Overview of the immunology of protection from COVID-19 vaccines

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Vaccine protection is observed across variants of concern - despite loss of neutralization.
How does the immune system **collaborate** to drive protection against viral infection?

- Monocytes
- Macrophages
- Neutrophils
- NK cells
- T cells

**Steps:**
- Initial Infection
- Spread
- Dissemination
Correlates of immunity against COVID-19

**Natural Immunity**
- Antibodies are sufficient, but not required for protection
- Antibody quality (neutralization + Fc-functions) modulate disease
- Cross-reactive T cells modulate disease severity
- Neutropenia, diabetes, BMI, age, sex, associated with severe disease
- Interferons are critical for protection

**Vaccine Induced Immunity**
- Binding and neutralizing antibodies are correlates of immunity at peak immunogenicity
- High titers are required to block transmission
- Immunity against severe disease persists after neutralizing antibodies wane
  - Memory B and T cells persist
- The first vaccine exposure imprints immunity, affecting future antibody evolution

**Hybrid Immunity**
- Infection associated priming induces tissue resident immunity and more effective antibody isotypes
- Infection associated immunity may have superior, albeit still imperfect, cross-reactivity
- Infection associated priming or boosting may reshape the landscape of innate immune cells at the respiratory barrier
- Infection associated priming may broaden the immune response to additional viral antigens (nucleocapsid, etc.) or across Spike

Interferons are critical for protection.
Multiple tissue-resident immune mechanisms are likely key to protection against this rapidly evolving virus.

1. Tissue resident plasma cells are needed to persistently produce high titer antibody isotype responses.

2. Long-lived binding opsinophagocytic antibodies create a bottleneck to control variant viruses that escape neutralization.

3. Long-lived tissue resident T cells are key to rapid clearance of infected cells.

4. Tissue resident memory B cells respond to variants, generating variant specific neutralizing responses.
Conclusions

• SARS-CoV-2:
  • While the design of a transmission blocking vaccine against SARS-CoV-2 remains an aspirational dream, due to its high $R_0$, current vaccines attenuate disease through a multi-cellular mechanism.
  • Because we understand this mechanism of disease control, we can now design next-generation vaccines able to relieve symptomatology as well as prevent death.

• Pathogen X:
  • Understanding immunity at the portal of entry and site of viral replication is key to the design of vaccines against prototypical pathogens.
  • The explosion of immunological tools must be weaved in strategically to inform vaccine development, rather than explain vaccine deficiencies, to accelerate global deployment of highly effective vaccines.