DERLEME REVIEW

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COMPREHENDING COVID-19: IMMUNOPATHOGENIC MECHANISMS OF CYTOKINE ACTION

COVID-19'U ANLAMAK: SİTOKİN ETKİSİNİN İMMÜNOPATOJENİK MEKANİZMALARI

Elisha Apatewen AKANBONG[1], Alparslan Kadir DEVRİM[1], Ali ŞENOL[1], Tuba DEVRİM[2]

[1] Kırıkkale University, School of Veterinary Medicine, Department of Biochemistry, Kırıkkale, TURKEY
[2] Kırıkkale University, School of Medicine, Department of Medical Pathology, Kırıkkale, TURKEY

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Öz

Sitokin salınım sendromu (SSS) veya sitokin fırtınası, SARS-CoV-2 tarafından başlatılabilen, bağışıklık sisteminin orantısız tepkisinden kaynaklanan proinflamatuar sitokinlerin aşırı üretiminin bir sonucudur. SARS-CoV-2'nin neden olduğu COVID-19, sitokinlerle korelasyon göstermektedir. SARS-CoV-2, yaygın dağılım gösteren makrofajlar ve mast hücreleri sayesinde IL-1 üretimini tetiklemektedir. IL-1 ise, IL-6 ve TNF-α üretimlerini etkileme eğilimindedir. COVID-19 şiddetinin ilerlemesi, IL-6 gibi bazı sitokin düzeylerini etkiler. IL-6, SSS oluşumundan başlıca sorumlu olan sitokindir. SSS, COVID-19 ile ilgili komplikasyonların ve COVID-19 ile ilişkili ölümlerin ana nedenidir. Bu zamana kadar literatürde bildirilmiş verilere rağmen, SARS-CoV-2 ve sitokinler arasındaki ilişki tam olarak aydınlatılmış değildir. Bu derleme ile söz konusu ilişkinin irdelenmesi amaçlamıştır. COVID-19 tedavisi sırasında sitokinlerin hedeflenmesi, hastaların hayatta kalma oranlarını artırma ve COVID-19 ile ilişkili ölümleri azaltma potansiyelini taşımaktadır. COVID-19 hastalığında, sitokin salınım mekanizmalarına ve salınan sitokinlerin etkilerine odaklanılmasının, özellikle T lenfositler üzerindeki etkilerinin ve IFN-γ üretiminin irdelenmesinin, hastalığın ölümcül etkilerini azaltmaya yardımcı olabileceği düşünülmektedir.

Anahtar Kelimeler: COVID-19, Sitokinler, Sitokin Salınım Sendromu, Sitokin Fırtınası

Abstract

Cytokine release syndrome (CRS) or cytokine storm is as a result of the excess production of pro-inflammatory cytokines which is due to the disproportionate response of the immune system which can be instigated by SARS-CoV-2. COVID-19 which is caused by SARS-CoV-2 has a correlation with cytokines. SARS-CoV-2 instigates the production of IL-1 by ubiquitous macrophages and mast cells. IL-1 tends to influence the production of IL-6 and TNF-α. The progression of COVID-19 severity influences the level of certain cytokines such as IL-6. IL-6 is the cytokine chiefly responsible for the occurrence of CRS. CRS is the cause of COVID-19-related complications and the main cause of COVID-19-related deaths. Despite the data reported in the literature so far, the relationship between SARS-CoV-2 and cytokines has not been fully elucidated. The aim of the present review is to examine the relationship in question. Targeting cytokines during COVID-19 treatment has the potential to increase patient survival and reduce COVID-19-related deaths. It is concluded that focusing on the mechanisms of cytokine release and the effects of released cytokines, especially examining the effects on T lymphocytes and IFN-γ production in COVID-19 disease, may help reduce the lethal effects of the disease.

Keywords: COVID-19, Cytokines, Cytokine Release Syndrome, Cytokine Storm

Sorumlu yazar ve iletişim adresi /Responsible author and contact address: T.D. / tubadevrim@gmail.com
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ORCID IDs of the authors: E.A.A: 0000-0002-2556-7236; A.K.D: 0000-0002-3293-7290; A.Ş: 0000-0003-4080-7776; T.D: 0000-0002-5321-2002

Introduction

Coronavirus disease 2019 (COVID-19) is caused by the novel human coronavirus, Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). SARS-CoV-2 belongs to the family Coronaviridae, which is an enveloped, positive-sense, and single-stranded RNA genome (1). Following its emergence in December 2019 in Wuhan-China, it rapidly spread to more than 196 countries. Due to its rapid spreading nature, the World Health Organization (WHO) declared it a global health emergency (2, 3). Research suggests that SARS-CoV-2 has a zoonotic origin and bats are major reservoirs of coronaviruses similar to the SARS-CoV-2. The transmission of SARS-CoV-2 from human to human may be via direct contact such as coughing and sneeze droplets, which may lead to the generation of aerosols, from an infected human. Again, contaminated surfaces such as door handles contribute to the indirect transmission of the virus (4). SARS-CoV-2 attacks and replicate in the upper and lower respiratory tract with infected individuals manifesting symptoms within 2 weeks. Thus, it has an incubation period of 2 weeks (5). According to WHO, as cited by Darif et al. (2) infected individuals show symptoms ranging from mild (and may recover without any special treatment) to moderate depending on their immune status. However, older individuals and people with chronic diseases like diabetes, chronic respiratory disease, cancer, and cardiovascular disease are more susceptible to developing severe symptoms due to compromised immunity. In such patients, the infection may result in pneumonia and acute respiratory distress syndrome (ARDS) eventually, leading to organ failure which ultimately may lead to death (4).

Cytokines, which were previously referred to as lymphokines and monokines to depict their cellular sources were subsequently named 'cytokines' when it was obvious that almost all nucleated cells could synthesize and respond to them (6). The term cytokine stems from two Greek words: cyto (cell) and kinos (movement) (7). Generally, Cytokines are low molecular weight proteins secreted by immune cells, endothelial cells, fibroblasts, and other stromal cells (8) with pleiotropic and cell-specific functions including; cellular communications and the coordination of cellular responses (9,10). Also, they provide growth, differentiation, inflammatory or anti-inflammatory signals to relevant cells, and most often, they are released during defined periods in response to stimuli (11,12). Cytokines have their extent of an effect being short due to their limited half-life in circulation. Typically, cytokines exert an autocrine or paracrine effect (11,13). Nonetheless, they may also signal distant cells thus, may exhibit an endocrine activity (14).

The expression of cytokines' gene is tightly regulated under basal homeostatic conditions and often not continuous. In other words, the constitutive expression of cytokines' gene is often absent. However, the transcription and translation rates of cytokines' gene may be affected by a variety of stimuli (9) such as growth factors, foreign stimuli, and/or cytokines (15). Cytokines are essential in the activation of immune cells, in other words, they contribute tremendously to immunity. Nonetheless, when their release is not regulated, they influence the occurrence of many inflammatory diseases (15) and cytokine release syndrome (CRS) or cytokine storm (17). CRS is a result of the excess production (exaggeration) of pro-inflammatory cytokines which is due to the disproportionate response of the immune system which can be instigated by SARS-CoV-2. CRS has been implicated in the severity and occurrence of deleterious effects of COVID-19 in some patients (2,18,19). Despite that, the relationship between SARS-CoV-2 and cytokines has not been well elucidated hence, this review aimed to achieve that.

Initiation of Cytokine Release by SARS-COV-2

Angiotensin-converting enzyme 2 receptor (ACE 2) is expressed on the surface of the cell membranes of epithelial cells of the respiratory tract. SARS-CoV-2 binding to this receptor instigates the release of pro-inflammatory cytokines. The hormone angiotensin II (Ang II) aside from being a vasoconstrictor, also stimulates pro-inflammatory responses thus, the release of cytokines including IL-6, IL-8, and TNFα by up-regulating NF-κβ. Ang 1-7 is a vasodilator that occurs from Ang II under the modulatory influence of ACE 2, the main modulator of the renin-angiotensin system (RAS). Hence, the blockade of Ang 1-7 production as a result of the inhibition or elimination of ACE 2 leads to an increase in the levels of Ang-II, which in turn causes the exaggeration of pro-inflammatory cytokines. Also, Ang 1-7 hormone triggers the release of anti-inflammatory cytokines by cells hence, prevents lung damage (20). SARS-CoV-2 infection inhibits the activities of ACE 2 via the ADAM Metallopeptidase Domain 17 (ADAM 18). This eventually results in the liberation of the membrane-bound ACE 2 in a soluble form (sACE2). The mitigation of ACE 2 production or release by SARS-CoV-2 which is mediated by the ADAM 17 hinders the synthesizes of Ang 1-7 from Ang II. Thus, the level of Ang II in the COVID-19 patients' increase which tends to increase or exacerbate the pro-inflammatory response in the

patients and eventually causes the organ or multi-organ failure to occur in COVID-19 patients (20). Aside from the virus itself, its degraded products can equally trigger the occurrence of CRS. The recognition of the SARS-CoV-2 by the germline-encoded host sensors, pattern recognition receptors (PRRs) play a vital role in the release of cytokines to stimulate both innate and adaptive immune responses (21).

In addition, CRS is a condition common in COVID-19 patients and this abnormality seems to be initiated by IL-1. SARS-CoV-2 induces the secretion of IL-1 by ubiquitous macrophages and mast cells (MCs) (22) and the secretion of IL-1 induced by SARS-CoV-2 is high in both severe and non-severe patients unlike in non-infected individuals (23). Following its secretion, it also triggers the secretion of TNF-α and IL-6 (22). IL-6 is largely the cause of CRS. IL-6 has two main receptors; IL-6R and the soluble form, SIL-6R. It also has two main signaling pathways namely; the classical and trans-signaling pathways. In COVID-19 patients, IL-6 binds to the SIL-6R (trans-signaling pathway) forming the IL-6/SIL-6R complex which results in the activation of gp130. The activation of the gp130 leads to the instigation of many intracellular pathways such as the Janus kinase (JAK)/signal transducers, transcription activation (STAT), and the phosphatidylinositol-3 kinase pathway thus, causing the release of pro-inflammatory cytokines by all cells (2,24).

IL-6 also induces the synthesis and production of positive acute phase reactants such as serum amyloid A (SAA) which is also capable of triggering the overexpression of cytokines (CRS) and this contributes to the reasons why individuals with chronic diseases such as diabetes are at more risk of encountering COVID-19 severity. Aside from that, the production of SAA induced by IL-6 subsequently causes more complications such as reduced pulmonary and tissue gas exchange via red blood cell (RBC) agglutination, atypical coagulopathy by binding to fibrinogen and high-density lipoprotein (HDL) dysfunction or atherosclerosis by binding to lipoproteins (Summarized in figure 1) (25,27).

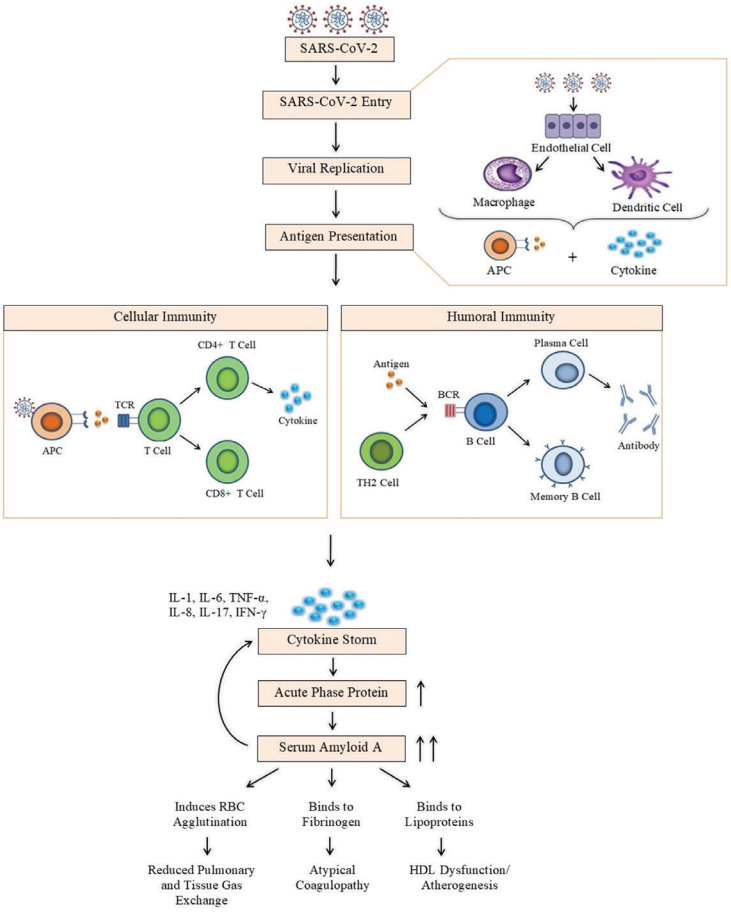

Figure 1
Schematic representation of SARS-CoV-2 induced cytokine release and the relationship with further complications (25,27).

In addition to the effect of IL-6 on positive acute phase reactants, it also instigates the transcription of C-reactive protein (CRP) gene in hepatocytes and high levels in CRP during the early stage of COVID-19 have been implicated in lung damage and the severity of the disease. CRP has also been found in high levels in patients with severe COVID-19 evolution (in which several organ systems were affected), and also in dead patients. CRP can contribute to the occurrence of severe outcomes of COVID-19 via the activation complement, induction of pro-inflammatory cytokines production and apoptosis (26).

Cytokine Storm In Covid-19

Evidence suggests that infections, including the novel human coronavirus, SARS-CoV-2 instigate immune response exaggeration or hyperactivity which causes CRS or cytokine storm. CRS is due to the activation of many white blood cells such as B cells, T cells, neutrophils, macrophages, monocytes, dendritic cells, NK cells, and other cells of the infected tissues including epithelial and endothelial cells, which consequently release high amounts or excess amounts of pro-inflammatory cytokines (28,29). This abnormality involves the overexpression of chemokines, colony-stimulating factors (CSFs), interleukins (ILs), interferons (IFNs), and tumor necrosis factor-alpha (TNF-α). Increasing evidence implicate cytokine storm in the exacerbation or severity of COVID-19 infection in patients and has been recognized as the major cause of ARDS. Furthermore, cytokine storm and its associated complications have been referred to as the major cause of COVID-19-related deaths (4,19,30,31).

There is a correlation between immune response and the progression of COVID-19 severity. It has been proven that T lymphocytes; CD4+ T cells and CD8+ T cells reduced absolute count in all COVID-19 patients (mild, moderate, and severe) but there was a marked decrease in the severe patients. This implies that there is a negative correlation between these cells and the progression of severity. Accompanying that was a marked elevation in the levels of IL-6, IL-10, IL-2R, and TNF-α. Contrary, there was a lower expression of IFN-γ (32) and this probably was a result of the decrease in the absolute count of the CD4+ T cells. Again, the absolute counts of T lymphocytes (CD4+ and CD8+ T cells) and B cells have been reported to have decreased gradually in severe and extremely severe COVID-19 patients with the severe patients having higher counts than the extremely severe patients. Despite that, the percentage of IFN-γ producing CD8+ T cells increased in both severe and extremely severe patients than in mild patients. Also, the percentage of IFN-γ producing CD4+ T cells increased in extremely severe patients. Consequently, the counts and function of T lymphocytes which includes the production of IFN-γ in COVID-19 patients are inconsistent. Moreover, the expression of IL-6, IL-10, and IL-2R increased in extremely severe patients (33). Furthermore, in a study conducted on 50 COVID-19 patients, it was observed that the production and activity of IFN-α were low in both severe and critically ill patients and there was no production of IFN-β. These variations were associated with persistent blood viral load and overexpressed inflammatory response. Accompanying these variations was an increase in the production and signaling of TNF-α and IL-6 (34).

COVID-19 patients in extremely severe conditions have high levels of systematic cytokines including IL-6, IL-8, IL-10, IL-2R, TNF-α (Table 1). Higher serum levels of IL-6, IL-10, IL-2, IL-4, TNF-α, and IFN-γ were observed in COVID-19 patients. However, the serum levels of IL-6 and IL-10 were significantly higher in the critical patients' group of the study. In addition, the serum levels of IL-10 positively correlated with the amount of C-reactive protein (CRP) (35). A study conducted on 43 adult COVID-19 patients (28 milds and 15 severe patients) revealed that IL-6 significantly varied among the 2 groups with the severe group having the highest level of IL-6. Also, IL-6 was closely related to the occurrence of COVID-19 severity in adult patients (36). In a study on a death group (68 carcasses) and a discharged group (82 volunteers), who initially tested positive for COVID-19, the laboratory results revealed that the IL-6 level of the death group was significantly higher than that of the discharged group. After confirming the results by conducting an autopsy, it was suggested that SARS-CoV-2-activated CRS might be the cause of COVID-19 mortalities (37). Liu et al. (38) reported that 38 cytokines out of the total plasma cytokines measured in 12 COVID-19 patients elevated significantly. Also, 17 cytokines associated with SARS-CoV-2 load, and 15 of the cytokines had a strong correlation with lung injury. This included M-CSF, IL-10, IFN-α2, IL-4, IP-10, IL-7, IL-1ra, G-CSF, IL-12, IFN-γ, IL-1α, IL-2, HGF, PDGF-BB, and IL-17. The TH17 cells produce IL-17 in the lungs in response to viruses which includes SARS-CoV-2, leading to the induction of cytokines production to enhance the recruitment of immune cells to the inflammation site (2,39). IL-17 demonstrates its inflammatory activity via the activation of IL-6 and IL-8 producing cells such as fibroblastic cells, epithelial and endothelial cells (2). IL-17 in conjunction with IL-6 mitigates the apoptosis of virally infected cells hence, influencing the persistent survival of the virus as the virus gets

Table 1 Levels of COVID-19 severity and their effects on cytokines.

COVID-19 Cases	Effect on Cytokines		Reference
	Increase	Decrease	
Moderate	IL-2R, IL-6, IL-10, TNF-α and IFN- γ	-	Chen et al., 2020 (32)
Severe	IL-2R, IL-6, IL-10, and TNF-α (*)	IFN- γ	
Severe	IFN-γ–producing CD8+ T cells	-	Wang et al., 2020 (20)
Critical	IL-6, IL-10 and IL-2R IFN-γ–producing $CD8^+$ T cells and IFN-γ–producing $CD4^+$ T cells	-	
Severe	TNF-α and IL-6	IFN-α and no IFN-β	Hadjaji et al., 2020 (31)
Critical	TNF-α and IL-6	IFN-α and no IFN-β	
Moderate	TNF-α, IFN-γ, IL-2, IL-4, IL-6 and IL-10	-	Han et al., 2020 (34)
Severe	TNF-α, IFN-γ, IL-2, IL-4, IL-6 and IL-10	-	
Critical	TNF-α, IFN-γ, IL-2, IL-4, IL-6 (*) and IL-10 (*)	-	
Mild	IL-6	-	Gao et al., 2020 (35)
Severe	IL-6 (*)	-	
Carcases	IL-6 (*)	-	Ruan et al., 2020 (36)
Discharged individuals	IL-6	-	
Severe	M-CSF, IL-10, IFN-α2, IL-4, IP-10, IL-7, IL-1ra, G-CSF, IL-12, IFN-γ, IL-1α, IL-2, HGF, PDGF-BB and IL-17	-	Liu et al., 2020 (36)
COVID-19 patients	IL-17	-	Ryzhakov et al., 2011; Darif et al., 2021 (2,38)

(*)=Extremely higher

to replicate itself. Again, their synergism promotes CD8+ T cell-mediated target destruction (40).

Circulating biomarkers such as the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR) and lymphocyte-to-monocyte ratio (LMR) can represent inflammatory and immune status of COVID-19 patients. NLR, PLR and LMR are useful predictors used in the prognosis of systemic inflammation and are used widely in the prognosis of viral pneumonia. NLR elevates in severely ill COVID-19 patients. Thus, NLR is associated

with COVID-19 severity and can be used as an independent prognostic biomarker for poor clinical outcomes (41). Also, in a meta-analysis conducted on 29 studies, severe patients were reported to have had increased levels of NLR (42). PLR level is a novel, cost-effective and readily available prognostic biomarker for COVID-19 severity. Its level increases in response to the severity of COVID-19 and this has been demonstrated in a meta-analysis where the severe group presented higher levels of PLR than the non-severe group (43). LMR level seems to have a negative correlation with COVID-19 severity. Higher levels of NLR and lower levels of LMR have been observed in severe COVID-19 patients. Conversely, higher levels of LMR were observed in patients with mild or moderate COVID-19 cases. Although, levels of NLR, PLR and LMR are helpful in the prognosis of COVID-19, normal reference ranges for NLR, PLR and LMR remain elusive (44).

Extrapolating from the above, targeting cytokines during treatment can reduce the progression rate of COVID-19 disease in COVID-19 patients and decrease COVID-19 caused mortalities. For instance, tocilizumab is a recombinant humanized IL-6 receptor antagonist that can hamper IL-6 from binding to its receptor. Tocilizumab is mainly used in the treatment of rheumatoid arthritis but can be used during COVID-19 treatment since CRS is largely caused by IL-6 (45). This has been demonstrated by Xu et al. (45) where tocilizumab was reported to have provided encouraging results when it was used to treat 21 patients (severe and critical).

Aside from that, other alternatives such as corticosteroids therapy maybe adopted in the treatment of COVID-19. Corticosteroids are steroid hormones with anti-inflammatory effects, and are commonly used to suppress inflammation. The proper administration of glucocorticoids to severe SARS patients ameliorated their condition via the reduction of fever, relieving of infiltrated radiation of the lungs and improving oxygenation. However, the administration of glucocorticoids should be timed properly and the dosage should be carefully taken. A too early administration of glucocorticoids inhibits the body's defence mechanism thereby causing an increase in viral load and ultimately, leading to a surge in consequences. Hence, glucocorticoids are used mainly in the treatment of critically ill COVID-19 patients suffering from cytokine storm. Its timely administration to critically ill COVID-19 patients mitigated the occurrence of ARDS and protects the organs of patients (46). Intravenous immunoglobulin therapy also has a dual potential of immune substitution and immunomodulation. However, the relevance of its application in COVID-19 patients has not been confirmed (47). Chloroquine has been reported to inhibit the production and release of TNF and IL-6 hence, chloroquine can suppress cytokine storm in COVID-19 patients. Again, the stem cell therapy can also prevent cytokine storm in patients. The mesenchymal stem cells (MSC) aside from their self-renewal potential, they have a strong anti-inflammatory and immune regulatory functions. MSC can inhibit the abnormal activation of T lymphocytes and macrophages, and can also activate their differentiation into regulatory T cells and anti-inflammatory macrophages, respectively. MSC can also inhibit the production of pro-inflammatory cytokines like TNF-α, IL-1, IL-6, IL-12 and IFN-γ (46).

Conclusion

Just as it is in all infections, COVID-19 infection stimulates the release of cytokines but some patient groups manifest an exaggerated cytokine response, thus, the occurrence of cytokine storm. Also, the progression of COVID-19 severity has an influence on the level of certain cytokines mainly, IL-6. Hence, cytokines are relevant in the diagnosis of COVID-19, and targeting them during treatment at the right time to the right patient could yield more positive results. Cytokine storm causes COVID-19-related complications and it is the main cause of COVID-19-related deaths. Considering the reported preliminary data in the literature on cytokine release caused by COVID-19 infection, it is concluded that future studies focusing on the effect of this infection on T lymphocytes and the IFN-γ levels produced by them would provide very significant findings.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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