Immunometabolic Reprogramming by Caloric Restriction Leads to Protection from SIV in Rhesus Macaques

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BACKGROUND

- Nutrient metabolism regulates HIV-1 replication, antiviral immunity, and chronic inflammation.
- However, modulating metabolic processes relevant to HIV-1 through small molecule drugs suffer from limitations relating to potency and toxicity.
- Caloric restriction (CR) is a safe modality with known anti-inflammatory and anti-aging effects.
- CR has led to positive outcomes in mice infected with Plasmodium sp. and Mycobacterium tuberculosis (Mtb).
- We therefore hypothesized that CR could improve viral control in SIV-infected rhesus macaques (RM).

METHODS



Figure 1. Implementation of caloric & time-restricted feeding

Six, middle-aged adult, non-obese, male and female rhesus macaques were given ad libitum access to food at defined hours of the day (800-1600) and daily chow intake was recorded within time-restricted (TR) feeding conditions. Following this, their caloric intake was reduced sequentially by 10% until a state of 30% caloric restriction (CR) was achieved.

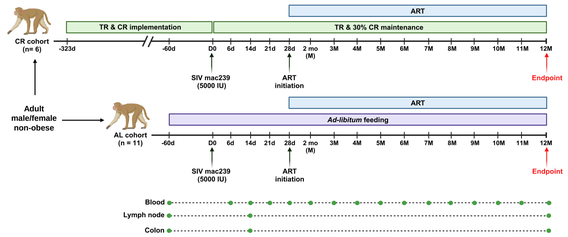


Figure 2. SIV infection of CR and AL-fed macaques

Following 4 months of CR and TR, animals were infected i.v. with 5000 IU of SIVmac239, left untreated for 28 days, and then received a 10-month daily ART regimen while maintaining dietary regulation. CR animals were compared to a group of age-, gender-, and enrollment weight-matched RMs (n=10) that had ad lib access to food at all hours of the day. Blood, lymphoid tissues, and colon were sampled longitudinally.

Caloric and time restricted feeding in rhesus macaques leads to broad metabolic reprogramming and significantly improves SIV disease outcomes[a]

RESULTS

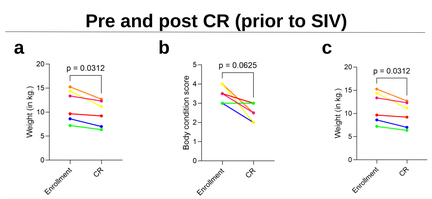


Figure 3. CR resulted in modest weight loss: (a) Weight, **(b)** body condition scores (5=obese,, 1=emaciated), and **(c)** plasma glucose levels (mg/dL) (*right*) at enrollment and after 3 months of 30% CR.

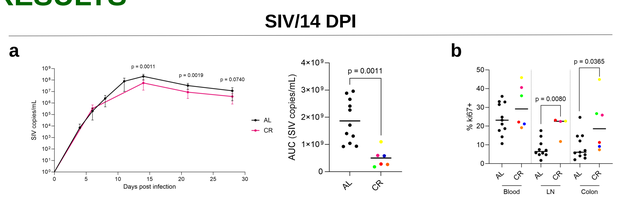


Figure 4. CR reduced plasma viral load and enhanced CD8+ T cell cycling at sites of early SIV replication: (a) PCR quantification of SIV viral copies in the blood (*left*) and the corresponding area under the curve (AUC) (*right*). **(b)** %ki67+ CD8+ Tcm (central memory) across different tissues.

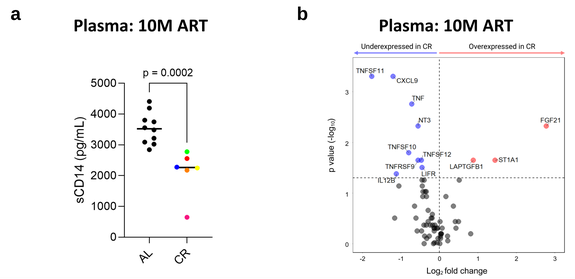


Figure 7. CR preserves gut barrier integrity and reduces systemic inflammation during ART: (a) Plasma levels of gut barrier integrity marker: soluble CD14 (sCD14). **(b)** Plasma levels of cytokines and chemokine measured via Olink Assay.

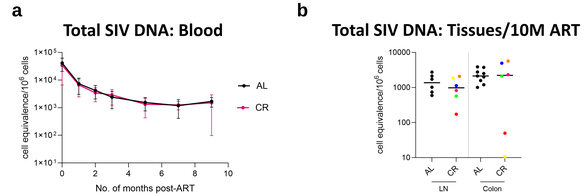


Figure 8. Promoting GI repair and reducing systemic inflammation with CR does not lead to lower SIV reservoirs during ART: (a) PCR quantification of SIV gag DNA in the blood during ART. **(b)** PCR quantification of SIV gag DNA in lymph nodes (LN) and colon at 10M ART. Data is expressed as cell equivalence per million CCR5+ CD4+ T cells.

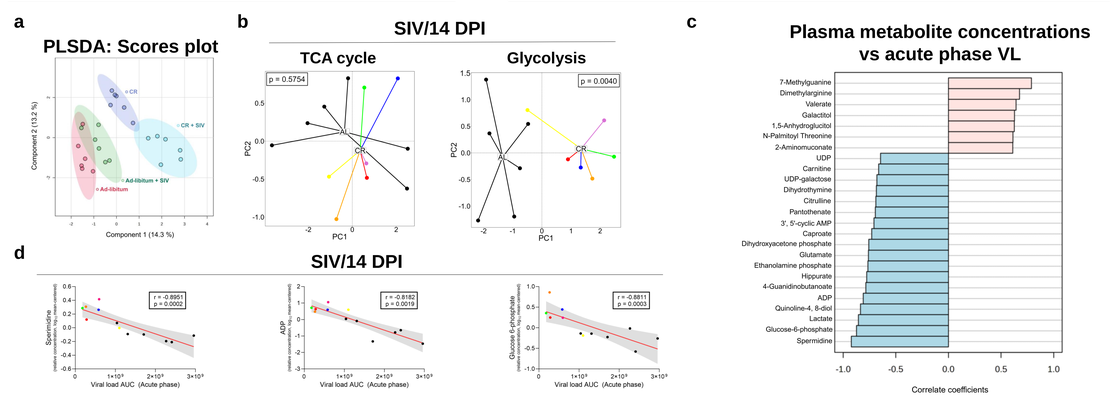


Figure 5. CR skews the acute phase metabolic response to SIV towards glycolysis, which is associated with protection: (a) PLSDA analysis of plasma metabolome (326 metabolites). **(b)** PCA plot of plasma TCA cycle and glycolytic metabolites at 14 dpi. **(c)** Correlation between plasma metabolites and viral load AUC. **(d)** LASSO regression revealed a set of 3 metabolites: Spermidine (*left*), ADP (*middle*), Glucose 6-phosphate (*right*) whose levels in plasma best predicted acute phase viremia.

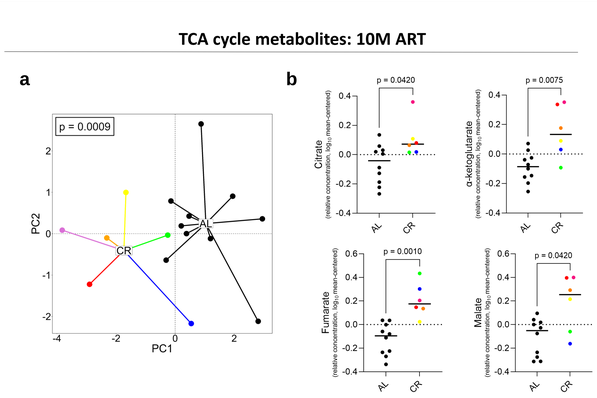


Figure 9. The plasma metabolome shifts from favoring glycolysis during acute SIV to favoring the TCA-cycle during ART: (a) PCA plots of key TCA cycle metabolites in the plasma and **(b)** their relative concentrations.

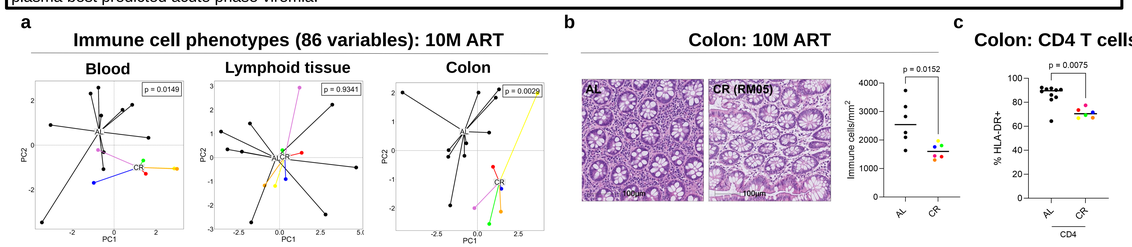


Figure 6. CR reduces immune infiltration and CD4 T cell activation in the colon during ART: (a) PCA plots of immune phenotypes across different tissues at 10M ART. **(b)** Representative image of H&E staining of colon (*left*) and quantification of immune cells/mm2 (*right*) at 10M ART. **(c)** Percentage of HLA-DR+ CD4+ T cells in the colon at 10M ART.

CONCLUSIONS

- CR was safe and well tolerated, even during acute SIV.
- CR reduced acute phase VL and increased the cycling of CD8+ T cells at sites of SIV replication.
- Plasma metabolomes were glycolytically skewed in CR and correlated inversely with acute phase viremia.
- CR improved gut reconstitution and reduced systemic inflammation during ART.
- Inflammatory markers were decoupled from persistence of the SIV reservoir.