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Commentary

# Following the elite: Targeting immunometabolism to limit HIV pathogenesis

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Few people living with HIV (PLWH) have undetectable plasma viral load, preserved $CD4^+$ T cell counts, low HIV reservoir and limited immune activation/inflammation in the absence of antiretroviral therapy (ART). These individuals are called elite controllers (ECs) and represent a heterogeneous minority amongst PLWH. However, overtime, some of them lose HIV control. ECs who maintain viral control are called persistent controllers (PCs) while those who lose viral control are called transient controllers (TCs). As the underlying causes remain poorly understood, identifying factors associated with spontaneous loss of control will benefit HIV cure research [1,2].

Immunometabolism is rising to fame as the underlying mechanisms between metabolic reprogramming and immune response, thus providing a novel perspective of immunity in health and disease.

In this issue of *EBioMedicine*, Tarancón-Diez et al. investigated the metabolic pathways linked with the spontaneous loss of control in HIV ECs [3]. Using metabolomics, investigators from the Spanish AIDS Research Network compared plasma metabolites and lipids in persistent and transient controllers. Before losing control, TCs showed an increase in aerobic glycolysis, dysregulated mitochondrial activity, oxidative stress and immunological activation. Plasma levels of valine were found to differentiate TCs from PCs. Valine and related catabolic intermediates that could enter the tricarboxylic acid (TCA) Krebs cycle were elevated due to a switch from oxidative phosphorylation to glycolysis. In addition, lipid profiles characterized loss of viral control. Metabolites and lipid variations were associated with reduced HIV specific immune response demonstrated by a lower proportion of polyfunctional anti-HIV-Gag $CD8^+$ T-cells in TCs compared to PCs.

An immune response requires a massive amount of energy to allow cell proliferation, maturation, and production of effector molecules. Upon activation, both $CD4^+$ and $CD8^+$ T cells switch from a "resting state" of oxidative phosphorylation to glycolysis, allowing for a faster albeit more "costly" means to produce energy. In the same line, Valle-Casuso et al. found that metabolically active $CD4^+$ T cells are susceptible to HIV infection, regardless of their activation status [4]. Interestingly, targeting glycolysis and glutamine metabolism prevented HIV acquisition and viral production in $CD4^+$ T cells *in vitro*. Furthermore, investigators showed that inhibiting glycolysis induced higher levels of cell death in HIV-infected cells compared to uninfected cells. These converging findings pave the way for novel therapeutic strategies targeting immunometabolism to prevent HIV infection and reduce HIV reservoir size [4].

Importantly, an increase in glycolysis during HIV infection is not only restricted to T cell activation as monocytes, macrophages and dendritic cells also increase their ability to catabolize glucose upon detection of microbial products [5].

Hocini et al. recently found on a large number of patients strong HIV-specific immune responses and low inflammation in ECs compared to ART-treated patients, especially in CD4 and CD8 T cells [6]. This work also confirmed higher polyfunctionality of $CD8^+$ T cells in ECs [7]. Moreover, Chowdbury et al. described a distinct program of signaling pathways in $CD8^+$ T cells from ECs with higher activation of pathways regulated by mammalian target of rapamycin (mTOR), phosphoinositide 3 kinase/Protein kinase B (PI3K/AKT) and eukaryotic initiation factor 2 (eIF2) [8]. These pathways are particularly implicated in the regulation of proliferation and cellular metabolism.

Increased aerobic glycolysis is a hallmark of cellular proliferation and thus an underlying feature of cancer. However, modulating immunometabolism has proven difficult for cancer therapies. For instance, after promising results in mice models, recent trials showed no effect of indoleamine-2,3-deoxygenase (IDO) inhibitors in people with cancer [9].

The role of immunometabolic pathways in the pathogenesis of HIV infection is flourishing as technical advances are allowing for more precise measurements of metabolic activities in immune cells. Metabolic targeted therapies aiming at decreasing inflammation and HIV reservoir size in ART-treated PLWH are currently being tested in clinical trials with the immunosuppressive drug sirolimus/rapamycin (ClinialTrials.gov NCT02440789) and the anti-diabetic medication Metformin (NCT02659306) [10].

Overall, Tarancón-diez et al. [3] demonstrated the relevance of immunometabolism in HIV-infection and highlighted it as a potential therapeutic tool to enhance immune response with the hope to clear HIV from reservoirs.

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## Conflict of interest

The authors have no conflict of interest to disclaim.

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