SARS-CoV-2 Infected Macaques Exhibit Microbial Translocation Across Intestinal Mucosa

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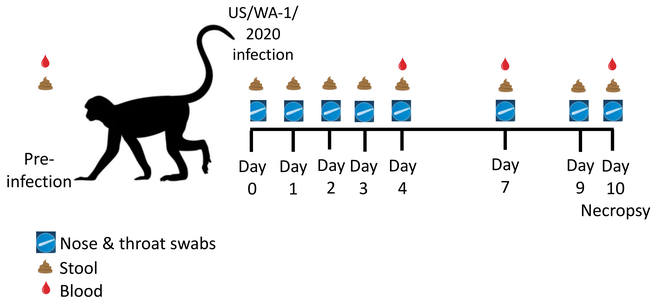
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BACKGROUND

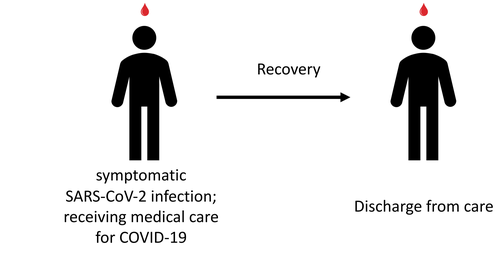
SARS-CoV-2 infections may include gastrointestinal symptoms such as nausea and diarrhea. However, intestinal pathology has not been extensively described in humans or animal models. Here we examine gut pathology and corresponding inflammation in SARS-CoV-2 infected rhesus macaques and humans.

METHODS

- 14 rhesus macaques were infected with SARS-CoV-2 intranasally and intratracheally
- Sampling for 6 animals was performed according to the schedule below, with additional plasma from 8 animals collected pre-infection and at day 10
- Colon and mesenteric lymph nodes were taken at necropsy; tissues were fixed for histological analyses and processed into single cell suspension

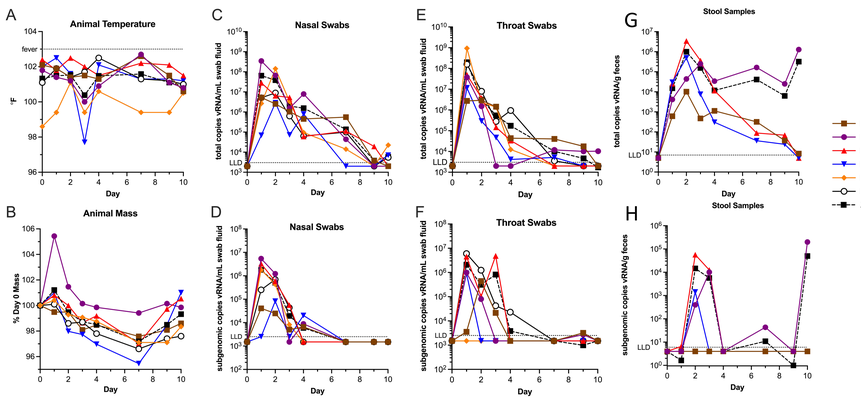


- Additionally, SARS-CoV-2 infected individuals were sampled cross-sectionally with two time points per individual: during the symptomatic phase of infection and following recovery

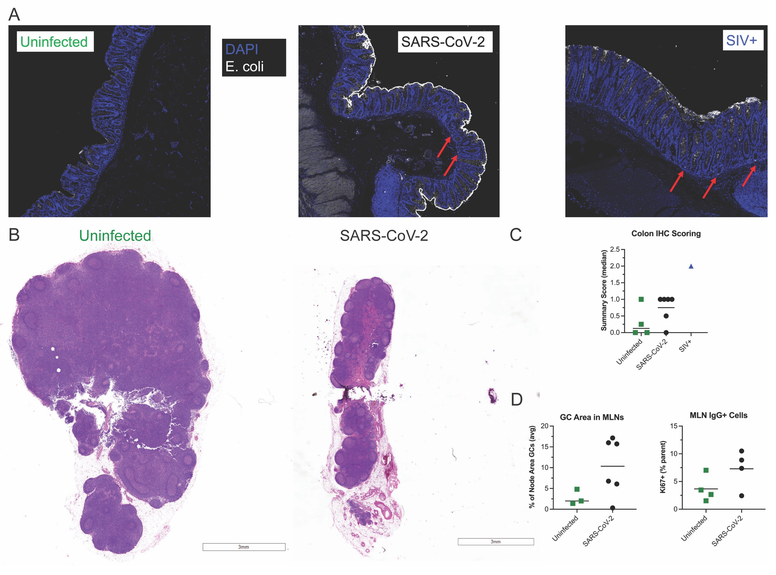


Mild SARS-CoV-2 infection in non-human primates nonetheless induces microbial translocation in the gut and corresponding systemic inflammation

RESULTS: MILD INFECTION IN MACAQUES COUPLED WITH VIRAL RNA IN STOOL AND MODEST MICROBIAL TRANSLOCATION IN COLON

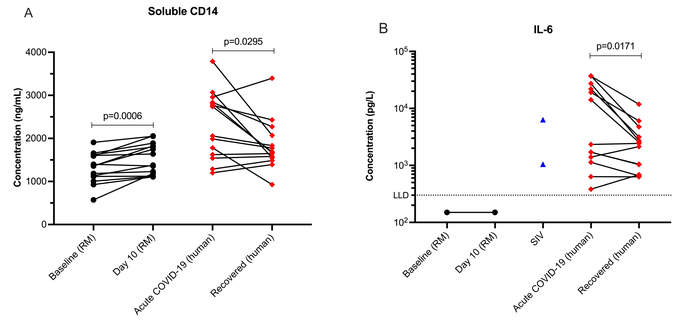


A) Intrarectal temperatures of 6 macaques. None experienced fever (temperature >103°F).
B) Animal change in mass, expressed as percent of Day 0 mass. Loss <5%.
C) Total viral RNA (vRNA) load in nasal swab fluid.
D) Subgenomic vRNA (sgvRNA) load in nasal swab fluid. sgvRNAs are viral mRNAs and indicate replication.
E) Total vRNA in throat swab fluid.
F) sgvRNA in throat swab fluid.
G) Total vRNA in stool samples.
H) sgvRNA in stool samples.



A) Immunohistochemisty (IHC) images for uninfected (left), SARS-CoV-2 infected (center), and SIV infected (right) colon tissue of rhesus macaques. Microbial products translocated across the gut epithelial layer are indicated with red arrows.
B) Hematoxylin and eosin (H&E) staining of mesenteric lymph nodes (MLN) from uninfected (left) and SARS-CoV-2 infected (right) macaques.
C) Median summary scores of microbial translocation in uninfected, SARS-CoV-2 infected, and SIV infected colon tissue stained by IHC and represented in **A**. Median scores are reported for 1-7 images per animal independently scored by 4 individuals without indication of the infection group at scoring.
D) Germinal center area as a percent of the total MLN area determined from H&E slides shown in **B** (left). Percent of MLN IgG+ cells Ki67+ (right) as determined with flow cytometry.

RESULTS: SYSTEMIC INFLAMMATORY MARKERS IN MACAQUES AND HUMANS



A) Soluble CD14 (sCD14) in rhesus macaques and humans. sCD14 is produced by activated monocytes/macrophages and indicates an inflammatory response to microbes or microbial products. Wilcoxon matched-pairs test performed.
B) IL-6 in rhesus macaques and humans. LLD=lower limit of detection of assay. All macaque samples during SARS-CoV-2 infection were below LLD for IL-6, although SIV+ controls were detectable. Wilcoxon matched-pairs test performed.

CONCLUSIONS

Despite mild infection, rhesus macaques with SARS-CoV-2 shed viral RNA in feces and experienced modest microbial translocation across the gut epithelium with a corresponding increase in sCD14. Symptomatically infected individuals likewise experienced a significant decrease in sCD14 and IL-6 following recovery from COVID-19, suggesting that SARS-CoV-2 infection causes gastrointestinal pathology that may contribute to systemic inflammation noted in COVID-19.

ACKNOWLEDGEMENTS

We are indebted to the efforts of the NIH Tuberculosis Imaging Program, the NIH Animal Center team, and the Yerkes National Primate Research Center animal care team for their exemplary management of study infections and attention to animal welfare.

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