COVID-19: Pathophysiology

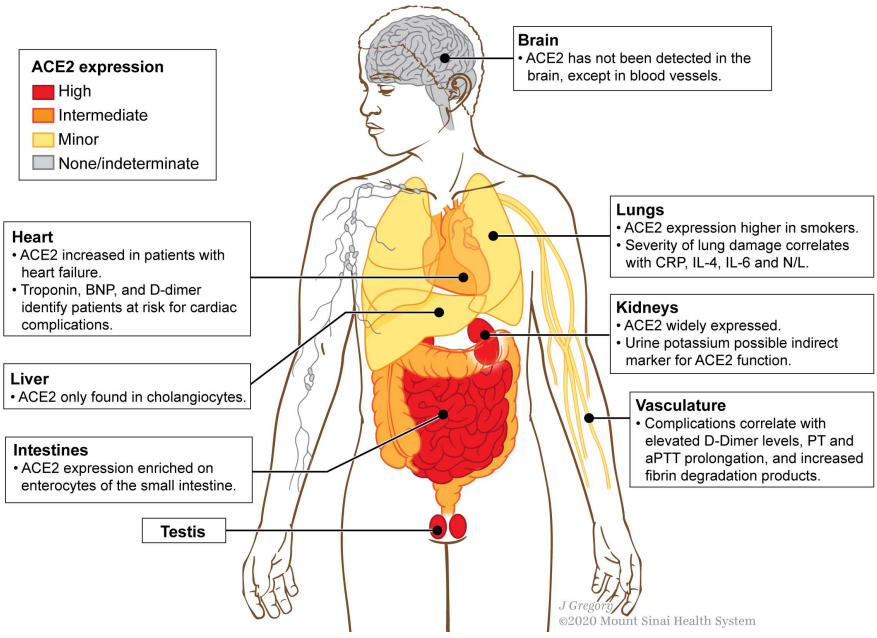
SARS-CoV-2 enters cells via ACE2 receptor:

Pathophysiology of SARS-CoV-2

ACE2

- Negative regulator of the renin-angiotensin-aldosterone system (RAAS)
- Promotes vasodilation via conversion of ATII to angiotensin 1-7
- Ubiquitously expressed by multiple organ tissues, with local regulatory function
  - > Lung
  - > Heart & vasculature
  - > Kidney
  - > Intestines
  - > Liver
  - > Brain

ACE2 is also described to modulate β-cell activity in the pancreas.



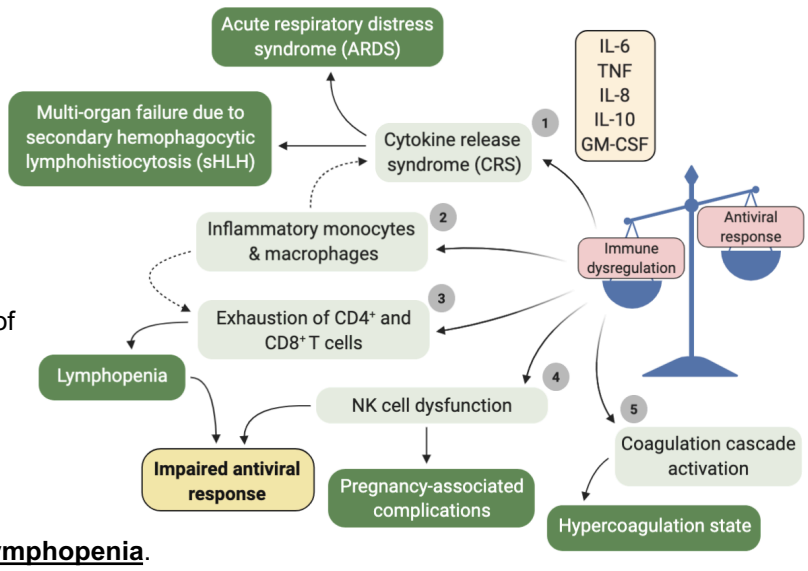
SARS-CoV-2 binds the ACE2 receptor, disabling the ACE2 signaling axis…

… may explain potential gendered differences in the mortality and susceptibility of male and female cases.

… may explain the range of COVID-19 symptoms at onset, including **headache**, **diarrhea**, **hepatic dysfunction**, **stroke**, and **hypertension**.

… can explain major COVID-19-associated complications, where ACE2 is vital in its niches, including **cardiac injury**, **gastrointestinal symptoms**, **endocrinopathy**, and **meningitis**.

Immune Dysregulation in COVID-19



1. COVID-19 patients present with a delayed interferon response.

   Elevated levels of pro-inflammatory cytokines are also detected in many COVID-19 patients.

2. Inflammatory monocytes and macrophages are present in the lungs of COVID-19 patients. These cells also infiltrate the lung and extrapulmonary organs from the blood during disease.

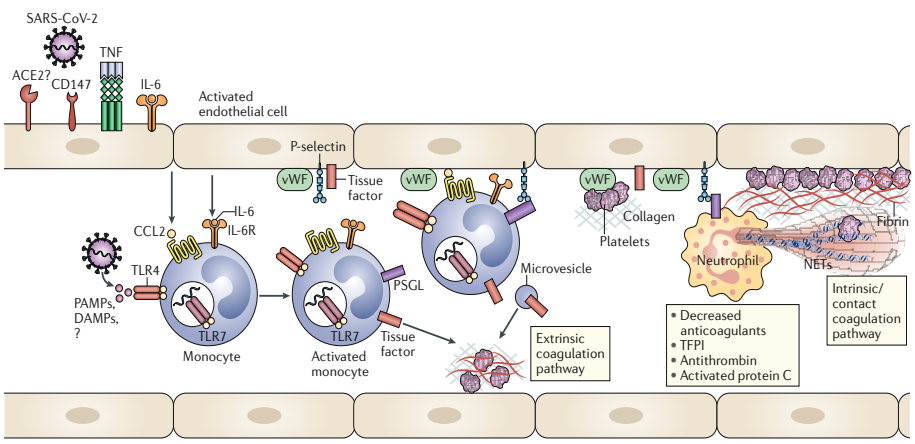
   These cells have been described to produce the inflammatory cytokines.

3. COVID-19 patients present with **<u>pan-lymphopenia</u>**.

   Analysis of surface markers show up-regulation of co-inhibitory receptors (i.e., PD-1, CTLA-4) that are characteristic of exhausted T cells seen during chronic viral infection.

4. NK cell dysfunction is described in COVID-19 patients.

   This may have implications for pregnancy-associated complications seen in pregnant COVID-19 patients, including **<u>maternal vascular malperfusion</u>** (+ delayed villous maturation, chorangiosis, intervillous thrombi).



5. **<u>Elevated D-dimers</u>**, **<u>low platelet counts</u>**, and evidence of endothelial cell damage suggest a hypercoagulative state in COVID-19 patients. **<u>Pulmonary microthrombi</u>** have also been described to contribute to lung pathology.

References:

1. Vabret, N., et al. Immunology of COVID-19: Current State of the Science. *Immunity* (2020), https://doi.org/10.1016/ j.immuni.2020.05.002
2. Merad, M. and Martin, J.C. Pathological inflammation in patients with COVID-19: a key role for monocytes and macrophages. *Nature Reviews Immunology* (2020). https://doi.org/10.1038/s41577-020-0331-4