Immunology and Pathogenesis of COVID-19

Eileen Scully, MD, PhD
Assistant Professor of Medicine
Johns Hopkins University
Baltimore, Maryland

Financial Relationships With Commercial Entities

Dr Scully has no financial relationships with ineligible companies relevant to the content of this talk. (Updated 04/30/21)

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Learning Objectives

After attending this presentation, learners will be able to:

- Describe the features that contribute to different outcomes of SARS-CoV-2 infection
- Describe the basic kinetics of immune responses to SARS-CoV-2
- List some features of immune dysfunction associated with COVID-19

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How does immunopathogenesis help in a pandemic?

- Mechanisms of disease may be a more direct pathway to therapeutics
- COVID-19 is novel, but likely will have shared features with emerging pathognes
- Pandemic dynamics may advance the understanding of the pathogenesis of post-infectious sequelae

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What determines the outcome of SARS-CoV-2 infection?

Pre-Infection (host)

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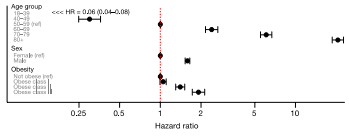
What determines the outcome of SARS-CoV-2 infection?

- Age and sex/gender
- Baseline immune status
- Comorbid conditions
- Genomics
- (Vaccination status)



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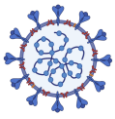
Williamson E et al., *Nature*, 584:430-6 (2020)

What determines the outcome of SARS-CoV-2 infection?



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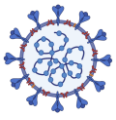
What determines the outcome of SARS-CoV-2 infection?

Infection (virus)



- Immune stimulating/evasion features
- Exposure/inoculum
- Potential role of viral variants

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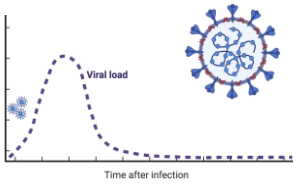
Viral dynamics after infection with SARS-CoV-2

- Multiple studies predict a genearl pattern of viral rise and then resolution on upper respiratory tract specimens



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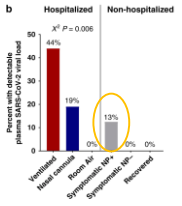
Wolfel et al., *Nature* 581, 465–469(2020)
He X., et al., *Nat Med* 26, 672–675 (2020)

Viral dynamics after infection with SARS-CoV-2

- *Viral dissemination?*
  - Sites of measurement of SARS-CoV-2
- *Denominantors?*
  - Quantification of viral material



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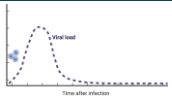
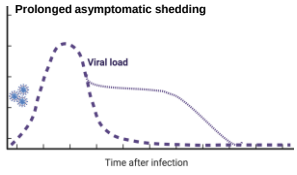
Fajnzylber et al. *Nat Commun* 11, 5493 (2020);Chen et al., *Clin Inf Diseases* 71,8 1937-1942(2020)

Viral dynamics after infection with SARS-CoV-2

- Even confined to the upper respiratory tract, alternate patterns have been observed





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Wolfel et al., *Nature* 581, 465–469(2020)
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Viral dynamics after infection with SARS-CoV-2

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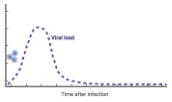

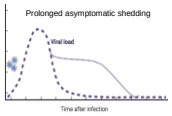

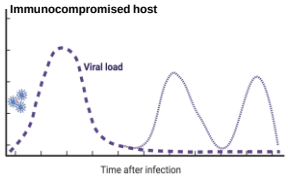

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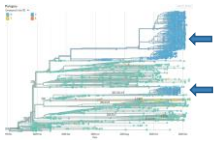
Wolfel et al., *Nature* 581, 465–469(2020)
He X., et al., *Nat Med* 26, 672–675 (2020)
Choi et al., N Engl J Med 383:2291-2293 (2020)

Viral variants?

- B.1.1.7 variant:
  - 14 nonsynonymous point mutations, 3 del
  - 8 in Spike, including N501Y in the RBD



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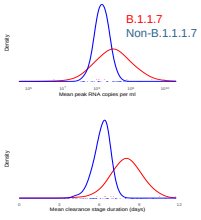
Hodcroft and Neher; https://nextstrain.org/groups/neherlab/ncov/S.N501; Davies et al., *Science*, 372: eabg3055, 2021; Kissler et al. medrxiv, 2021; https://doi.org/10.1101/2021.02.16.21251535;

Viral variants?

- B.1.1.7 variant:
  - 14 nonsynonymous point mutations, 3 del
  - 8 in Spike, including N501Y in the RBD
- Longitudinal virus sampling B.1.1.7 vs Non:
  - Peak VL. C_t 19.0 vs C_t 20.2
  - Infection duration 13 days vs 8.2 days



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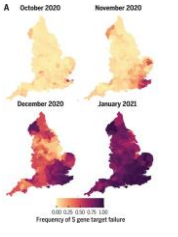
Hodcroft and Neher; https://nextstrain.org/groups/neherlab/ncov/S.N501; Davies et al., *Science*, 372: eabg3055, 2021; Kissler et al. medrxiv, 2021; https://doi.org/10.1101/2021.02.16.21251535;

Viral variants?

- Modeling the cause of enhanced spread – hypotheses?
  - Increased transmissibility
  - Longer infectious period
  - Immune escape
  - Increased susceptibility in children
  - Shorter generation time



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Davies et al., *Science*, 372: eabg3055, 2021;

Viral variants?

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  - Longer infectious period*
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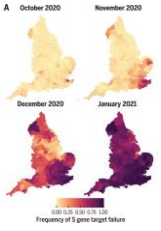

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Davies et al., *Science*, 372: eabg3055, 2021;

Viral variants?

- Is there increase risk of severe disease/death?

	Frampton et al, Lancet Inf Dis 2021	Challen et al, BMJ 2021	Davies et al, Nature 2021	Grint et al, Eurosurveillance 2021
Population	Hospitalized patients with confirmed COVID-19	Public health dataset, community-based testing	Public health dataset, community-based testing	Public health dataset, community and hospital-based testing
Timeframe	Nov-Dec 2020	Oct 2020-Jan 2021	Nov 2020-Jan 2021	Nov 2020-Jan 2021
Number of participants	341	109,812	1,146,534	184,786
Age	Median 60 (IQR 47-75)	Mean 46.3 (SD 11.0)	1-54y (80%); 55-69 (15%); >=70 (4.6%)	Median 38 (IQR 24-52)
Detection	Whole genome	S dropout	S dropout	S dropout
Controls	Non-B.1.1.7 patients	S positive	S positive	S positive
Primary outcome	WHO>4, mortality at 28d	Mortality at 28d	Mortality at 28d	Mortality at 28d
Severe disease	36.9%	?	?	?
Mortality	16.2%	0.3%	0.9%	0.5%
Effect of lineage on mortality	No difference	HR 1.64 (95% CI 1.32-2.04)	HR 1.55 (95% CI 1.39-1.72)	HR 1.67 (95% CI 1.34-2.09)

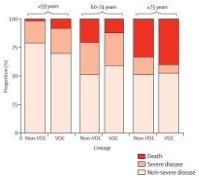

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Table adapted from Ong et al., *Lancet Infect Dis*, 2021;Davies et al., *Nature*, 2021. https://doi.org/10.1038/s41586-021-03426-1; Challen et al *BMJ* 2021; Grint et al, *Eurosurveillance*, 2021; Frampton et al., *Lancet Infect Dis*, 2021. https://doi.org/10.1016/S1473-3099(21)00170-5

Summary of virus factors/questions

- Specific viral features may be linked to transmissibility and replication/clearance dynamics
- Host features (e.g. immunodeficiency) can change the shape of viral decline curves

Unknown: do early features of viral dissemination or virus specific features contribute to longterm outcomes

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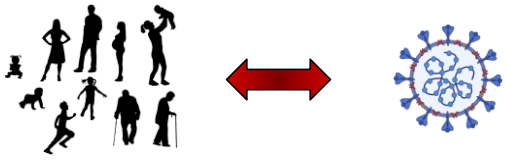
The host-pathogen interface: immune responses



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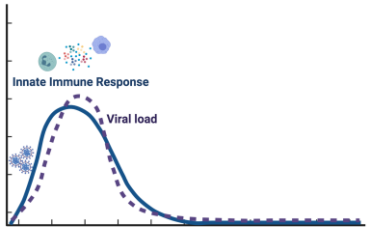
The host-pathogen interface: immune responses



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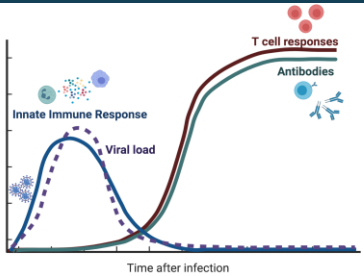
The host-pathogen interface: immune responses



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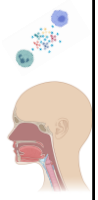
Innate immune activation to SARS-CoV-2 infection

- Early responses are local to the upper respiratory epithelium.



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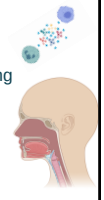
Mick, E et al., *Nat Commun* **11,** 5854 (2020).

Innate immune activation to SARS-CoV-2 infection

- Early responses are local to the upper respiratory epithelium.
- 234 patients with acute respiratory illnesses tested for SARS-CoV-2 with nasal swab-> metagenomic sequencing
  - 93 SARS-CoV-2
  - 41 other respiratory viruses
  - 100 no pathogen identified



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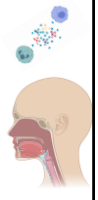
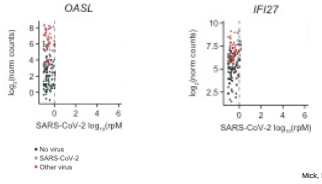
Mick, E et al., *Nat Commun* **11,** 5854 (2020).

Innate immune activation to SARS-CoV-2 infection

- Findings:
  - Induction of interferon response genes in two patterns





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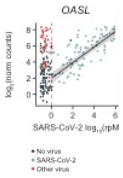

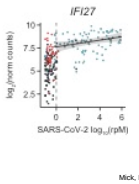

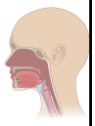

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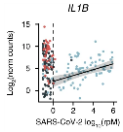
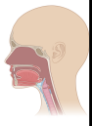
Mick, E et al., *Nat Commun* **11,** 5854 (2020).

Innate immune activation to SARS-CoV-2 infection

- Findings:
  - Induction of interferon response genes in two patterns
  - Activation of inflammasome genes linked to VL
  - Cell recruitment (neutrophils/mono) < other viruses





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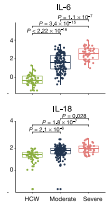
Mick, E et al., *Nat Commun* **11,** 5854 (2020).

Innate immune activation to SARS-CoV-2 infection

- In analyses of systemic cytokine levels as measure of innate immune responses:



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Lucas et al., *Nature* 584:463-471, 2020

Innate immune activation to SARS-CoV-2 infection

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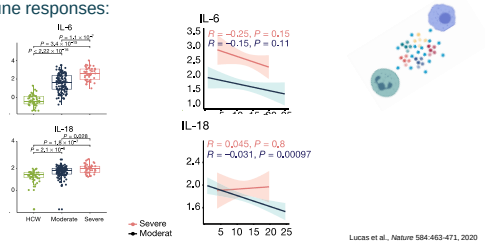

Lucas et al., *Nature* 584:463-471, 2020

Innate immune activation to SARS-CoV-2 infection

- Genetic studies suggest the importance of antiviral innate responses:
  - 4 young male patients with severe COVID
  - Rare putative loss of function mutations in TLR7 with downstream decreases in *IRF7, ISG15, IFNB1*

van der Made CI, et al., *JAMA*. 324:663–673, 2020; Zhang Q et al., *Science*. 370: eabd4570, 2020

Innate immune activation to SARS-CoV-2 infection

- Genetic studies suggest the importance of antiviral innate responses:
  - 4 young male patients with severe COVID
  - Rare putative loss of function mutations in TLR7 with downstream decreases in *IRF7, ISG15, IFNB1*
  - 659 severe patients vs 534 asymptomatic/mild
  - Tested 13 loci involved in TLR3 and IRF7 dependent induction and amplification of type I IFNs
  - 3.5% of patients with severe COVID-19 had genetic defects in 8/13 candidate loci in the type I IFN pathway

van der Made CI, et al., *JAMA*. 324:663–673, 2020; Zhang Q et al., *Science*. 370: eabd4570, 2020

Innate immune activation to SARS-CoV-2 infection

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  - Rare putative loss of function mutations in TLR7 with
  - induction and amplification of type I IFNs
  - 3.5% of patients with severe COVID-19 had genetic defects in 8/13 candidate loci in the type I IFN pathway

Antiviral interferon responses are deficient in a subset of patients with severe disease -> implicating this pathway in productive/efficient viral control responses.

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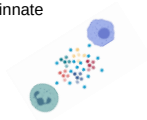
van der Made CI, et al., *JAMA*. 324:663–673, 2020; Zhang Q et al., *Science*. 370: eabd4570, 2020

Innate immune activation to SARS-CoV-2 infection

- As with other respiratory viruses, SARS-CoV-2 induces a local interferon response, with some variations in specific features
- Inflammasome activation is also a feature of disease, and may be associated with higher viral loads/more severe disease
- Rare genetic mutations suggest that interferon and innate responses are critical in control of SARS-CoV-2



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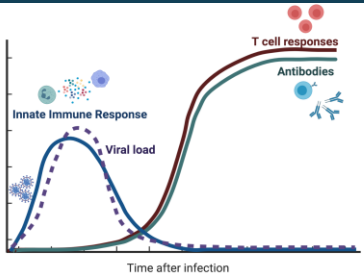
Adaptive immunity to SARS-CoV-2



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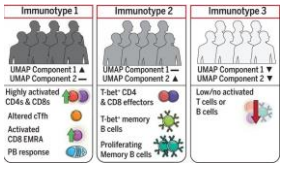
Adaptive immunity to SARS-CoV-2

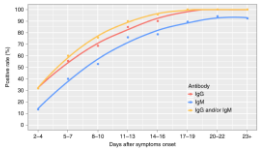
- Robust T cell responses are elicited in the majority of cases that have been studied
- Extensive immune profiling has suggested some patterns of response



Mathew, D et al., *Science* 369: 6508(2020); Moderbacher, CR et al., *Cell* 183:996-1012 (2020)

Antibody responses to COVID-19

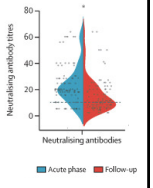
- Antibody to SARS-CoV-2 is detectable in majority at 19d after symptom onset
- Some variation in titer, target and antibody type
- Relationship to disease severity and patient characteristics
- ? Extrafollicular B cell responses in severe disease -> pattern consistent with autoimmune activation*



[1]DLong, Q-X et al., *Nature Med*, 26:845-848, 2020; Moderbacher, CR et al., Cell (2020) 183:4: P996-1012; Ogega C. et al, *J Clin Invest*, 2021,131(7):e145516; Woodruff M et al., *Nature Immunology* 21:1506–1516(2020); Klein et al, *J Clin Invest*, 2020:130(11):6141-6150

Persistence of protective immunity: antibodies

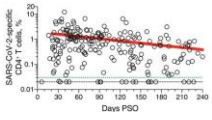
- Neutralizing antibody titers
  - Early studies suggest lower antibody titers in asymptomatic disease ? More likely to lose neutralizing titers[1]
  - 30K cohort of mild to moderate disease, ~90% with neutralizing titers, -> subset of 121 recalled patients modest decline at 5 months[2]
  - Post-hospitalization cohort follow up with modest declines in titer ~6months post infection[3]

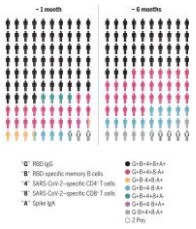


[1]Long, QX et al., *Nature Med*, 26:1200-1204, 2020
[2]Wajnberg et al., *Science*, 370:1227-30, 2020
[3]Huang et al., *Lancet*, 397: 220–232. 2021

Persistence of protective immunity: T cells/Ab

- Antigen specific T cell responses persist with moderate declines over time
- 8 months after COVID-19 infection, ~90% of individuals have 3/5 memory immune responses





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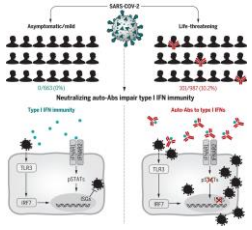
[1]Dan JM et al., *Science*, 26:1200-1204, 2020

Dysfunctional immune responses

- Autoantibody responses to interferon identified in cases of severe disease



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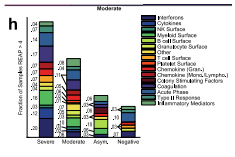
Bastard, P et al. *Science* 23 Oct 2020 370:6515: eabd4585

Dysfunctional immune responses

- Autoantibody responses to interferon identified in cases of severe disease
- Autoantibody (IgM) targeting ACE2
- Increased frequency of ANA and antiphospholipid antibodies
- Novel method associated frequency of autoreactive antibodies with severity of COVID-19



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Bastard, P et al. *Science* 23 Oct 2020 370:6515: eabd4585; ; Casciola-Rosen et al., https://doi.org/10.1101/2020.10.13.20211664
Gao, ZW et al, Autoimm Rev, 2021 10.1016/j.autrev.2021.102754; Wang et al., bioxiv, 2020 https://doi.org/10.1101/2020.12.10.20247205

What does immunomodulatory therapy tell us?

- Dexamethasone
  - RECOVERY trial -> benefit in patients with hypoxia
- Tocilizumab (IL-6 receptor monoclonal antibody)
  - RECOVERY trial -> benefit in hospitalized patients with hypoxia and elevated CRP

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N Engl J Med 2021; 384:693-704; https://doi.org/10.1101/2021.02.11.21249258

What does immunomodulatory therapy tell us?

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  - RECOVERY trial -> benefit in patients with hypoxia
- Tocilizumab (IL-6 receptor monoclonal antibody)
  - RECOVERY trial -> benefit in hospitalized patients with hypoxia and elevated CRP

Unknown how these treatments impact immune dysfunction but suggest that there is a component of dysfunctional inflammation that contributes to disease severity.

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N Engl J Med 2021; 384:693-704; https://doi.org/10.1101/2021.02.11.21249258

Immunological mechanisms for Long COVID?

- Autoreactivity
- Viral remnants?
- Immunologic setpoint

Questions:
- Will immunomodulatory treatment impact the rate of Long COVID
- Vaccine induced improvement?
- Autoreactive disease lasting versus transient?

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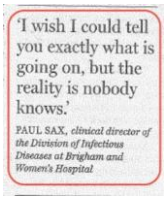
Conclusions


'I wish I could tell you exactly what is going on, but the reality is nobody knows.'

PAUL SAX, *clinical director of the Division of Infectious Diseases at Brigham and Women's Hospital*

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Boston Globe, April 29, 2021

Question-and-Answer Session