Antigen-specific adaptive immunity to SARS-CoV-2 in acute COVID-19 and associations with age and disease severity

ATS COVID-19 Seminar
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Previous study (Grifoni et al, *Cell* 2020) demonstrated that SARS-CoV-2-specific CD4 and CD8 T cells are detectable in recovered COVID-19 cases.

There is also a substantial fraction of the population with cross-reactive T cells.
Major knowledge gaps in understanding immunity to SARS-CoV-2

- How much of an adaptive immune response is there to COVID-19?
- What kind of immunity is important against COVID-19?
- Why do some people get severely ill and some people have mild disease?
Major knowledge gaps in understanding immunity to SARS-CoV-2

Assess all three arms of adaptive immunity across a wide-range of disease severity to better understand SARS-CoV-2 protective immunity

- Enrolled 54 subjects: 24 acute COVID-19, 15 convalescent COVID-19, 15 unexposed
- SARS-CoV-2-specific abs, including neutralizing abs
- Antigen-specific CD4 and CD8 T cells
- 22-parameter immunophenotyping panel
Antibody responses in acute COVID-19

- **RBD IgG titer**
  - Unexp: 10^5, Ac: 10^6, Co: 10^3
  - R = 0.88, p <0.0001

- **RBD IgA titer**
  - Unexp: 10^5, Ac: 10^6, Co: 10^3
  - R = 0.84, p <0.0001

- **Spike IgG titer**
  - Unexp: 10^5, Ac: 10^6, Co: 10^3

- **Spike IgA titer**
  - Unexp: 10^5, Ac: 10^6, Co: 10^3

- **PSV Neutralizing Titer**
  - Unexp: 10^5, Ac: 10^6, Co: 10^3

- **Live Neutralizing Titer**
  - Unexp: 10^0, Ac: 10^1, Co: 10^2

- **RBD IgG+IgA Titer**
  - Unexp: 10^5, Ac: 10^6, Co: 10^3

**Cell, 2020**
SARS2-specific CD4 T cell responses in acute COVID-19

Activation-induced marker (AIM) assays provide a cytokine-independent and highly sensitive measure of antigen-specific T cell responses.
Antiviral CD4 T cell responses in acute COVID-19

Secreted cytokines

intracellular cytokines
SARS2-specific cT_{FH} responses in acute COVID-19
SARS2-specific CD8 T cell responses in acute COVID-19
Adaptive immunity associations with disease severity

**Adaptive Immunity (ADIM) score**

SARS2-specific:
- Neutralizing antibodies
- CD4 T cells
- CD8 T cells

Subject negative for neutralizing antibodies
Coordinated adaptive immunity is protective immunity

Spearman correlogram
Age is a major COVID-19 risk factor, and part of that risk is weak adaptive immunity.
What about age may be causal in the poor adaptive immune response to COVID-19?
Age is a major COVID-19 risk factor

Naive T cell abundance is one immunological component of that risk

Statistics
Full data set (Ac, Co, Unexp)
COVID-19 disease (Ac, Co)
Acute COVID-19

Cell, 2020
Strong SARS-CoV-2-specific T cell responses associated with lower COVID-19 disease severity
CXCL10 may be a biomarker of poor CD4 and CD8 T cell responses to SARS2

Additional COVID-19 relationships with adaptive immunity
T cell and antibody responses in ‘average’ cases of COVID-19 look like protective immune responses and largely match antiviral immune response expectations.

Coordinated adaptive immunity is protective immunity:
- Responses involving multiple arms of adaptive immunity were better than partial responses
- We observed no convincing evidence of causal negative associations of adaptive immunity with disease severity

Age is a major COVID-19 risk factor, and adaptive immunity shortcomings are part of that problem
- Poorly coordinated antibody and T cell response
- Limited naive T cell repertoire
Potential implications for vaccine design

- Ideal vaccine: nAbs alone or nAbs + T cells?
- Role of pre-existing cross-reactive T cells in this coordinated adaptive response?
- Interplay of innate and adaptive immune responses?
  - Balancing immunosenescence with inflammaging
# Acknowledgements

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