HIV gp120 Alters the Human Macrophage Immunometabolic Response to *Mycobacterium tuberculosis*, and Impairs TNFα Secretion

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INTRODUCTION

- HIV co-infection is a major driver of the TB epidemic[1].
- People living with HIV (PLWH) remain at increased risk of TB despite successful treatment with antiretroviral therapy (ART)[2].
- Reprogramming of cellular metabolism remains central to host defence against TB[3], yet its role in HIV is less clear[4].
- Macrophage metabolism of TB/HIV co-infection remains largely unstudied[5], yet represents an important avenue of potential therapeutic intervention.
- We examined the effect of HIV co-infection on the host immunometabolic response to Mtb infection using HIV envelope glycoprotein 120 (gp120) as a model of HIV infection.
- HIV gp120 freely circulates in the serum of PLWH, despite treatment with ART[6], and therefore represents a good model of chronic treated HIV infection.

METHODS

- Peripheral blood mononuclear cells were isolated from buffy coats and monocyte-derived macrophages (MDM) were matured by plastic adherence.
- MDM were stimulated with HIV *env* gp120 for 24hr prior to bioenergetic analysis on the Agilent Seahorse XF24 Analyser.
- Bioenergetic flux analysis was performed using two Mtb infection protocols: an acute injection protocol, whereby MDM received an injection of gamma-irradiated Mtb (iH37Rv) in real-time; and a MitoStress protocol, whereby MDM were infected with iH37Rv 30 minutes prior to bioenergetic analysis.
- Cytokines were measured using sandwich ELISA.
- Data was analysed in Microsoft Excel®. Figures were generated in GraphPad Prism®. Appropriate statistical analyses were performed using GraphPad Prism® software, with $p < 0.05$ defined as statistical significance.

RESULTS

Human monocyte-derived macrophages (MDM) were stimulated in real-time with irradiated Mtb. HIV *env* gp120 pre-treatment at low (100ng/ml, purple) and high (5,000ng/ml, red) dose altered the immediate oxygen consumption (OCR) and extracellular acidification (ECAR) rate responses to Mtb (**A**). Overall OCR and ECAR are further demonstrated by area under the curve analysis (**B**).These metabolic alterations shifted the energetic phenotype from glycolytic to energetic (**C**). (n = 8)

Fig. 1

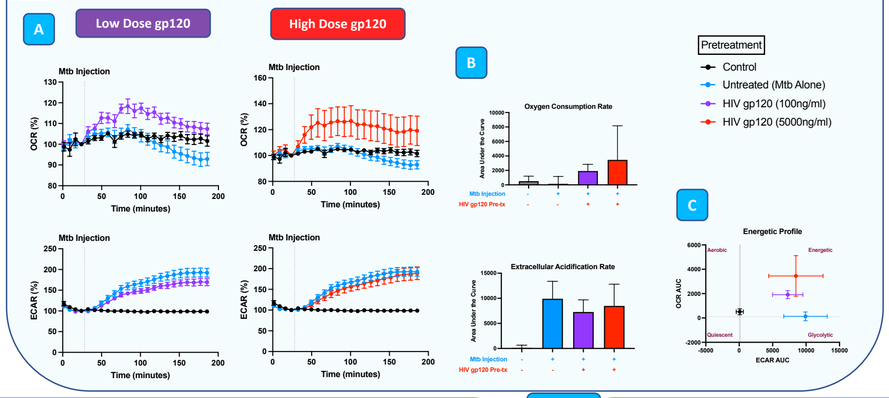


Fig. 2

Further examination of mitochondrial respiration by Mitochondrial Stress Test (**A**) demonstrated trends towards decreased maximal respiration (**C**) and spare respiratory capacity (**D**), and increased non-mitochondrial respiration (**E**) in HIV *env* gp120 pre-treated groups. (n = 3)

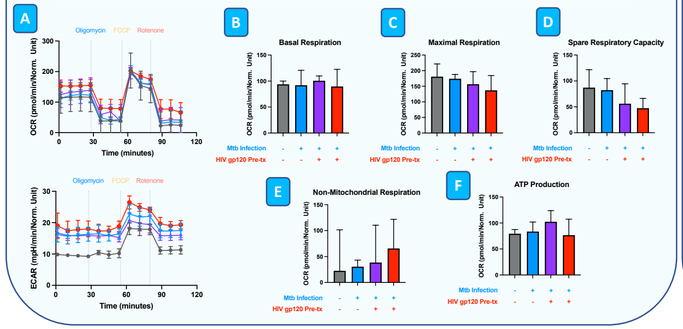
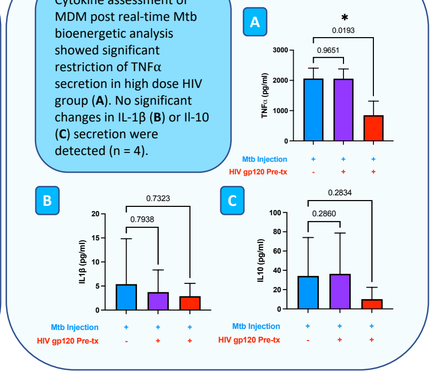


Fig. 3

Cytokine assessment of MDM post real-time Mtb bioenergetic analysis showed significant restriction of TNFα secretion in high dose HIV group (**A**). No significant changes in IL-1β (**B**) or Il-10 (**C**) secretion were detected (n = 4).



CONCLUSIONS

- Mtb infection of human macrophages induces a metabolic profile consistent with increased glycolysis and TCA cycle rewiring, which has been shown to be crucial for host defence against Mtb[7].
- Our data demonstrates that pre-treatment of human MDM with HIV *env* gp120 alters this Mtb-induced metabolic profile.
- HIV *env* gp120 circulates freely in the serum of people with HIV who are treated with antiretroviral therapy[6], potentially enabling persistent stimulation of HIV-uninfected cells.
- We demonstrate that low dose gp120 significantly alters the immediate metabolic phenotype of human MDM upon Mtb infection.
- In-depth interrogation of cellular oxygen consumption demonstrated a trend towards decreased maximal respiration and spare respiratory capacity, and increased non-mitochondrial respiration in both low and high dose gp120 groups.
- TNFα is considered one of the most critical cytokines in host defence against Mtb[8], yet the relationship between TNFα and macrophage immunometabolism remains a novel paradigm[9].
- We find that high dose gp120 significantly impairs human MDM TNFα secretion in response to Mtb infection.
- These HIV-induced changes in the macrophage immunometabolic response to Mtb might help explain the persistent risk of TB infection in people living with HIV, despite adequate treatment.

ACKNOWLEDGEMENTS

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