



## Cytokine Storming in COVID-19

**Attapon Cheepsattayakorn<sup>1\*</sup> and Ruangrong Cheepsattayakorn<sup>2</sup>**<sup>1</sup>10<sup>th</sup> Zonal Tuberculosis and Chest Disease Center, Chiang Mai, Thailand<sup>2</sup>Department of Pathology, Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand**\*Corresponding Author:** Attapon Cheepsattayakorn, 10<sup>th</sup> Zonal Tuberculosis and Chest Disease Center, Chiang Mai, Thailand.**Received:** April 25, 2020**Published:** June 16, 2020© All rights are reserved by **Attapon Cheepsattayakorn and Ruangrong Cheepsattayakorn.**

During viral infection, cytokines play an important role in immunopathology with the first line of defense against viral infection via rapid and well-coordinated innate immune response. *In vitro* studies reveal that delayed release of cytokines and chemokines occurs in respiratory epithelial cells, macrophages and dendritic cells (DCs) at the early stage of severe-acute-respiratory-syndrome coronavirus (SARS-CoV) infection, including COVID-19 infection. At the later stage of infection, these cells secrete low levels of the antiviral factors-interferons (IFNs) and high levels of proinflammatory cytokines (interleukin (IL)-1 $\beta$ , IL-6, and tumor necrosis factor (TNF) and chemokines (C-C motif chemokine ligand (CCL-2, CCL-3 and CCL-5. SARS-CoV-2 or COVID-19 infects human airway epithelial cells, DCs, human peripheral blood monocyte (HPBM)-derived macrophages, and THP-1 cells (a monocyte cell line) and elevates levels of proinflammatory cytokines and chemokines.

After COVID-19 infection, plasmacytoid DCs are induced to secrete a large amount of IFNs. Acute respiratory distress syndrome (ARDS) is developed by the airway epithelial cells, DCs, HPBM-derived macrophages, and THP-1 cells secretion of several proinflammatory cytokines, such as IL-6, IL-8, IL-1 $\beta$ , reactive oxygen species (ROS) and chemokines (CCL-2, CCL-3, CCL-5, IFN $\gamma$ -induced protein-10 (IP-10)). Following COVID-19 infection, dysregulation of cytokine and chemokine response and high virus titer cause an inflammatory cytokine storming that is accompanying by pulmonary immunopathological changes.

High levels of several inflammatory cytokines (IL-1B, IFN- $\gamma$ , IP-10 and monocyte chemoattractant protein-1 (MCP-1) may activate the T-helper type 1 (Th1) cell response that is a key event in specific immune activation. COVID-19 can also elevate the levels of Th2 cell-secreted cytokines (such as IL-4 and IL-10), that inhibit the inflammatory response. The severity of COVID-19 patients correlates with the serum levels of IL-2R and IL-6 (i.e., critically ill COVID-19 patients > severely ill COVID-19 patients > normal

COVID-19 patients). COVID-19 patients with intensive care unit (ICU) admission demonstrate high serum levels of granulocyte-stimulating factor, IP-10, MCP-1, MIP-1 A, and TNF- $\alpha$ , compared to the general ward patients.

In conclusion, excessive and prolonged cytokine/chemokine response in some COVID-19 infected patients, called “cytokine storm” can contribute to ARDS or multiple organ dysfunction and death. The key of the treatment success is the timely control of the early stage of cytokine storm by cytokine antagonists and immunomodulators, including the reduction of the pulmonary inflammatory cell infiltration.

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