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BRIEF REVIEW

Do You Know the Pathophysiology of Cytokine Storm During COVID-19?

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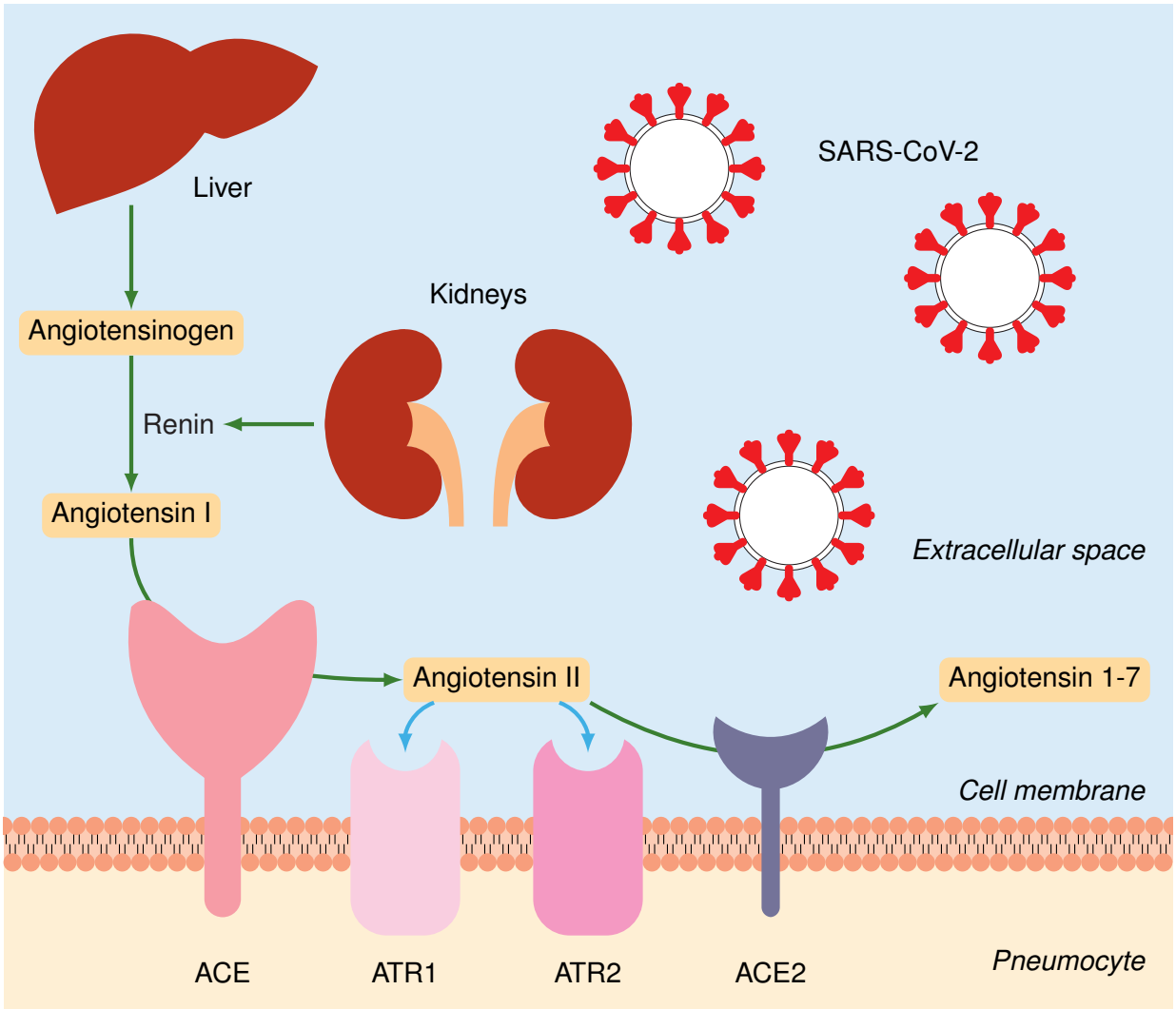

Figure 1. Angiotensinogen is synthesized by the liver. Renin cleaves angiotensinogen to angiotensin I, which is further processed to angiotensin II by angiotensin-converting enzyme (ACE). Angiotensin II undergoes further metabolism by the carboxypeptidase angiotensin-converting enzyme 2 to form Angiotensin (1-7).

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the causative pathogen of the COVID-19 pandemic. It has a single-stranded positive-sense RNA genome.[1, 2] COVID-19 illness usually lasts 7–10 days. Occasionally, it induces a potentially dangerous, variable-intensity, host-mediated, immune-inflammatory response called a cytokine storm.[3]

The pathophysiology of a cytokine storm's immune dysregulation is incompletely understood. Infected patients frequently exhibit an increase in serum cytokine levels, sometimes called "cytokine release syndrome".[4] Elevated cytokine concentrations are linked to rapidly deteriorating health.[4, 5] Examples of these cytokines include tumor necrosis factor α (TNF-α), monocyte chemoattractant protein 1, interleukin-1beta (IL-1β), IL-2, IL-6, IL-7, IL-17, IL-18, granulocyte colony–stimulating factor, macrophage colony–stimulating factor, C-X-C motif chemokine ligand 10, macrophage inflammatory protein 1 alpha, and chemokine ligand 2.[6, 7]

Angiotensin-converting enzyme 2, the primary receptor for SARS-CoV-2, is originally a part of the renin-angiotensin system.[8] The liver produces angiotensinogen, which is then cleaved by renin to angiotensin I and then converted to angiotensin II by angiotensin-converting enzyme. Angiotensin-converting enzyme 2 converts angiotensin II into angiotensin (1-7) (**Figure 1**).[9] Angiotensin-converting enzyme 2 is abundantly present in the lungs and other human tissues, explaining the multiorgan pathophysiology of SARS-CoV-2 infections.[8]

Angiotensin II binds to the angiotensin type I receptor, causing vasoconstriction and inflammation that damage tissues. By contrast, angiotensin (1-7) has anti-inflammatory and vasodilatory properties that balance the effects of angiotensin II.[9] SARS-COV-2 binding to angiotensin-converting enzyme 2 receptor induces its downregulation and abrogation of interferon (IFN) antiviral defense mechanisms by impaired or delayed IFN-1 response.[1]

Viral entry into host cells initiates an inflammatory signaling cascade that can eventually leads to a cytokine storm. Two important feedback loops involved in the production of a cytokine storm are contributed by nuclear factor kappa B (NF-κB) and IFN-1 pathways.[10] NF-κB is a transcription factor activated to induce the production of proinflammatory cytokines and IFN-1.[10, 11] Pro-inflammatory cytokines, such as IL-6, IL-2, TNF-α, and INF-γ, in return activate Janus kinase/signal transducers and activators of transcription (JAK/STAT) and NF-κB, inducing more production of proinflammatory cytokines.[11] IFN-1 can also activate pathways, initiating the transcription of interferon-stimulated genes (ISGs) to produce anti-virus mediators; it also unconventionally activates inflammatory pathways such as NF-κB and expression of proinflammatory cytokines and paradoxical hyperinflammation occurring during COVID-19.[11]

The IFN-1 response is the initial defense against viral infections and regulates immunity.[12] High viral loads, defective IFN signaling pathways, insufficient IFN response, the presence of IFN auto-antibodies, or advanced patient age may result in viral persistence.[13] Most people with severe COVID-19 have pre-existing comorbidities, such as hypertension, diabetes, obesity, and cardio-pulmonary diseases.[12]

Patients requiring mechanical ventilation are often documented to have had elevated cytokine levels.[5, 14] These pro-inflammatory cytokines are the main source of tissue injury, formation of thromboemboli, acute respiratory dysfunction, multiorgan failure, and acquired hemophagocytic lymphohistiocytosis, all occasionally present during COVID-19 illness.[15] An index of severe inflammation includes lymphocytopenia, prolonged prothrombin time, hyperferritinemia, elevated D-dimer levels, and/or ground-glass lung opacities depicted on computerized tomography.[4]

Therapeutic interventions dampen the cytokine storm by targeting the inflammatory cytokines and other associated signaling pathways. Understanding the pathophysiology is critical to research aimed at mitigating cytokine storm.

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