Pathophysiology and Infection Cycle of SARS-CoV-2

SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus 2) is a novel, enveloped, **positive-sense single-stranded RNA virus** belonging to the **Coronaviridae family**, responsible for the global COVID-19 pandemic. It primarily targets the **respiratory system** and can lead to **multisystem involvement**, especially in severe cases.

Infection Cycle of SARS-CoV-2

The SARS-CoV-2 infection follows a multi-step cycle:

1. **Viral Entry (Invasion)**
2. **Viral Replication**
3. **Direct Cytopathic Effects**
4. **Dysregulated Immune Response (Cytokine Storm)**

Viral Entry (Invasion)

- The **spike (S) glycoprotein** on the SARS-CoV-2 surface is critical for **cell entry**.
- The **S protein is cleaved into S1 and S2 subunits** by **host proteases**.
  - **S1** binds to the **angiotensin-converting enzyme 2 (ACE2)** receptor on host epithelial cells (abundant in lungs, heart, kidneys).
  - **S2** mediates **membrane fusion**, aided by **TMPRSS2 (Transmembrane Serine Protease 2)**.
- The virus enters cells via **endocytosis** or **membrane fusion**.

? **High-Yield Note** : ACE2 not only facilitates viral entry but also modulates the renin-angiotensin system, influencing inflammation and vasoconstriction.

Viral Replication and Protein Synthesis

- After entry, **viral RNA** is released into the cytoplasm.
- The **5? two-thirds** of the genome encodes two **polyproteins** : **pp1a** and **pp1ab**, which are cleaved by viral proteases:
  - **3CLPro (Main Protease, Mpro)**
  - **PLPro (Papain-like Protease)**
- These polyproteins are processed into **16 non-structural proteins (nsps)** that form the **replication-transcription complex (RTC)**.
- The RTC synthesizes:
  - Full-length **negative-sense RNA** template
  - Subgenomic RNAs for structural proteins

Structural proteins (encoded at the 3? end):

- **Spike (S)** – mediates host cell entry

- **Envelope (E)** – viral assembly and release
- **Membrane (M)** – gives virus its shape
- **Nucleocapsid (N)** – binds RNA genome
- **Assembly** occurs in the **endoplasmic reticulum-Golgi intermediate compartment (ERGIC)** .
- Virions are released via **exocytosis** .

Direct Cytopathic Effects

- Viral replication causes **apoptosis and necrosis** of infected epithelial and endothelial cells, particularly in the **alveoli** .
- This leads to **alveolar damage** , **impaired gas exchange** , and in severe cases, **multi-organ injury** due to widespread viral dissemination.

Dysregulated Immune Response (Cytokine Storm)

- Viral antigens are processed by **antigen-presenting cells (APCs)** , triggering the release of pro-inflammatory **cytokines and chemokines** , including:
  - **IL-1**
  - **IL-6**
  - **CXCL10**
  - **TNF-?**
- An exaggerated immune response— **cytokine storm syndrome** —causes widespread **tissue damage** , especially in the lungs, leading to:
  - **Acute Respiratory Distress Syndrome (ARDS)**
  - **Multiorgan Failure**

? **Clinical Insight** :

- The severity of COVID-19 correlates strongly with **immune dysregulation** , not just viral load.
- Patients with comorbidities (e.g., obesity, diabetes, cardiovascular disease) are more prone to cytokine storm.

Therapeutic Interventions Based on Pathogenesis

- **IL-6 Inhibitors** : Block the cytokine storm and prevent lung injury in severe COVID-19 cases.
  - **Tocilizumab** and **Sarilumab**
- **Corticosteroids** (e.g., dexamethasone): Reduce mortality in patients requiring supplemental oxygen or mechanical ventilation.
- **Antivirals** (e.g., Remdesivir): Target the viral RNA-dependent RNA polymerase.
- **Monoclonal Antibodies** : Target spike protein, blocking viral entry.
- **Hydroxychloroquine** : Initially explored for its immunomodulatory effects, but **no longer recommended** due to lack of efficacy and safety concerns (per current guidelines from WHO and NIH).