COVID-19 associated glomerular diseases: Pathogenesis and treatment

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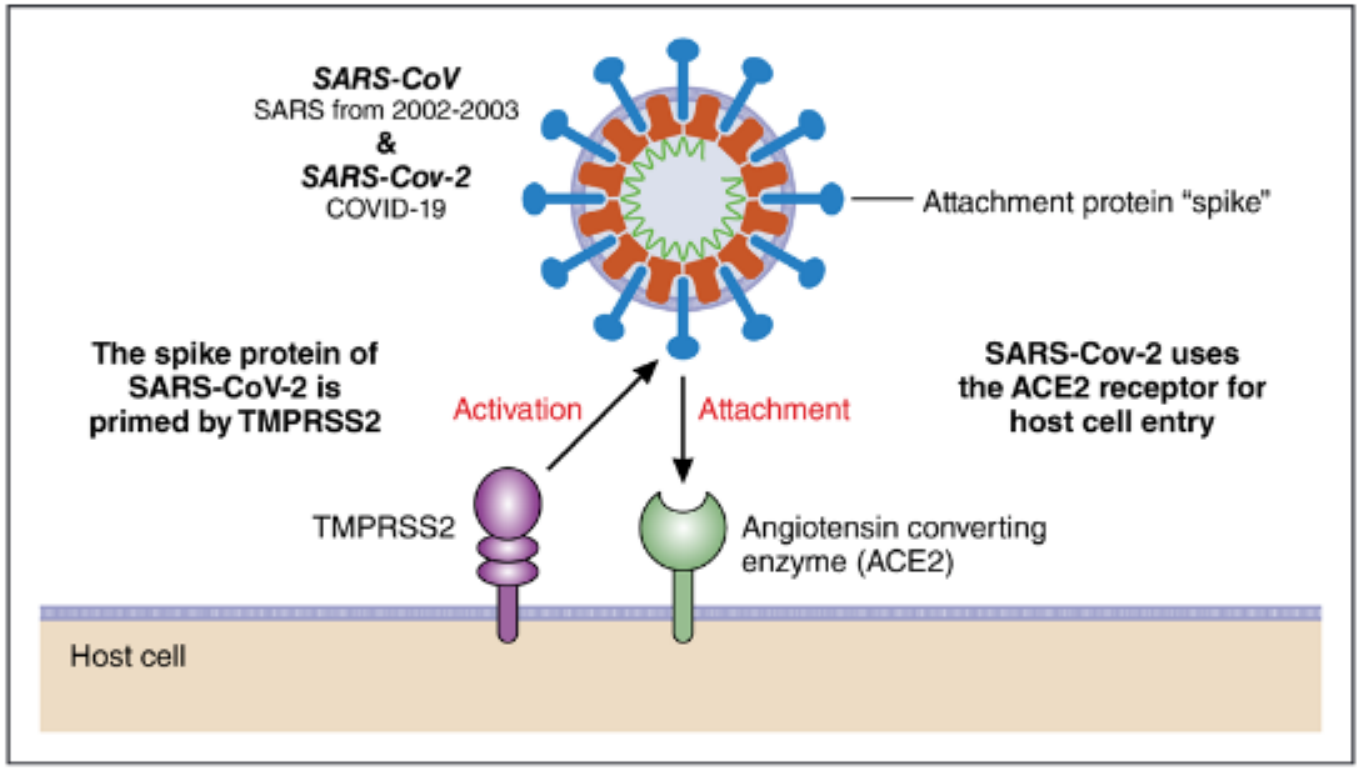
Does SARS-CoV-2 infection of glomerular cells cause injury?

- ACE2 & TMPRSS2 expression high in proximal tubules
- ACE2 & TMPRSS2 expression much lower in podocytes, other glomerular cells
- Unclear how SARS-coV-2 would gain access to podocytes



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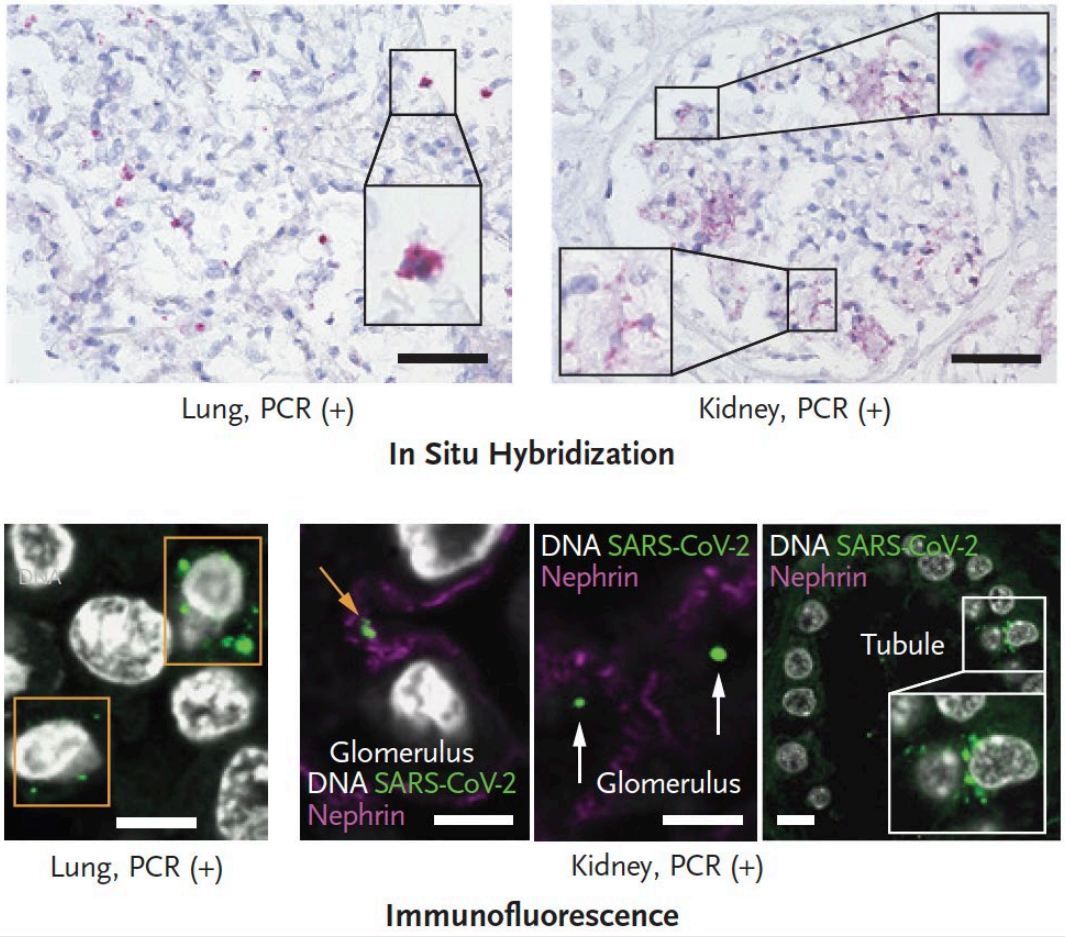
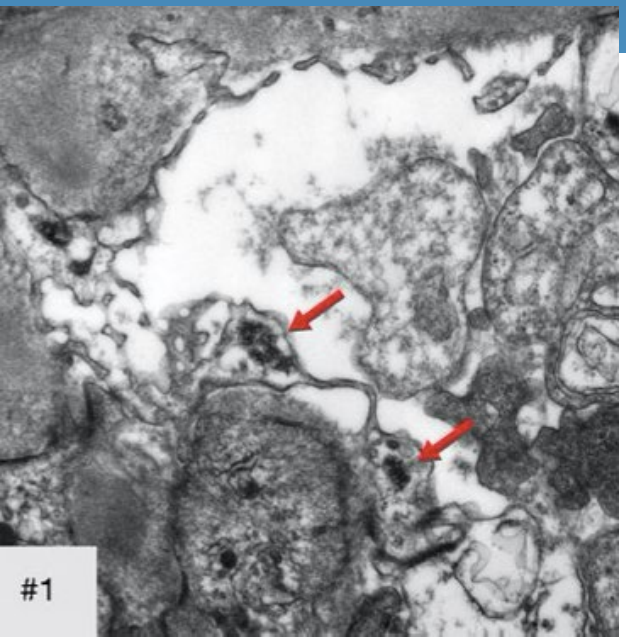
Issues with studies reporting SARS-coV-2 particles, protein, and/or viral RNA in glomeruli

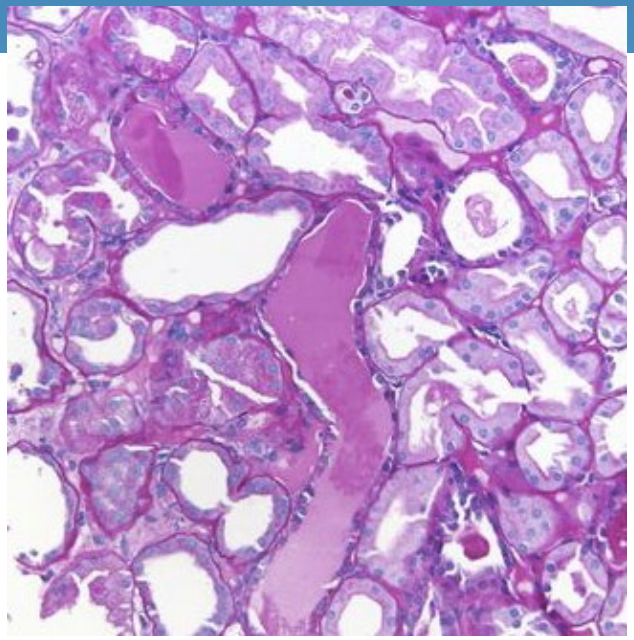
- Studies reporting SARS-coV-2 in kidney have technical limitations that may cause false positives:
  - PCR prone to false positives due to amplification of RNA fragments from dead virus
  - Insufficient specificity of antibodies used for immunostaining poor antigen specificity
  - RNA in situ hybridization prone to false positives due to autolysis of autopsy kidney specimens and insufficient specificity of probes
  - Normal organelles can look like viral particles on EM

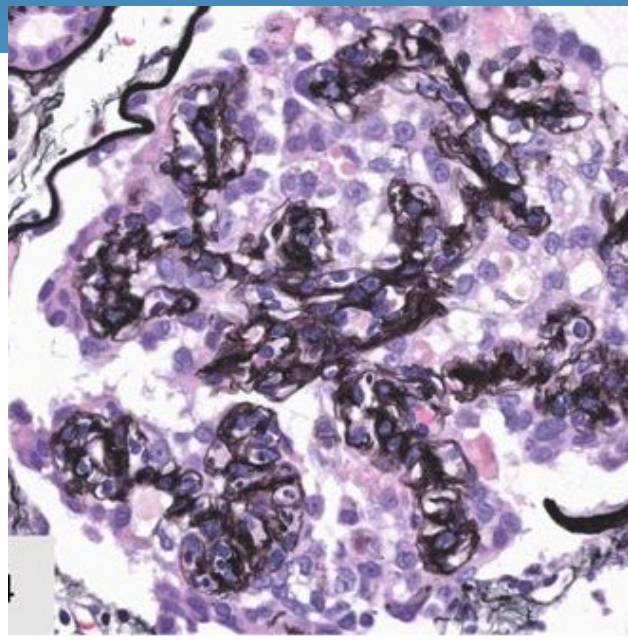
Puelles, et al. *NEJM*, 2020



COVID-19 associated collapsing glomerulopathy







Histological features of COVID-19 associated CG

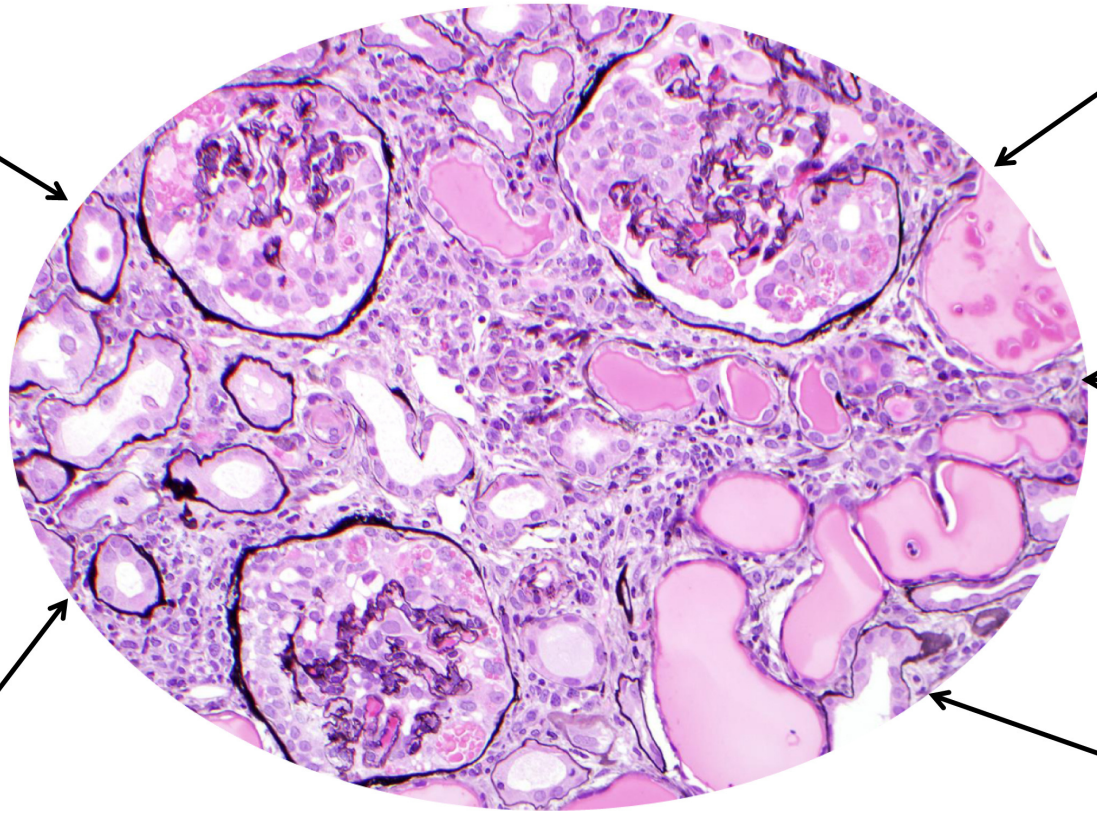
- Acute tubular injury, microcystic tubules
- Glomerular tuft collapse
- Parietal epithelial cell hypertrophy and hyperplasia
- Extensive foot process effacement
- Tubuloreticular inclusions (“interferon footprints”)

Wu, et al. *J Am Soc Nephrol*. 2020.

COVID-19 associated collapsing glomerulopathy looks identical to CG occurring in other settings

Genetic variants:
- **Nuclear genome**
  - APOL1
  - WDR73
  - PDSS2
  - AMRF2
- **Mitochondrial genome**
  - COQ2
  - COQ6

Infections:
- **Viral**
  - HIV-1
  - HTLV1
  - CMV
  - Parvovirus B19
  - EBV
  - Coxsackie B
  - Dengue
  - Zika
  - SARS-CoV-2
- **Others**
  - Malaria
  - Schistosoma
  - Pulmonary tuberculosis

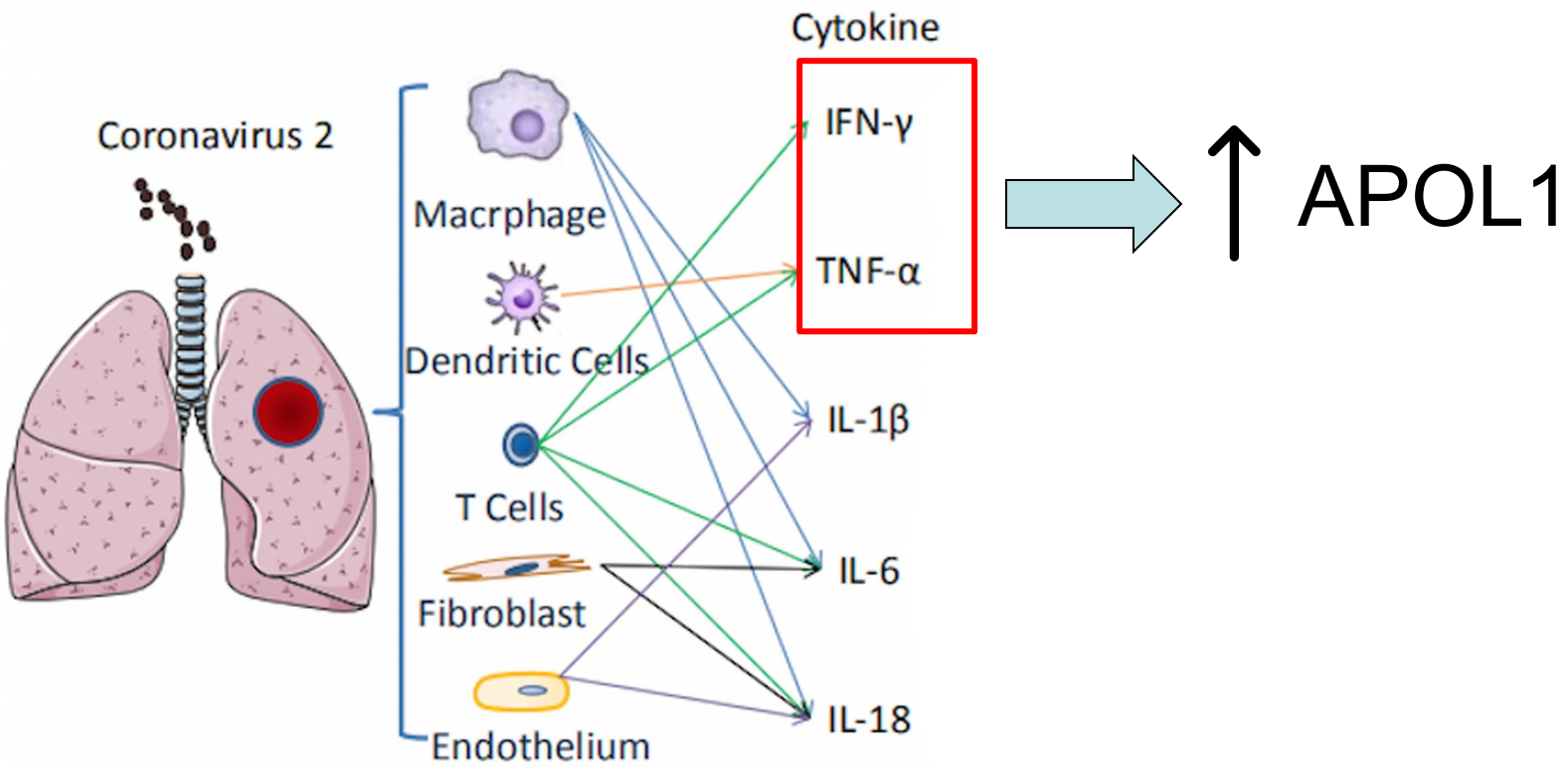


Medications:
- Pamidronate
- Interferons
- Anthracyclines

Systemic diseases:
- SLE
- ANCA vasculitis
- Still's disease
- Hemophagocytic syndrome
- Behcet syndrome
- Malignancy (lymphoma, leukemia, myeloma)

Acute glomerular ischemia:
- Thrombotic microangiopathy
- Atheroembolic disease
- Sickle cell disease
- Hydrophilic polymer embolism

Immune mechanisms of COVID-19 associated glomerular injury



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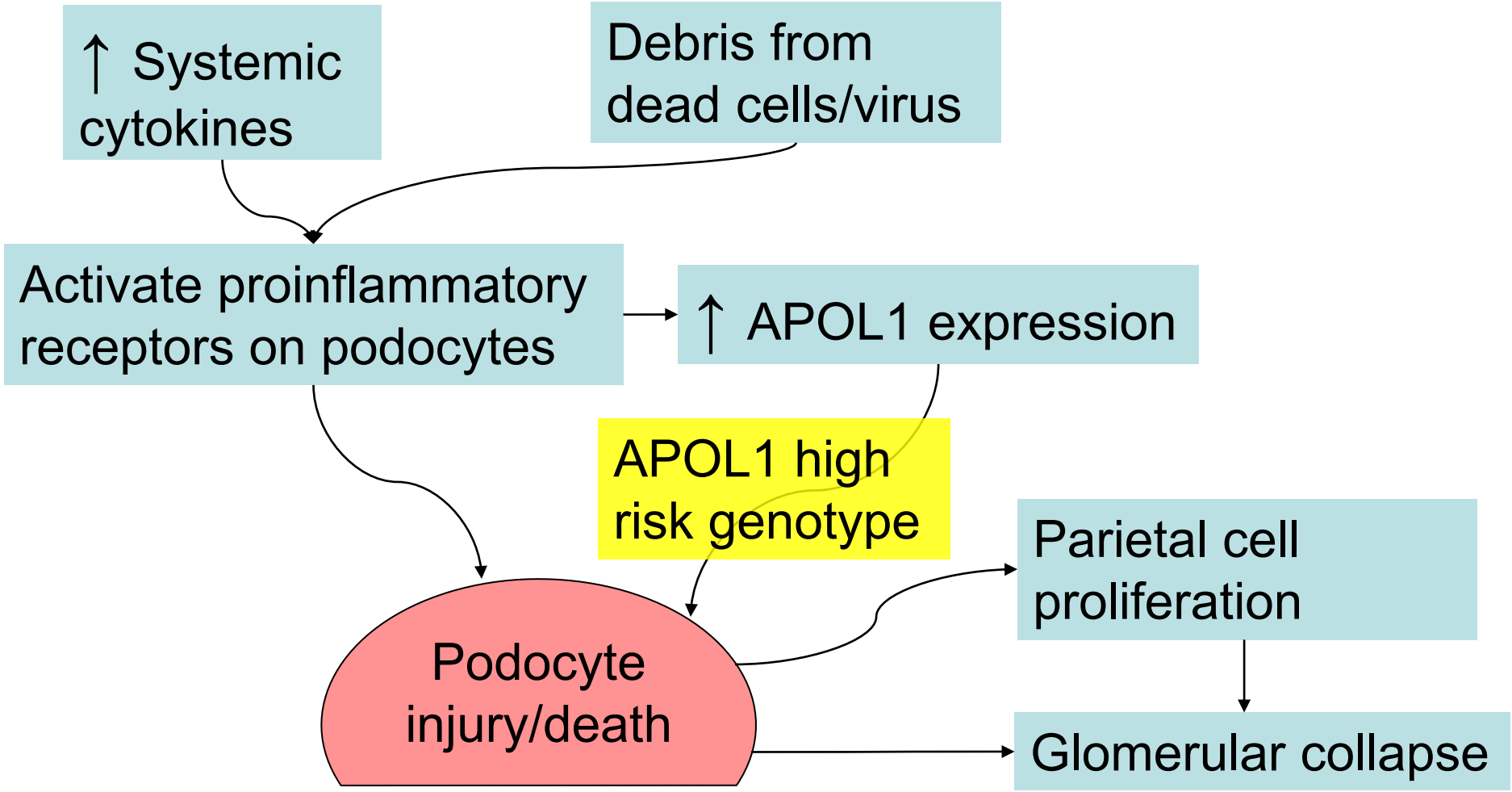
Sun, et al. Cytokine & Growth Factor Rev, 2020

Immune mechanisms of COVID-19 associated glomerular injury

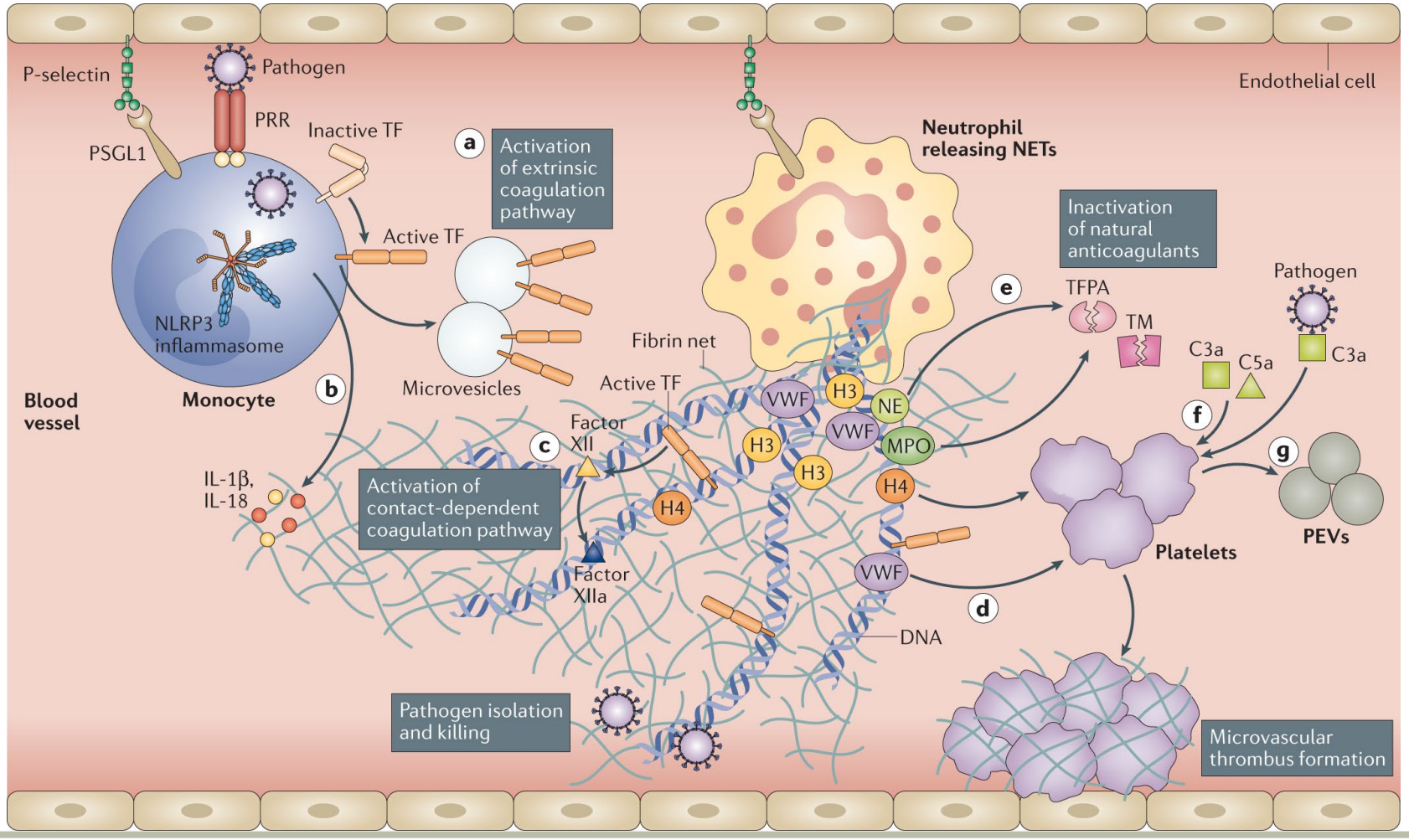


Role of APOL1 in COVID-19 associated collapsing glomerulopathy

- Most patients with COVID-19 associated CG who underwent APOL1 genotyping found to have high risk genotype (G1/G1, G1/G2, G2/G2)
- Heterozygosity for risk alleles does not appear to increase risk
- One transplant recipient with high-risk genotype developed COVID-19 associated CG in kidney from donor with low-risk genotype
  - Suggests either:
    - COVID-19 can sometimes cause CG independent of APOL1 genotype OR
    - In setting of COVID-19, liver derived APOL1 in plasma may mediate kidney injury

Shetty, *JASN*, 2021; Ferlicot, *Nephrol Dial Transpl*, 2021; Kudose, *JASN*, 2020; Wu, *JASN* 2020

Role of immunothrombosis in COVID-19 associated thrombotic microangiopathy



Bonaventura, Nat Rev Immunol, 2021

Treatment of COVID-19 associated glomerular disease: Collapsing glomerulopathy

- Kidney function and proteinuria improve in many patients up to 90 days following resolution of infection
  - Acute tubular injury also present in most CG cases
    - Monitor for recovery of kidney function if requiring kidney replacement therapy
  - Supportive therapy with strict control of blood pressure and volume status
- Consider immunosuppression in patients with severe nephrotic syndrome or persistent severe proteinuria that persists after resolution of infection
  - No controlled studies of treatment for COVID-19 associated glomerular diseases

Treatment of other COVID-19 associated glomerular diseases

- Thrombotic microangiopathy
  - Supportive care
  - Evaluate for predisposing factors (medications, complement factor deficiencies, etc)
  - Case reports/small case series suggest possible benefit of plasmapheresis and/or complement inhibition with eculizumab in selected cases
- The optimal approach to treatment of other COVID-19 associated glomerular diseases remains to be determined

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Sharma, *JASN*, 2020; Laurence, *Clin Immunol*, 2020

Summary of pathogenesis and treatment of COVID-19 associated glomerular diseases

- Dysregulated activation of systemic inflammation is likely the most important contributor to glomerular injury
- It remains unclear if SARS-CoV-2 infects glomerular cells and if it occurs, whether infections causes disease
- Collapsing glomerulopathy occurs primarily in persons with APOL1 high risk genotypes
- COVID-19 associated thrombotic microangiopathy is multifactorial with important role for “immunothrombosis”
- In addition to supportive therapy, immunosuppression may be appropriate in selected patients with persistent severe glomerular disease after resolution of COVID-19