The grace of aging with ART: *Ex vivo* dendritic cell-based immunotherapy restores HIV-specific functional CD8$^+$ T-cells

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The Nobel Prize in Physiology or Medicine 1953 was shared between Sir Hans Adolf Krebs, a German-British biochemist, and Fritz Albert Lipmann, a German-American biochemist for their pioneer work on metabolism.[1] The former earned it for his discovery of tricarboxylic (TCA) or Krebs cycle, and the later earned it for his discovery of coenzyme A that completed the gap in the initial Krebs cycle. TCA cycle being a major source of energy for cells plays an important role in aerobic respiration in the mitochondria. Emerging evidence places this cycle at the forefront of immunometabolism during health and disease as several of its metabolites such as acetyl-CoA and α-ketoglutaric acid are involved in immune regulation.[2]

HIV elite controllers (ECs) are rare and heterogenous group of people living with HIV (PLWH), who are characterized by the spontaneous control of viral replication and by the metabolic profiles that enhance CD8$^+$ T-cell cytotoxic function.[3] While, HIV control is durable in most of the persistent ECs, it is lost in transient ECs. Such changes in viral control have been associated with metabolomic signature comprising of TCA cycle, glycolysis and amino acid pathways.[4] Therefore, a thorough understanding of the immunometabolism of ECs represents a promising strategy towards a functional HIV cure. As metabolic plasticity and glycolytic activity are crucial for anti-HIV CD8$^+$ T-cell responses,[3] two studies have reported on elevated TCA cycle function in ECs.

Masip et al. reported among ECs with long-term viral and immunological HIV control vs no-long-term control to have elevated plasma levels of α-ketoglutaric acid.[5] This TCA cycle metabolite activates the mammalian target of rapamycin (mTOR) complex which is a regulator of cytotoxic function and glycolysis. Metformin, a proglycolytic anti-diabetic medication, acts by inhibiting mTOR by enhancing AMP-activated protein kinase. Metformin is also associated with anti-aging, anti-cancer and immune boosting properties.[6,7] Furthermore, Isnard et al. reported lower plasma levels of extracellular acyl-coenzyme A binding protein, a marker of optimal autophagic function and longevity in animal models, in ECs compared to ART-naÿve or ART-treated PLWH.[8]

In a recent issue of *eBioMedicine,* a study by Calvet-Mirabent et al. analyzed two subgroups of PLWH based on the duration of antiretroviral therapy (ART) below 10 years (n = 31) or above (n = 18).[9] These two groups differed in CD8$^+$ T-cell immunometabolic phenotypes and their ability to respond to *ex vivo* adjuvant-primed autologous monocyte-derived dendritic cell (MDDC) immunotherapy. Cytotoxic CD8$^+$ T-cells clearing HIV infected CD4$^+$ T-cells after DC immunotherapy were enriched only in PLWH who were on ART for 10+ years. In addition, CD8$^+$ T-cells in this group had lower expression levels of programmed cell death protein 1 (PD-1) and T-cell immunoreceptor with Ig and ITIM domains (TIGIT) checkpoint inhibitory receptors along with preserved metabolism, and central memory T-cell subsets. In contrast, dysfunctional CD8$^+$ T-cells unable to respond to adjuvant-activated DC therapy were enriched in PLWH on ART for less than 10 years, displaying higher proportions of PD1$^+$ TIGIT$^+$ cells and reduced mitochondrial fitness. Of note, DC immunotherapy in combination with the use of anti-PD1 and anti-TIGIT antibodies and metformin restored functionality of CD8$^+$ T-cells in this group. The study limitations include a small sample size and exclusion of other markers of CD8$^+$ T cell activation such as TNF-α. On the contrary, a variety of *in vitro* and *ex vivo* functional assays performed on patient samples strengthened the study.

Guo et al. by analyzing the transcriptome of CD4$^+$ T-cells of PLWH linked elevated oxidative phosphorylation

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(OXPHOS) pathway with disease progression. Inhibition of OXPHOS by metformin, which targets TCA, directly suppressed HIV-1 replication in $CD4^+$ T-cells.[10] Planas et al. reported that metformin in non-diabetic PLWH on ART reduced residual HIV-1 gene transcription in the gut-reservoir, but not in the blood where the drug concentration was very low. Metformin concentration in the gut vs in other tissues, such as liver and lymph nodes constitutes a potential limitation of this drug.[7] Altogether, these studies suggest that metformin may be a candidate for block and lock strategies, as this commercialized anti-diabetic drug enhances $CD8^+$ T-cell function and reduces low level of HIV replication that persists on ART.

The work by Calvet-Mirabent et al.[9] is encouraging as long-term ART can further improve immune response. In addition, adjuvant-primed autologous MDDC combined with metformin represents potential therapeutic option in different groups of PLWH with a shorter or a longer duration of ART. Along these lines, research on immunometabolism in the context of HIV is gaining momentum owing to the advances in molecular medicine. Finally, developments in DC-based HIV-1 vaccine may pave the way towards a functional HIV cure.

Contributors

VM and JPR drafted the commentary. VM, JA, and JPR contributed to the literature search. All authors contributed in writing and critical editing of the commentary. All the authors reviewed the final version of the commentary and approved its submission.

Declaration of interests

All authors have no conflicts of interest to declare.

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