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Contribution of cART to the modulation of IKAROS expression in PLWH

Background: People living with HIV (PLWH) can live long, healthy lives on combined antiretroviral therapy (cART). Though these drugs can lower viral load to undetectable amounts, PLWH receiving treatment still face greater risk of secondary illnesses, chronic inflammation, cancer, and other diseases. Previous work from the Peruzzi lab detailed a role by which an attenuation in the expression of the transcription factor IKAROS leads to immune and metabolic dysregulation of monocyte derived macrophages (MDMs) from PLWH. These MDMs did not establish endotoxin tolerance in response to lipopolysaccharide (LPS) challenge. Rather, they showed hyperresponsiveness with increased pro inflammatory cytokines and increased oxidative phosphorylation beyond those of controls.

Objective: Determine if THP1 cells and primary MDMs from HIV (-) controls receiving cART shows downregulation of IKAROS and metabolic changes consistent with those from PLWH derived MDMs.

Methods: Western blots were used to determine the expression of IKAROS in the human THP1 monocytic cell line and MDMs from HIV (-) controls treated or untreated with cART for 3 or 5 days, respectively. The antiretroviral drug treatments were tenofovir (TDF), emtricitabine (EMT), and raltegravir (RAL) administered individually and in combination (cART). To test the effect of cART on metabolic reprogramming, metabolic profiles under mitochondrial and glycolysis stress on the same sets of samples were performed using a seahorse bioanalyzer.

Results: Relative to the untreated group, THP1 cells in the TDF, EMT, and cART treatment conditions consumed more oxygen at baseline. The TDF and cART treatments exhibited greater maximal respiration and spare respiratory capacity. Similarly, the extracellular acidification rate for the TDF, EMT, and cART treatment groups exceeded UNT at baseline and had a greater glycolytic capacity. MDMs treated with cART showed reduced levels of IKAROS and increased mitochondrial respiration compared to untreated cells.

Conclusions: THP1 cells and MDMs obtained from HIV (-) controls exposed to antiretroviral drugs exhibit similar metabolic dysregulation to PLWH MDMs. Increases in both glycolysis and oxidative phosphorylation along with a reduction of IKAROS suggests a hyperactive cell biased toward an inflammatory response. This is consistent with previous work in the Peruzzi lab.