Interferon Resistance of Emerging SARS-CoV-2 Variants

University of Colorado Anschutz Medical Campus

Kejun Guo[1], Bradley S Barrett[1], Kaylee Mickens[1,2], Kim J Hasenkrug[3], and Mario L Santiago[1,2]

[1] *Division of Infectious Diseases, Dept. of Medicine, Univ. of Colorado AMC, Aurora, CO 80045*
[2] *Dept. of Immunology and Microbiology, Univ. of Colorado AMC, Aurora, CO 80045*
[3] *Rocky Mountain Laboratories, NIAID, NIH, Hamilton, MT 59840*

Abstract

- The emergence of SARS-CoV-2 variants with enhanced transmissibility, pathogenesis and resistance to vaccines presents urgent challenges for curbing the COVID-19 pandemic.
- Studies that documented a critical role for interferon responses in the early control of SARS-CoV-2 infection, combined with the presence of viral genes that limit these responses, suggest that interferons may also influence SARS-CoV-2 evolution.
- We compared the potency of 17 different human interferons against 5 viral lineages sampled throughout the course of the global outbreak.
- Our data revealed increased interferon resistance in emerging SARS-CoV-2 variants, indicating that evasion of innate immunity is a significant driving force for SARS-CoV-2 evolution.

Methods

- Cell line: A549-ACE2
  - A549 (human alveolar type II) cells transduced to stably express codon-optimized human ACE2
- Virus isolates (lineage):
  - USA-WA1/2020 (A)
  - Germany/BavPat1/2020 (B)
  - New York-PV-0841/2020 (B.1)
  - USA/CA_CDC5574/2020 (B.1.1.7)
  - hCoV-19/England/204820464/2020 (B.1.1.7)
  - hCoV-19/South Africa/KRISP (B.1.351)
- SARS-CoV2 quantitative RT-PCR:
  - Official CDC SARS-CoV-2 N1 primers and TaqMan probe set were used.

Results

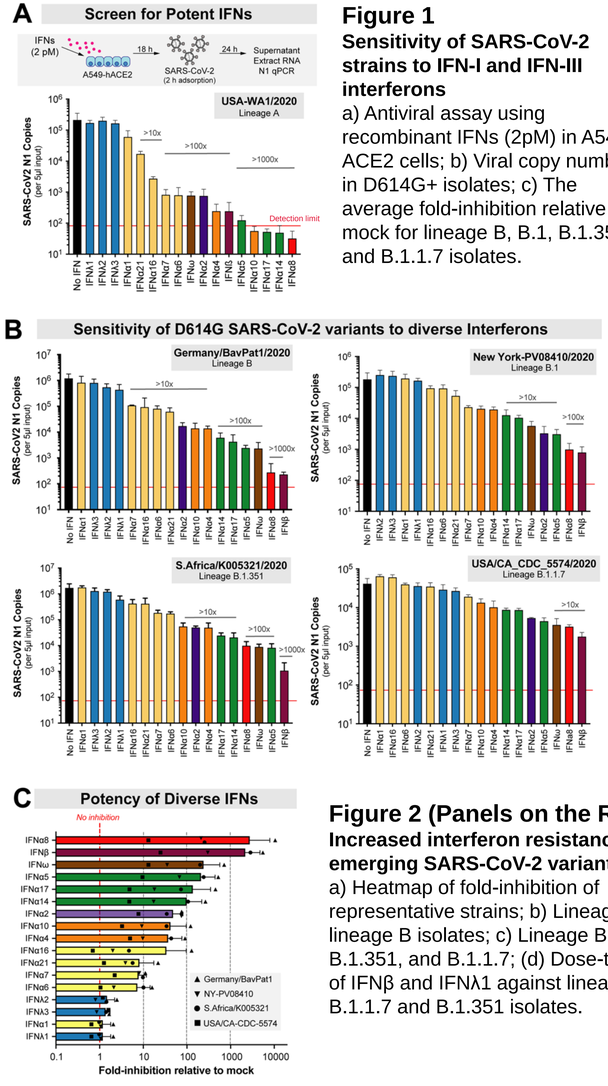

Figure 1
Sensitivity of SARS-CoV-2 strains to IFN-I and IFN-III interferons
a) Antiviral assay using recombinant IFNs (2pM) in A549-ACE2 cells; b) Viral copy numbers in D614G+ isolates; c) The average fold-inhibition relative to mock for lineage B, B.1, B.1.351, and B.1.1.7 isolates.

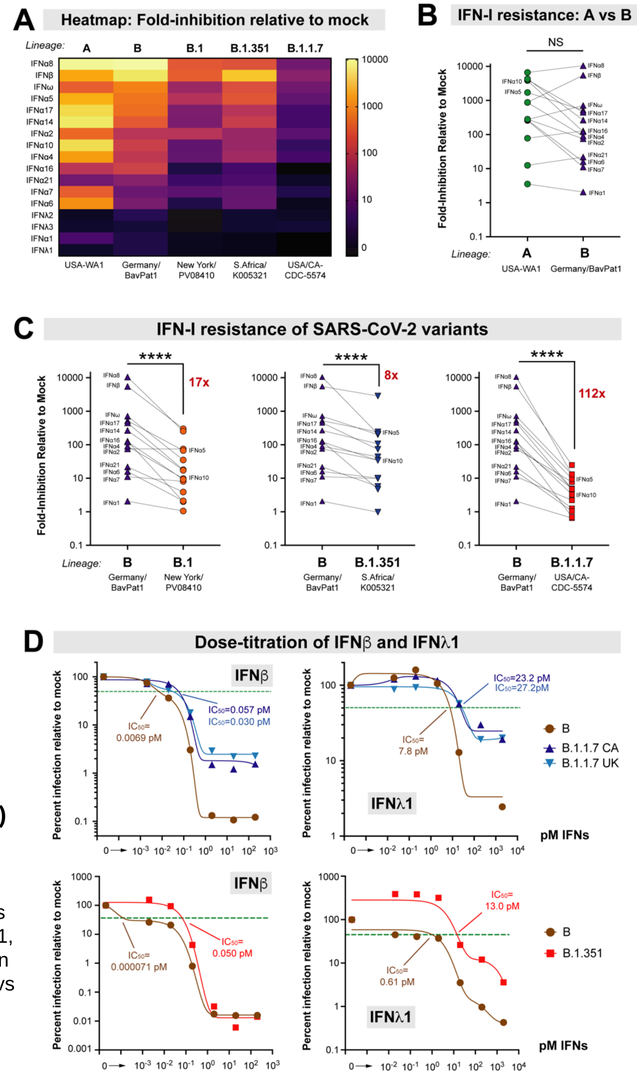

Figure 2 (Panels on the Right)
Increased interferon resistance of emerging SARS-CoV-2 variants.
a) Heatmap of fold-inhibition of representative strains; b) Lineage A vs lineage B isolates; c) Lineage B vs B.1, B.1.351, and B.1.1.7; (d) Dose-titration of IFNβ and IFNλ1 against lineage B vs B.1.1.7 and B.1.351 isolates.

Conclusions

- IFNλ requires higher doses to achieve similar antiviral effect *in vivo*.
- IFNβ is highly potent antiviral against SARS-CoV-2.
- IFNα8 has shown similar anti-SARS-CoV-2 potency as IFNβ
- Our data revealed a concerning trend for emerging SARS-CoV-2 variants to resist antiviral interferon responses.

Implications

- **Interferon resistance may contribute to the rapid emergence of variants such as B.1.1.7.**
- Other than spike protein mutations, emerging variants exhibited mutations in nucleocapsid and non-structural proteins NSP3, NSP6, and NSP12, which were shown to antagonize IFN signaling in cells.
- It will be important to identify the virus mutations that drive IFN resistance and their underlying mechanisms.

Disclosures

- The current study has been submitted to BioRxiv as a pre-print: *https://www.biorxiv.org/content/10.1101/2021.03.20.436257v1*