Disrupted alpha-ketoglutarate homeostasis trained monocyte-derived macrophages towards M2-like phenotype increase HIV infectivity in treated infection

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**Abstract**

Cells of the myeloid lineage, particularly monocytes and macrophages, play a key role in HIV infection by contributing to viral replication, immune response, and maintaining immune balance during suppressive therapy. We hypothesized that metabolic reprogramming and altered chemokine signaling in people living with HIV (PWH) on long-term antiretroviral therapy (ART) affect monocyte transport and polarization due to ongoing inflammation. Therefore, the present study aimed to identify the mechanism of impaired monocyte/macrophage function in PWH on suppressive ART that can lead to clinical intervention strategies to improve health. Single-cell RNA sequencing, immune-phenotyping, and metabolic modeling identified altered expression of chemokine and metabolite receptors and altered metabolic flux in PWH monocytes that amplify altered monocyte migration. The plasma secretome revealed a nonclassical inflammatory microenvironment in PWH. Integrative multi-omics and single-cell proteomics of differentiated monocyte-derived macrophages (MDMs) detected metabolic reprogramming orchestrated by α -ketoglutarate (AKG) that affected macrophage function and HIV infection. Increased levels of AKG in plasma were shown to occur in PWH under ART. Therefore, when differentiating MDM with serum from the PWH or AKG, macrophage function was found polarized towards an M2-like state. AKG alone was shown to increase CCR5 levels and increase HIV-1 infection in MDM. Here, we show systems biology-driven identification and ex vivo assays of impaired macrophage polarization due to metabolic training, which leads to a low-grade nonclassical inflammatory environment in PWH.