MULTI-OMICS ANALYSES REVEAL IMMUNOMETABOLIC REPROGRAMMING-DEPENDENT HIV-1 REPLICATION

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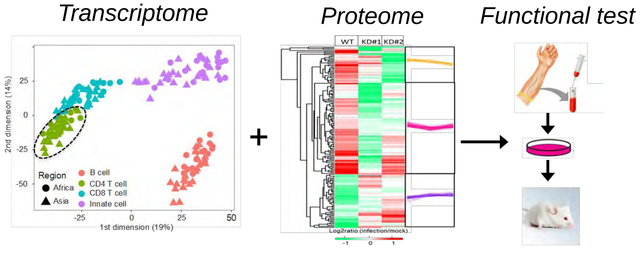
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BACKGROUND

Immune cells metabolism (immunometabolism) is altered in HIV-1 infected individuals and it is associated with viral replication, immune abnormalities and complications. But, the causative metabolic signatures for HIV-1 disease outcomes are lacking and the mechanisms underlying how HIV-1 infection reprograms immunometabolism is elusive. So, it is of emerging importance to dissect the cross talk between HIV-1 infection and metabolic influxes at the molecular level. The nucleotide-binding, leucine-rich-repeat –containing protein NLRX1 is a novel host factor identified by our group for HIV-1 replication in myeloid cells. Since NLRX1 expresses in CD4 T cells and mainly resides in mitochondria, thus presents a high potential to shape metabolism. We are testing whether NLRX1 has an interaction with the immunometabolism to impact HIV-1 replication in CD4 T cells in this study.

METHODS

- First, we analyzed CD4 T cell transcriptomic data of HIV-1+ patients to search the association between metabolic pathways and HIV-1 set point viral load.
- Second, we suppressed the metabolic pathways by pharmacological inhibitors and test the impact in HIV-1 replication in primary CD4 T cell cultures and human CD4 T cell-reconstituted humanized mice.
- Third, we silenced *NLRX1* gene expression in human CD4 T cells and tested its impact in the metabolic influx and HIV-1 replication.



Research methodology scheme

RESULTS

Oxidative phosphorylation (OXPHOS) level correlates with HIV-1 set point viral load

Fig. 1. Gene Set Enrichment Analysis (GSEA) was used to test the association of metabolic pathways with set point viremia levels in the Asian and African RV217 cohorts. Bar-plot represents positively (red) and negatively (blue) correlated pathways.

Elevation of OXPHOS in HIV-1 infected CD4 T cells is dependent on NLRX1

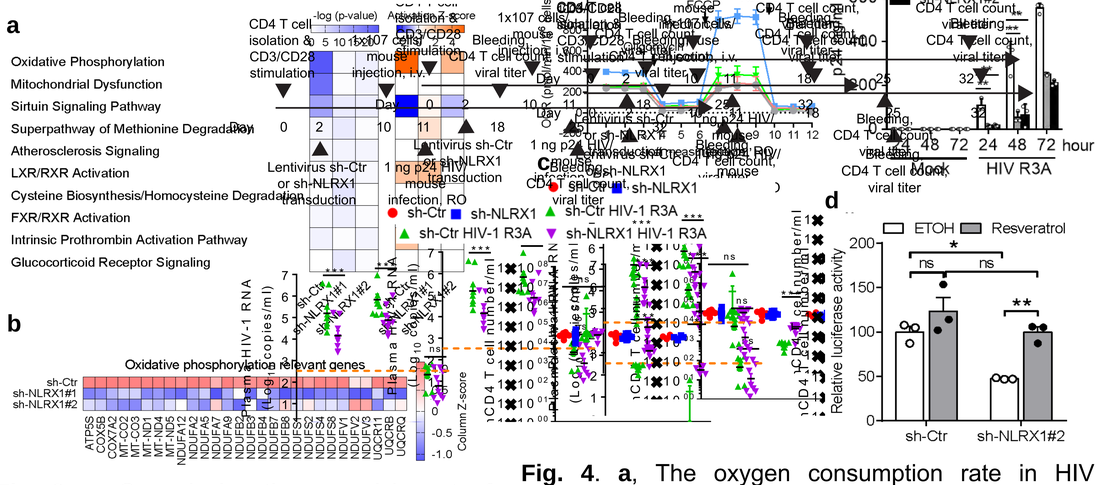


Fig. 3. **a**, Canonical pathway enrichment of differentially expressed genes (infection/mock, fold change ≥2). **b**, Expression change of gene products involved in oxidative phosphorylation (infection/mock, fold change ≥2)..

Inhibition of OXPHOS suppresses HIV-1 replication in both primary CD4 T cells and humanized mice

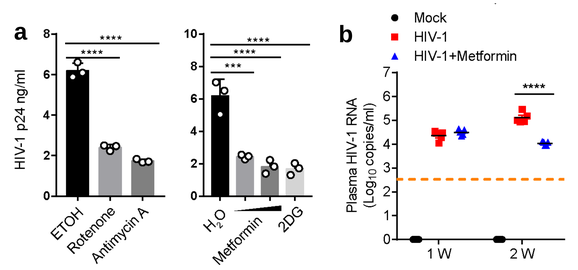
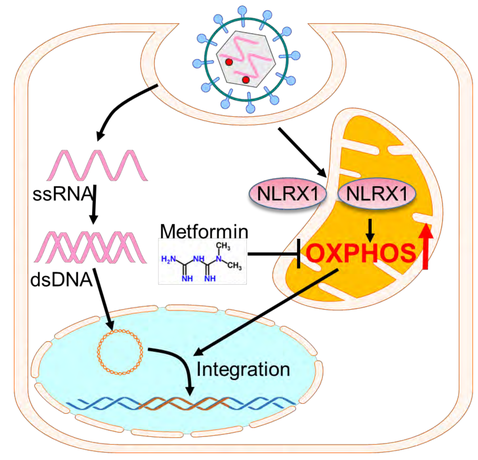


Fig. 2. **a**, Human primary CD4 T cells were infected with HIV-1 clinical isolates under the treatment of metabolism inhibitors and cell-released virions were assessed by p24 ELISA. **b**, Mice reconstituted with human CD4 T cells were infected by HIV CCR5/CXCR4 dual tropic strain R3A under the treatment of metformin. HIV viremia were assessed.

NLRX1 promotes HIV-1 replication via OXPHOS

Fig. 4. **a**, The oxygen consumption rate in HIV infected Jurkat T cells. **b, c**, HIV-1 virion release in NLRX1-silenced and control human CD4 T cells (**b**) and those cells reconstituted mice (**c**). **d**, HIV-1-Luc replication in NLRX1-silenced and control human CD4 T cells under the induction of OXPHOS by resveratrol.

CONCLUSIONS



- Oxidative phosphorylation (OXPHOS) is up-regulated in HIV-1 infected CD4 T cells and directly correlates with HIV-1 set point viral load.
- Inhibiting OXPHOS by FDA-approved drug metformin suppresses HIV-1 replication in primary CD4 T cells and humanized mice.
- NLRX1 contributes to the elevation of OXPHOS in HIV-1 infected CD4 T cells.
- Silencing NLRX1 reduces HIV-1 replication in CD4 T cells, which can be restored by enforcing OXPHOS.

This study discovered a mechanism of HIV-1-regulated elevation of OXPHOS, thus raise the promise of controlling HIV-1 replication by targeting the NLRX1-OXPHOS axis.

ACKNOWLEDGEMENTS

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