Immune responses to COVID-19 infection

Objectives

- Acquire working knowledge of the course of an immune response in mild and severe COVID-19 infections
- Understand the potential benefits and limitations of plasma therapy
- Understand the impact and benefits of widespread COVID-19 antibody screening
- Understand the challenges involved in achieving herd immunity while minimizing morbidity and mortality

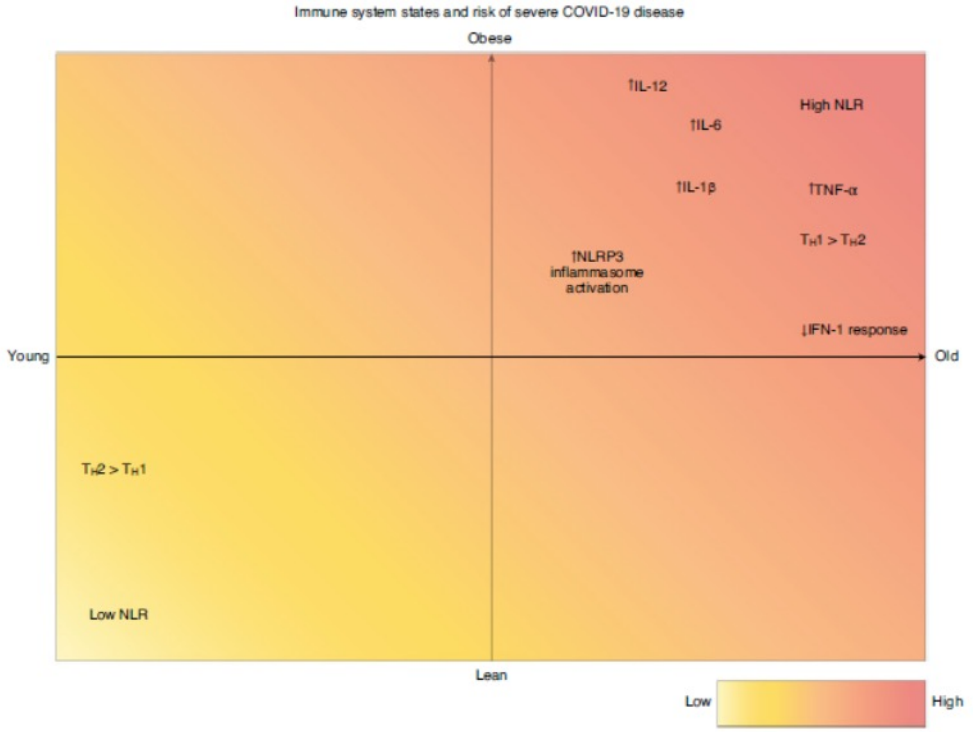
Course of immune response in non-severe COVID-19 infection

- An early case report tracked immune parameters through COVID-19 infection and recovery
- Stimulation of strong IgG and IgM antibody responses by day 9
- Increase in frequency of antibody-secreting cells, T_{FH} cells
- Rapid increase in activated ($CD38^+$ $HLA\text{-}DR^+$) CD8 T cells from day 7 (3.57%) to day 9 (11.8%)
- SARS-COV-2 virus undetectable from day 7
- Minimal levels of inflammatory cytokines – patient did not experience ARDS or require supplemental oxygenation

Known risk factors for mild versus severe COVID-19 infection

- Age – children rarely suffer from severe infection, whereas the elderly (>70 years) are high risk for severe COVID-19
- Sex – males are more likely to suffer from severe COVID-19, whereas females are more likely to suffer from long COVID

- Disease severity correlates with higher neutrophil to lymphocyte ratio (NLR), which also positively correlates with advancing age and obesity
- NLR is indicative of low grade inflammation, and is associated with other immune markers that are associated with severe COVID-19 course, notably IL-6, IL-12 and IL-1β secretion ("inflammaging")
- High serum IL-6, IL-8 and TNFα have been associated with disease severity and reduced survival



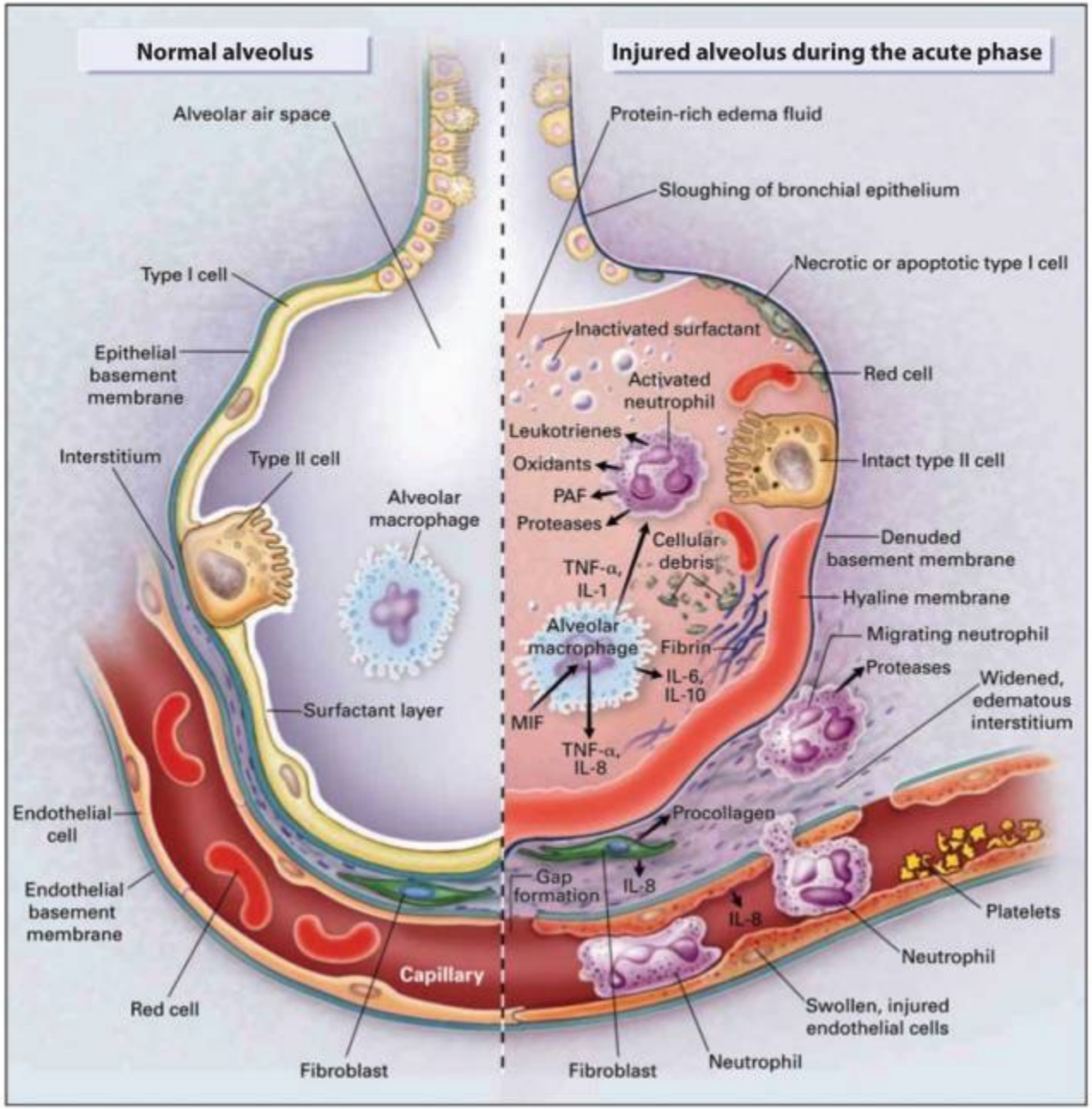
P. Brodin, Nature Medicine 27:28-33, January 2021

Severe COVID-19 immunopathology and ARDS

- ARDS is the main cause of death from COVID-19 infection, associated with multi-organ failure
- Hallmark of ARDS is an uncontrolled systemic inflammatory response, commonly known as a cytokine storm (cytokine release syndrome)
- Increased serum IL-6 and CRP; patients needing ICU care have elevated innate cytokines IP-10, MCP-1, MIP-1A, TNFα
- Pattern is similar to that observed for SARS and MERS
- Most clinical trials of tocilizumab (anti-IL-6R) for patients with severe COVID-19 have given inconclusive results
- In the RECOVERY trial, 4,116 adults hospitalized with COVID-19 were randomly assigned to tocilizumab or usual care (SE Gupta, DE Leaf, Lancet 397:1599-1601, May 1, 2021)
  - 14% were receiving mechanical ventilation, and 82% were receiving systemic corticosteroids
  - Primary outcome of all-cause mortality was 35% in patients receiving usual care and 31% in patients given tocilizumab ($p = 0.0028$)
- Dexamethasone treatment results in lower mortality among patients receiving mechanical ventilation or oxygen support, but not among those with no respiratory support (NEJM 384:693-704, Feb 25, 2021)

Innate immune responses and ARDS

- Macrophage activation leads to release of inflammatory cytokines
- TNFα and IL-1β lead to neutrophil chemotaxis and activation
- https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3108259/



Antibody responses from COVID-19 patients

- Chinese study tested plasma and monoclonal antibodies from patients for reactivity to viral Spike protein receptor-binding domain (RBD)
- Found potent neutralizing activity
- Surprisingly, there was no cross-reactivity with SARS Spike protein RBD, although there was substantial plasma cross-reactivity with non-RBD Spike protein domains
- Lack of RBD cross-reactivity is a puzzle, since SARS, and SARS-COV-2 both bind the ACE2 target cell receptor

Does plasma therapy work?

- Early study - treatment of 5 critically ill COVID-19 patients with convalescent plasma suggested some benefit (JAMA, March 27, 2020)
- All 5 patients were on mechanical ventilation
- Following transfusion, body temperature normalized within 3 days in 4 of 5 patients
- $Pa0_2$ and $Fi0_2$ improved
- Viral loads decreased and became negative within 12 days

Treatment with convalescent plasma from recovered COVID-19 patients

- Need to recruit recovered COVID-19 patients for plasma donation
- Should also screen for neutralizing antibody titers
- Early randomized trials on hospitalized patients provided weak evidence of clinical efficacy – problems with heterogeneity of plasma product
- Recent trial of high titer plasma therapy to prevent severe infection in elderly patients <72 hours after onset of symptoms concluded that treatment limited progression of COVID-19
- Plasma treatment should be considered for high-risk patients (and immunodeficient patients)
- LM Katz, NEJM 384:666-668.2021, DOI: 10.1056/NEJMe2035678

Monoclonal antibodies for COVID-19 treatment

- FDA has issued emergency use authorizations (EUA) for monoclonal antibody treatment for patients at high risk of progressing to severe COVID-19, hospitalization, or both
- Casirivimab and imdevimab, administered together (EUA issued November 21, 2020)
- Bamlanivimab and etesevimab, administered together (EUA issued February 9, 2021)
- Specific for receptor-binding domain of SARS-CoV-2 Spike protein

Antibody tests to confirm COVID-19 infection

- Antibodies tell you about the history of infection!
- Essential tool to understand the epidemiology of COVID-19
- Can be used to track incidence of asymptomatic or mild cases that would otherwise be undetected
- Can help to determine whether an individual (or even an entire community) needs to be subject to continued restrictions
- One caveat - it's not yet known whether immunity to COVID-19 is protective and durable
- https://www.sciencemag.org/news/2020/02/singapore-claims-first-use-antibody-test-track-coronavirus-infections
- https://abcnews.go.com/Health/antibody-testing-colorado-town-provide-forward/story?id=69856623

Herd immunity

- The idea that if a sufficient number of people become immune, transmission will be limited, and those who are still vulnerable will be less likely to become infected
- Minimum threshold figure is about 60%, based on $1-(1/R_0)$ formula, where the R_0 value is 2.5. For comparative purposes, the R_0 for measles is 18 (!), giving a herd immunity threshold of >94% (that's why MMR vaccination is so important)
- Herd immunity can be achieved through vaccination, or continued spread of disease through a community
- Briefly touted as a long-term benefit in the Netherlands and UK, by controlling spread of virus (flattening the curve) while protecting the vulnerable
- https://www.forbes.com/sites/joshuacohen/2020/03/27/caught-between-herd-immunity-and-national-lockdown-holland-hit-hard-by-covid-19/#fcbf0eb3557c
- Logistically impossible to protect elderly and vulnerable, as their care-takers would be potentially contagious younger people
- We will reach a point of herd immunity eventually, but it will take time, and the cost in morbidity and mortality will be high
- Historically, herd immunity is best achieved through effective vaccination programs