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An enlightening role for cytokine storm in coronavirus infection

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A B S T R A C T

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) outbreak in Wuhan, China has dispersed rapidly worldwide. Although most patients present with mild fever, cough with varying pulmonary shadows, a significant portion still develops severe respiratory dysfunction. And these severe cases are often associated with manifestations outside the respiratory tract. Currently, it is not difficult to find inflammatory cytokines upregulated in the blood of infected patients. However, some complications in addition to respiratory system with the coronavirus disease 2019 (COVID-19) are impossible to explain or cannot be attributed to virus itself. Thus excessive cytokines and their potentially fatal adverse effects are probably the answer to the multiple organ dysfunctions and growing mortality. This review provides a comprehensive overview of the mechanisms underlying cytokine storm, summarizes its pathophysiology and improves understanding of cytokine storm associated with coronavirus infections by comparing SARS-CoV-2 with severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV).

Keywords:
Coronavirus disease 2019 (COVID-19)
Cytokine storm
Multiple organ dysfunctions
Inflammatory cytokines
Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)

1. Introduction

A novel coronavirus named “severe acute respiratory syndrome coronavirus 2” (SARS-CoV-2) by the World Health Organization (WHO) is blamed for the recent pneumonia outbreak that started in December 2019 in Wuhan, Hubei, China [1]. The rapid epidemic spread of this highly contagious virus, to date, have caused around 91,554 cases across the globe [2]. Some clinical physicians and researchers noticed that infected patients, especially severe patients, are liable to progress into respiratory failure and many of them even have suffered from multiple organ injuries, involving respiratory tract, gastrointestinal tract, kidney, liver, heart, etc. [3–6]. The pathogenesis of these complications has not been elucidated as information on the clinical features of infected patients is limited. However, we are easy to discover relevant tracks in the long history of epidemic disease.

Cytokine storm is a potentially fatal immune condition and caused by a large number of inflammatory mediators derived from unchecked feed forward immune activation and amplification [7,8]. If left untreated, cytokine storm can lead to severe pathological complications including sepsis, shock, tissue damage, multiple organ failure and ultimately death [7–11]. The factors sparking the cytokine storm are heterogeneous but infection is the most frequent cause clinically [12]. In graft versus host disease cytokine storm is also known as hypercytokinemia, a high inflammatory response causing injury of vascular endothelial cells and alveolar epithelial cells, as well as infiltration of neutrophils and macrophages into lung [13]. Recently, hypercytokinemia was seen in severe COVID-19.

Abbreviations: SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; CoV, coronavirus; WHO, World Health Organization; ALI, acute lung injury; ARDS, acute respiratory distress syndrome; CNS, central nervous system; COVID-19, coronavirus disease 2019; MERS, Middle East respiratory syndrome; SARS, severe acute respiratory syndrome; IL, interleukin; IFN, interferons; TNF, tumor necrosis factor; MCP, monocyte chemoattractant protein; IL-1RA, IL-1 receptor antagonist; IP-10, IFN-γ-inducible protein-10; Th, helper T cell; DC, dendritic cell; NK, natural killer cell; B, B lymphocyte; Th2, T-helper-2 cell; BMSC, bone marrow stromal cell; Th1, T-helper-1 cell; PBMC, peripheral blood mononuclear cell; CCL, chemokine ligand; CXCL, chemokine (C-X-C motif) ligand; GCSF, granulocyte colony stimulating factor; GMCSF, granulocyte-macrophage colony-stimulating factor; FGF, fibroblast growth factor; PDGF, platelet derived growth factor; VEGF, vascular endothelial growth factor; MCP1A, macrophage Inflammatory Protein 1 Alpha; MIP1B, macrophage Inflammatory Protein 1 beta; PRRs, pattern recognition receptors; TLRs, Toll-like receptors; PAMPs, pathogen-associated molecular patterns; CRP, C-reactive protein; NLR, neutrophil-to-lymphocyte ratio; COVID-SS, COVID-19 related cytokine storm syndrome; ACE2, angiotensin-converting enzyme 2; NF-κB, nuclear factor κB; JAK, Janus kinase; STAT, signal transducer and activator of transcription; IRF3, IFN regulatory factor-3.

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https://doi.org/10.1016/j.clim.2020.108615
Received 19 February 2020; Received in revised form 20 October 2020; Accepted 21 October 2020
Available online 23 October 2020
Evidence from coronavirus disease 2019 (COVID-19) patients indicated that serum inflammatory markers increased excessively, especially in severe patients with some obvious complications, and the term of COVID-19 related cytokine storm syndrome (COVID-CSS) emerged to denote patients with markedly excessive immune activation [3–6, 14]. Previously, SARS-CoV, MERS-CoV, Ebola and other virus have been demonstrated to induce hypercytokinemia and contributes to the high fatality rate [9, 11, 15]. Studies also support the cytokine storm rather than virus is the real killer, triggering the immune system to attack the human body systemically and fiercely [8, 16]. Herein, we comprehensively reviewed the current literature regarding the physiology of cytokine storm in the context of coronavirus infection and also discussed about the complicated interactions among the cytokine storm, immune response and organ functions. We hope to provide some inspirations to SARS-CoV-2 therapeutics and present evidence that could help understand some unexplainable complications.

2. Definition of cytokine storm

Cytokines are a large number of small signaling proteins secreted by immune cells for the purpose of intercellular communication, taking part in cell proliferation and differentiation, regulating immune and inflammatory responses, and being main executors of the cytokine storm [17, 18]. Cytokine storm generally describes that pro-inflammatory cytokines are releasing excessively and uncontrollably during severe infection [7, 8]. In most cases, multiple cytokines have positive implications in promoting disease progression, such as providing a defense against pathogens, modulating the inflammatory process and facilitating tissue repair, thus present as a complex, overlapping and cross-linked interplay [19]. Whereas, this can be detrimental if excessive. A cytokine storm can bring severe damages to the host and lung is always the first to be affected, such as diffuse alveolar damage, hyaline membrane formed, increased pulmonary capillary permeability and alveolar exudative inflammation, etc. [18, 20]. The direst consequences of all lies in that lung injury disrupts immune system and further results in multiple organ dysfunctions [21].

3. The origin of cytokine storm

Inflammatory response is the first line of defense that protects human from infection or damage, responding to endogenous or exogenous challenges by activating both innate and adaptive immune responses [22]. The main signs for inflammation usually consist of heat, redness, swelling and pain [23]. In terms of classical self-limiting inflammatory response, four steps are included: (1) recognition of the infectious agents; (2) recruitment of immune cells and other components; (3) clearance of the infection; (4) retrogression of inflammation [24] (Fig. 1A). However, the procedure doesn’t fit into certain pathogens since they are so cunning that they have developed strategies to deceive the immune system and thus unable to induce an effective and defensive immune response [25–27]. On the contrary, some microorganisms cannot be neglected as they could hyperstimulate the immune system and give rise to so-called cytokine storm [28] (Fig. 1B). This extremely dangerous pathogen, like SARS-CoV-2, MERS-CoV and SARS-CoV, can hamper the elimination of infection and induce severe tissue damages [29–32]. Throughout the process, numerous cytokines with pro-inflammatory/anti-inflammatory properties act on different parts of the inflammatory response.

More specifically, cytokine storm is triggered by some signaling pathways. Viral spike protein, like SARS-CoV spike protein, firstly binds...
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inflammatory cytokines (IL-1β) elevated significantly in critically ill COVID-19 patients [4,5,37]. The correlative facts that excessive immune response play an irreplaceable role as well as extensive lung damage [39,40]. Also, compared to mild- and IFN-γ patients, severe patients had higher levels of pro-inflammatory cytokines was followed by the increased number of neutrophil and monocyte [42]. High level of cytokines and chemokines was followed by the increased number of neutrophil and monocyte in lungs as well as blood, suggesting that immunocompetent cells possibly participate in lung pathology [30,41].

Two early researches of SARS-CoV-2 also reported the cytokine response. According to a set of data from Jin Yin-tan Hospital, a COVID-19 designated hospital in Wuhan, patients infected with SARS-CoV-2 had higher concentrations of TNF-α, IFN-γ, IP10, MCP-1, IL-1RA, IL-1β, IL-7, IL-8, IL-10, GCSF, GMCSF, basic FGF, PDGF, VEGF, MIP1A and MIP1B than healthy adults [4]. Moreover, the levels of IL-2, IL-7, IL-10, GCSF, MCP-1, IP-10, MIP1A, and TNF-α were significantly higher in intensive care unit (ICU) patients than those in non-ICU patients, suggesting that cytokine storm was more likely to happen in severe patients and associated with disease severity [4]. Intriguingly, both T-helper-1 (Th1) cell and T-helper-2 (Th2) cytokines were activated and this indicated Th2 cytokines suppressing inflammation were also involved in this process, which differs from SARS-CoV-2 infection [4,39]. Another research group from Chongqing reported the abnormal cytokines in peripheral blood of SARS-CoV-2 infected patients as well. Specifically, 30.39% of the mild patients had higher IL-6 value than normal, but this proportion for severe patients was up to 76.19%, which was significantly greater than normal levels, whereas IL-6 showed larger increases, even more than 1000 fold over the normal. Paralleled studies found markedly to angiotensin-converting enzyme 2 (ACE2) for virus entry, and then viral RNAs, one of the most important pathogen-associated molecular patterns (PAMPs), are identified by the pattern recognition receptors (PRRs) mainly consisting of the family of Toll-like receptors (TLRs) [33]. Downstream transcription pathways, including nuclear factor κB (NF-κB), JAK (Janus kinase)/STAT (signal transducer and activator of transcription), IRF3 (IFN regulatory factor-3) are subsequently activated to fight the virus [34-36].

4. Cytokine responses during coronavirus infection

Infection is often the root of cytokine storm. Though no direct evidence can demonstrate that pro-inflammatory cytokines involve in pathogenesis of coronavirus, some patients with severe disease provide the correlative facts that excessive immune response play an irreplaceable role [3,4,37,38]. SARS-CoV-2 has caused a mounting number of COVID-19 cases in Wuhan. It is noteworthy that a group of cytokines elevated significantly in critically ill COVID-19 patients [4,5,37].

Early studies of SARS patients showed that increased amounts of pro-inflammatory cytokines (IL-1β, IL-6, IL-12, MCP-1, IP-10, IL-8, TNF-α and IFN-γ) in serum were connected with severe pulmonary inflammation as well as extensive lung damage [39,40]. Also, compared to mild patients, severe patients had higher levels of pro-inflammatory cytokines (IL-1β, IL-6, IL-12, IFN-γ and TGF-β) and chemokines (IL-8, CCL2, CXCL9 and CXCL10), and among them, the classic anti-inflammatory cytokine, IL-10, was at comparatively low level [39]. In addition, elevation of IFN-α, IFN-γ and IFN-stimulated genes (CXCL10 and CXCL2) was observed in patients with lethal SARS [29,39,40]. Similarly, MERS-CoV was also demonstrated to induce increased levels of pro-inflammatory cytokines (MCP-1, IFN-α, IFN-γ, IL-10, TNF-α, IL-1RA, IL-6, IL-15 and IL-17) [41,42]. Researchers also found pro-inflammatory cytokines (IFN-α and IL-6) and chemokines (IL-8, CCL5 and CXCL10) in patients with severe MERS increased more than those with mild or moderate disease [42]. High level of cytokines and chemokines was followed by the increased number of neutrophil and monocyte in lungs as well as blood, suggesting that immunocompetent cells possibly participate in lung pathology [30,41].

Table 1

Main characteristics of cytokine profile during different coronavirus infections.

| Major cytokines | Origin | Major actions | COVID-19 | MERS | SARS |
|-----------------|--------|---------------|----------|------|------|
| TNF-α           | Th, Monocyte, Macrophages, DC, NK, B, Mastocytte | Proinflammatory; activates cytotoxic T-lymphocytes | ↑ [4] | ↑ [41] | ↑ Healthy group(n = 12):3.77(3.40)ng/L SARS group(n = 24):4.79(14.48)ng/L [40] |
| IL-1β           | Monocyte, Macrophages, DC, NK, B, Endotheliocyte | Growth and differentiation of lymphocytes; proinflammatory; cytokine expression | ↑ [4] | ↑ [4] | ↑ SARS group(n = 20): 7.8 ng/L [39] |
| IL-6            | Th-2, Monocyte, Macrophage, DC, BMSC | Differentiation of stem cells and lymphocytes; proliferation of T-lymphocytes; proinflammatory | ↑↑ Mild group(n = 102):13.41 ± 1.84 ng/L | ↑ [42] | ↑ SARS group(n = 20): >3.9 ng/L [39] |
| IL-RA           | Synovial tissue, PBMC | Inhibit IL-1, anti-inflammatory | ↑ [4] | ↑ [42] | ↑ SARS group(n = 20): 7.8 ng/L [39] |
| IFN-α           | Leukocyte | Antiviral properties; regulation MHC II | ↑ [4] | | |
| IFN-β           | Th, B, Macrophage, Mastocyte | Proinflammatory or anti-inflammatory; promote tissue repairing | ↑ [42] | | |
| IFN-γ           | Th1, Tc1, NK | Antiviral properties; regulation of innate immunity; antiproliferative effects | ↑ [4] | ↑ [41,43] | ↑ SARS group(n = 20): 15.6 ng/L [39] |
| IL-8            | Monocyte, Macrophage, Endotheliocyte | Control of chemotaxis; leukocyte recruitment | ↑ [4] | ↑ [43] | ↑ SARS group(n = 20): >5.0 ng/L [39] |
| IL-10           | Th2, Monocyte, Macrophage | Cytokine inhibition; immunosuppression; anti-inflammatory | ↑ [4] | | Healthy group(n = 12):6.28(3.49)ng/L SARS group(n = 24): 431.23(78.51)ng/L [40] |
| IP-10           | CD4+ T, CD8+ T, NK | Control of chemotaxis; leukocyte or lymphocyte recruitment; proinflammatory | ↑ [4] | ↑ [43] | ↑ [39] |
| MCP-1           | Endotheliocyte, Fibrocyte, Monocyte, Macrophage, B | Chemotactic for monocytes and T-lymphocytes; proinflammatory | ↑ [4] | ↑ [43] | ↑ [39] |

Abbreviations: COVID-19, coronavirus disease 2019; MERS, Middle East respiratory syndrome; SARS, severe acute respiratory syndrome; IL, interleukin; IFN, interferons; TNF, tumor necrosis factor; MCP, monocyte chemotactant protein; IL-1RA, IL-1 receptor antagonist; IP-10, IFN-γ-inducible protein-10; Th, helper T cell; DC, dendritic cell; NK, natural killer cell; B, B lymphocyte; Th2, T-helper-2 cell; BMSC, bone marrow stromal cell; Th1, T-helper-1 cell; PBMC, peripheral blood mononuclear cell.
elevated IL-6 ranging from 100 to 10,000 pg/mL in severe patients [43–46]. While the emerging coronaviruses present similar clinical symptoms, the laboratory findings are characterized by distinct cytokine profiles (Table 1).

Clinically, it is urgent to diagnose or discern cytokine storm in COVID-19. Result from a global meta-analysis including 33 laboratory biomarkers indicated that elevated serum levels of IL-6 and ferritin, positively and significantly correlated with white blood cells and inversely correlated with lymphocyte and platelet counts, could provide a diagnostic clue for COVID-19 [47]. In another study, severe symptoms were characterized by high levels of IL-6, fibrinogen, sialic acid, C-reactive protein (CRP) and neutrophils [48]. Also, higher neutrophil-to-lymphocyte ratio (NLR) and decreased lymphocyte counts may indicate the dysregulated immune response [48]. Some large studies imply that an IL-6 threshold ≥ 80 pg/mL has predictive value in COVID-CSS outcomes [43, 49, 50]. Though IL-6 measurement became an inexpensive and simple assay for many clinical laboratories to evaluate prognosis of COVID-19, the value of it has been challenged. This is because COVID-19 IL-6 had a relatively low median level in several studies [51]. The temporal heterogeneity makes it difficult to specify effects of IL-6, but treatment with IL-6 blockade is perhaps more informatively [14]. Cytokine modulators have been purposed as therapeutic strategy to mitigate the COVID-19. Such drugs include anti-TNF-α agents, corticosteroids, IL-1 inhibitors, IL-6 receptor antagonists, JAK inhibitors, chloroquine, hydroxychloroquine and azithromycin and some of them have shown clinical benefit [52–63].

5. Cytokine storm involving in multiple organ failures

Cytokine storm could affect all the vital organs of the human body. Acute lung injury (ALI) is a common consequence of a cytokine storm and always associated with confirmed or suspected infections in the lung or other organs [29]. The main characteristic of ALI is inflammatory cell (granulocyte and monocyte) infiltration followed by collagen distribution and deposition [64,65]. Virus-induced lung injury could rapidly progress to ALI or acute respiratory distress syndrome (ARDS), a severe form of ALI, as seen with SARS-CoV and highly pathogenic influenza virus infections [66,67]. Some crucial cytokines in cytokine storm (e.g. IL-1β and TNF-α) drive pro-inflammatory activity in patients with lung injury [68]. Intensive inflammation originated from lungs can have other systemic effects, for instance, the severe lung injury combined with mechanical ventilation makes for cell apoptosis in renal tubular epithelial and renal dysfunction [69].

Systemic effects for cytokine storm starts from local inflammation spilling over into the circulation, producing systemic sepsis, as marked by persistent hyperpyrexia or hypothermia, leukocytosis or leukopenia, thrombocytopenia and often hypotension [70]. Study reported, among the COVID-19 patients, 25% of them had leukopenia and 5% had thrombocytopenia [4]. When it comes to histopathological changes, the highly pathogenic influenza virus (H5N1 and H7N9) was researched most deeply, but more attention has been devoted to coronavirus in recent decades [71,72]. Studies showed SARS-CoV infection induces ALI that may progress rapidly to life-threatening ARDS [73]. MERS-CoV infection could result in a more severe pneumonia than SARS-CoV infection [74].

In addition to pulmonary lesions, a cytokine storm could involve in nervous system, digestive system urinary systems, cardiovascular system and other areas [75–77]. Currently, part of patients with COVID-19 manifested intestinal sign, nervous system symptom, renal damage, hepatic lesion and even cardiac injury, besides respiratory problems [3–5,78]. Zhongnan Hospital of Wuhan University reported common complications among the 138 infected patients, including shock (8.7%), ARDS (19.6%), arrhythmia (16.7%), and acute cardiac injury (7.2%) [3]. Moreover, the ICU patients were more likely to get one of these complications than non-ICU patients [3]. Earlier, Jin Yin-tan Hospital of Wuhan had suggested patients in ICU were more likely to report...
dizziness, abdominal pain, and anorexia compared with the non-ICU patients [4]. Besides, a remarkable reduction of lymphocytes, especially T lymphocytes, was observed, suggesting the cytokine storm have caused changes in peripheral immune cells, as does SARS-CoV-2 [3, 5, 7, 8]. Actually, many of the similar signs or symptoms have been reported in SARS and MERS. Patients infected with either MERS-CoV or SARS-CoV both had diarrhea [8, 9]. In addition to respiratory symptoms, gastrointestinal distress and neurological sequelae have been seen in MERS patients [81]. As to SARS, the most severe cases died after the onset of non-specific symptoms (e.g. cough, myalgia and dyspnea) [82, 83]. And follow-up studies revealed that immunopathologic damage resulting from exaggerated immune response, rather than unbridled viral replication, is the lethal cause [29, 84]. Studies on cytokine responses in extra-respiratory organs or tissues during coronavirus infection are insufficient, but in the field of influenza virus, systemic cytokine responses have been demonstrated to increase the severity of influenza [71, 72, 83]. Severe influenza virus infections are associated with central nervous system (CNS) and cardiovascular disease [84, 85]. The associated clinical manifestations with cytokine storm are shown in Fig. 2.

6. Conclusions
After several years of silence, appearance of SARS-CoV-2 alarms researchers about the dreadful consequences of inordinate immune response. This virus has caused a widespread and fast-spread epidemic that poses a major threat to global public health. As a recently emerging and highly contagious coronavirus, SARS-CoV-2 remains mysterious and thus current treatments continue to tapp down symptoms rather than address causes. Several studies have demonstrated that cytokine storm following infection could be the most crucial factor for exacerbation and even death of patients. Therefore, in the present review, we suggested appropriate immunomodulation therapy might become a potential complement to supportive treatment and have present review, we suggested appropriate immunomodulation therapy and its role in severe dengue, Semin. Immunopath. 39 (2017) 563–574, https://doi.org/10.1016/j.semirolpath.2017.02.003.

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