Latent viruses as drivers of chronic illness

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LIINC

RECOVER
Researching COVID to Enhance Recovery

UCSF University of California San Francisco

NASEM Workshop: Infection Associated Chronic Illnesses
June 2023

ZUCKERBERG SAN FRANCISCO GENERAL Hospital and Trauma Center

LIINC: Long-term Impact of Infection With Novel Coronavirus

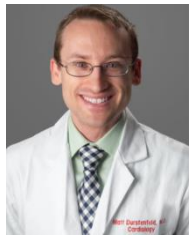
Built on UCSF SCOPE infrastructure, now supporting RECOVER

- **> 800 participants**
- **Detailed longitudinal phenotyping**
- **> 50K specimens banked**
- **> 50 collaborations**


Michael Peluso


Tim Henrich


Priscilla Hsue


Matt Durstenfeld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Carina Marquez


Dan Kelly


Lekshmi Santhosh

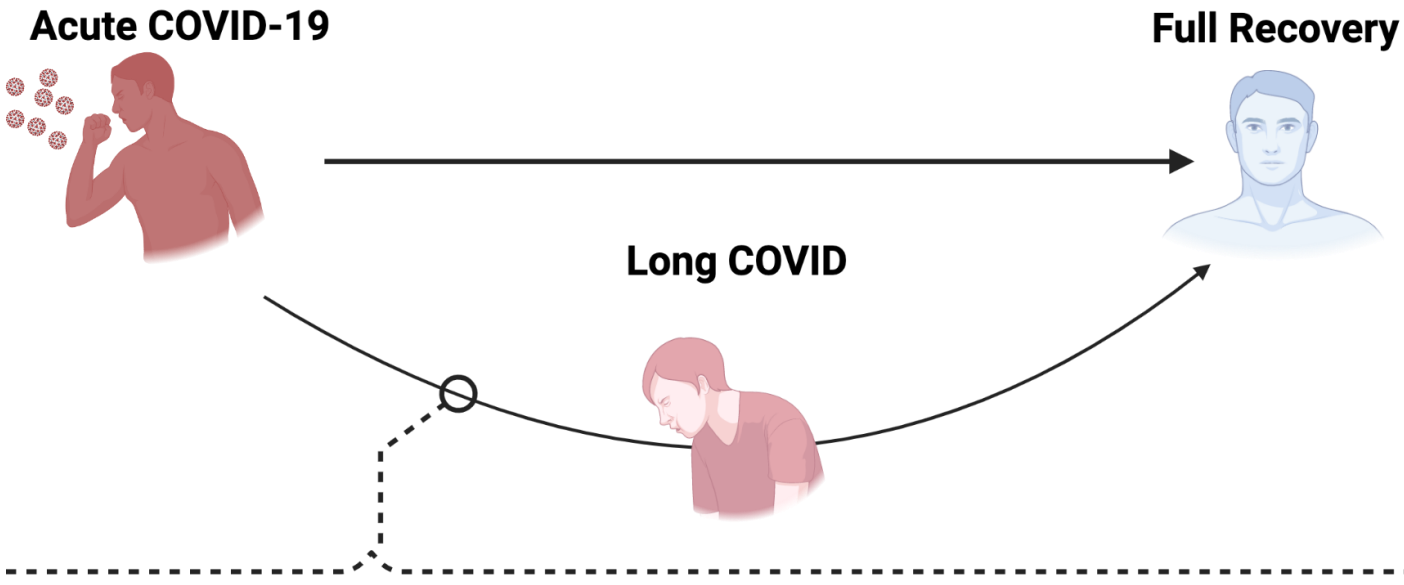

Nadia Roan

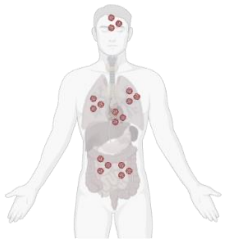

Joanna Hellmuth


Jeff Martin

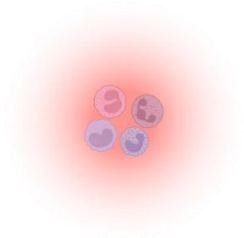

Steven Deeks

Proposed Mechanisms of Long COVID

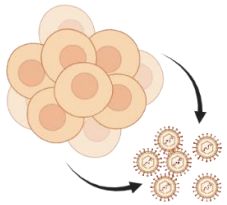




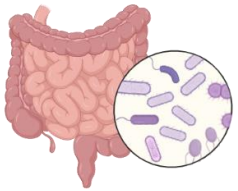
Viral Persistence



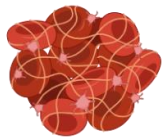
Inflammation/ Immune Dysregulation



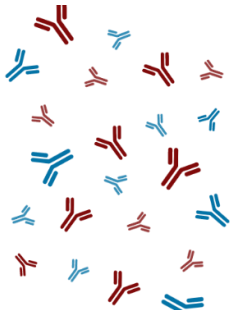
Viral Co-infection Reactivation



Microbial Translocation



Microvascular Dysfunction



Autoimmunity

Peluso & Deeks Trends in Immunology 2022; Images: Biorender

Latent Virus Reactivation

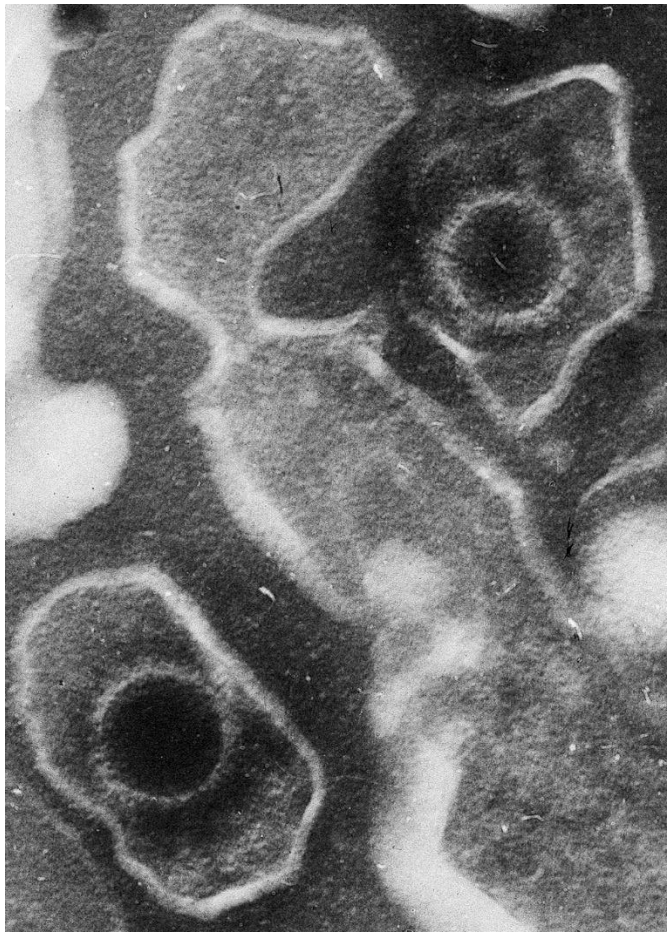
- Herpesviruses achieve latency
  - HSV-1 and -2 (herpes)
  - VZV (shingles)
  - Epstein-Barr Virus (EBV)
  - Cytomegalovirus (CMV)
  - HHV-6

I will focus on these two

- Other viruses: Hepatitis B, HIV, HTLV, adenovirus, BK virus, SARS-CoV-2 (?)

- Some other organisms: bacteria (syphilis, tuberculosis), fungal organisms (histoplasmosis), protozoa (leishmania, toxoplasma)

Epstein-Barr Virus in Human Disease



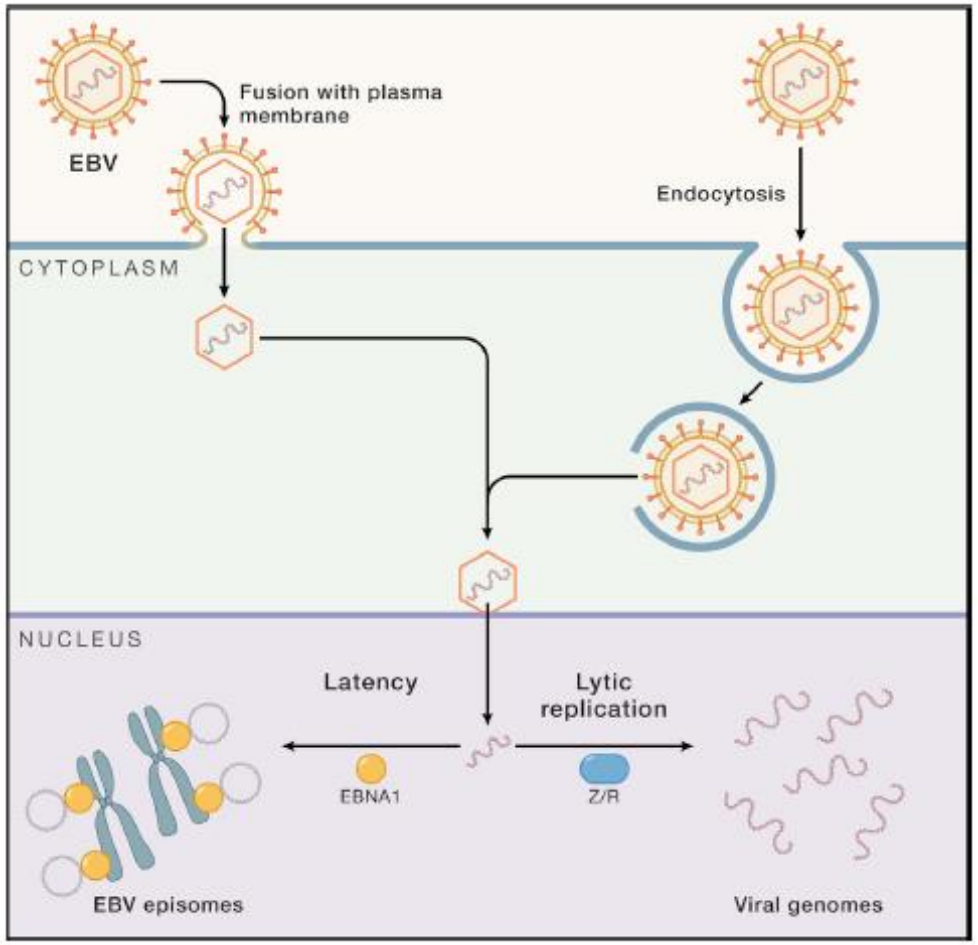
Gross PLoS Biology 2005

- Herpesvirus harbored by 95% of adults
- Infects B cells, resides in memory B cells
- Initial infection leads to mononucleosis
- Association w/ hematologic, epithelial malignancy

Epstein-Barr Virus in Human Disease

- Latent phase:
  - Episome tethered to chromatin by EBNA1
  - Minimal gene expression
  - Normal cellular division → passively replicates
  - Certain conditions → reactivates, lytic cycle

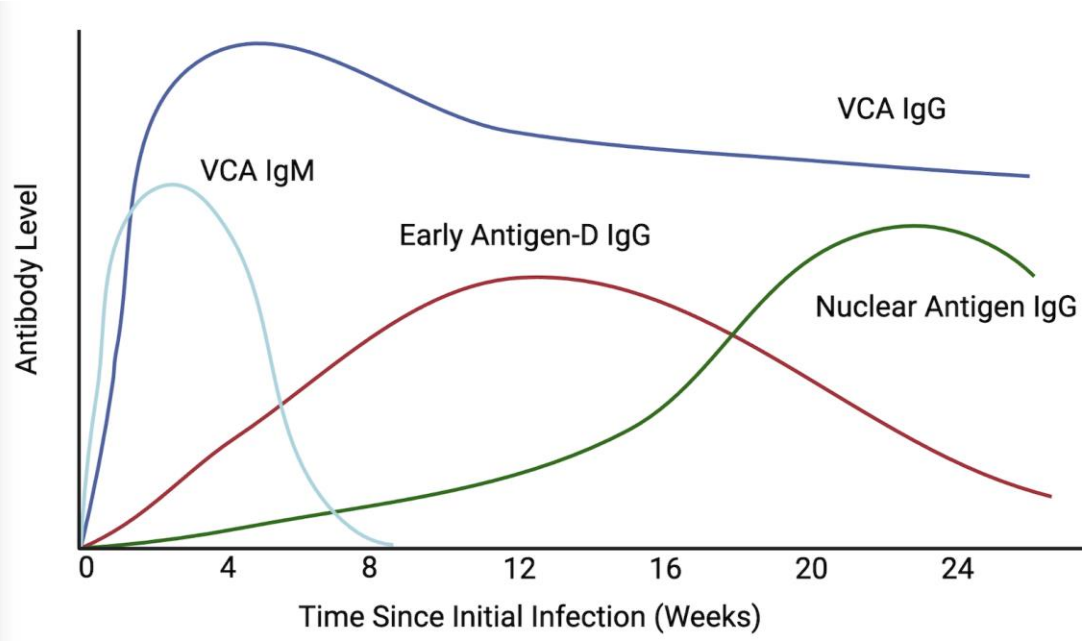
- Lytic phase:
  - Reactivates and expresses all viral genes
  - Cell death and production of infectious progeny
  - Inhibited by ganciclovir, acyclovir, foscarnet
  - Rarely treated directly



Damania et al Cell 2022

Initial Immune Responses to EBV

- Innate and adaptive responses
  - NK cells recognize infected cells
  - B cells produce IgM, IgG, IgA
  - CD8+ T cells recognize viral peptides (over half of CD8+ T cells in newly infected people can be directed at anti-EBV responses)



Peluso et al JCI 2023

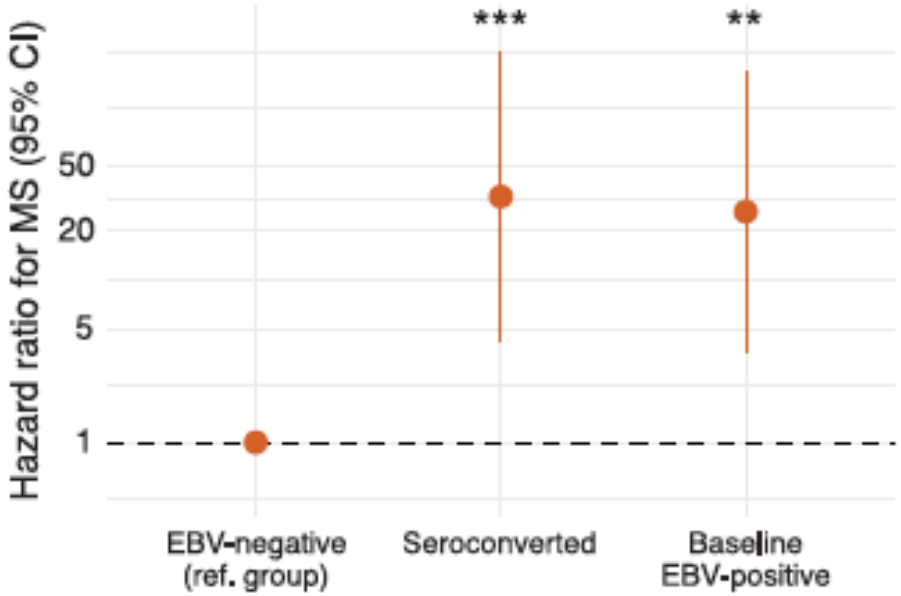
EBV in Autoimmune Diseases

- Associations with many autoimmune conditions but limited causal connections or utility for therapeutics
- Lupus (SLE): Anti-EBNA1 antibodies cross-react with SLE autoantigens
- Rheumatoid arthritis: increased EBV viral DNA in blood, increased EBV-infected B lymphocytes

Lanz Nature 2022, Lunemann J Exp Med 2008, Serafini J Exp Med 2007

EBV in Multiple Sclerosis

- U.S. military study (n=10 million)
  - EBV-infected 32x more likely to develop MS
- Molecular mimicry: EBNA1 antibodies cross-react with glial proteins in CSF
- Autopsy: EBV-infected B/plasma cells in post-mortem MS brain specimens
- Not really reactivation, but rather EBV infection during a certain vulnerable people may increase MS risk



Bjornevik Science 2022, Lanz Nature 2022, Lunemann J Exp Med 2008, Serafini J Exp Med 2007

EBV in ME/CFS

- Herpesviruses have frequently been associated with ME/CFS
- Presence of viral genome sequences or elevated antibody titres
- Overall mixed results with lots of heterogeneity
  - Methodologic differences
  - Limited characterization of ME/CFS in some studies
  - Subtypes of ME/CFS

Shikova J Med Virol 2020, Jason Neuropsychol Rev 2005, Zhang J Clin Pathol 2010

Does treating EBV in ME/CFS help?

- Limited studies of valganciclovir
  - Single arm study showing 9/12 experienced symptomatic improvement, sustained after treatment
  - Randomized study (n=30) showing 7x odds of improvement in fatigue and cognitive function
  - Retrospective (n=61) showing improvement in physical or cognitive function in half of patients receiving therapy
    - High baseline antibody responses and longer treatment length more likely to respond
- Has not been studied at scale, but a signal may exist

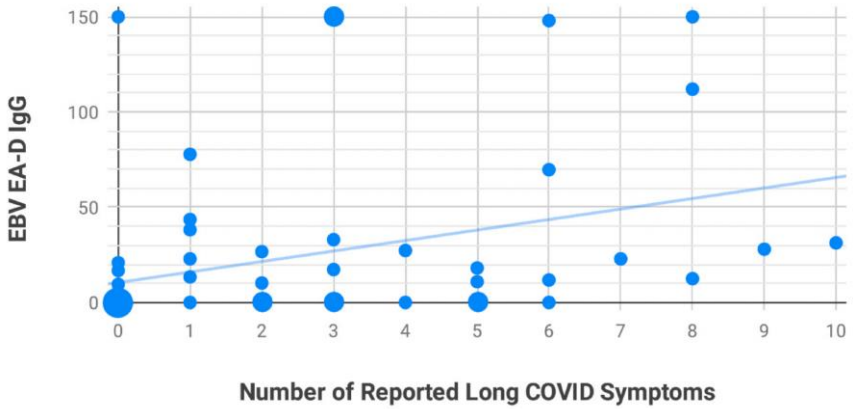
Kogelnik 2006, Watt J Med Virol 2012, Montoya J Med Virol 2013

Initial Observations in Long COVID

pathogens

Investigation of Long COVID Prevalence and Its Relationship to Epstein-Barr Virus Reactivation

- 20/30 Long COVID participants vs 2/20 recovered had serologic evidence suggesting recent EBV reactivation
- Higher EBV titres associated with more symptomatic Long COVID phenotypes



Cell

Multiple early factors anticipate post-acute COVID-19 sequelae

- EBV viremia during early infection associates with later development of PASC (cognitive, fatigue, etc.)
- Little persistent shedding

JCI The Journal of Clinical Investigation

Chronic viral coinfections differentially affect the likelihood of developing long COVID

LIINC

Tim Henrich

Peter Hunt

- 280 people with confirmed SARS-CoV-2 infection
- Pre-vaccine, ancestral through Delta variants
- Mostly outpatients
- Obesity (60%), hypertension (19%), asthma (17%), diabetes (9%)
- Half men, half women
- Median 4 months post-COVID

- Defined Long COVID as any post-COVID symptom
- Examined phenotypes of Long COVID (fatigue, neurologic, cardiac, GI)

Peluso JCI 2023

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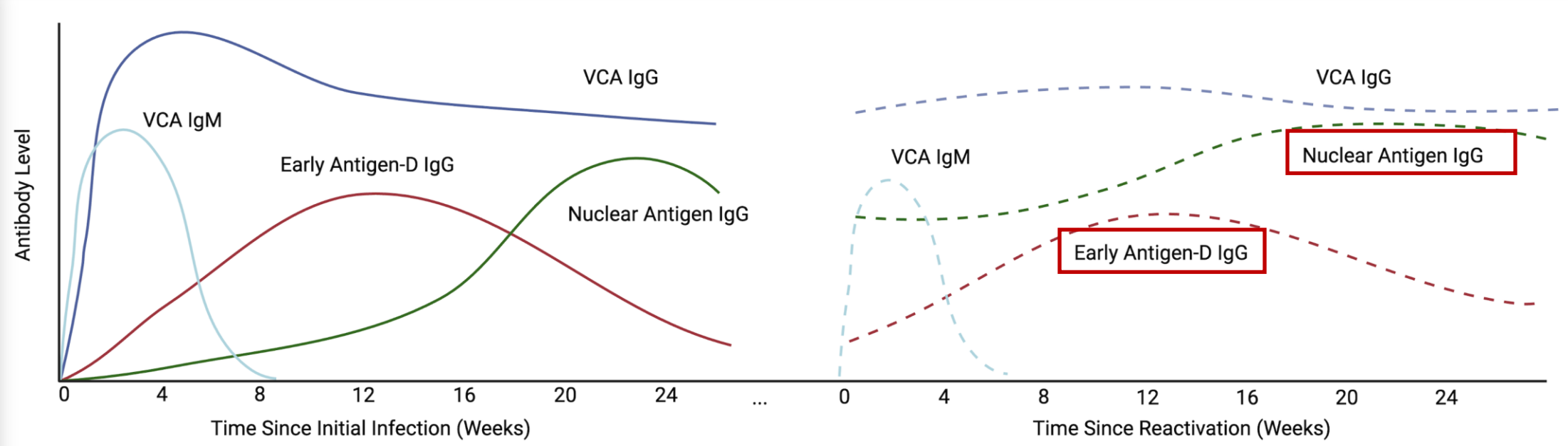
Chronic viral coinfections differentially affect the likelihood of developing long COVID



- VCA IgM (current reactivation): uncommon
- EA-D IgG (recent reactivation): 36%
- High level EBNA IgG (high burden): 40%
- EBV PCR (circulating EBV): 0%

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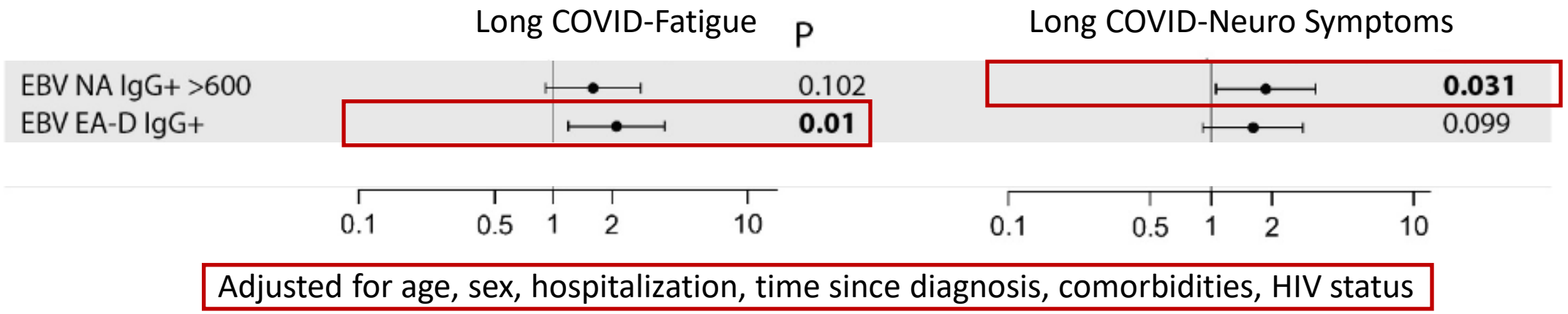
Chronic viral coinfections differentially affect the likelihood of developing long COVID



Adjusted for age, sex, hospitalization, time since diagnosis, comorbidities, HIV status

Those with serologic evidence suggesting recent EBV reactivation had 2.5x the odds of Long COVID fatigue.

Those with serologic evidence of high-level EBV responses had 2x the odds of Long COVID neurologic symptoms (e.g., brain fog)

No clear relationship with cardiopulmonary or GI symptoms

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The Journal of Infectious Diseases

Reduced Exercise Capacity, Chronotropic Incompetence, and Early Systemic Inflammation in Cardiopulmonary Phenotype Long Coronavirus Disease 2019 FREE

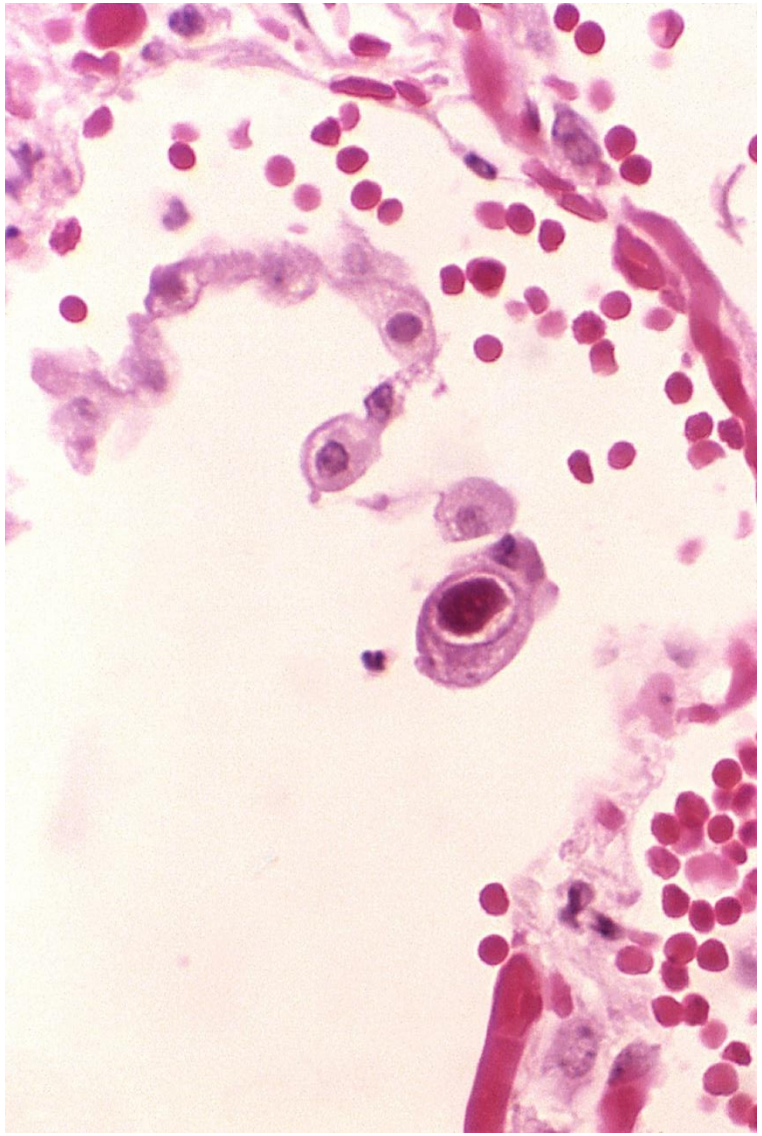
LIINC

- CPET in 60 LIINC participants with and without cardiopulmonary symptoms
- Strong association between EBV reactivation (EA-D IgG) and cardiopulmonary symptoms
- EBV reactivation associated with chronotropic incompetence and lower heart rate reserve (objective CPET measures)

Durstenfeld JID 2023

Cytomegalovirus in Human Disease

- Another herpesvirus that infects 60% of adults in developed countries
- Usually controlled by a vigorous immune response (high proportion of immune cells target CMV)
- Like EBV, can cause a mononucleosis-like illness
- Can reactivate in immunocompromised hosts (transplant, etc.)
- Generally, CMV seropositivity thought to be negative



CDC Image Library

Initial Observations in COVID and Long COVID

CROI
Conference on Retroviruses and Opportunistic Infections

DIFFERENTIAL ASSOCIATION OF CYTOMEGALOVIRUS WITH ACUTE AND POST-ACUTE COVID-19

- CMV seropositivity associated with 1.9x odds of hospitalization during acute COVID-19 (p=0.01).
- Among those hospitalized with acute COVID-19, CMV seropositivity associated with higher plasma SARS-CoV-2 N antigen levels (median 936 vs. 323 pg/ml, p=0.03)

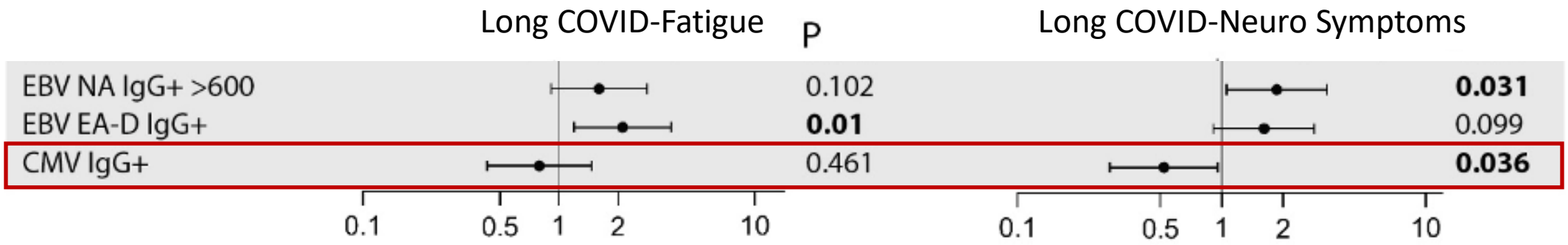
Cell

Multiple early factors anticipate post-acute COVID-19 sequelae

- Found more CMV-specific cytotoxic T cells in those with acute COVID-19 compared to healthy controls, suggesting bystander activation
- Increased cellular responses associated with GI PASC

JCI The Journal of Clinical Investigation

Chronic viral coinfections differentially affect the likelihood of developing long COVID



Adjusted for age, sex, hospitalization, time since diagnosis, comorbidities, HIV status

In contrast with EBV, CMV serostatus consistently associated with decreased odds of Long COVID across multiple symptom phenotypes

Why would this be?

Peluso JCI 2023

Cytomegalovirus and Immune Responses

Science Translational Medicine

Cytomegalovirus infection improves immune responses to influenza

- CMV-infected young adults had better immune responses to influenza vaccine

european journal of neurology

the official journal of the european academy of neurology

Cytomegalovirus seropositivity is associated with reduced risk of multiple sclerosis—a presymptomatic case–control study

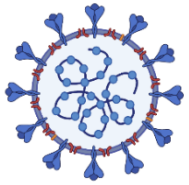
- EBV and HHV-6 both increased odds of MS in subgroups
- CMV serostatus associated with 30% decreased odds of MS (OR=0.7)

Differential Effects of EBV and CMV in Long COVID: Why?

- EBV acting via inflammatory and autoimmune pathways?
- EBV and CMV compartmentalized differently (B cells vs myeloid cells)?
- CMV immunoregulatory effects (viral IL-10) altering immune perturbations that would otherwise drive Long COVID?

Differential Effects of EBV and CMV in Long COVID

Acute COVID-19



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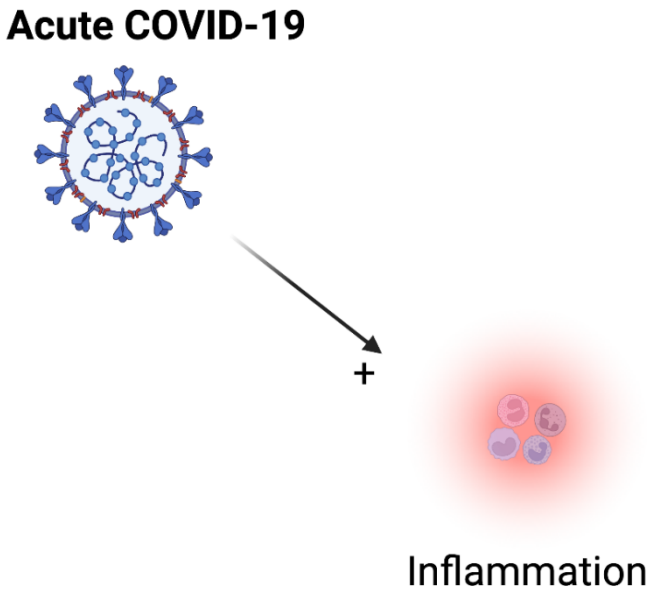
Differential Effects of EBV and CMV in Long COVID



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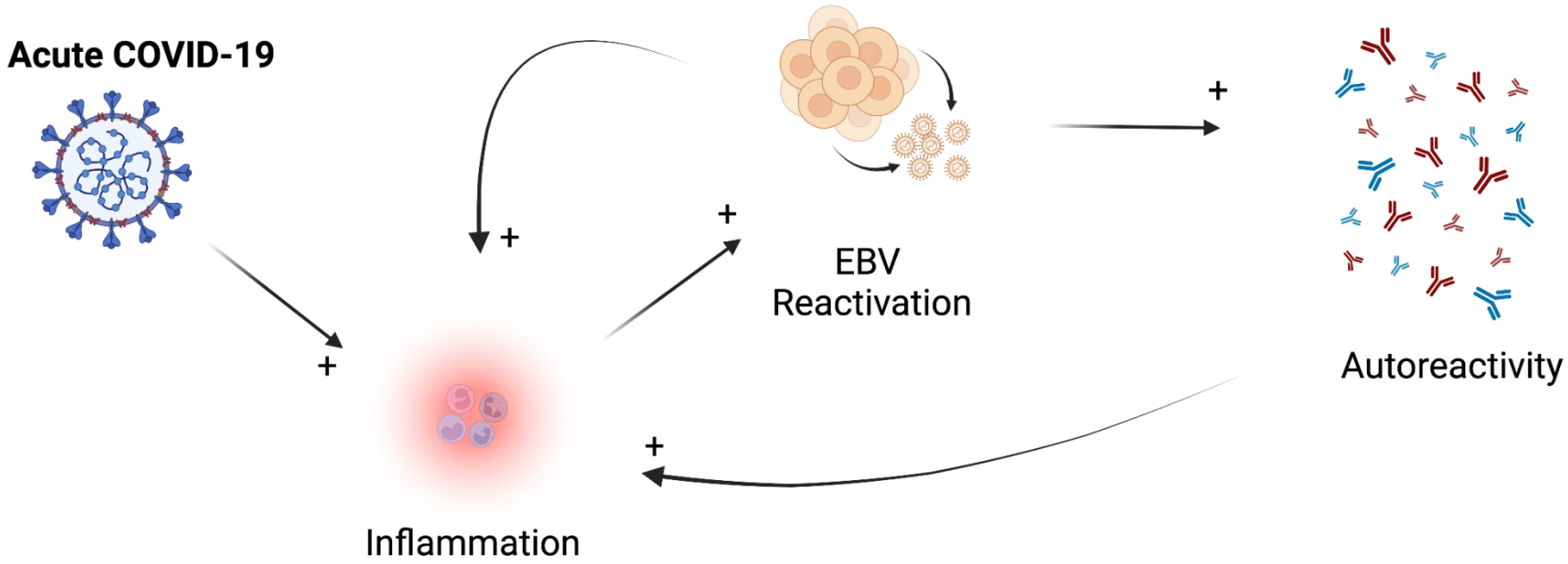
Differential Effects of EBV and CMV in Long COVID



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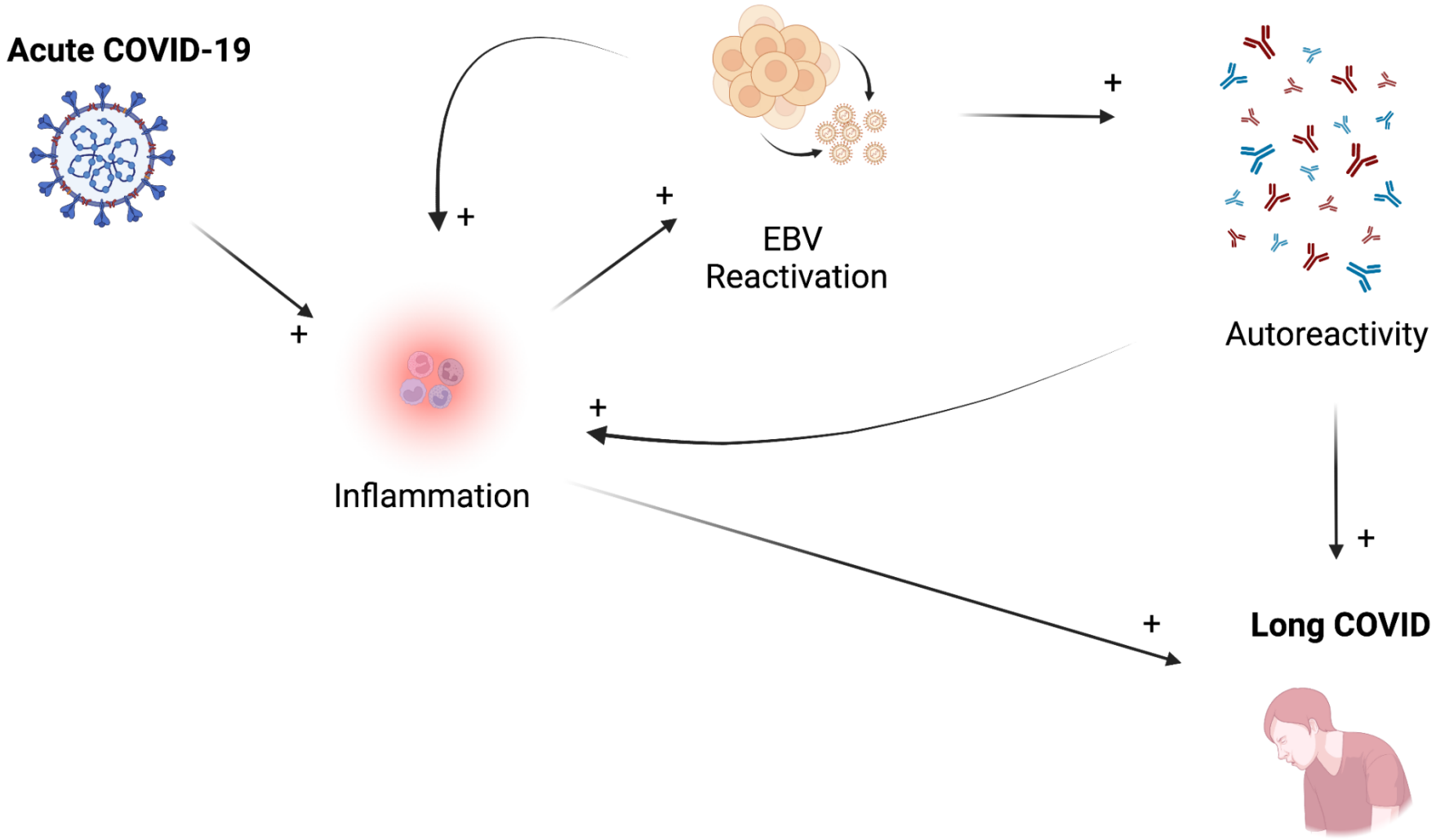
Differential Effects of EBV and CMV in Long COVID



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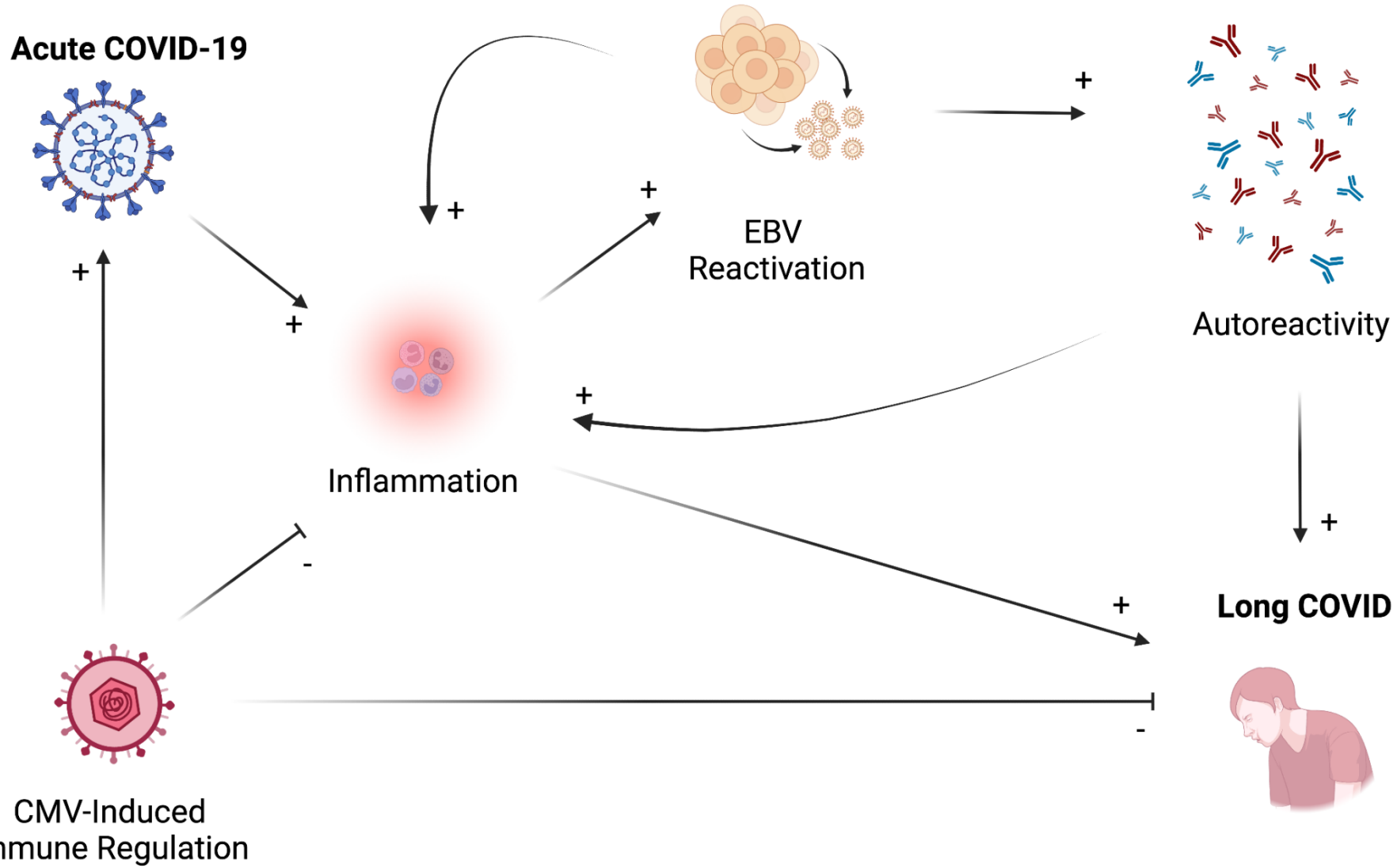
Differential Effects of EBV and CMV in Long COVID



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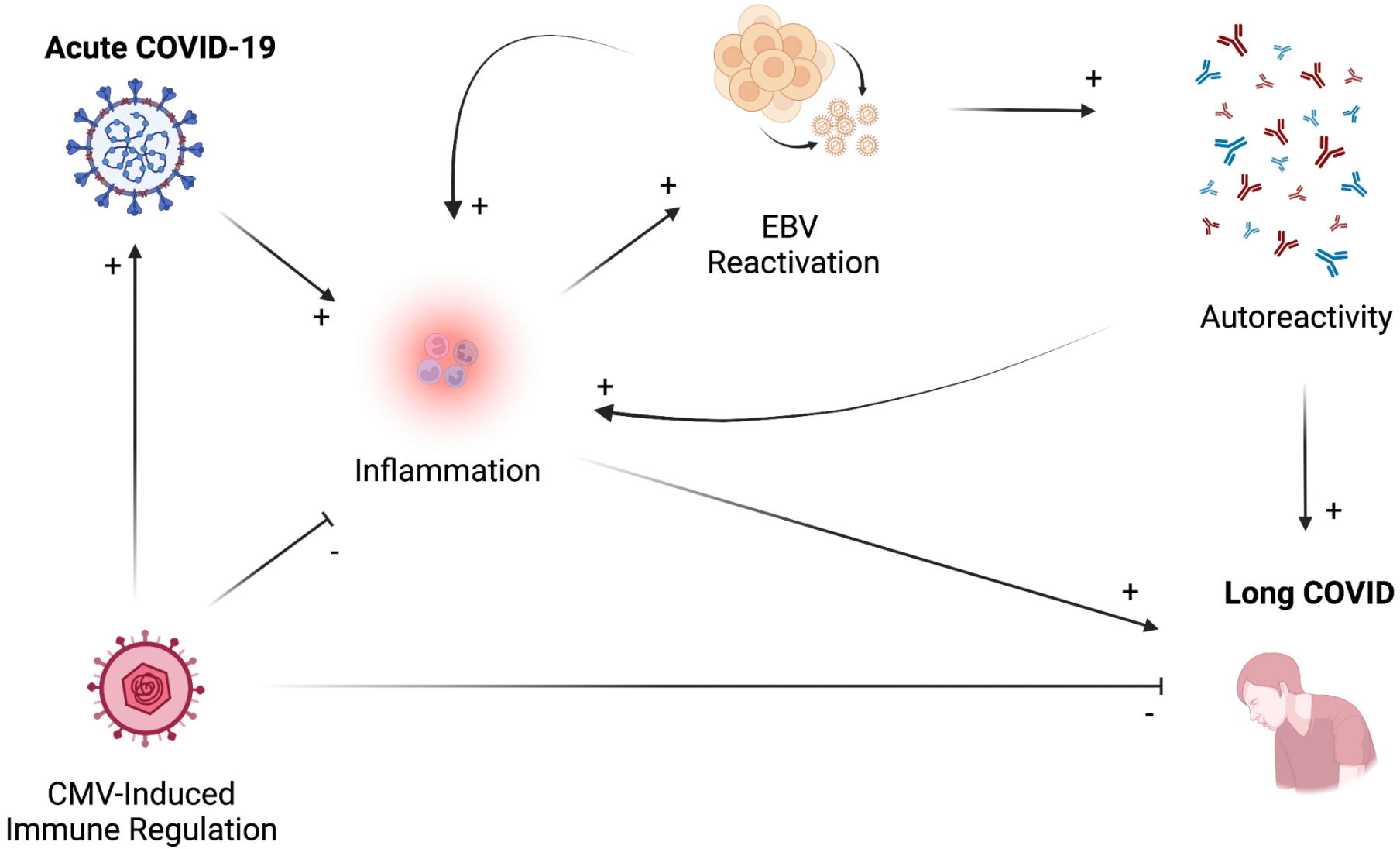
Differential Effects of EBV and CMV in Long COVID



Can further superimpose less directly connected mechanisms like viral persistence, platelet activation

EBV and CMV in Long COVID: Next Steps

- Study of outpatients with acute COVID-19 via UCSF/CDC FIND-COVID cohort
- Tissue studies, efforts to link EBV with autoimmunity
- Would EBV anti-viral treatment be of benefit?
  - Treatment during acute phase?
  - Relative benefit compared to SARS-CoV-2 antivirals?
  - Treatment during post-acute phase?
  - Anti-CMV effects of EBV treatments
  - Likely would require very large studies
- Would other types of EBV treatment (targeting infected cells but not active virus) be effective?

Summary

- Latent viral infections interact in complex ways in those who get sick with other infections. This is incompletely understood.
- There is growing evidence that these infections associate with Long COVID.
- Physicians have been trained to be skeptical about the role of these viruses.
- This skepticism needs to be re-examined and overcome. A specific focus on these questions (and funding) is needed to overcome this.
- Getting answers for Long COVID may help determine the role these viruses play in other infection-associated chronic illnesses.

Acknowledgements

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LIINC

RECOVER Researching COVID to Enhance Recovery


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amfAR MAKING AIDS HISTORY

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