Cytokine Release Syndrome in Pathogenesis and Treatment of COVID-19

As of July 2022, based on the reported data from the world health organization (WHO), there have been more than six million deaths related to the coronavirus disease 2019 (COVID-19) in the world. It has been recognized that one leading cause of morbidity and mortality in COVID-19 patients is cytokine release syndrome upon severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection [1]. Such viral infection potentially causes excessive activation of inflammatory and immune responses in the patients and remarkable production of various cytokines and chemokines, including interleukin (IL)-1β, IL-2, IL-4, IL-6, IL-7, IL-8, IL-10, IL-17, tumor necrosis factor (TNF)-α, interferon (IFN)-γ, chemokine C-C motif ligand (CCL)2, CCL3, chemokine C-X-C motif ligand (CXCL)10, and granulocyte-macrophage colony-stimulating factor (GM-CSF), etc. [2]. The elevated circulating levels of pro-inflammatory cytokines and chemokines have been reported to be associated with the clinical symptoms of COVID-19, particularly those in moderate and severe patients, such as fever, disseminated intravascular coagulation, pneumonia, acute respiratory distress syndrome, tissue damage, multiorgan failure, and death eventually [3].

Many efforts have been made so far to develop potential therapies to treat moderate and severe COVID-19 patients by targeting cytokine release syndrome. Different therapeutic agents have been shown to relieve the cytokine release syndrome in pre-clinical studies and/or clinical trials, such as anakinra, baricitinib, chloroquine, emapalumab, etanercept, glucocorticoids, hydroxychloroquine, tocilizumab, and synthetic progestogen, etc. [4-6]. Of note, the United States Food and Drug Administration (FDA) issued an emergency use authorization (EUA) for tocilizumab to treat certain hospitalized adults and pediatric patients with COVID-19 in June 2021. Undoubtedly, effective management of cytokine release syndrome represents a promising strategy to improve the outcomes of COVID-19 patients, particularly those with moderate and severe diseases.

To provide a timely and latest understanding with regard to the involvement of cytokine release syndrome in the pathogenesis of COVID-19 and potentially relevant therapies, this mini-thematic issue was organized to collect the opinions from experts from different regions across the world, and the current review articles were reported timely for this pandemic disease.

Sagulkoo et al. from Thailand reviewed the current understanding of the immunogenetic etiology and pathophysiology of COVID-19 and associated cytokine storm. The authors also constructed and analyzed protein-protein interaction networks based on the NOD-like receptor protein 3 (NLRP3) and IL-18 variants and all genes that were established in severe COVID-19. Their work predicted many useful drug targets to prevent the onset of severe COVID-19. The SARS-CoV-2 innate immune evasion and the involvement of MYD88 and MAVS in the pathophysiology of severe COVID-19 were also predicted by their network analysis [7]. Another review by Simões et al. from Brazil summarized the modulation of P2X7 purinergic receptor in the main organs that were directly affected by SARS-CoV-2 and by the associated cytokine storm, with emphasis on the heart, brain, lung, liver and kidney. Given the ability of the P2X7 receptor to modulate hyper-inflammatory responses associated with COVID-19, many antagonists of this receptor were proposed to be promising agents for the treatment of cytokine release syndrome and cytokine production in COVID-19 [8]. In addition, Cure et al. from Turkey discussed the relationship between Na+/H+ exchanger (NHE) activation and cytokine production in COVID-19. SARS-CoV-2 infection was found to increase angiotensin II levels and overstimulate NHE. The prolonged activation of NHE contributed to excessive production of cytokines, which further increased NHE overstimulation and worsened this scenario. Based on their findings, NHE was considered a potential therapeutic target for mitigating cytokine release syndrome in COVID-19 [9].

In summary, the three reviews published in this mini-thematic issue have covered different aspects related to the mechanisms of cytokine release syndrome in COVID-19 and potential therapeutic targets and agents. We believe that the knowledge and information presented in this special issue are indeed valuable for those basic and clinical scientists working in the field to better understand the pathogenesis of COVID-19 and to develop safe and effective therapies, particularly for moderate and severe patients.

REFERENCES


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