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"Assessment of metabolic profile in monocytes from PLWH and role of cART in increasing mitochondrial respiration and glycolysis"

Human Immunodeficiency Virus (HIV) is a retrovirus that attacks the immune cells of the body, specifically $CD4^+$ T cells, macrophages, and dendritic cells. To mitigate viral replication in patients, combined antiretroviral therapy (cART) is administered daily. Such treatment, while not completely eliminating the virus from infected individuals, greatly increases the life span of these patients and reduces the risk of further transmission through a reduction of viral load and restoration of the $CD4^+$ T cell count. However, People Living with HIV (PLWH) undergoing cART still have a dysfunctional immune system that may lead to secondary illnesses, including cancer.

Monocytes and macrophages are key players of the innate immune system. When monocytes are exposed to consecutive treatments with microbial products such as the fungal β-glucan or the lipopolysaccharides (LPS) of gram-negative bacteria, epigenetic and metabolic remodeling lead to the development of trained or tolerant phenotypes. Trained cells are characterized by an increased production of pro- inflammatory cytokines (called hyper-responsiveness), such as IL-6, IL-1β, and TNF-α. In contrast, tolerant phenotypes are characterized by hypo-responsiveness upon the same exposure to LPS.

IKAROS, a transcription factor encoded by the IKZF1 gene, is a master regulator of hematopoiesis, as well as lymphocyte differentiation and function. Our laboratory has previously found that monocytes from PLWH display hyper-responsiveness to consecutive LPS treatments and are incapable of establishing a tolerant phenotype compared to HIV^- control cells. Furthermore, our laboratory has identified IKAROS as a critical factor in this imbalanced immune response. Since trained immunity is linked to metabolic reprogramming, we sought to investigate whether cART can alter the metabolism of monocytes and whether IKAROS has a role in the cART-mediated effects.

We utilized $CD14^+/CD16^-$ monocytes from PLWH and HIV^- controls, as well as the THP-1 monocytic cell line and found that monocytes from PLWH or from HIV^- controls treated with cART had increased mitochondrial respiration and glycolysis compared to untreated controls. In addition, THP-1 cells treated with cART displayed a metabolic profile comparable to the one of PLWH. Similar to our previous data obtained in PLWH, Western blot analysis of THP-1 cells treated with cART showed a reduced expression of IKAROS. Altogether, our data suggest that cART could be responsible for the increased metabolism in PLWH. Future experiments are aimed at understanding the role of IKAROS in the cART-induced dysfunctional responses in monocytes.