NON-HUMAN PRIMATE MODEL OF LONG-COVID: IMMUNE INSIGHTS OF GLYCOMETABOLIC DYSFUNCTIONS

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BACKGROUND

- We investigated the immune basis of long-term glycometabolic disruptions in a non-human primate model of SARS-CoV-2 infection.

A major consequence of COVID-19 is long-term metabolic complications (metabolic PASC or Long COVID) following acute disease resolution. However, the mechanisms underlying the links between COVID-19 and glycometabolic disruptions remain unclear.

METHODS

- 15 African green monkeys (AGM; *Chlorocebus aethiops*) were infected with SARS-CoV-2 (Wuhan stain), 5 received the BNT162b2 vaccine 4-days post infection. All animals were monitored for 18 weeks **(Fig. 1A)**.
- Plasma proteins were analyzed using antibody binding oligonucleotide amplification technology (Proximity Extension Assay) **(Fig. 1B)**.
- STRING was used to identify enriched protein networks **(Fig. 1B)**.

Our SARS-CoV-2 AGM model validates phenotypes of **metabolic PASC** and offers an opportunity to mechanistically study the **immunometabolic manifestations** of PASC. Vaccination post-infection may improve long-term glycometabolic homeostasis.



RESULTS

- The presence of genomic SARS-CoV-2 RNA in pharyngeal and nasal swabs confirmed infection of AGMs (**Fig. 2**).
- Hyperglycemia is observed as early as 3 days post-infection and is maintained over the study period. Vaccination post-infection has favorable metabolic effects (**Fig. 3**).
- Plasma analytes linked to chemotaxis networks are differentially regulated early and late post-infection (**Fig. 4-5**). Among these GDNF is positively associated with blood glucose (**Fig. 6**).
- Hyperglycemia may be linked at least in part to dysregulated liver glucose homeostasis (**Fig. 7**).

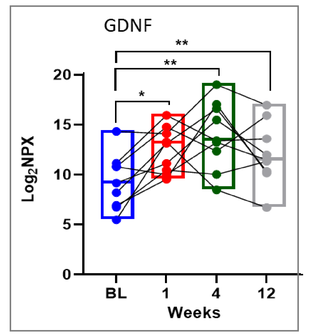


Figure 6. Glial Neurotrophic Factor (GDNF) is persistently elevated in SARS-CoV-2 infected unvaccinated AGMs, and positively correlates with blood glucose levels over time.

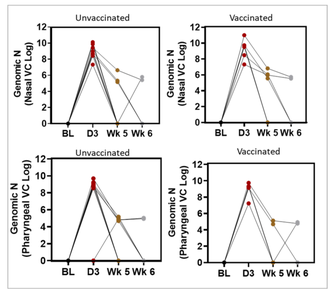
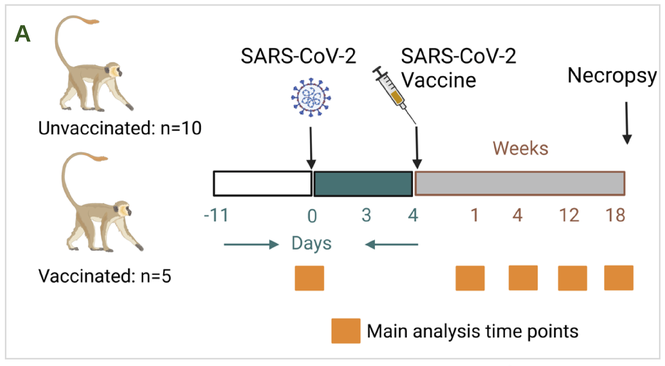


Figure 2. Kinetics of nasal and pharyngeal genomic RNA in unvaccinated and vaccinated animals.



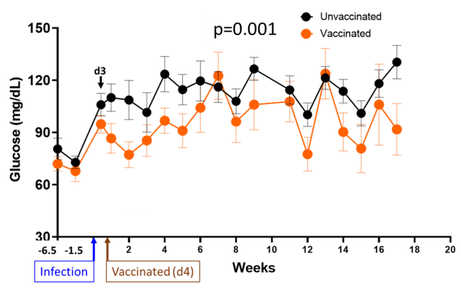


Figure 3. SARS-CoV-2 infection induces early-onset hyperglycemia that persists. PERMANOVA reveals vaccinated animals have lower glucose levels over time.



Figure 1. AGMs were infected with SARS-CoV-2 and evaluated over 18 weeks (A). Plasma protein assay and network analysis identified deferentially regulatory pathways.

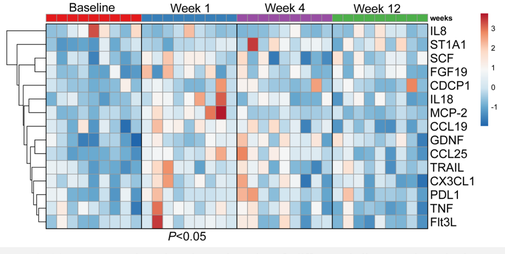


Figure 4. Heat map showing how levels of differentially regulated plasma analytes at week 1 change over time.

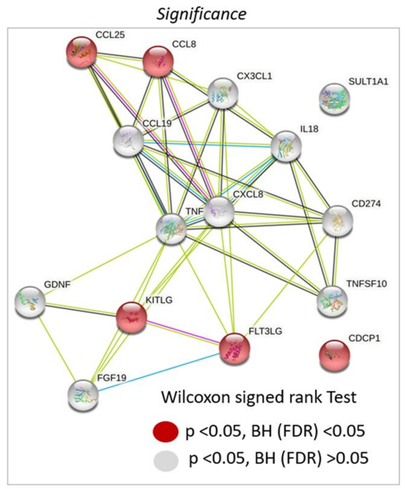
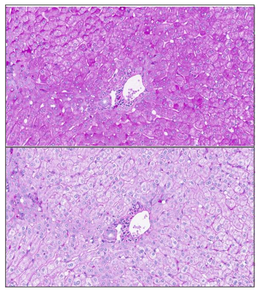


Figure 5. STRING analysis identifies *regulation of chemokine migration* as the top ranked functionally enriched network (FDR=1.38E-06). Circles represent differentially regulated analytes at week 1. FDR<0.05 (red), raw p <0.05 (grey).



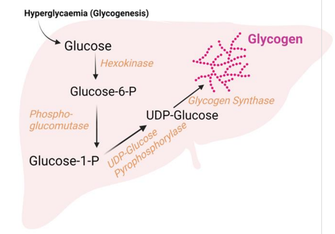


Figure 7. (A) Schiff's stain (for glycogen) of liver without (upper panel) or with diastase treatment (lower panel). (B) Increased levels of liver glycogen at necropsy in animals infected short term (4 weeks study; PMID: 33171111) or long-term (18 weeks). (C) Prosses involved in glycogen storage in liver. Increased glycogen storge and induction of glycogenolysis may contribute to persisted hyperglycemia in infected AGMs.

CONCLUSIONS

- Our AGM model validates phenotypes of metabolic PASC and offers an opportunity to mechanistically study the manifestations of PASC.
- Vaccine-preventable early insults by metabolic-regulating immune factors may contribute to long-term dysregulated liver and systemic glucose homeostasis during PASC.
- These immune factors warrant further investigation for their mechanistic links to PASC.

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