic pathways is crucial to support the function and differentiation state of $CD8^+$ T cells. Whereas naive $CD4^+$ and $CD8^+$ T cells are metabolically quiescent, T cell receptor activation leads to upregulation of central carbon metabolism pathways such as glycolysis and the tricarboxylic acid (TCA) cycle. However, T_M cell differentiation is associated with sustained TCA-cycle activity and a decrease in aerobic glycolysis[3].

HIV infection is dependent on both the expression of CD4 and metabolic activation, thus partly explaining why activated $CD4^+$ T cells are more permissive to HIV infection than naive CD4 T cells[4–6] (Fig. 1b). Although metabolic activity and enhanced expression of metabolite transporters have been shown to enhance HIV infection rates of $CD4^+$ T cells[6], the rate-limiting metabolic pathways fed by glucose and glutamine remained to be identified. In an effort to more precisely delineate the metabolic requirements of HIV infection, Clerc et al. assessed which changes in the central carbon metabolic pathways, after activation, contribute to increased HIV infection of $CD4^+$ T cells[4]. The authors show that glutamine-depleted cultures of $CD4^+$ T cells are much less susceptible to HIV infection. The addition of a cell-permeable analogue of α-ketoglutarate (αKG) overcomes glutamine depletion, thus suggesting that this TCA intermediate is an important player during HIV infection in $CD4^+$ T cells (Fig. 1a). Whether this effect of αKG is mediated by a mechanism relying on TCA flux downstream, thereby driving the electron-transport chain to generate more ATP, or by altered activity of enzymes that depend on αKG as a cofactor, remains to be elucidated. In addition, depleting glucose from the medium and preventing glucose carbons from entering central metabolism through inhibition of the first kinase in glycolysis, hexokinase, both block HIV infection[4,5]. In stark contrast, specifically blocking aerobic glycolysis through lactate dehydrogenase (LDH) inhibition increases HIV infection (Fig. 1a). During inhibition of LDH, glucose carbons can no longer be secreted as lactate. To determine the allocation of these carbons, the authors used carbon tracing and measured redirection into the pentose-phosphate pathway (PPP), a crucial metabolic pathway for nucleotide synthesis (glucose-derived carbon redirection into the PPP is blocked during hexokinase inhibition). This redirection could be partially mediated by the changes in the redox state of the cells after inhibition of LDH. Of note, the addition of exogenous nucleotides did not compensate for HIV infectiousness during glutamine depletion, whereas it did rescue $CD4^+$ T cell proliferation. Thus, the induction of proliferation after activation by the availability of nucleotides is insufficient to allow HIV infection in the absence of glutamine. Although glutamine-derived nitrogen is important for nucleotide biosynthesis, this result is consistent with the importance of glutamine-derived carbons to assimilate into TCA metabolites such as αKG.

Previous work has shown that inhibition of the mitochondrial pyruvate transporter complex also nullifies $CD4^+$ T cell infection by HIV[5], thus suggesting that shunting carbons from pyruvate into lactate can negatively affect the ability of HIV to infect $CD4^+$ T cells. However, Clerc et al. observed that the addition of extracellular lactate to $CD4^+$ T cell cultures enhanced HIV infection[4], thus suggesting that it is not lactate per se but rather the allocation of carbons from pyruvate that inhibits the infectious mechanism. In addition, import of glucose carbons into the TCA cycle

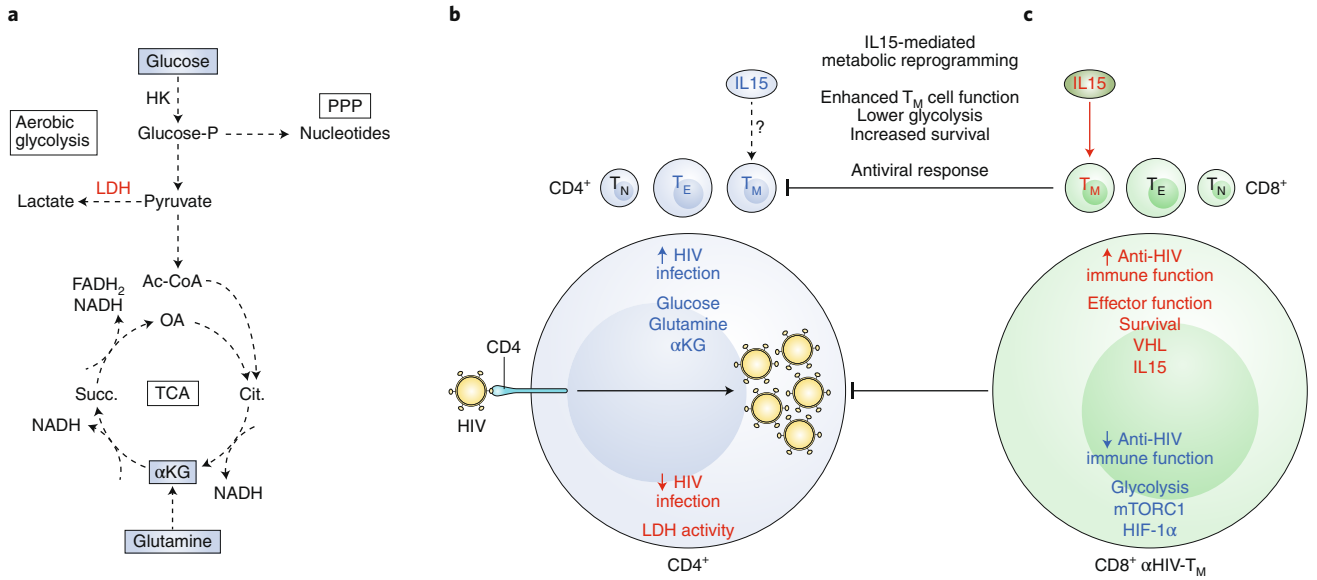

Fig. 1 | Metabolic requirements for HIV infection and antiviral T cell immunity. a, Glucose and glutamine fuel anabolic and catabolic metabolism in T cells after activation. Carbons from glucose are secreted as lactate as a result of aerobic glycolysis. Carbons of glucose and glutamine can enter the mitochondrial TCA cycle and ultimately lead to the generation of the cofactors NADH and $FADH_2$, which drive the electron-transport chain to produce ATP. HK, hexokinase; P, phosphate; Ac-CoA, acetyl-coenzyme A; OA, oxaloacetate; succ., succinate; cit., citrate. **b**, Depletion of glutamine leads to a decrease in HIV infection, which can be overcome by addition of αKG. The generation of lactate from pyruvate in $CD4^+$ T cells by LDH is a negative regulator of infection. T_N, naive T cell. **c**, Within the $CD8^+$ T_M compartment, αHIV-T_M cells are able to control infection in some patients. This control is associated with proper metabolic programming and a transcriptional profile associated with T_E cell function, survival and high *VHL* expression. T_M cells from ART-treated patients in whom HIV infection is not controlled are associated with higher glycolysis, an effect probably mediated by the key modulators of glycolytic metabolism mTORC1 and HIF-1α. Treatment of these cells with the cytokine IL15 leads to metabolic-pathway engagement associated with enhanced anti-HIV function. Factors in blue benefit HIV infection (**a**,**b**) or blunt αHIV-T_M cell function (**c**); factors in red negatively affect HIV infection (**a**,**b**) or benefit αHIV-T_M cell function (**c**).

was augmented by LDH inhibition[4]. This import could be mediating the differences in HIV infection, perhaps by increasing the generation of αKG from glucose.

Another study in this issue examined HIV-infected individuals exhibiting spontaneous immune control of the infection, which protected them against immune dysfunction and increased viral load. To elucidate the mechanism by which immune control is regulated, Angin et al. compared HIV-specific $CD8^+$ T_M (αHIV-T_M) cells from spontaneous controllers to HIV-specific $CD8^+$ T cells from individuals on ART who were unable to control the infection[7]. Transcriptional profiling at the single-cell level revealed gene signatures related to enhanced glycolysis, proliferation and exhaustion in dysfunctional αHIV-T_M cells. In contrast, αHIV-T_M cells from spontaneous HIV controllers showed a single-cell transcriptional profile associated with survival and effector T cell functions. Key regulators of glycolysis in T cells, such as hypoxia inducible factor 1 alpha (HIF-1α) and mechanistic target of rapamycin complex 1 (mTORC1), were differentially expressed between the groups, and αHIV-T_M cells from non-controllers presented a more glycolytic phenotype. In support of the gene-expression differences, the αHIV-T_M cells of spontaneous HIV controllers were metabolically flexible and less dependent on glucose.

Because T_M differentiation can be enhanced by dampening glycolysis during activation of $CD8^+$ T cells[8], the non-controlling αHIV-T_M might simply maintain the incorrect metabolic profile and consequently yield non-functional αHIV-T_M cells. The enhanced expression of glycolytic programs might be more reflective of terminally differentiated $CD8^+$ T cells, as substantiated by the enhanced expression of inhibitory receptors commonly associated with T cell exhaustion[7]. Although deletion of the Von Hippel–Lindau tumour suppressor (*Vhl*) and constitutive glycolytic engagement in mouse T cells has been shown not to be detrimental to the generation of effector T_M cells with antiviral activity during chronic infections[9], the data presented by Angin et al. suggest that higher expression of *VHL*, which suppresses glycolysis, is a hallmark of long-lived functional αHIV-T_M cells, which efficiently suppress HIV infection in autologous $CD4^+$ T cells.

To substantiate the importance of metabolic flexibility, the authors metabolically reprogrammed the non-controlling αHIV-T_M cells in patients undergoing ART. This reprogramming was achieved by ex vivo treatment with IL15, a cytokine that drives T_M differentiation in vitro in both human and mouse cells[3]. Treatment of non-controller αHIV-T_M cells with IL15 led to decreased expression of glycolysis-associated genes, upregulated effector function and enhanced control of HIV-infected $CD4^+$ T cells. A note of caution with using IL15 in vivo relates to the ability of $CD4^+$ T cells to also respond to IL15. This cytokine was previously shown to enhance HIV infection of $CD4^+$ cells[10]. IL15 signalling would also result in lower aerobic glycolysis and increased oxidative metabolism, thus implying that systemic treatment with IL15 might make $CD4^+$ T cells more permissive to HIV infection and lead to undesired increases in viral load (Fig. 1b). One such complication has been shown in a model of simian immunodeficiency virus infection in macaques, in which treatment with IL15 increased the viral set point and progression to acquired immunodeficiency syndrome in some animals[11]. Perhaps the development of a synthetic cytokine[12] might avoid the unwanted $CD4^+$ T cell effects and specifically enhance the function of αHIV-T_M by targeting IL15 to $CD8^+$ cells in vivo.

An adoptive therapy approach in which αHIV-T_M cells are metabolically reprogrammed ex vivo would also circumvent these complications, but how long this enhanced metabolic phenotype would be preserved in vivo is unclear. Thus, the question remains as to whether IL15-mediated metabolic reprogramming could be used as a one-off therapy to induce immunologically protective long-lived αHIV-T_M cells.

These two studies expand understanding of the metabolic obligations in HIV infection of $CD4^+$ T cells and the ability to engage non-controlling αHIV-T_M cells by reprogramming their metabolism. Integrating these data might bring researchers closer to designing a treatment modality that limits increasing viral load in the $CD4^+$ T cells of HIV-infected patients while simultaneously engaging existing αHIV-T_M cells to move a step further in the direction of removing the viral reservoir altogether. ❐

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Competing interests

The author declares no competing interests.